REVIEW

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Congenital systemic candidiasis: a comprehensive literature review and meta-analysis of 44 cases

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Abstract

Systemic candidiasis is a frequent complication in neonatal units, but congenital systemic candidiasis is an unusual diagnosis, observed in both full-term and preterm infants, with less than 50 cases reported to date. Congenital candidiasis presents with a wide spectrum of symptoms, ranging from diffuse skin eruptions to severe systemic disease, resulting in fetal demise or early neonatal death. Although management guidelines have been published almost two decades ago, due to the rarity of this type of infection, conclusive recommendations are difficult to establish, since they are based on anecdotal experience. In this paper, we present a comprehensive meta-analysis of the current scientific knowledge regarding congenital candidiasis, which spans 54 years and includes a total of 44 cases.

Keywords: congenital systemic candidiasis, cutaneous congenital candidiasis, neonatal death, preterm birth, stillbirth, preterm premature rupture of the membranes.

Introduction

Candidiasis is defined as infection with fungi of the *Candida* genus. Congenital candidiasis is a rare entity in which intrauterine infection with *Candida* spp. is evident at birth. It may be localized (congenital cutaneous candidiasis), presenting as an extensive skin rash, which eventually results in widespread desquamation, or generalized (congenital systemic candidiasis), which usually lacks cutaneous involvement and presents with respiratory distress, meningitis, sepsis, and death.

Unlike nosocomial systemic candidiasis, which is a common problem in neonatal intensive care units worldwide, congenital systemic candidiasis is an extremely rare disease reported both in full-term and preterm infants, with less than 50 cases published in the medical literature to date.

Candida vaginitis occurs in approximately 25% of all pregnancies, without causing any obstetric complications [1]. Rarely, ascending infection from the lower maternal genital tract may occur, resulting in placental candidiasis. The extent of infection is usually limited to fungal chorioamnionitis and funisitis, with no fetal involvement. When it occurs, congenital neonatal infection is usually limited to cutaneous involvement, but life-threatening disseminated candidiasis may occur, especially in preterm infants. Infections limited to the placenta and/or umbilical cord or to the skin respond well to minimal antifungal therapy and almost always have favorable outcomes. On the other hand, systemic dissemination of congenital candidiasis is a severe cause of early-onset sepsis, involving a high mortality rate (35%).

Preterm infants are predisposed to *Candida* infections mainly due to the immaturity of their immune system. Congenital candidiasis is rare and must be distinguished from other conditions presenting with pustular lesions at birth, in order to avoid severe complications, which may have lifelong repercussions.

Aim

In this paper, we develop a meta-analysis of all previously reported cases of systemically disseminated congenital candidiasis in the English literature, regarding gestational age and weight at delivery, duration of membrane rupture, extent of infection and association with an intrauterine foreign body, in the attempt to picture a comprehensive clinical and morphological spectrum of this extremely rare disease.

Methods

Multiple *PubMed* surveys using various combinations of the following terms: "congenital", "intrauterine", "*Candida*", "candidiasis", "candidemia", "systemic", "invasive" and "disseminated" revealed a total of 43 cases published in English journals, as far back as year 1966, mainly as isolated case reports and short case series. Most search results included reports of perinatal nosocomial infections with *Candida* spp. or congenital cutaneous infections with *Candida* spp. showing no signs of systemic involvement. We also identified series of cases including congenital systemic candidiasis and congenital cutaneous candidiasis. Only cases with confirmed systemic infection have been included in this study. Systemic infection has been defined as having a positive blood, urine, and/or cerebrospinal fluid culture for *Candida* spp., or demonstration of *Candida* in histopathological (HP) or culture specimens obtained at autopsy.

Results

Tables 1 and 2 summarize the main characteristics of the 44 infants with congenital systemic candidiasis identified in the English literature [1–40].

