

Review

Not peer-reviewed version

Invasive Candida Infections in the NICU. Risk Factors and New Insights in Prevention

Niki Dermitzaki , [Maria Baltogianni](#) , [Efrosini Tsekoura](#) , [Vasileios Giapros](#) *

Posted Date: 9 July 2024

doi: 10.20944/preprints202407.0540.v1

Keywords: invasive candida infections; neonatal candidiasis; antifungal prophylaxis; fluconazole prophylaxis



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Review

Invasive Candida Infections in the NICU. Risk Factors and New Insights in Prevention

Niki Dermitzaki ¹, Maria Baltogianni ¹, Efrosini Tsekoura ² and Vasileios Giapros ^{1,*}

¹ Neonatal Intensive Care Unit, School of Medicine, University of Ioannina, Ioannina, Greece

² Paediatric Department, "Asklepieion Voula's" General Hospital, Athens, Greece

* Correspondence: vgiapros@uoi.gr, tel: +302651099325

Abstract: Invasive Candida infections represent a significant cause of morbidity and mortality in neonatal intensive care units (NICUs), with a particular impact on preterm and low birth weight neonates. In addition to prematurity, several predisposing factors for Candida colonization and dissemination during NICU hospitalization have been identified, including prolonged exposure to broad-spectrum antibiotics, central venous catheters, parenteral nutrition, corticosteroids, H2 antagonist administration and poor adherence to infection control measures. According to the literature, the implementation of antifungal prophylaxis, mainly fluconazole, in high-risk populations has proven to be an effective strategy in reducing the incidence of fungal infections. This review aims to provide an overview of risk factors for Candida invasive infections and current perspectives regarding antifungal prophylaxis use. Recognition and reduction of exposure to these modifiable risk factors, in conjunction with the administration of antifungal prophylaxis, has been demonstrated to be an effective method for preventing invasive candidiasis in susceptible neonatal populations.

Keywords: invasive candida infections; neonatal candidiasis; antifungal prophylaxis; fluconazole prophylaxis

1. Introduction

1.1. Epidemiology

Invasive *Candida* infections represent a significant cause of morbidity and mortality in the neonatal intensive care unit (NICU) population, with a reported incidence of 0.5-2% [1,2]. Preterm and very low birth weight (VLBW) neonates are at a particularly high risk of invasive *Candida* infections, with the incidence inversely correlated with gestational age (GA) and birth weight (BW) [3]. The rate of these infections varies significantly between NICUs and different geographic locations. Concerning the most susceptible neonatal population, the extremely low birth weight neonates (ELBW), an incidence of 2 to 20% has been described [3–10]. A recent prospective study, involving 10,501 neonates of GA <29 weeks and late-onset sepsis (LOS) reported that fungal microorganisms were detected in 5.1% of cases; however in the subgroup of neonates of GA <23 weeks the proportion of fungal infections rose to 10% [2].

Following the increased incidence of invasive fungal infections in the 1980s and 1990s, which was attributed to the improved survival of preterm neonates, a gradual decrease has been reported subsequently, probably due to the increased use of antifungal prophylaxis, empirical antifungal treatment, and the reduced use of antimicrobial agents [9,11–13]. A retrospective study of data from 322 NICUs over a 14-year period, revealed a decline in the incidence of invasive neonatal fungal infections. The annual incidence decreased from 3.6 to 1.4 per 1000 patients among the study population and the reduction was more pronounced as the birth weight declined (from 82.7 to 23.8 per 1000 infants with BW <750g) [9].

Invasive fungal infections in neonates, especially VLBW, are associated with significant morbidity and mortality. A mortality rate of 30% has been described in preterm and low birth weight neonatal populations [5,12–15]. Death or adverse neurodevelopmental outcome was observed in 73% of a cohort of 320 ELBW neonates with IC [5]. A retrospective Canadian study compared the outcome of extremely preterm neonates with IC, infection by other pathogens, and neonates with no history of infection and concluded that mortality and adverse neurological outcome were significantly higher in the group of neonates with IC than in the other two groups (50% vs 23,3% vs 22,2% and 44.2% vs 21.6% vs 14.8% respectively) [14].

1.2. Microbiology

Although over a hundred species of *Candida* have been identified, the majority of *Candida* infections in all age groups are presumed to be caused by just five species (*Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*) [13,16,17]. In neonatal cohorts, *Candida albicans* is the most frequently isolated strain (40-60%) responsible for invasive infections, with *Candida parapsilosis* (20-40%) and *Candida tropicalis* (1-6%) following in prevalence [1,5,8,12,13,18–20].

1.3. Colonization

Neonates admitted to the NICU, particularly VLBW neonates, represent a population with a relatively high frequency of *Candida* colonization [21,22]. The colonization by *Candida* species represents an initial necessary step in the pathogenesis of invasive infection, providing a repository for subsequent dissemination under predisposing conditions [22,23].

Candida species colonize the skin, the gastrointestinal tract, and the genitourinary system. Acquisition of colonization in the neonatal population can be either vertical or horizontal [13,23,24]. A number of studies have identified vaginal delivery as a risk factor for neonatal colonization [24–30]. The incidence of vaginal *Candida* colonization is known to increase during pregnancy, particularly in the last trimester, and the reported prevalence varies considerably in the literature ranging from 5.6 to 69.2% [24,31]. In a cohort of 102 preterm and VLBW neonates delivered either vaginally or by cesarean section, 12.8% of vaginally delivered neonates were detected to be colonized within the first week of life, whereas none of the cesarean-delivered group. It is noteworthy that all mothers of the colonized preterm were also colonized by the same species. The risk of neonatal colonization was found to be correlated with the duration of PROM and inversely correlated with birth weight [24]. The higher risk of perinatal colonization as gestational age and birth weight decline has been described in several studies [29,32]. Another study of a population consisting of term neonates reported a 25% prevalence of colonization in the group of neonates delivered vaginally and a 3.6% prevalence in the group delivered by cesarean section. However, although concordance in the species isolated from maternal and neonatal specimens was detected in almost a quarter of cases in the vaginal birth group, when genotype and phenotypic profiles were examined concordance rates fell to 6%. In the caesarean-delivered group, no concordance was noted. The authors concluded that transmission during the birth process is not the primary source of neonatal colonization [31].

In addition to transmission during the birth process, horizontal acquisition of *Candida spp* can occur from the NICU environment. The most common sources of transmission are the hands of healthcare providers, contaminated equipment, or intravenous preparations [13,29,33]. This mode of transmission represents the primary source of *Candida parapsilosis* infection, as it has been reported as the most common strain isolated from the hands of healthcare providers. Conversely, *C. parapsilosis* is rarely implicated in vertical transmission [13,24,33].

Colonization is considered to be the initial step in the pathogenesis of IC. However, colonization does not necessarily lead to dissemination and systematic infection [23]. It is estimated that more than 60% of VLBW are colonized during the first month of their NICU hospitalization [35]. The incidence of invasive fungal infections in colonized VLBW neonates ranges from 8-23% [21,22,24,29]. Therefore, the recognition of additional predisposing factors for disseminated disease is crucial as it could aid in the identification of high-risk neonates.

2. Materials and Methods

We searched the Pubmed database for relevant studies on risk factors of invasive candidiasis and antifungal prophylaxis up to May 2024. The following keywords were used: “neonatal invasive candidiasis”, “neonate”, “invasive candidiasis risk factors”, “fluconazole prophylaxis”, “nystatin prophylaxis”, and “antifungal prophylaxis”. We also screened the reference lists of the retrieved articles to identify relevant articles that the initial search might not have covered. Ultimately, 80 articles were found, and 52 out of that 80 were included in the present narrative review, specifically randomized control trials, systematic reviews, narrative reviews, and observational studies.

3. Risk Factors

3.1. Prematurity and Low Birth Weight

Invasive *Candida* infections are rarely observed in neonates with normal birth weight. In a large retrospective study including neonates from 302 NICUs with a birth weight above 1500g, IC was reported in 0.06% of neonates [36]. Notably, the risk of systemic *Candida* infection increases with decreasing gestational age and birth weight [37]. Predisposing factors, in addition to their prolonged stay in the NICU and increased need for invasive procedures, include their relative immunodeficiency and immature skin and mucosal barriers [1,38]. ELBW neonates are at increased risk of disseminated *Candida* infection and rates of up to 20% have been reported [10]. Even in this high-risk population, the prevalence varies according to birth weight. Benjamin et al., in a multicenter prospective study including ELBW neonates, reported an IC rate of 3.4% in neonates with BW 750-100g and 11.4% in neonates with BW less than 750g [5].

3.2. Type and Number of Colonization Sites

Several studies have indicated a correlation between the type and number of colonization sites and the risk of progression to IC [21,22,24,29]. In a cohort of 201 VLBW neonates, colonized by *Candida* spp. at any time during their hospitalization, colonization of central venous catheter (CVC) and colonization in more than three sites were identified as independent risk factors for the progression to IC [21]. Mahieu et al. reported that no cases of IC were detected in neonates colonized at the skin exclusively. However, the prevalence of IC in neonates with gastrointestinal colonization was 16.6%, and when both aforementioned sites were colonized, the incidence was 41.7% [29]. Manzoni et al. reported a threefold increase in the incidence of IC in neonates colonized in more than three sites. Moreover, they observed that certain sites of colonization, such as urine and catheters, are associated with a fourfold increased risk of IC compared to other sites, including the skin, nasopharynx secretions, and gastric aspirates [22].

