

Invasive Candidiasis in Newborns Report of Cases and Review of Literature Diagnosis, Treatment and Prevention

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Abstract

Introduction: Neonatal invasive candidiasis is associated with significant morbidity and mortality, currently there is greater survival of critically ill newborn patients predominantly premature newborns, and then it has increased invasive fungal infections reports, being a common problem present in the neonatal intensive care units (NICU).

Objective: This review proposes to carry out actions to prevent, give treatment and monitor invasive candidiasis in the newborn infant. by reviewing the cases reported in the HMI GV Edo de Mex. And in that way determine the modalities in which this condition occurs. Consequently, make an effective and timely management

Methods: The review of the documented cases of critically ill patients diagnosed with Invasive Candidiasis, Hospitalized in the NICU area from October 2016 to February 2019, was carried out retrospectively, identifying as factors of risk those previously described being the main ones, prematurity, use of central vascular lines, exposure to broad spectrum antibiotics, as well as forms of presentation, gestational age, sex and weight of affected patients.

Results: In this Institution during the year 2018 there were a total of 3585 births of which 8.89% (n = 319) required hospitalization for different causes, the main one being: Prematurity, In this article the incidence of invasive candidiasis in the same time span of the sample, adding a total of 29 patients (n = 29) 8 of these hospitalized in the year 2018, corresponding to a 0.22% of the income, of the total of patients (n = 29) the gestational ages were report between week 29 to 40 of gestation, and weights from 1000 g - 2800 grams. In relation to the sex of the patients, it predominated in the masculine in 62.06% (n = 18) and feminine in 37.9% (n = 11). The largest number of affected patients presented between week 30 - 34. The whole of the sample cited 100% (n = 29) course with invasive Candidiasis = Neonatal Sepsis, In addition some patients attended with invasion to other devices and systems, causing endocarditis (n = 2) (6.8%), neuroinfection: (n = 1) (3.4%), hepatic colonization (n = 1) (3.4%) and Urosepsis n = 1 (3.4%), discarding in all of them intraocular injury.

They were treated with antifungal schemes according to clinical practice practices in Mexico: fluconazole, amphotericin, B dextrolicolate, Caspofungin and finally Voriconazole in patients with *Candida* spp. Resistant to the previously mentioned medications. The above according to the form of presentation and prior consent of the parents.

The final decrease in n = 3 cases unfortunately and given the seriousness and acuteness with which the disease was presented was the death of patients, otherwise high at home with respective references for follow-up in the third level of health care.

Conclusions: Neonatal Sepsis secondary to *Candida* spp in the Newborn is an important cause of morbidity and mortality in the NICU. In a newborn with risk factors and suspected infection, it is recommended to initiate an intentional search, with study and tracking of all the diana organs, when confirming the presence by blood culture and other indicators, specific antifungal treatment should be provided according to location or systems affected and the central vascular access lines should be removed within 24 hours to avoid colonization of the fungus. with the implementation of Essential Actions of patient safety, as a method for the prevention of nosocomial infections.

Those patients who had repercussions to other target organs, were directed to their exit to Hospitals that have the medical elements to continue treatment (at Cardiovascular and Neurological level).

As soon as its impact exists in Neurodevelopment, it is necessary to initiate a long-term surveillance scheme.

Besides that, more studies are needed to evaluate the toxicity of Voriconazole in the newborn.

It is working jointly with the authorities, both health and government, to carry out care in an effective and timely way, as well as insisting totally in the culture of prevention of premature birth.

Keywords: *Candia* spp; Neonatal Invasive Candidiasis (NIC); Newborn; Neonatal Intensive Care Unit (NICU); Preterm Infants

Introduction

Invasive candidiasis is an important cause of sepsis in the Neonatal Intensive Care Unit, whose incidence has increased considerably in recent decades in developing countries, due to the increase in survival of critically ill, predominantly preterm infants, and it is also associated with an increase in morbidity and mortality, including alterations in neurodevelopment in the long term. The frequency is variable according to each Hospital Center and the complexity of the patients that are managed with limited reports in Latin America. For this reason, this article is of greater relevance in order to establish an adequate surveillance, prevention, diagnosis and management strategy.

Epidemiology

According to data obtained in the literature, *Candida* spp is the main microorganism causing opportunistic fungal infections in the hospital environment. Its incidence is inversely proportional to birth weight. Globally, it varies from 2.6% to 13.2% in patients with low weight (< 1000g) [1,2].

Mortality in the extreme premature infant is reprinted up to 20%, despite the appropriate antifungal treatment and up to 60% of them develop significant neurological sequelae [1-4].