Table 1 – ***Clinical features of infants with systemic congenital candidiasis***

Case No.	Author(s), Country (year) [Reference No.]	Fetal gender	GA [weeks]	BW [g]	Foreign body	ROM [hours]	Delivery method
1.	Dvorak & Gavaller, USA (1966) [2]	NA	32	2736	None	0	CS
2.	Albarracin *et al.*, Canada (1967) [13]	F	24	800	None	>48	SVD
3.	Aterman, Canada (1968) [24]	F	22	440	None	0	SVD
4.	Lopez & Aterman, Canada (1968) [34]	F	28	1219	None	0	SVD
5.	Misenhimer & Garcia-Bunuel, USA (1969) [35] – Case #1	M	26	1070	IUD	24–48	SVD
6.	Misenhimer & Garcia-Bunuel, USA (1969) [35] – Case #2	F	24	800	IUD	<12	SVD
7.	Ho & Aterman, Canada (1970) [36]	NA	16	75	IUD	<12	SA
8.	Schirar *et al.*, France (1974) [37]	M	20	650	Cerclage	0	SVD
9.	Brandsma *et al.*, Netherlands (1975) [38]	NA	20	360	IUD	0	SA
10.	Levin *et al.*, Israel (1978) [39] – Twin #2	F	29	520	None	>48	SVD
11.	Buchanan *et al.*, UK (1979) [3]	F	25	NA	IUD	0	SVD
12.	Johnson *et al.*, USA (1981) [4]	F	27	1080	None	0	SVD
13.	Nagata *et al.*, Japan (1981) [5]	F	35	2530	None	>48	SVD
14.	Delprado *et al.*, Australia (1982) [6]	M	34	2275	IUD	12–24	CS
15.	Bittencourt *et al.*, Brazil (1984) [7]	M	19	110	IUD	0	SA
16.	Mamlok *et al.*, USA (1985) [8]	F	36	2560	None	>48	SVD
17.	Smith *et al.*, USA (1988) [9]	NA	16	104	IUD	>48	IL
18.	Donders *et al.*, Belgium (1991) [10]	F	22	450	IUD	12–24	SVD
19.	Ng *et al.*, Hong Kong (1994) [11]	F	24	815	Cerclage	0	SVD
20.	Barone & Krilov, USA (1995) [12]	F	39	NA	None	0	CS
21.	Nichols *et al.*, Australia (1995) [14]	M	25	760	IUD	0	SVD
22.	Roqué *et al.*, USA (1999) [1]	M	20	398	IUD	25-48	IL
23.	Waguespack-LaBiche *et al.*, USA (1999) [15]	M	25	520	None	>48	IL
24.	Arai *et al.*, Japan (2002) [16] – Twin #1	M	29	1118	None	0	CS
25.	Aldana-Valenzuela *et al.*, Mexico (2005) [17]	F	39	2540	None	0	CS
26.	Krallis *et al.*, Greece (2006) [18] – Twin #1	F	26	425	None	NA	SVD
27.	Krallis *et al.*, Greece (2006) [18] – Twin #2	M	26	535	None	NA	SVD
28.	Baradkar *et al.*, India (2007) [19]	M	26	1800	None	NA	NA
29.	Carmo *et al.*, Australia (2007) [20] – Twin #1	F	32	1694	None	12–24	CS
30.	Meizoso *et al.*, Spain (2008) [21]	F	28	500	IUD	0	IL
31.	Wang *et al.*, Taiwan (2008) [22] – Case #1	F	34	2012	None	NA	CS
32.	Wang *et al.*, Taiwan (2008) [22] – Case #2	M	38	3390	None	NA	CS
33.	Haase *et al.*, Germany (2009) [23]	F	33	1530	None	NA	SVD
34.	Tiraboschi *et al.*, Argentina (2010) [25]	F	27	1020	None	<12	CS
35.	Nouri-Merchoui *et al.*, Tunisia (2011) [26]	F	35	NA	None	NA	SVD
36.	Li *et al.*, Taiwan (2012) [27]	F	26	770	None	>48	SVD
37.	Pineda *et al.*, USA (2012) [28] – Twin #1	M	29	1440	None	12–24	CS
38.	Pineda *et al.*, USA (2012) [28] – Twin #2	M	29	1370	None	12–24	CS
39.	Siriratsivawong *et al.*, USA (2014) [29]	M	37	NA	None	<12	SVD
40.	Chen *et al.*, Taiwan (2015) [31] – Twin #1	M	30	1664	None	<12	SVD
41.	Chen *et al.*, Taiwan (2015) [31] – Twin #2	F	30	1488	None	<12	SVD
42.	Oberhauser *et al.*, Switzerland (2017) [32]	M	25	920	None	0	CS
43.	Lee *et al.*, Malaysia (2017) [33] – Twin #1	F	29	1650	None	0	SVD
44.	Georgescu *et al.*, Romania (2019) [40] – Our case	M	30	1100	None	<12	SVD

BW: Birth weight; CS: Caesarean section; F: Female; GA: Gestational age; IL: Induced labor; IUD: Intrauterine device; M: Male; NA: Not available; ROM: Rupture of membranes; SA: Spontaneous abortion; SVD: Spontaneous vaginal delivery.