3.3. Broad-Spectrum Antibiotics

Broad-spectrum antibiotics represent a significant modifiable risk factor for IC [13]. It is well established that antibiotics suppress the normal gastrointestinal bacterial flora, thereby limiting its competitive action that would normally prevent the overgrowth of *Candida*. This effect is probably more pronounced in the immature gut microbiota of neonates [39]. The increased density of *Candida* predisposes to translocation across the intestinal epithelium and dissemination [13,23,37,39]. Several studies have identified an association between the use of broad-spectrum antibiotics, more commonly third-generation cephalosporins and carbapenems, and the development of systemic *Candida* infections in neonates [5,10,35–37,40,41]. Among different NICUs, the incidence of IC in ELBW has been shown to correlate with the average use of broad-spectrum antibiotics per neonate, predominantly third-generation cephalosporins [10]. Moreover, it has been reported that in neonates with a birth weight <1500 g, a 2.9-7.3% decrease in episodes of IC is observed for every 10% reduction in broad-spectrum antibiotic use [9].

3.4. Central Venous Catheters

Central venous catheters penetrate epithelial barriers allowing for the invasion of *Candida* in normally sterile sites. In addition, the capacity of *Candida spp.* for adhesion and biofilm formation on devices protects them from the host's immune response and antifungal agents [13,37,41]. Therefore, central venous catheters, widely used in VLBW neonates during their NICU stay, represent a significant risk factor for developing systemic candidiasis [5,13,37,38,40–43]. It has been reported that the risk of IC increases with each additional day that a central catheter remains in place [43]. A recent retrospective study in a cohort of very preterm and VLBW neonates demonstrated that the risk of colonization of peripherally inserted central catheters (PICC) lines was associated with the duration of antibiotics and parenteral nutrition, and the administration of corticosteroids postnatally [44]. Furthermore, due to the ability of drug-resistant biofilm formation, the delayed removal of catheters in ELBW neonates with IC has been identified as a factor that prolongs the duration of fungemia, increases the risk of end-organ involvement, adverse neurodevelopmental outcome, and mortality [5,41].

3.5. Corticosteroids

Corticosteroids are widely used in the NICUs to reduce pulmonary morbidity among preterm neonates, by preventing or managing chronic lung disease [45]. It is well established, that corticosteroids exert immunosuppressive effects, including a decreased circulating T-lymphocyte count, suppressed cytokine responses, and impaired cell-mediated immunity [13,46]). Several studies have indicated a potential association between the administration of steroids and the risk of IC in preterm neonates [13,46–49]. A retrospective case-control study of neonates with a birth weight <1250g identified dexamethasone administration during the first two weeks of life as a risk factor for systemic candidiasis [46].

3.6. Histamine Type 2 Receptor (H2) Antagonists

H2 antagonists act by inhibiting gastric acid secretion. Alkalization modifies the normal bacterial flora and promotes gastric colonization and proliferation of gram-negative bacteria and fungus, and subsequently their translocation across the gastrointestinal tract. Moreover, H2 antagonists can exert immunomodulatory effects by influencing neutrophil activity [13,23,38,41,50]. Saiman et. al, in a prospective multicenter study, reported that the administration of H2 antagonists in neonates was associated with a twofold increased risk of systemic candidiasis [38].

3.7. Gastrointestinal Pathologies

Gastrointestinal pathologies, including necrotizing enterocolitis (NEC), congenital malformations, and prior abdominal surgeries, represent significant risk factors for the development of systemic fungal infections. The disruption of the mucosal and epithelial intestinal barrier allows the translocation of colonizing *Candida* in the gastrointestinal tract and into the bloodstream [4,12,13,43]. The association between gastrointestinal pathologies and IC in the neonatal population has been demonstrated in several studies [4,26,36,40,43,51].

3.8. Parenteral Nutrition

Parenteral nutrition represents a fundamental aspect of the care provided to ELBW neonates during their stay in the NICU. However, it is a recognized predisposing factor for bacterial and fungal infections in the neonatal population [5,37,38,52,53]. Specifically, lipid emulsion has been shown to facilitate the proliferation of *Candida* and its capacity to form biofilms on indwelling catheters [54]. Furthermore, contamination during the preparation of parenteral nutrition has been reported as a potential causative factor in *Candida* outbreaks in NICUs [55]. Saiman et. al identified parenteral nutrition as a predisposing factor for systematic Candidemia and this association was observed independently of central venous catheter use [38].

4. Prevention

In addition to their relative immunodeficiency and immature skin and mucosal barriers, preterm and low birth weight neonates represent a population frequently exposed to a variety of predisposing factors that pose them to a particular risk for acquiring fungal infections during their prolonged stay in NICU. Given the potential adverse effects of *Candida* infections on survival and neurodevelopment in this immature population, it is evident that primary prevention represents a crucial aspect.

4.1. Fluconazole Prophylaxis

In the prevention of candidiasis, in addition to the minimization of exposure of most susceptible neonates to potential predisposing factors, the prophylactic administration of antifungal agents represents a widely used approach (10956). The most commonly used agent is fluconazole, a long half-life azole with good tissue penetration [57,58]. Fluconazole prophylaxis has been studied since the 1990s in immunocompromised adult and pediatric populations [59]. The first randomized control trials (RCTs) regarding the efficacy of fluconazole prophylaxis in susceptible neonatal populations were published in 2001 and reported potentiated results for its utility in the prevention of colonization and invasive infections [60,61]. Since then, several RCTs and retrospective studies with historical control cohorts have examined the efficacy, the optimal dosing regimen, the adverse effects, and the resistance pattern [62] (Table 1).

Table 1. Studies investigating the efficacy of fluconazole prophylaxis.

Author	Study	Population	Dosing	Colonization	IC	Mortality attributable to <i>Candida</i>	Overall mortality
Kicklighter, 2001 [61]	RCT	100 VLBW (50 fluconazole, 50 placebo)	6mg/kg/72h 7d 6mg/kg/24h 8-28d	15.1% vs 60% (p=0.0005)	4% vs 4%	ND	ND
Kaufman, 2001 [60]	RCT	100 ELBW (50 fluconazole, 50 placebo)	3mg/kg/72h 1-2wk, 3mg/kg/48h 3-4wk, 3mg/kg/24h 5-6wk (iv)	22% vs 60% (p=0.002)	0% vs 20% (p=0.008)	ND	8% vs 20% (p=0.22)
Manzoni, 2006 [63]	Pre-post cohort study	465 (225 fluconazole, 240 control)	6mg/kg/72h for 7d, 6mg/kg/48h until 30d VLBW, 45d ELBW or discharge (iv/per os)	26.4% vs 71.9% ELBW (p<0.0001) 22% vs 35% VLBW (P=0.01)	4.4% vs 16.7% (p<0.0001)	0% vs 1.7% (p=0.7)	ND
Aghai, 2006 [64]	Pre-post cohort study	177 ELBW (140 fluconazole, 137 control)	3mg/kg/72h 1-2wk, 3mg/kg/48h 3-4wk, 3mg/kg/24h 5-6wk (iv)	ND	0% vs 6.6% (p=0.006)	ND	25.7% vs 39.4% (p=0.02)

Parikhi, 2007 [65]	RCT	120 VLBW (60 fluconazole, 60 placebo)	3mg/kg/72h 7d 3mg/kg/24h 8-28d	19% vs 50% (p<0.001)	26.7% vs 25% (p=0.835)	ND	ND
Manzoni, 2007 [66]	RCT	363 VLBW (112 fluconazole 6mg/kg, 104 placebo)	6mg/kg/72h 2 wk 6mg/kg/48h until 4wk VLBW, 6 wk ELBW, or 3mg/kg/72h 2 wk 3mg/kg/48h until 4wk VLBW, 6 wk ELBW	9.8% vs 29.3% (p<0.001) 7.7% vs 29.3% (p<0.001)	2.7% vs 13.2% (p=0.005) 3.3% vs 13.2% (p=0.02)	0% vs 1.9% (p=0.23) 0% vs 1.9% (p=0.57)	8% vs 9.4% (p=0.81) 8.7% vs 9.4% (p=1)
Aziz, 2010 [67]	Pre-post cohort study	262 ELBW (163 fluconazole, 99 control)	3mg/kg/72h 1-2wk, 3mg/kg/48h 3-4wk, 3mg/kg/24h 5-6wk Or 3mg/kg biweekly	ND	1.8% vs 7.1% (p=0.045)	ND	9.2% vs 5.1% (p>0.05)
Benjamin, 2014 [68]	RCT	362 BW<750g (188 fluconazole, 175 placebo)	6mg/kg biweekly until 42d (iv/per os)	ND	3% vs 9% (p=0.02)	ND	14% vs 14% (p=0.98)
Kirpal, 2015 [69]	RCT	75 VLBW (38 fluconazole group, 37 placebo)	6mg/kg/48h for 7d, 6mg/kg/24h until 28d or discharge (iv)	ND	21% vs 43.2% (p<0.05)	2.6% vs 18.9% (p<0.05)	ND
Lee, 2016 [70]	Pre-post cohort study	423 ELBW (264 fluconazole, 159 control)	3mg/kg biweekly for 4wks (iv or per os)	33.9% vs 59.1% (p<0.001)	5.0% vs 4.4% (p=0.80)	3.2% vs 11.5% (p=0.32)	11.7% vs 16.4% (p=0.18)
Silva-Rios, 2019 [71]	Pre-post cohort study	893 neonates (484 ELBW universal fluconazole prophylaxis, 409 VLBW targeted prophylaxis)	3mg/kg/72h (iv or per os)	ND	3.7% vs 7.1% (p=0.04)	0% vs 17.1% (p=0.015)	ND
Zhang, 2021 [35]	Pre-post cohort study	196 VLBW (113 fluconazole, 83 control)	6mg/kg biweekly, 4 wks VLBW, 6 wks ELBW or discharge (iv)	ND	15.9% vs 45.8% (p<0.001)	2% vs 4% (p=0.69)	ND

VLBW: very low birth weight; ELBW: extremely low birth weight, iv: intravenous, ND: no data.