They are identified as risk factors for development of invasive candidiasis in NICU: prematurity and extreme prematurity, attributed to the immaturity of their immune system, low weight, use of invasive procedures such as placement of central vascular accesses, total parenteral nutrition, mechanical ventilation, exposure to management with broad-spectrum antibiotics (including third-generation cephalosporins and carbapenems) [1-3], lack of adherence to the essential actions of patient safety in the appropriate hand-washing technique of health personnel, use of postnatal corticosteroids and antacids in addition to the associated comorbidity (such as necrotizing enterocolitis) [2,3]. Finally, it has been described associated with patients with pathology who require abdominal surgical treatment.

Colonization by *Candida* spp is considered a risk factor for progression to Invasive Candidiasis, with variation in the percentage of colonized extreme newborns of 7-28%, in different series. Manzoni, *et al.* reported a rate of progression of 7.2% in patients colonized by *Candida* spp in three or more sites versus 7.2% in those non-colonized terminal RNs (< 0.001). There were no significant differences in the progression to CI in those NB with colonization of a site [5,6]. In Mexico there is very little data on colonization by *Candida* spp.

Clinical manifestations

In the neonate, they are generally nonspecific, including alimentary intolerance, abdominal distension, systemic inflammatory response data, hypothermia, respiratory distress, hemodynamic instability and blood level: alterations in the leukocyte count, in addition to the presence of severe thrombocytopenia with or without active bleeding, any level. The presence of fever is not very frequent, even in systemic disease. Hyperglycemia associated with thrombocytopenia has also been described in disseminated fungal infections [7].

The main target organs of invasive candidiasis are genitourinary tract, eyeballs, central nervous system, liver spleen, heart. The manifestations vary according to the affected area.

Diagnosis

When having the only suspicion of Invasive Candidiasis or having a positive Hemoculture to *Candida* spp, it is mandatory to start a search for invasive fungal disease.

Detailed clinical examination including ocular fundus, paraclinical examinations (Table 1) [7-9].

	Test Type	Alterations	Observations
Physical exploration	Complete and detailed		Include ocular Fund (rule out endophthalmitis)
General exams	Hemogram	Significant platelet count decrease	<100,000/mm ³
	Glycemia	Hyperglycemia	presence or recent history
	Study of renal and hepatic function	Must be performed prior to the use of anti-fungal treatment	According to result adjustment of medications
Microbiological study	Central or peripheral blood cultures	2 to obtain a higher isolation rate	Having a negative blood culture does not rule out the presence of Candida spp
	Central blood culture	If it is positive, it is considered associated with the device and should be removed.	Taken from central venous catheter
	Urinalysis and urine culture	Must be taken by sterile technique and bladder catheterization Pseudohyphaeal search	Positive cultivation with the presence of > 10 ⁴ ufc/ml
	Study of cerebrospinal fluid	Gram stain, cytochemical and culture with seeding blood agar and Sabouraud.	
Direct Mycological Exam		Cultivation of any affected area	
	Molecular diagnostic techniques	Polymerase chain reaction	Under evaluation
	<i>In vitro</i> susceptibility	It must be performed on all the isolates	Fundamental for adjustment of antifungal treatment.
Ultrasound	Ultrasound Transfontanelle	Discard presence of cerebral fungomas	May reveal the presence of ventricular dilation, calcifications or fungal balls,
	Abdominal	Search for fungomas	Defines parenchymal, renal, hepato-splenic or peritoneal compromise. Abdominal
	Cardiac	Vegetations	must be done intentionally. Discard Endocarditis Cardiaca

Table 1: Diagnosis.

Treatment

Start immediately, with fungicide medications, should be individualized according to evolution and complications in patients (Table 2).

Medication	Dose	
Amphotericin B desoxicolato	0.5 - 1 mg/ kg/ day	Infusion 4 hours
Anfotericina B liposomal	3 - 5 mg/ kg/ day	
Caspofungin	25 mg/m ² sc/ day	After discarding commitment of CNS.
Micafungin	10 mg/kg/day or 15 mg/kg/day if it affects CNS (Central Nervous System)	No available in Mexico
Fluconazole	6 mg/kg/day requires loading dose 12 mg/kg/d	
Voriconazole	3 mg/kg/To every 12hr Requires loading dose	It was generally used in cases of infection resistant to treatment with other antifungals.

Table 2: Treatment of invasive candidiasis in neonates.

The location and extent of infection, *in vitro* susceptibility of the isolate, mechanism of action and toxicity related to the drug, as well as previous use of prophylaxis should be assessed [4].

Amphotericin B-d has been for years the drug of choice in the treatment of Invasive Candidiasis in N, having minor adverse effects in older children or adults [10]. It is important to emphasize that the penetration of cerebrospinal fluid in neonates ranges from 40 - 90% of the concentrations found in plasma [11]. It has been suggested that there is a lower frequency of renal involvement in the pediatric population, especially in extreme preterm infants. However, the studies are inconclusive [12,13].