Table 2 – ***Clinical features of infants with congenital systemic candidiasis***

Case No.	Maternal history of vaginal discharge	Maternal therapy during pregnancy	Blood, urine or tissue culture specimens	Organ involvement confirmed by culture or histopathological examination (except blood/urine)	Fetal outcome (survival time)
1.	NA	NA	*C. albicans*	L, GI, K	Fatal (34 hours)
2.	NA	NA	*C. albicans*	S, L, GI	Fatal (NA)
3.	No	No	*C. albicans*	UC, L, GI	Fatal (six hours)
4.	No	No	*C. albicans*	UC, GI	Fatal (13 hours)
5.	Yes	No	NA	FM, L	Fatal (29 hours)
6.	Yes	No	*C. albicans*	L, GI	Fatal (114 hours)
7.	No	No	NA	FM, L, GI	Abortion
8.	Yes	NA	*C. albicans*	UC, FM, P, L, GI	Stillborn
9.	No	No	*C. albicans*	UC, FM, P, S, L, GI, LN	Abortion
10.	No	AB	*C. albicans*	P, B	Stillborn
11.	Yes	Yes (NA)	NA	UC, S, L	Stillborn
12.	Yes	No	*C. albicans*	P, S, L, B	Fatal (14 days)
13.	Yes	NA	*C. albicans*	P, L	Fatal (one hour)
14.	Yes	Yes (NA)	*C. albicans*	UC, FM, P, S, L, LIV	Fatal (90 minutes)
15.	Yes	AF	NA	UC, FM, P, S, L, GI	Abortion
16.	Yes	AB	*C. albicans*	UC, FM, P, L	Fatal (14 hours)
17.	No	No	NA	L, GI	Abortion
18.	No	No	*C. albicans*	UC, FM, P, L	Stillborn
19.	No	CORT	*C. albicans*	L, GI	Survival
20.	No	CORT	*C. albicans*	S, B	Survival
21.	No	No	*C. tropicalis*	FM, P, L	Stillborn
22.	No	No	*C. albicans*	FM, P, B, LIV	Stillborn
23.	No	AB	*C. parapsilosis* + *C. albicans*	S, L, GI	Survival
24.	No	No	*C. glabrata*	S, L, GI	Survival
25.	Yes	Insulin	*C. albicans*	S, L	Survival
26.	No	CORT	*C. parapsilosis*	L, GI	Fatal (72 hours)
27.	No	CORT	*C. albicans*	L, GI	Fatal (22 hours)
28.	NA	NA	*C. albicans*	B	Survival
29.	No	AB	*C. albicans*	P, L, LIV	Fatal (22 hours)
30.	Yes	AF	*C. albicans*	UC, FM, L, GI	Stillborn
31.	Yes	NA	*C. albicans*	S, L	Survival
32.	No	No	*C. albicans*	S	Survival
33.	No	No	*C. albicans*	S	Survival
34.	No	No	*C. albicans*	UC, P	Survival
35.	No	AB	*C. albicans*	S	Survival
36.	No	No	*C. albicans*	S, H, K	Fatal (128 days)
37.	No	AB	*C. kefyr*	UC, FM, P	Survival
38.	No	AB	*C. kefyr*	UC, FM, P	Survival
39.	No	AB	*C. albicans*	UC, P, S	Survival
40.	No	No	*C. albicans*	P, S, L	Fatal (81 hours)
41.	No	No	*C. albicans*	P, K	Survival
42.	No	AB + CORT	*C. albicans*	S, K	Survival
43.	Yes	No	*C. albicans*	L	Fatal (32 hours)
44.	No	No	*C. albicans*	L, GI, K, LIV, SPL, B	Fatal (76 hours)

AB: Antibiotics; AF: Antifungal; B: Brain; CORT: Corticosteroids; FM: Fetal membranes; GI: Gastrointestinal tract; H: Heart; K: Kidney; L: Lungs; LIV: Liver; LN: Lymph node; NA: Not available; P: Placenta; S: Skin; SPL: Spleen; UC: Umbilical cord.