4.1.1. Efficacy

Neonates have a unique opportunity for the beneficial effects of fluconazole prophylaxis, which differs from those observed in pediatric and adult populations. At birth, the majority of VLBW neonates are not yet colonized or have low-density colonization. This offers an opportunity for antifungal medication to act, either by preventing colonization or reducing the proliferation of the yeast in already colonized patients [59,72]. It is noteworthy that in the absence of antifungal prophylaxis up to 60% of VLBW neonates will be colonized by *Candida* until the third week of life [8472]. Several studies have indicated a significant reduction in the incidence of colonization in vulnerable neonatal populations following the administration of fluconazole prophylaxis [60,61,63,65,66,70]. In a recent systematic review and meta-analysis by Anaraki et al., which included 7 studies with the outcome of colonization rate, a significant decrease in the *Candida* colonization rate was reported in VLBW neonates who received fluconazole prophylaxis [73].

The efficacy of fluconazole prophylaxis regarding the reduction of systematic *Candidiasis* incidence in high-risk neonates has been recognized in a number of RCTs and retrospective studies [35,60,63,64,66,67,69,71,74,75]. It is worth noting that in the majority of these studies, the incidence of IC in the control group is high (up to 45%), which is higher than that typically observed in developed countries at present. Consequently, the benefit of fluconazole prophylaxis may be overestimated and less pronounced in NICUs with a lower incidence of systemic candidiasis [76,77]. It has been proposed that in settings with an incidence of IC of approximately 16%, the number needed to treat for benefit (NTTB) is 11 [78]. However, in a multicenter RCT of neonates with a birth weight <750g with a low rate of probable or definitive IC in the control group (9%), although no significant difference was observed regarding the composite outcome of death or IC between the two groups, the rate of IC was significantly lower in the fluconazole-administered group. This suggests that high-risk neonates in low-risk settings might benefit from antifungal prophylaxis [68].

In other studies, despite the lower colonization rate among neonates receiving fluconazole prophylaxis, the incidence of IC was not observed to differ in the prophylaxis group. Two of these studies reported a low incidence of IC in the control group (4%), while the other, conducted in India, found that non-albicans *Candida* spp. were responsible for almost all invasive infections [61,65,70].

A recent meta-analysis by Xie et al. demonstrated a significant reduction in the risk of IC and in-hospital mortality associated with fluconazole prophylaxis (RR=0.37, p=0.0006 and RR=0.75, p=0.004 respectively) [79].

Current guidelines by the Infectious Diseases Societies of North America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend routine fluconazole prophylaxis in ELBW in NICUs with a high incidence of IC (>10%) [17,80]. In settings where the incidence of IC is lower (>2%), an individualized approach with risk factor estimation is advised [80].

4.1.2. Dosing

The optimal dosing regimen for fluconazole prophylaxis remains inconclusive. The dosing interval varies substantially among studies, ranging from daily to biweekly administration [76]. In an RCT, Kaufman et al. reported that twice-weekly administration is as effective for *Candida* prophylaxis in ELBW neonates as more frequent dosing [81]. Furthermore, a pharmacokinetic analysis demonstrated that adequate serum levels can be achieved with biweekly administration [82]. Less frequent dosing is associated with less fluconazole exposure and probably lessens the risk of drug resistance [76,81].

With regard to the dosage, the majority of studies employ a dose of either 3 mg/kg or 6 mg/kg [83]. Manzoni et.al, in a multicenter RCT, demonstrated that both doses are equivalent in their effectiveness in preventing IC [66]. Moreover, in their meta-analysis, Leonart et al. reported that the effectiveness of the prophylaxis was not affected by the dose administered (3, 4, or 6 mg/kg/dose). The authors concluded that, given the greater potential for adverse effects, antifungal resistance, and higher cost associated with higher doses, a lower dose (3 mg/kg/dose) should be recommended [83].

Another aspect of fluconazole prophylaxis administration that varies among studies is the cessation time. In most studies, prophylaxis in ELBW is continued until the chronological age of 28 or 42 days (table 1). The results of a meta-analysis indicate that prophylaxis until the 42nd postnatal day may be more efficacious [84]. The IDSA and ESCMID guidelines both recommend a dosage of 3 to 6 mg/kg administered intravenously or orally twice weekly for 6 weeks [17,80].

4.1.3. Adverse effects

Several studies have evaluated the potential risk of adverse effects associated with fluconazole, including abnormal liver tests, cholestasis, sepsis, and NEC. These studies have found no significant association between fluconazole and these adverse effects [35,60,61,63,66–69]. Nevertheless, although fluconazole appears to be safe for neonates, it is advisable to use lower doses to avoid potential adverse events and drug reactions. In a prospective study, Kaufman et al. evaluated the neurodevelopmental outcome of VLBW neonates who received fluconazole prophylaxis, at the age of 8 to 10 years old and observed no association between fluconazole and adverse neurodevelopment [85].

4.1.4. Resistance

The potential emergence or predominance of *Candida spp.* with native or acquired resistance to fluconazole represents a significant concern regarding the strategy of fluconazole prophylaxis in high-risk neonates [74,86]. Studies in susceptible adult populations have demonstrated the emergence of resistant strains following antifungal prophylaxis [86]. Although still inconclusive, the data from studies in neonatal populations are more reassuring, probably because the development of resistance is associated with the length of drug exposure, the cumulative dose, and the proportion of admitted patients in the unit receiving prophylaxis concomitantly. Previous RCTs have demonstrated the lack of emergence of resistant strains [60,61,87]. A meta-analysis conducted by Ericson et al. indicated that there was no significant difference in the resistant strains isolated in the prophylaxis and control groups [76]. Moreover, in a single-center retrospective study from Italy, no change in fungal ecology was detected over 20 years, including 4 years before the implementation of the fluconazole prophylaxis strategy and 16 years after [86].

A recent multicenter RCT in ELBW neonates reported a clinically insignificant higher minimum inhibitory concentration (MIC) of isolated *Candida* colonization species after fluconazole prophylaxis administration [74]. Furthermore, in a recent retrospective study by Zhang et al., although no completely resistant species were detected, isolates with significantly higher MICs were observed in the group of neonates that received prophylaxis. This is likely due to the high proportion of *Candida glabrata*, a strain with a higher propensity for resistance development. Lee et al. observed a higher, though not statistically significant, incidence of IC fluconazole-resistant *C. parapsilosis* in ELBW infants following five years of routine fluconazole prophylaxis [70].

The aforementioned evidence suggests that fluconazole prophylaxis appears to be a safe and effective strategy to reduce IC in high-risk neonates. However, an alternative approach to anti-fungal prophylaxis has been suggested in cases of colonization with azole-resistant *Candida* species, such as *Candida auris*, or NICUs with a high prevalence of resistant strains. In these settings, micafungin prophylaxis may be a suitable option [62,88,89]. Micafungin is the sole echinocandin approved by both the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for use in infants. However, its use is limited due to the potential hepatotoxicity and the paucity of data regarding pharmacokinetics in the neonatal population [90].

5. Nonabsorbable Antifungal Agents

Nonabsorbable antifungal agents, such as nystatin and miconazole oral gel, are not systemically absorbed and aim to reduce the density of fungal colonization in the gastrointestinal tract and subsequent dissemination [80,91].

A number of RCTs and prospective studies have reported a reduced incidence of IC in VLBW and ELBW populations with oral nystatin prophylaxis administration in comparison to no prophylaxis [91–94] (Table 2). A meta-analysis indicated that nystatin prophylaxis was associated with a significant reduction in IC. However, the presence of methodological weaknesses and heterogeneity of the studies included precludes a conclusive interpretation of the results [97]. Oral nystatin and oral or intravenous fluconazole have demonstrated similar efficacy in RCTs that include VLBW and ELBW neonates [95,96]. The current IDSA and ESCMID guidelines recommend the use of oral nystatin 100,000 UI q8, as an alternative to fluconazole for the prophylaxis of fungal infections in susceptible neonates when fluconazole is unavailable or if resistant species have been isolated [17,80].

A significant limitation to the use of oral nystatin is that VLBW and ELBW neonates frequently present with medical conditions that preclude the use of oral preparations, including hemodynamic instability, feeding intolerance, and gastrointestinal diseases [17,62]. Moreover, a potential increased risk of NEC is associated with nystatin administration due to its hyperosmolar composition [97].