The lipid formulations of Amphotericin B as Amphotericin Liposomal (L-amB) Amphotericin of lipid complex (ABDC) are an alternative with similar spectrum of action and less nephrotoxicity. Most of the publications correspond to case series or retrospective works [14,15].

Echinocandins (Caspofungin or Micafungin), are also recommended in the treatment of IC in neonates, proving to be more effective than Amphotericin Bd, its use is not recommended when there is CNS compromise, due to the absence of conclusive studies evaluating its efficacy in this ethereal group [16].

Fluconazole is an agent belonging to the group of triazoles, with fungistatic effect, so according to the literature should be reserved for patients with urinary candidiasis, who has negative blood culture, or for newborns with stable clinical condition and whose *Candida* spp is susceptible to this drug [17].

Voriconazole is an antifungal drug from the group of triazole derivatives. It is used in the treatment of systemic infections or caused by resistant fungi. shows a broad spectrum of *in vitro* activity, with activity against *Candida* spp. No response to treatment with other medications. It has recently developed, the experience of its use in newborns is limited [18,19].

It was reserved only to be used in cases in which there was no response to the established management.

Treatment time: depends on the location and spread of the infection, clinical response and negativization of the cultures. A strict clinical and microbiological follow-up is essential in each case, on average it should be prolonged for 14 - 21 days after obtaining at least two consecutive negative blood cultures. It has been described that up to 20% of cases can a negative blood culture followed by positive blood cultures [19]. Therefore, it is necessary to have at least two to suspend antifungal therapy.

There are limited data in newborns to support the utility of associating a second antifungal to therapy, but it should not be ruled out. If required.

Methods

The review of the documented cases of critically ill patients diagnosed with Invasive Candidiasis, Hospitalized in the NICU area from October 2016 to February 2019, was carried out retrospectively, identifying as factors of risk those previously described being the main ones, prematurity, use of central vascular lines, exposure to broad spectrum antibiotics, as well as forms of presentation, gestational age, sex and weight of affected patients.

Discussion

In the Maternal and Child Hospital (GV) Edo Mex, during the year 2018 there were a total of 3585 births of which 8.89% (n = 319) required hospitalization for different reasons, the main one being: Prematurity, In this article Document the incidence of invasive candidiasis in the same time period of the sample, adding a total of 29 patients (n = 29) 8 of these hospitalized in the year 2018, corresponding to a 0.22% of the income, of the total of patients (n = 29) gestational ages are reported between week 29 to 40 of gestation, and weights from 1000g - 2800 grams. In relation to the sex of the patients, it predominated in the masculine in 62.06% (n = 18) and feminine in 37.9% (n = 11). The largest number of affected patients presented between week 30 - 34. The whole of the sample cited 100% (n = 29) course with invasive Candidiasis = Neonatal Sepsis, In addition some patients attended with invasion to other devices and systems, causing endocarditis (n = 2) (6.8%), neuroinfection: (n = 1) (3.4%), hepatic colonization (n = 1) (3.4%) and Urosepsis n = 1 (3.4%), discarding in all of them intraocular injury (Figures 1-3).