Seven authors reported twin pregnancies [16, 18, 20, 28, 31, 33, 39]. In three of these cases, both twins suffered systemic infection with *Candida* spp. [18, 28, 31]. Among the remaining four cases, only one twin suffered systemic infection, while the other twin was either unaffected or featured only cutaneous manifestations [16, 20, 33, 39]. As already mentioned, unaffected twins or twins with cutaneous rash and no systemic involvement have been excluded from this study. Surprisingly, all cases in which both twins were equally affected were dichorionic diamniotic pregnancies, while cases where only one twin was affected were mainly monochorionic diamniotic pregnancies.

At least 14 (34.15%) mothers had an intrauterine foreign body in place, either in the form of cervical cerclage or an intrauterine device (IUD). The presence of an intrauterine body was associated with congenital systemic candidiasis in babies weighing less than 1000 g (12 out of 14), suggesting that the foreign body could predispose the infant to invasive candidiasis and

subsequent preterm birth during the first two trimesters of gestation.

There were five (11.36%) miscarriages, 35 (79.55%) preterm deliveries and four (9.09%) full-term deliveries. Most women entered spontaneous labor (54.55%). There were three (6.82%) spontaneous abortions, 12 (27.27%) pregnancies delivered by Caesarean section and four (9.09%) cases were labor was induced therapeutically. There were 17 (38.64%) live births with subsequent fatal outcome, 11 (25%) cases of abortion/stillbirth and 16 (36.36%) cases in which the newborn survived. In fatal cases, survival ranged from 90 minutes to 128 days. All pregnancies with a total duration of ruptured membranes of more than 48 hours were fatal (n=7), but so were most of the pregnancies with intact membranes (11 out of 16). However, this information was not available in seven cases.

Gestational age ranged between 16 and 39 weeks, with an average of 27.86 weeks and a standard deviation of 5.84. Birth weight ranged between 75 g and 3390 g, with an average of 1180.95 g and a standard deviation of 809.87.

In at least 14 (34.15%) cases, a maternal history of vaginal discharge has been confirmed and 13 of them had fatal outcome. During pregnancy, nine (21.95%) patients received antibiotics, five (12.19%) patients received corticosteroids and only two (4.88%) patients received antifungal therapy, but fetal outcome did not appear to be meaningfully impacted by any of those medications.

Based on the information in our meta-analysis, typical sites of infection were those in direct contact with the amniotic fluid: umbilical cord, fetal membranes, placental surface, fetal skin, lungs, and gastrointestinal tract. Among the 44 cases identified in the scientific literature, there was only one case with involvement of the fetal heart and one case with involvement of the lymph nodes. Georgescu *et al.* (2019) reported the only case with involvement of the fetal spleen [40]. Organ involvement confirmed by culture and/or HP examination is summarized in Figure 1.

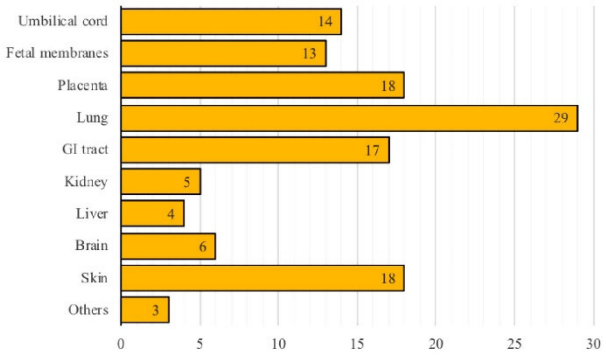

Figure 1 – ***Organ involvement confirmed by culture and/or histopathological examination. GI: Gastro-intestinal.***