The efficacy of miconazole oral gel as an antifungal prophylaxis has been previously investigated in an RCT involving 600 neonates. The incidence of *Candida* colonization was significantly lower in the miconazole prophylaxis group compared to the placebo group. However, no significant difference was observed in the incidence of IC, which can be attributed, at least in part, to the low rates of IC in the study cohort (2% and 2.6% in the miconazole and placebo groups, respectively) [98].

Table 2. Studies investigating the efficacy of nystatin prophylaxis.

Author	Type of study	Population	Colonization	IC	Mortality
Sims, 1998 [92]	RCT	67 VLBW (33 nystatin, 34 control)	12% vs 44% (p<0.01)	6% vs 32% (p<0.001)	12% vs 20% (p<0.05)
Howell, 2009 [94]	Prospective multicenter surveillance	12607 VLBW (7738 nystatin, 4868 control)	ND	0.54% vs 1.23% (p<0.01)	ND
Aydemir, 2010 [95]	RCT	278 VLBW (94 nystatin, 93 fluconazole, 91 placebo)	11.7% vs 10.8% vs 42.9% (p<0.01)	4.3% vs 3.2% vs 16.5% (p<0.01)	8.5% vs 8.4% vs 12.1% (p=0.64)
Mersal, 2013 [96]	RCT	57 VPT<30wks and/or <1200g (24 nystatin, 33 fluconazole)	12% vs 8%	0% vs 0%	
Rundjan, 2020 [91]	RCT	95 VLBW/VPT (47 nystatin, 48 placebo)	29.8% vs 56.3% (p=0.009)	0% vs 10.4% (p=0.056)	14.9% vs 18.8% (p=0.616)

VLBW: very low birth weight; VPT: very preterm, ND: no data.

6. Probiotics

It has been postulated that probiotics may inhibit the colonization and proliferation of *Candida* in the intestinal tract. This is thought to occur through competition for colonization sites, alteration of mucosal barrier permeability, and immune-mediated responses [99,100]. A meta-analysis of seven RCTs indicated that probiotics may have a beneficial effect in reducing *Candida* colonization in preterm neonates. However, data regarding the efficacy of probiotics in preventing IC in the NICUs were inconclusive [100]. Two RCTs in VLBW populations compared two different strains of

probiotics, *Lactobacillus reuteri* and *Saccharomyces boulardii*, to nystatin prophylaxis and both demonstrated similar efficacy regarding colonization and IC reduction. Additionally, in both trials, the probiotic group demonstrated a reduced incidence of bacterial sepsis and feeding intolerance [101,102]. Conversely, a recent multicenter cohort study demonstrated that the incidence of IC was significantly higher in preterm neonates exposed to probiotics than in the control group [103]. In conclusion, the effect of probiotics in the prevention of IC in preterm neonates, and the optimal strain, dosage, and duration of administration, remain controversial [162].

7. Lactoferrin

Bovine lactoferrin, a glycoprotein known to enhance the maturation of the intestinal barrier and the immunological properties of the intestinal mucosa, has been demonstrated to exert antifungal activities by disrupting the fungal cell membrane [104,105]. In a multicenter RCT, Manzoni et al. observed a significantly reduced incidence of IC in VLBW neonates receiving bovine lactoferrin alone or in combination with *Lactobacillus rhamnosus* GG, in comparison to the placebo group. The rate of fungal colonization in both groups was found to be similar [104]. Nevertheless, a recent large RCT did not demonstrate any benefit regarding IC with lactoferrin administration [106]. According to the current IDSA and ESCMID guidelines, bovine lactoferrin (100 mg/d) administered alone or in combination with *Lactobacillus rhamnosus* may be efficacious as a prophylactic measure for IC [17,80].

5. Conclusions

Invasive *Candida* infections in the NICUs represent a significant challenge. Preterm and low birth weight neonates are at particularly high risk of disseminated disease. The potentially detrimental effects of IC in this vulnerable population on survival and neurodevelopment underscore the need to recognize and avoid modifiable risk factors, such as extensive use of broad-spectrum antibiotics, central venous catheter use, corticosteroid administration, and poor compliance with hygiene measures. Antifungal prophylaxis with fluconazole in high-risk neonatal populations, especially in settings with a high prevalence of fungal infections has been proven to be an efficacious measure to reduce the incidence of *Candida* colonization and progression to disseminated disease. In conclusion, the development of strategies to minimize exposure to risk factors and integration in clinical practice in the NICUs, along with antifungal prophylaxis in cases when it is indicated, has been demonstrated to be an effective approach to reducing the incidence of IC.

Author Contributions: Conceptualization, M.B., and E.T.; writing—original draft preparation, N.D.; writing—review and editing, M.B., E.T. and V.G.; supervision, V.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Weimer, K.E.D.; Smith, P.B.; Puia-Dumitrescu, M.; Aleem, S. Invasive fungal infections in neonates: A review. *Pediatr Res*, **2022**, *91*, 404–412. <https://doi.org/10.1038/s41390-021-01842-7>. PMID: 34880444.
2. Flannery, D.D.; Edwards, E.M.; Coggins, S.A.; Horbar, J.D.; Puopolo, K.M. Late-Onset Sepsis Among Very Preterm Infants. *Pediatrics*. **2022**, *150*, e2022058813. <https://doi.org/10.1542/peds.2022-058813>. PMID: 36366916; PMCID: PMC11151779.
3. Calley, J.L.; Warris, A. Recognition and diagnosis of invasive fungal infections in neonates. *J Infect*, **2017**, *74*, Suppl 1:S108–S113. [https://doi.org/10.1016/S0163-4453\(17\)30200-1](https://doi.org/10.1016/S0163-4453(17)30200-1). PMID: 28646949.
4. Barton, M.; O'Brien, K.; Robinson, J.L.; Davies, D.H.; Simpson, K.; Asztalos, E.; Langley, J.M.; Le Saux, N.; Sauve, R.; Synnes, A.; et al. Invasive candidiasis in low birth weight preterm infants: Risk factors, clinical course and outcome in a prospective multicenter study of cases and their matched controls. *BMC Infect Dis*. **2014**, *14*, 327. <https://doi.org/10.1186/1471-2334-14-327>. PMID: 24924877; PMCID: PMC4063435.
5. Benjamin, D.K. Jr.; Stoll, B.J.; Fanaroff, A.A.; McDonald, S.A.; Oh, W.; Higgins, R.D.; Duara, S.; Poole, K.; Laptook, A.; Goldberg, R. National Institute of Child Health and Human Development Neonatal Research