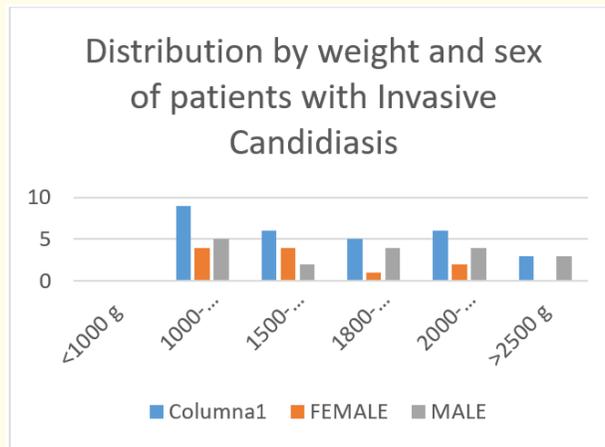


Figure 1

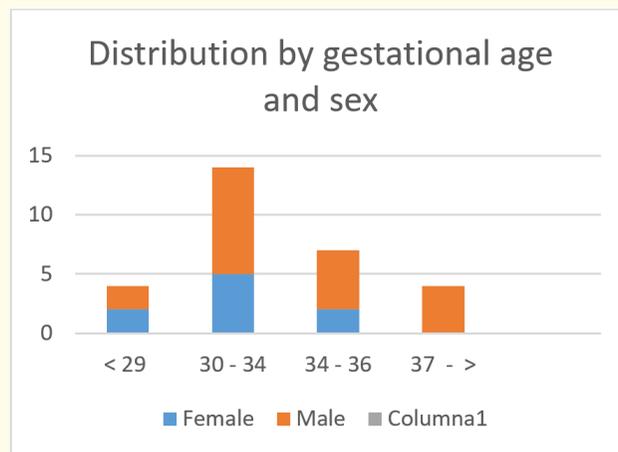


Figure 2

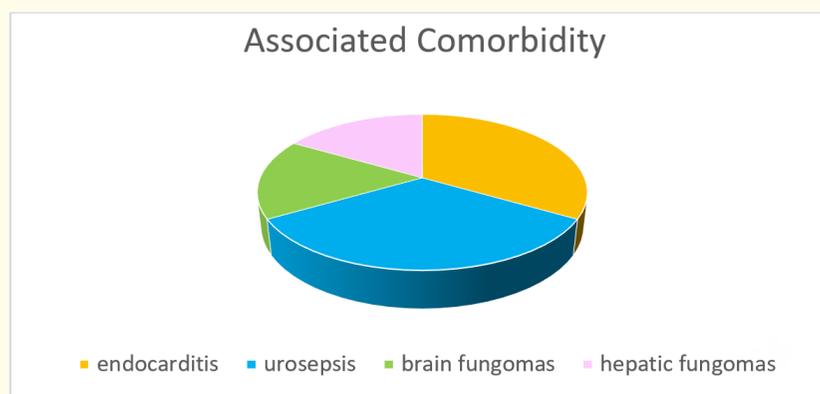


Figure 3

Antifungal schemes were treated according to clinical practice guidelines of Health in Mexico: Fluconazole, Amphotericin, B dexosicolate, Caspofungin and finally Voriconazole. There was no availability of Liposomal Amphotericin B in patients with *Candida* spp. Resistant to the aforementioned drugs. The above according to the form of presentation and prior consent of the parents. Of all the patients (n = 29), management was induced with Fluconazole before the suspicion of Infection by *Candida* in 100% of the cases, having the confirmation by means of blood cultures were staggered when having Amphotericin B in n = 18 cases (62.06%), management with Caspofungin due to lack of response to treatment: n = 8 (27.5%) Voriconazole was used as a second-line antifungal agent in the face of resistance to amphotericin and not having echinocandins at a specific time, in a total of 12 patients (41.3%), Caspofungin was not used in the management of Neuroinfection, which could be resolved with Amphotericin Bd (Figure 4).

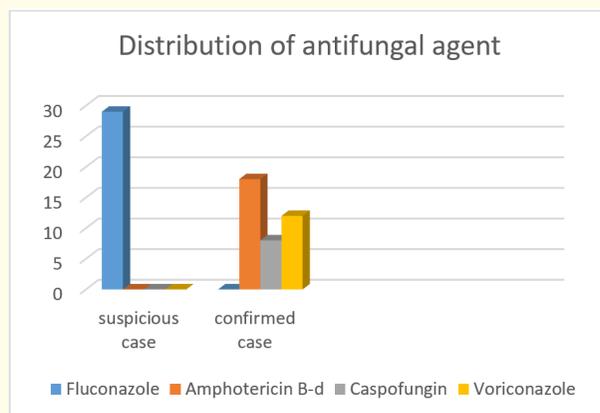


Figure 4

The final outcome in n = 3 cases unfortunately and given the severity and acuteness with which the disease was presented was the death of patients, otherwise high at home with respective referrals for follow-up in the 3rd level of health care.

Conclusions

Neonatal Sepsis secondary to *Candida* spp in the Newborn is an important cause of morbidity and mortality in the NICU. In a newborn with risk factors and suspected infection, it is recommended to initiate an intentional search, with study and tracking of all the white organs, when confirming the presence through blood culture and other indicators, specific antifungal treatment must be provided according to affected organs and/or systems.

Remove the central vascular access lines associated with the presence of *Candida* infection within 24 hours.

To make known and implement Essential Actions of patient safety, as a method of prevention of nosocomial infections. Specifically, in the technique of hand washing and the 5 moments of application of said procedure, watch is carried out.

It is essential to have the specific indication of broad-spectrum antibiotics, to avoid their indiscriminate use.

There are specific antifungal drugs, already documented, but in the presence of resistances to the management of them, further studies are required to evaluate efficacy and toxicity of Voriconazole. There is little evidence.

Those who had repercussions to other target organs, were directed to their exit to Hospitals that have the medical elements to continue treatment (at Cardiovascular and Neurological level).

As soon as its impact exists in Neurodevelopment, it is necessary to initiate a long-term surveillance scheme. To achieve document results.

It is working jointly with the authorities, both health and government, to carry out an effective and timely care, as well as fully insisting on the culture of prevention of premature birth.

Conflict of Interests

There is not conflict of interests.

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