Discussions

Congenital systemic candidiasis is an extremely rare disease and as more cases are recognized, additional and important evidence can be gained for a better understanding of this enigmatic clinical entity. The first case of *Candida* infection of the uterine contents during pregnancy was reported by Benirschke & Raphael, in 1958 [41]. They reported the case of a 36-year-old gravida II para I who gave birth to an anencephalic female infant with *C. albicans* chorioamnionitis confirmed by positive cultures from the fetal membranes and placenta. This is also the first and only association reported in the scientific literature between anencephaly and congenital candidiasis. However, no autopsy was performed and no information about fetal fluid or organ involvement is available. The first biologically confirmed congenital systemic infection with *Candida* spp. was published in *New England Journal of Medicine* by Dvorak & Gavaller, in 1966 [2], and was followed by a plethora of case reports and case series, including twin and singleton pregnancies (Tables 1 and 2). After a comprehensive review of all these reports, we have summarized in this paper the etiopathogenesis, risk factors, clinical presentation, methods of diagnosis, possible differential diagnoses, as well as treatment and outcome of congenital systemic candidiasis.

Etiopathogenesis

C. albicans is a common inhabitant and frequent pathogen of the female genital tract, especially during pregnancy [42]. In our meta-analysis, *C. albicans* was isolated from cultures in 34 cases, but as microbiological techniques improved, other *Candida* strains were identified as pathogens. Nichols *et al.* reported a case of *C. tropicalis* disseminated chorioamnionitis [14]. Krallis *et al.* [18] and Waguespack-LaBiche *et al.* [15] reported infections with *C. parapsilosis*. Arai *et al.* [16] reported a case of dichorionic diamniotic twin pregnancy in which one of the twins presented congenital infection with *C. glabrata*. Pineda *et al.* [28] reported a case of dichorionic diamniotic twin pregnancy in which both infants suffered congenital infection with *C. kefyr*.

Two different routes of intrauterine infection have been postulated [43]. If present in the maternal circulation, fungal microorganisms could reach the fetal circulation through the placenta. This route invariably results in a widespread pattern of visceral involvement, with prominent lesions mainly affecting the liver [43]. The alternate and more probable scenario is that microorganisms from the maternal genital tract might penetrate ruptured or intact fetal membranes and infect the amniotic fluid. This vaginal ascending route results in an inflammatory process primarily affecting the amniotic fluid and amniotic surface of the placenta and umbilical cord. The fetus develops cutaneous manifestations and is secondarily infected by swallowing and aspirating infected amniotic material. The most severely affected are the gastrointestinal and respiratory systems with subsequent systemic dissemination and multiorgan failure [43, 44]. Most importantly, *Candida* can penetrate intact fetal membranes and intrauterine infection can develop in the absence of symptomatic vaginal candidiasis [45].

Multiple studies conclude that the magnitude of secondary spread from the amnion varies considerably, based on the virulence of the microorganism, degree of contamination and fetal immune response [8, 37]. Premature, low birth weight infants with diminished fetal response have increased risk of dissemination and

death [46, 47]. Maternal risk factors include antibiotic therapy during labor, symptomatic vulvovaginal candidiasis, the use of intrauterine contraceptive devices and presence of cervical sutures during pregnancy [6, 35, 48]. However, none of these maternal risk factors can be used as a reliable predictor for the severity of congenital candidiasis [44].

Spreading of the infection to the lungs, pharynx, and the colonization of the digestive tract, as reported in our case, occurred due to inhaling and swallowing infected amnionic fluid. Hematogenous spread to the liver, kidney, spleen, and brain was probably favored by the immature immune system of the preterm infant.

Risk factors

Congenital candidiasis appears in the setting of *Candida* vulvovaginitis, which affects approximately 25% of all pregnant women [49, 50]. Although frequently present in the vagina, less than 1% of placentas are confirmed with *Candida* on the fetal surface [51]. Among these cases, congenital cutaneous infection of the fetus is rare and systemic involvement is exceptional. The reason why some infants born from women with vulvovaginitis develop congenital candidiasis, while others do not, remains unknown. Chen *et al.* published the first molecular evidence of congenital systemic candidiasis associated with maternal *Candida* vaginitis [30]. They encountered a premature infant with congenital invasive candidiasis in whom isolates of *C. albicans* from the blood and oral cavity of the infant as well as vagina of the mother were available for genotyping analysis. Both isolates from the infant and the mother shared an identical pulsed-field gel electrophoresis pattern, while the three control strains belonged to three different genotypes, distinct from the genotype of the case infant. Similar results using the same method have been subsequently reported by Tiraboschi *et al.*, in 2010 [25].