- Network. Neonatal candidiasis among extremely low birth weight infants: Risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics*. **2006**, 117, 84-92. <https://doi.org/10.1542/peds.2004-2292>. PMID: 16396864.
6. Hundalani, S.; Pammi, M. Invasive fungal infections in newborns and current management strategies. *Expert Rev Anti Infect Ther*. **2013**, 11, 709-21. <https://doi.org/10.1586/14787210.2013.811925>. Epub 2013 Jul 5. PMID: 23829639.
 7. Cohen, J.F.; Ouziel, A.; Matczak, S.; Brice, J.; Spijker, R.; Lortholary, O.; Bougnoux, M.E.; Toubiana, J. Diagnostic accuracy of serum (1,3)-beta-d-glucan for neonatal invasive candidiasis: Systematic review and meta-analysis. *Clin Microbiol Infect*. **2020**, 26, 291-298. <https://doi.org/10.1016/j.cmi.2019.09.010>. Epub 2019 Sep 17. PMID: 31539634.
 8. Clerihew, L.; Lamagni, T.L.; Brocklehurst, P.; McGuire, W. Invasive fungal infection in very low birthweight infants: National prospective surveillance study. *Arch Dis Child Fetal Neonatal Ed*. **2006**, 91, F188-92. <https://doi.org/10.1136/adc.2005.082024>. Epub 2005 Dec 6. PMID: 16332924; PMCID: PMC2672702.
 9. Aliaga, S.; Clark, R.H.; Laughon, M.; Walsh, T.J.; Hope, W.W.; Benjamin, D.K.; Kaufman, D.; Arrieta, A.; Benjamin, D.K. Jr.; Smith, P.B. Changes in the incidence of candidiasis in neonatal intensive care units. *Pediatrics*. **2014**, 133, 236-42. <https://doi.org/10.1542/peds.2013-0671>. Epub 2014 Jan 20. PMID: 24446441; PMCID: PMC3904270.
 10. Cotten, C.M.; McDonald, S.; Stoll, B.; Goldberg, R.N.; Poole, K.; Benjamin, D.K. Jr. National Institute for Child Health and Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics*. **2006**, 118, 717-22. <https://doi.org/10.1542/peds.2005-2677>. PMID: 16882828.
 11. Fridkin, S.K.; Kaufman, D.; Edwards, J.R.; Shetty, S.; Horan, T. Changing incidence of Candida bloodstream infections among NICU patients in the United States: 1995-2004. *Pediatrics*. **2006**, 117, 1680-7. <https://doi.org/10.1542/peds.2005-1996>. PMID: 16651324.
 12. Ting, J.Y.; Roberts, A.; Synnes, A.; Canning, R.; Bodani, J.; Monterossa, L.; Shah, P.S. Canadian Neonatal Network Investigators. Invasive Fungal Infections in Neonates in Canada: Epidemiology and Outcomes. *Pediatr Infect Dis J*. **2018**, 37, 1154-1159. <https://doi.org/10.1097/INF.0000000000001968>. PMID: 29561508.
 13. Kelly, M.S.; Benjamin, D.K. Jr.; Smith, P.B. The epidemiology and diagnosis of invasive candidiasis among premature infants. *Clin Perinatol*. **2015**, 42, 105-17. <https://doi.org/10.1016/j.clp.2014.10.008>. PMID: 25677999; PMCID: PMC4328135.
 14. Zhou, Q.; Kelly, E.; Luu, T.M.; Ye, X.Y.; Ting, J.; Shah, P.S.; Lee, S.K. Fungal infection and neurodevelopmental outcomes at 18-30 months in preterm infants. *Front Pediatr*. **2023**, 11:1145252. <https://doi.org/10.3389/fped.2023.1145252>. PMID: 37152326; PMCID: PMC10157087.
 15. Stoll, B.J.; Hansen, N.; Fanaroff, A.A.; Wright, L.L.; Carlo, W.A.; Ehrenkranz, R.A.; Lemons, J.A.; Donovan, E.F.; Stark, A.R.; Tyson, J.E.; et al. Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. *Pediatrics*. **2002**, 110, 285-91. <https://doi.org/10.1542/peds.110.2.285>. PMID: 12165580.
 16. Turner, S.A.; Butler, G. The Candida pathogenic species complex. *Cold Spring Harb Perspect Med*. **2014**, 4, a019778. <https://doi.org/10.1101/cshperspect.a019778>. PMID: 25183855; PMCID: PMC4143104.
 17. Pappas, P.G.; Kauffman, C.A.; Andes, D.R.; Clancy, C.J.; Marr, K.A.; Ostrosky-Zeichner, L.; Reboli, A.C.; Schuster, M.G.; Vazquez, J.A.; Walsh, T.J.; et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. **2016**, 62, e1-50. <https://doi.org/10.1093/cid/civ933>. Epub 2015 Dec 16. PMID: 26679628; PMCID: PMC4725385.
 18. Noni, M.; Stathi, A.; Vaki, I.; Velegraki, A.; Zachariadou, L.; Michos, A. Changing Epidemiology of Invasive Candidiasis in Children during a 10-Year Period. *J Fungi (Basel)*. **2019**, 5, 19. <https://doi.org/10.3390/jof5010019>. PMID: 30813283; PMCID: PMC6462917.
 19. Fu, J.; Ding, Y.; Wei, B.; Wang, L.; Xu, S.; Qin, P.; Wei, L.; Jiang, L. Epidemiology of Candida albicans and non-C.albicans of neonatal candidemia at a tertiary care hospital in western China. *BMC Infect Dis*. **2017**, 17, 329. <https://doi.org/10.1186/s12879-017-2423-8>. PMID: 28477628; PMCID: PMC5420153.
 20. Blyth, C.; Chen, S.C.; Slavin, M.A.; Serena, C.; Nguyen, Q.; Marriott, D.; Ellis, D.; Meyer, W.; Sorrell, T.C. Australian Candidemia Study. Not just little adults: Candidemia epidemiology, molecular characterization, and antifungal susceptibility in neonatal and pediatric patients. *Pediatrics*. **2009**, 123, 1360-8. <https://doi.org/10.1542/peds.2008-2055>. PMID: 19403503.
 21. Manzoni, P.; Farina, D.; Leonessa, M.; d'Oulx, E.A.; Galletto, P.; Mostert, M.; Miniero, R.; Gomirato, G. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. *Pediatrics*. **2006**, 118, 2359-64. <https://doi.org/10.1542/peds.2006-1311>. PMID: 17142519.
 22. Manzoni, P.; Farina, D.; Galletto, P.; Leonessa, M.; Priolo, C.; Arisio, R.; Gomirato, G. Type and number of sites colonized by fungi and risk of progression to invasive fungal infection in preterm neonates in neonatal intensive care unit. *J Perinat Med*. **2007**, 35, 220-6. <https://doi.org/10.1515/JPM.2007.055>. PMID: 17378718.
 23. Bendel, C.M. Colonization and epithelial adhesion in the pathogenesis of neonatal candidiasis. *Semin Perinatol*. **2003**, 27, 357-64. [https://doi.org/10.1016/s0146-0005\(03\)00059-4](https://doi.org/10.1016/s0146-0005(03)00059-4). PMID: 14626499.

24. Ali, G.Y.; Algothary, E.H.; Rashed, K.A.; Almoghanum, M.; Khalifa, A.A. Prevalence of *Candida* colonization in preterm newborns and VLBW in neonatal intensive care unit: Role of maternal colonization as a risk factor in transmission of disease. *J Matern Fetal Neonatal Med.* **2012**, *25*, 789-95. <https://doi.org/10.3109/14767058.2011.622005>. Epub 2011 Oct 17. PMID: 21919548.
25. Henderickx, J.G.E.; de Weerd, H.; Groot Jebbink L.J.; van Zoeren-Grobbe, D.; Hemels, M.A.C.; van Lingen, R.A.; Knol, J.; Belzer, C. The first fungi: Mode of delivery determines early life fungal colonization in the intestine of preterm infants. *Microbiome Res Rep.* **2022**, *1*, 7. <https://doi.org/10.20517/mrr.2021.03>. PMID: 38089064; PMCID: PMC10714301.
26. Shetty, S.S.; Harrison, L.H.; Hajjeh, R.A.; Taylor, T.; Mirza, S.A.; Schmidt, A.B.; Sanza, L.T.; Shutt, K.A.; Fridkin, S.K. Determining risk factors for candidemia among newborn infants from population-based surveillance: Baltimore, Maryland, 1998-2000. *Pediatr Infect Dis J.* **2005**, *24*, 601-4. <https://doi.org/10.1097/01.inf.0000168751.11375.d6>. PMID: 15999000.
27. Manzoni, P.; Maestri, A.; Leonessa, M.; Mostert, M.; Farina, D.; Gomirato, G. Fungal and bacterial sepsis and threshold ROP in preterm very low birth weight neonates. *J Perinatol.* **2006**, *26*, 23-30. <https://doi.org/10.1038/sj.jp.7211420>. PMID: 16355104.
28. Pappas, P.G.; Rex, J.H.; Lee, J.; Hamill, R.J.; Larsen, R.A.; Powderly, W.; Kauffman, C.A.; Hyslop, N.; Mangino, J.E.; Chapman, S.; NIAID Mycoses Study Group. A prospective observational study of candidemia: Epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis.* **2003**, *37*, 634-43. <https://doi.org/10.1086/376906>. PMID: 12942393.
29. Mahieu, L.M.; Van Gasse, N.; Wildemeersch, D.; Jansens, H.; Ieven, M. Number of sites of perinatal *Candida* colonization and neutropenia are associated with nosocomial candidemia in the neonatal intensive care unit patient. *Pediatr Crit Care Med.* **2010**, *11*, 240-5. <https://doi.org/10.1097/PCC.0b013e3181b808fb>. PMID: 19794324.
30. Waggoner-Fountain, L.A.; Walker, M.W.; Hollis, R.J.; Pfaller, M.A.; Ferguson, J.E. 2nd, Wenzel, R.P.; Donowitz, L.G. Vertical and horizontal transmission of unique *Candida* species to premature newborns. *Clin Infect Dis.* **1996**, *22*, 803-8. <https://doi.org/10.1093/clinids/22.5.803>. PMID: 8722935.
31. Caramalac, D.A.; da Silva Ruiz, L.; de Batista, G.C.; Birman, E.G.; Duarte, M.; Hahn, R.; Paula, C.R. *Candida* isolated from vaginal mucosa of mothers and oral mucosa of neonates: Occurrence and biotypes concordance. *Pediatr Infect Dis J.* **2007**, *26*, 553-7. <https://doi.org/10.1097/INF.0b013e31806166d7>. PMID: 17596793.
32. Johnsson, H.; Ewald, U. The rate of candidaemia in preterm infants born at a gestational age of 23-28 weeks is inversely correlated to gestational age. *Acta Paediatr.* **2004**, *93*, 954-8. PMID: 15303812.
33. Reef, S.E.; Lasker, B.A.; Butcher, D.S.; McNeil, M.M.; Pruitt, R.; Keyserling, H.; Jarvis, W.R. Nonperinatal nosocomial transmission of *Candida albicans* in a neonatal intensive care unit: Prospective study. *J Clin Microbiol.* **1998**, *36*, 1255-9. <https://doi.org/10.1128/JCM.36.5.1255-1259.1998>. PMID: 9574687; PMCID: PMC104810.
34. Bendel CM. Nosocomial neonatal candidiasis. *Pediatr Infect Dis J.* **2005**, *24*, 831-2. <https://doi.org/10.1097/01.inf.0000178291.40568.ef>. PMID: 16148852.
35. Zhang, D.; Xie, D.; He, N.; Wang, X.; Dong, W.; Lei, X. Prophylactic Use of Fluconazole in Very Premature Infants. *Front Pediatr.* **2021**, *9*, 726769. <https://doi.org/10.3389/fped.2021.726769>. PMID: 34660487; PMCID: PMC8517516.
36. Lee, J.H.; Hornik, C.P.; Benjamin, D.K. Jr.; Herring, A.H.; Clark, R.H.; Cohen-Wolkowicz, M.; Smith, P.B. Risk factors for invasive candidiasis in infants >1500 g birth weight. *Pediatr Infect Dis J.* **2013**, *32*, 222-6. <https://doi.org/10.1097/INF.0b013e3182769603>. PMID: 23042050; PMCID: PMC3578110.
37. Fu, J.; Wang, X.; Wei, B.; Jiang, Y.; Chen J. Risk factors and clinical analysis of candidemia in very-low-birth-weight neonates. *Am J Infect Control.* **2016**, *44*, 1321-1325. <https://doi.org/10.1016/j.ajic.2016.03.026>. PMID: 27566876.
38. Saiman, L.; Ludington, E.; Pfaller, M.; Rangel-Frausto, S.; Wiblin, R.T.; Dawson, J.; Blumberg, H.M.; Patterson, J.E.; Rinaldi, M.; Edwards, J.E.; et al. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr Infect Dis J.* **2000**, *19*, 319-24. <https://doi.org/10.1097/00006454-200004000-00011>. PMID: 10783022.
39. Esaiassen, E.; Fjalstad, J.W.; Juvet, L.K.; van den Anker, J.N.; Klingenberg, C. Antibiotic exposure in neonates and early adverse outcomes: A systematic review and meta-analysis. *J Antimicrob Chemother.* **2017**, *72*, 1858-1870. <https://doi.org/10.1093/jac/dkx088>. PMID: 28369594.
40. Yu, Y.; Du, L.; Yuan, T.; Zheng, J.; Chen, A.; Chen, L.; Shi, L. Risk factors and clinical analysis for invasive fungal infection in neonatal intensive care unit patients. *Am J Perinatol.* **2013**, *30*, 589-94. <https://doi.org/10.1055/s-0032-1329688>. Epub 2012 Dec 31. PMID: 23277386.
41. Kaufman, D.; Fairchild, K.D. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. *Clin Microbiol Rev.* **2004**, *17*, 638-80, table of contents. <https://doi.org/10.1128/CMR.17.3.638-680.2004>. PMID: 15258097; PMCID: PMC452555.

42. Roilides, E. Invasive candidiasis in neonates and children. *Early Hum Dev.* **2011**, 87 Suppl 1:S75-6. <https://doi.org/10.1016/j.earlhumdev.2011.01.017>. Epub 2011 Jan 20. PMID: 21251769.
43. Feja, K.N.; Wu, F.; Roberts, K.; Loughrey, M.; Nesin, M.; Larson, E.; Della-Latta, P.; Haas, J.; Cimiotti, J.; Saiman L. Risk factors for candidemia in critically ill infants: A matched case-control study. *J Pediatr.* **2005**, 147, 156-61. <https://doi.org/10.1016/j.jpeds.2005.02.021>. PMID: 16126040; PMCID: PMC2031014.
44. Zhang, L.; Yang, L.; Dong, W.; Liu, X.; Lei, X.; Zhang, L. Risk factors and clinical analysis of peripherally inserted central catheter-related fungal colonization in premature infants. *Sci Rep.* **2021**, 11, 20897. <https://doi.org/10.1038/s41598-021-00120-0>. PMID: 34686686; PMCID: PMC8536761.
45. Cummings, J.J.; Pramanik, A.K.; Committee on fetus and newborn. Postnatal Corticosteroids to Prevent or Treat Chronic Lung Disease Following Preterm Birth. *Pediatrics.* **2022**, 149, e2022057530. <https://doi.org/10.1542/peds.2022-057530>. PMID: 37917016.
46. Pera, A.; Byun, A.; Gribar, S.; Schwartz, R.; Kumar, D.; Parimi, P. Dexamethasone therapy and Candida sepsis in neonates less than 1250 grams. *J Perinatol.* **2002**, 22, 204-8. <https://doi.org/10.1038/sj.jp.7210699>. PMID: 11948382.
47. Adams-Chapman, I.; Bann, C.M.; Das, A.; Goldberg, R.N.; Stoll, B.J.; Walsh, M.C.; Sánchez, P.J.; Higgins, R.D.; Shankaran, S.; Watterberg, K.L.; et al. Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. *J Pediatr.* **2013**, 163, 961-7.e3. <https://doi.org/10.1016/j.jpeds.2013.04.034>. PMID: 23726546; PMCID: PMC3786056.
48. Stoll, B.J.; Temprowsa, M.; Tyson, J.E.; Papile, L.A.; Wright, L.L.; Bauer, C.R.; Donovan, E.F.; Korones, S.B.; Lemons, J.A.; Fanaroff, A.A.; et al. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics.* **1999**, 104, e63. <https://doi.org/10.1542/peds.104.5.e63>. PMID: 10545589.
49. Botas, C.M.; Kurlat, I.; Young, S.M.; Sola, A. Disseminated candidal infections and intravenous hydrocortisone in preterm infants. *Pediatrics.* **1995**, 95, 883-7. PMID: 7761215.
50. Santos, V.S.; Freire, M.S.; Santana, R.N.S.; Martins-Filho, P.R.S.; Cuevas, L.E.; Gurgel, R.Q. Association between histamine-2 receptor antagonists and adverse outcomes in neonates: A systematic review and meta-analysis. *PLoS ONE.* **2019**, 14, e0214135. <https://doi.org/10.1371/journal.pone.0214135>. PMID: 30947259; PMCID: PMC6448909.
51. Ballot, D.E.; Bosman, N.; Nana, T.; Ramdin, T.; Cooper, P.A. Background changing patterns of neonatal fungal sepsis in a developing country. *J Trop Pediatr.* **2013**, 59, 460-4. <https://doi.org/10.1093/tropej/fmt053>. Epub 2013 Jun 26. PMID: 23803724.
52. Zingg, W.; Tomaske, M.; Martin, M. Risk of parenteral nutrition in neonates--an overview. *Nutrients.* **2012**, 4, 1490-503. <https://doi.org/10.3390/nu4101490>. PMID: 23201767; PMCID: PMC3497007.
53. Chen, J.; Jiang, Y.; Wei, B.; Ding, Y.; Xu, S.; Qin, P.; Fu, J. Epidemiology of and risk factors for neonatal candidemia at a tertiary care hospital in western China. *BMC Infect Dis.* **2016**, 16, 700. <https://doi.org/10.1186/s12879-016-2042-9>. PMID: 27884125; PMCID: PMC5121934.
54. Swindell, K.; Lattif, A.A.; Chandra, J.; Mukherjee, P.K.; Ghannoum, M.A. Parenteral lipid emulsion induces germination of *Candida albicans* and increases biofilm formation on medical catheter surfaces. *J Infect Dis.* **2009**, 200, 473-80. <https://doi.org/10.1086/600106>. PMID: 19552524.
55. Guducuoglu, H.; Gultepe, B.; Otlu, B.; Bektas, A.; Yildirim, O.; Tuncer, O.; Berktaş M. *Candida albicans* outbreak associated with total parenteral nutrition in the neonatal unit. *Indian J Med Microbiol.* **2016**, 34, 202-7. <https://doi.org/10.4103/0255-0857.180303>. PMID: 27080773.
56. Kilpatrick, R.; Scarrow, E.; Hornik, C.; Greenberg, R.G. Neonatal invasive candidiasis: Updates on clinical management and prevention. *Lancet Child Adolesc Health.* **2022**, 6, 60-70. [https://doi.org/10.1016/S2352-4642\(21\)00272-8](https://doi.org/10.1016/S2352-4642(21)00272-8). Epub 2021 Oct 19. PMID: 34672994.
57. Leibovitz, E. Strategies for the prevention of neonatal candidiasis. *Pediatr Neonatol.* **2012**, 53, 83-9. <https://doi.org/10.1016/j.pedneo.2012.01.004>. Epub 2012 Mar 3. PMID: 22503254.
58. Momper, J.D.; Capparelli, E.V.; Wade, K.C.; Kantak, A.; Dhanireddy, R.; Cummings, J.J.; Nedrelow, J.H.; Hudak, M.L.; Mundakel, G.T.; Natarajan, G.; et al. Population Pharmacokinetics of Fluconazole in Premature Infants with Birth Weights Less than 750 Grams. *Antimicrob Agents Chemother.* **2016**, 60, 5539-45. <https://doi.org/10.1128/AAC.00963-16>. PMID: 27401564; PMCID: PMC4997840.
59. Kaufman, D.A. Fluconazole prophylaxis: Can we eliminate invasive *Candida* infections in the neonatal ICU? *Curr Opin Pediatr.* **2008**, 20, 332-40. <https://doi.org/10.1097/MOP.0b013e3282f79c48>. PMID: 18475105.
60. Kaufman, D.; Boyle, R.; Hazen, K.C.; Patrie, J.T.; Robinson, M.; Donowitz L.G. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med.* **2001**, 345, 1660-6. <https://doi.org/10.1056/NEJMoa010494>. PMID: 11759644.
61. Kicklighter, S.D.; Springer, S.C.; Cox, T.; Hulsey, T.C.; Turner, R.B. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. *Pediatrics.* **2001**, 107, 293-8. <https://doi.org/10.1542/peds.107.2.293>. PMID: 11158461.
62. Ferrando, G.; Castagnola, E. Prophylaxis of Invasive Fungal Infection in Neonates: A Narrative Review for Practical Purposes. *J Fungi (Basel).* **2023**, 9, 164. <https://doi.org/10.3390/jof9020164>. PMID: 36836279; PMCID: PMC9962596.