The presence of a foreign body, such as an IUD or cervical sutures, appear to be the most important risk factors associated with congenital systemic candidiasis and early preterm birth. Extensive instrumentation in the delivery room and invasive procedures, such as placement of an indwelling catheter in the neonatal period or an altered immune response, particularly neutrophil or macrophage function may increase the risk for subsequent development of systemic disease.

Diagnostic amniocentesis has preceded and may trigger the development of congenital cutaneous candidiasis [52]. Maternal age, parity, diabetes, nutrition, urinary tract infections, prolonged labor and tocolytic therapy do not appear to be risk factors for congenital candidiasis [53–59]. However, congenital candidiasis may precipitate premature rupture of membranes and preterm delivery. Although maternal diabetes is not considered a risk factor for congenital candidiasis [53], this is not a proven fact and further studies are needed before this condition is discarded.

Chen *et al.* described that first infants from premature twin pregnancies have higher risk of invasive candidiasis compared to the other twin, because they are the first to be affected by ascending infection, while the second twins are usually infected during delivery [31]. Thus, second twins are generally less severely affected than first twins, as observed in four out of the seven twin case reports we identified.

Barone & Krilov reported a case of *Candida* meningitis in a full-term infant with congenital cutaneous candidiasis from a mother with short-term prenatal Prednisone exposure [12]. Corticosteroids, which are a known risk factor for *Candida* infection, decrease neutrophil function and may have depressed the infant's immune function, allowing *Candida* dissemination.

Clinical presentation

Congenital candidiasis has a plethora of clinical features, ranging from a diffuse erythematous skin eruption with or without vesicles and pustules to systemic disease, with or without skin involvement, in which the lung and gastrointestinal tract are most frequently affected [60].

Skin lesions in congenital candidiasis typically present on the first day of life and sometimes can be delayed up to six days. The typical rash consists of a generalized eruption of 2 mm to 4 mm erythematous macules, papules and/or pustules. Carmo *et al.* [20] reported a case of congenital candidiasis without rash, presenting with overwhelming septic shock and neutropenia. They encountered a twin pregnancy in which the presenting twin succumbed due to candidemia with no signs or symptoms to suggest *C. albicans* infection. The other twin eventually developed florid pustulo-vesicular and markedly pruritic truncal rash, with diffuse erythroderma, but made a complete recovery under Amphotericin B therapy.

The most common manifestation of congenital systemic candidiasis is sepsis with respiratory distress. Once the symptoms are evident, the clinical course is so fulminant that even prompt initiation of antifungal therapy is rarely lifesaving [15, 20, 26].

Candidal meningitis is a frequent manifestation of congenital candidiasis, with limited information available on long-term neurodevelopment. The infants present cerebrospinal fluid alterations similar to those observed in other infections, such as tuberculosis, cryptococcosis and histoplasmosis [61–63]. In our meta-analysis, we identified four cases of *Candida* meningitis, two of which had favorable outcome [12, 19].

Diagnosis

Definitive diagnosis of invasive congenital candidiasis can be confirmed by fungal culture from a sterile body fluid from the newborn (such as blood, urine or cerebrospinal fluid, etc.) and/or microscopic demonstration of spores and pseudohyphae of *C. albicans* [22, 64]. Immunological evaluation generally does not reveal any specific defect and has no diagnostic significance.

The lesions in the umbilical cord are frequently associated with other lesions in the fetal adnexa. However, nowhere can the characteristic pathology be seen as clearly and as easily as in the umbilical cord, which should always be examined most carefully. Gross examination of the umbilical cord should reveal small, round, white-yellow lesions measuring 0.5–2 mm, clustered along the surface of the cord, sometimes penetrating deeply within the Wharton's jelly. The extraplacental membranes may feature diffuse yellow exudate on the fetal surface. Infrequently, the chorionic surface, intervillous space and sometimes even the chorionic villi may be affected.

Yeasts and pseudohyphae can be identified in routine Hematoxylin–Eosin (HE) staining but are best visualized using Periodic Acid–Schiff (PAS) or Gömöri Methenamine Silver stainings. In the umbilical cord, the inflammation usually has a wedge shape, with the wide base towards the surface of the cord and is composed of neutrophils, lymphocytes and histiocytes. Cellularity and micro-organisms tend to lower in density towards the center of the umbilical cord and rarely extend to the umbilical vessels [65].