63. Manzoni, P.; Arisio, R.; Mostert, M.; Leonessa, M.; Farina, D.; Latino, M.A.; Gomirato, G. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: A single-center, 6-year, retrospective cohort study. *Pediatrics*. **2006**, *117*, e22-32. <https://doi.org/10.1542/peds.2004-2227>. PMID: 16326690.
64. Aghai, Z.H.; Mudduluru, M.; Nakhla, T.A.; Amendolia, B.; Longo, D.; Kemble, N.; Kaki, S.; Sutsko, R.; Saslow, J.G.; Stahl, G.E Fluconazole prophylaxis in extremely low birth weight infants: Association with cholestasis. *J Perinatol*. **2006**, *26*, 550-5. <https://doi.org/10.1038/sj.jp.7211570>. PMID: 16940972.
65. Parikh, T.B.; Nanavati, R.N.; Patankar, C.V.; Rao, S.; Bisure, K.; Udani, R.H.; Mehta, P. Fluconazole prophylaxis against fungal colonization and invasive fungal infection in very low birth weight infants. *Indian Pediatr*. **2007**, *44*, 830-7. PMID: 18057479.
66. Manzoni, P.; Stolfi, I.; Pagni, L.; Decembrino, L.; Magnani, C.; Vetrano, G.; Tridapalli, E.; Corona, G.; Giovannozzi, C.; Farina, D.; et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med*. **2007**, *356*, 2483-95. <https://doi.org/10.1056/NEJMoa065733>. PMID: 17568029.
67. Aziz, M.; Patel, A.L.; Losavio, J.; Iyengar, A.; Berven, M.; Schloemer, N.; Jakubowicz, A.; Mathai, T.; McAuley, J.B. Efficacy of fluconazole prophylaxis for prevention of invasive fungal infection in extremely low birth weight infants. *Pediatr Infect Dis J*. **2010**, *29*, 352-6. <https://doi.org/10.1097/INF.0b013e3181bf8eb1>. PMID: 19934791.
68. Benjamin, D.K. Jr.; Hudak, M.L.; Duara, S.; Randolph, D.A.; Bidegain, M.; Mundakel, G.T.; Natarajan, G.; Burchfield, D.J.; White, R.D.; Shattuck, K.E.; et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: A randomized clinical trial. *JAMA*. **2014**, *311*, 1742-9. <https://doi.org/10.1001/jama.2014.2624>. PMID: 24794367; PMCID: PMC4110724.
69. Kirpal, H.; Gathwala, G.; Chaudhary, U.; Sharma, D. Prophylactic fluconazole in very low birth weight infants admitted to neonatal intensive care unit: Randomized controlled trial. *J Matern Fetal Neonatal Med*. **2016**, *29*, 624-8. <https://doi.org/10.3109/14767058.2015.1013933>. Epub 2015 Feb 24. PMID: 25708488.
70. Lee, J.; Kim, H.S.; Shin, S.H.; Choi, C.W.; Kim, E.K.; Choi, E.H.; Kim, B.I.; Choi, J.H. Efficacy and safety of fluconazole prophylaxis in extremely low birth weight infants: Multicenter pre-post cohort study. *BMC Pediatr*. **2016**, *16*, 67. <https://doi.org/10.1186/s12887-016-0605-y>. PMID: 27184665; PMCID: PMC4869366.
71. Silva-Rios, J.; Camargos, P.; Correa, L.; Romanelli, R. Prophylactic regimens with fluconazole for candidiasis in neonates under 1.500g: A retrospective chart review of two cohorts. *J Neonatal Perinatal Med*. **2019**, *12*, 29-36. <https://doi.org/10.3233/NPM-17121>. PMID: 30958318.
72. Kaufman, D.A. "Getting to Zero": Preventing invasive Candida infections and eliminating infection-related mortality and morbidity in extremely preterm infants. *Early Hum Dev*. **2012**, *88*, Suppl 2:S45-9. [https://doi.org/10.1016/S0378-3782\(12\)70014-2](https://doi.org/10.1016/S0378-3782(12)70014-2). PMID: 22633513.
73. Robati Anaraki, M.; Nouri-Vaskeh, M.; Abdoli Oskoei, S. Fluconazole prophylaxis against invasive candidiasis in very low and extremely low birth weight preterm neonates: A systematic review and meta-analysis. *Clin Exp Pediatr*. **2021**, *64*, 172-179. <https://doi.org/10.3345/cep.2019.01431>. Epub 2020 May 14. PMID: 32683818; PMCID: PMC8024115.
74. Autmizguine, J.; Smith, P.B.; Prather, K.; Bendel, C.; Natarajan, G.; Bidegain, M.; Kaufman, D.A.; Burchfield, D.J.; Ross, A.S.; Pandit, P. Effect of fluconazole prophylaxis on Candida fluconazole susceptibility in premature infants. *J Antimicrob Chemother*. **2018**, *73*, 3482-3487. <https://doi.org/10.1093/jac/dky353>. PMID: 30247579; PMCID: PMC6927883.
75. Chicella, M.F.; Woodruff, E.D.; Desai, M.M. A review of Candida prophylaxis in the neonatal intensive care population. *J Pediatr Pharmacol Ther*. **2011**, *16*, 237-45. <https://doi.org/10.5863/1551-6776-16.4.237>. PMID: 22768008; PMCID: PMC3385038.
76. Ericson, J.E.; Kaufman, D.A.; Kicklighter, S.D.; Bhatia, J.; Testoni, D.; Gao, J.; Smith, P.B.; Prather, K.O.; Benjamin, D.K. Jr.; Fluconazole Prophylaxis Study Team on behalf of the Best Pharmaceuticals for Children Act–Pediatric Trials Network Steering Committee; Fluconazole Prophylaxis Study Team on behalf of the Best Pharmaceuticals for Children Act–Pediatric Trials Network Steering Committee. Fluconazole Prophylaxis for the Prevention of Candidiasis in Premature Infants: A Meta-analysis Using Patient-level Data. *Clin Infect Dis*. **2016**, *63*, 604-10. <https://doi.org/10.1093/cid/ciw363>. Epub 2016 Jun 13. PMID: 27298330; PMCID: PMC4981761.
77. Hornik, C.D.; Bondi, D.S.; Greene, N.M.; Cober, M.P.; John, B. Review of Fluconazole Treatment and Prophylaxis for Invasive Candidiasis in Neonates. *J Pediatr Pharmacol Ther*. **2021**, *26*, 115-122. <https://doi.org/10.5863/1551-6776-26.2.115>. PMID: 33603574; PMCID: PMC7887891.
78. Fly, J.H.; Kapoor, S.; Bobo, K.; Stultz, J.S. Updates in the Pharmacologic Prophylaxis and Treatment of Invasive Candidiasis in the Pediatric and Neonatal Intensive Care Units: Updates in the Pharmacologic Prophylaxis. *Curr Treat Options Infect Dis*. **2022**, *14*, 15-34. <https://doi.org/10.1007/s40506-022-00258-z>. Epub 2022 May 16. PMID: 36329878; PMCID: PMC9629810.
79. Xie, J.; Zeng, J.; Zheng, S. The efficacy and safety of fluconazole in preventing invasive fungal infection in very low birth weight infants: A systematic review and meta-analysis. *Ital J Pediatr*. **2023**, *49*, 51. <https://doi.org/10.1186/s13052-023-01460-5>. PMID: 37106436; PMCID: PMC10142176.