Differential diagnosis

Based on the clinical presentation, the differential diagnosis of congenital candidiasis can be very extensive. Systemic infection may or may not be associated with cutaneous involvement. When mucocutaneous lesions are present, congenital candidiasis should be included in the differential diagnosis of other neonatal generalized maculopapular or pustular skin eruptions, such as: staphylococcal pustulosis, *Listeria monocytogenes* infection, impetigo, chickenpox, *Herpes simplex* virus infection, syphilis, *erythema toxicum neonatorum*, milia, Ritter's disease, Leiner's disease, *epidermolysis bullosa* and Langerhans cell histiocytosis [66].

Infants lacking mucocutaneous manifestations usually present with fever and severe respiratory distress, raising the possibility for neonatal bacterial infection and septicemia.

Treatment and outcome

In full-term infants, congenital cutaneous candidiasis almost invariably follows a self-limited, benign course, despite the presence of chorioamnionitis and funisitis. On the other hand, preterm infants with low birth weight have the highest risk for development of systemic disease. They may be stillborn or may present early in neonatal life with *in utero* acquired infection. Those with burn-like dermatitis are at particularly high risk for systemic infection and death [67–70]. The overall mortality of untreated systemic candidiasis ranges between 39% and 94%. Therefore, early diagnosis and treatment are crucial.

Prompt initiation of antifungal therapy appears to be the most important factor associated with survival in systemic infection [68–70]. Amphotericin B is the first-line agent for treatment of congenital systemic candidiasis [71]. Unfortunately, some patients do not show improvement and evolve to persistent candidemia and further clinical deterioration. In these cases, replacing Amphotericin B with Caspofungin, has been reported highly effective in controlling neonatal candidemia refractory to Amphotericin B therapy and a possible salvage therapy. Additional benefit may be provided by introduction of 5-Flucytosine. Use of Fluconazole may be considered when toxicity to Amphotericin B is prohibitive and the organism is susceptible, although data to support its use for treatment of systemic candidal infection in preterm infants are lacking.

Haase *et al.* detailed the clinical findings and successful treatment of *C. albicans* fungemia in a preterm infant with congenital ichthyosis (Harlequin baby) [23]. The infant developed systemic candidiasis refractory to liposomal Amphotericin B and was treated with echinocandin Caspofungin, which led to prompt eradication of *C. albicans* fungemia without serious side effects. Oberhauser *et al.* also reported positive results in treating refractory candidemia with echinocandin Micafungin [32].

Congenital cutaneous candidiasis should be considered an invasive *Candida* infection, especially in preterm infants. We believe that infants with suspected congenital candidiasis should be considered as candidates for systemic antifungal therapy in any of the following cases: (*i*) evidence of respiratory distress or other laboratory or clinical signs of sepsis in the immediate neonatal period; (*ii*) birth weight less than 1500 g; (*iii*) treatment with broad-spectrum antibiotics; (*iv*) extensive instrumentation during delivery or invasive procedures in the neonatal period; (*v*) positive systemic cultures; and (*vi*) evidence of an altered immune response.

We also believe that in cases with positive amniotic fluid *Candida* cultures, early aggressive therapy should be started before birth. Shalev *et al.* reported a case of intra-amniotic infection with *C. albicans* successfully treated *in utero* with antifungal drugs which had favorable outcome [72].

Conclusions

Invasive congenital candidiasis must be taken into consideration in newborns with unaccountable respiratory distress syndrome, fever, and poor response to antibiotic treatment, especially in the presence of maternal risk factors, such as history of vaginal discharge or presence of an intrauterine foreign body during pregnancy. In these cases, antifungal therapy should be initiated immediately, even in the absence of cutaneous involvement or placental culture/pathology results. Our meta-analysis revealed that the most reliable indicators for predicting disease extent and outcome were gestational age, fetal birth weight and symptomatology at birth. Infants with very early onset of severe respiratory symptoms died with histological evidence of *Candida* pneumonia. Cutaneous involvement, while usually indicative of localized disease, was associated with fatal outcome when one of these risk factors was also present.

Conflict of interests

The authors declare that they have no conflict of interests.

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