80. Hope, W.W.; Castagnola, E.; Groll, A.H.; Roilides, E.; Akova M, Arendrup MC, Arikan-Akdagli S, Bassetti M, Bille J, Cornely OA, Cuenca-Estrella M; et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: Prevention and management of invasive infections in neonates and children caused by *Candida* spp. *Clin Microbiol Infect.* **2012**, 18, Suppl 7:38-52. <https://doi.org/10.1111/1469-0691.12040>. PMID: 23137136.
81. Kaufman, D.; Boyle, R.; Hazen, K.C.; Patrie, J.T.; Robinson, M.; Grossman, L.B. Twice weekly fluconazole prophylaxis for prevention of invasive *Candida* infection in high-risk infants of <1000 grams birth weight. *J Pediatr.* **2005**, 147, 172-9. <https://doi.org/10.1016/j.jpeds.2005.03.036>. PMID: 16126045.
82. Wade, K.C.; Benjamin, D.K. Jr.; Kaufman, D.A.; Ward, R.M.; Smith, P.B.; Jayaraman, B.; Adamson, P.C.; Gastonguay, M.R.; Barrett, J.S. Fluconazole dosing for the prevention or treatment of invasive candidiasis in young infants. *Pediatr Infect Dis J.* **2009**, 28, 717-23. <https://doi.org/10.1097/INF.0b013e31819f1f50>. PMID: 19593252; PMCID: PMC2771384.
83. Leonart, L.P.; Tonin, F.S.; Ferreira, V.L.; Tavares da Silva Penteado, S.; de Araújo Motta, F.; Pontarolo R. Fluconazole Doses Used for Prophylaxis of Invasive Fungal Infection in Neonatal Intensive Care Units: A Network Meta-Analysis. *J Pediatr.* **2017**, 185, 129-135.e6. <https://doi.org/10.1016/j.jpeds.2017.02.039>. Epub 2017 Mar 10. PMID: 28285752.
84. Che, D.; Zhou, H.; Li, T.; Wu, B. Duration and intensity of fluconazole for prophylaxis in preterm neonates: A meta-analysis of randomized controlled trials. *BMC Infect Dis.* **2016**, 16, 312. <https://doi.org/10.1186/s12879-016-1645-5>. PMID: 27350534; PMCID: PMC4924264.
85. Kaufman, D.A.; Cuff, A.L.; Wamstad, J.B.; Boyle, R.; Gurka, M.J.; Grossman, L.B.; Patrick, P. Fluconazole prophylaxis in extremely low birth weight infants and neurodevelopmental outcomes and quality of life at 8 to 10 years of age. *J Pediatr.* **2011**, 158, 759-765.e1. <https://doi.org/10.1016/j.jpeds.2010.11.002>. PMID: 21168853.
86. Luparia, M.; Landi, F.; Mesini, A.; Militello, M.A.; Galletto, P.; Farina, D.; Castagnola, E.; Manzoni, P. Fungal Ecology in a Tertiary Neonatal Intensive Care Unit after 16 Years of Routine Fluconazole Prophylaxis: No Emergence of Native Fluconazole-Resistant Strains. *Am J Perinatol.* **2019**, 36, S126-S133. <https://doi.org/10.1055/s-0039-1691808>. Epub 2019 Jun 25. PMID: 31238373.
87. Healy, C.M.; Baker, C.J.; Zaccaria, E.; Campbell, J.R. Impact of fluconazole prophylaxis on incidence and outcome of invasive candidiasis in a neonatal intensive care unit. *J Pediatr.* **2005**, 147, 166-71. <https://doi.org/10.1016/j.jpeds.2005.04.016>. PMID: 16126043.
88. Chandramati, J.; Sadanandan, L.; Kumar, A.; Ponthenkandath, S. Neonatal *Candida auris* infection: Management and prevention strategies - A single centre experience. *J Paediatr Child Health.* **2020**, 56, 1565-1569. <https://doi.org/10.1111/jpc.15019>. Epub 2020 Jul 16. PMID: 32672390.
89. Sokou, R.; Palioura, A.E.; Kopanou Taliaka, P.; Konstantinidi, A.; Tsantes, A.G.; Piovani, D.; Tsante, K.A.; Gounari, E.A.; Iliodromiti, Z.; Boutsikou, T.; et al N. *Candida auris* Infection, a Rapidly Emerging Threat in the Neonatal Intensive Care Units: A Systematic Review. *J Clin Med.* **2024**, 13, 1586. <https://doi.org/10.3390/jcm13061586>. PMID: 38541815; PMCID: PMC10971333.
90. Bersani, I.; Piersigilli, F.; Goffredo, B.M.; Santisi, A.; Cairoli, S.; Ronchetti, M.P.; Auriti, C. Antifungal Drugs for Invasive *Candida* Infections (ICI) in Neonates: Future Perspectives. *Front Pediatr.* **2019**, 7, 375. <https://doi.org/10.3389/fped.2019.00375>. PMID: 31616647; PMCID: PMC6764087.
91. Rundjan, L.; Wahyuningsih, R.; Oeswadi, C.A.; Marsogi, M.; Purnamasari, A. Oral nystatin prophylaxis to prevent systemic fungal infection in very low birth weight preterm infants: A randomized controlled trial. *BMC Pediatr.* **2020**, 20, 170. <https://doi.org/10.1186/s12887-020-02074-0>. PMID: 32303210; PMCID: PMC7164192.
92. Sims, M.E.; Yoo, Y.; You, H.; Salminen, C.; Walther, FJ. Prophylactic oral nystatin and fungal infections in very-low-birthweight infants. *Am J Perinatol.* **1988**, 5, 33-6. <https://doi.org/10.1055/s-2007-999649>. PMID: 3276336.
93. Ozturk, M.A.; Gunes, T.; Koklu, E.; Cetin, N.; Koc, N. Oral nystatin prophylaxis to prevent invasive candidiasis in Neonatal Intensive Care Unit. *Mycoses.* **2006**, 9, 484-92. <https://doi.org/10.1111/j.1439-0507.2006.01274.x>. PMID: 17022766.
94. Howell, A.; Isaacs, D.; Halliday, R.; Australasian Study Group For Neonatal Infections. Oral nystatin prophylaxis and neonatal fungal infections. *Arch Dis Child Fetal Neonatal Ed.* **2009**, 94, F429-33. <https://doi.org/10.1136/adc.2008.157123>. Epub 2009 Mar 25. PMID: 19321509.
95. Aydemir, C.; Oguz, S.S.; Dizdar, E.A.; Akar, M.; Sarikabadayi, Y.U.; Saygan, S.; Erdev, O.; Dilmen, U. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. *Arch Dis Child Fetal Neonatal Ed.* **2011**, 96, F164-8. <https://doi.org/10.1136/adc.2009.178996>. PMID: 20659937.
96. Mersal, A.; Alzahrani, I.; Azzouz, M.; Alsubhi, A.; Alsawaigh, H.; Albshri, N.; Bajammal, M.; Avand, G.; Almahbosh, A. Oral Nystatin Versus Intravenous Fluconazole as Neonatal Antifungal Prophylaxis: Non-inferiority Trial. *J Clin Neonatol.* **2013**, 2, 88-92. <https://doi.org/10.4103/2249-4847.116408>. PMID: 24049751; PMCID: PMC3775143.

97. Austin, N; Cleminson, J.; Darlow, B.A.; McGuire, W. Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. *Cochrane Database Syst Rev.* **2015**, 10, CD003478. <https://doi.org/10.1002/14651858.CD003478.pub5>. PMID: 26497202; PMCID: PMC7154334.
98. Wainer, S.; Cooper, P.A.; Funk, E.; Bental, R.Y.; Sandler, D.A.; Patel, J. Prophylactic miconazole oral gel for the prevention of neonatal fungal rectal colonization and systemic infection. *Pediatr Infect Dis J.* **1992**, 11, 713-6. <https://doi.org/10.1097/00006454-199209000-00008>. PMID: 1448310.
99. Agrawal, S; Rao, S; Patole, S. Probiotic supplementation for preventing invasive fungal infections in preterm neonates--a systematic review and meta-analysis. *Mycoses.* **2015**, 58, 642-51. <https://doi.org/10.1111/myc.12368>. PMID: 26468692.
100. Hu, H.J.; Zhang, G.Q.; Zhang, Q; Shakya, S.; Li, Z.Y. Probiotics Prevent Candida Colonization and Invasive Fungal Sepsis in Preterm Neonates: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pediatr Neonatol.* **2017**, 58, 103-110. <https://doi.org/10.1016/j.pedneo.2016.06.001>. PMID: 27793494.
101. Oncel, M.Y.; Arayici, S.; Sari, F.N.; Simsek, G.K.; Yurttutan, S.; Erdeve, O.; Saygan, S.; Uras, N.; Oguz, S.S.; Dilmen, U. Comparison of Lactobacillus reuteri and nystatin prophylaxis on Candida colonization and infection in very low birth weight infants. *J Matern Fetal Neonatal Med.* **2015**, 28, 1790-4. <https://doi.org/10.3109/14767058.2014.968842>. Epub 2014 Oct 9. PMID: 25245226.
102. Demirel, G.; Celik, I.H.; Erdeve, O.; Saygan, S.; Dilmen, U.; Canpolat, F.E. Prophylactic Saccharomyces boulardii versus nystatin for the prevention of fungal colonization and invasive fungal infection in premature infants. *Eur J Pediatr.* **2013**, 172, 1321-6. <https://doi.org/10.1007/s00431-013-2041-4>. PMID: 23703468.
103. Gray, K.D.; Messina, J.A.; Cortina, C.; Owens, T.; Fowler, M.; Foster, M.; Gbadegesin, S.; Clark, R.H.; Benjamin, D.K. Jr.; Zimmerman, K.O.; et al. Probiotic Use and Safety in the Neonatal Intensive Care Unit: A Matched Cohort Study. *J Pediatr.* **2020**, 222, 59-64.e1. <https://doi.org/10.1016/j.jpeds.2020.03.051>. PMID: 32418818; PMCID: PMC7321859.
104. Manzoni, P.; Stolfi, I.; Messner, H.; Cattani, S.; Laforgia, N.; Romeo, M.G.; Bollani, L.; Rinaldi, M.; Gallo, E.; Quercia, M.; et al. Bovine lactoferrin prevents invasive fungal infections in very low birth weight infants: A randomized controlled trial. *Pediatrics.* **2012**, 129, 116-23. <https://doi.org/10.1542/peds.2011-0279>. Epub 2011 Dec 19. PMID: 22184648.
105. Fernandes, K.E.; Carter, D.A. The Antifungal Activity of Lactoferrin and Its Derived Peptides: Mechanisms of Action and Synergy with Drugs against Fungal Pathogens. *Front Microbiol.* **2017**, 8, 2. <https://doi.org/10.3389/fmicb.2017.00002>. PMID: 28149293; PMCID: PMC5241296.
106. Berrington, J.E.; McGuire, W.; Embleton, ND. ELFIN, the United Kingdom preterm lactoferrin trial: Interpretation and future questions. *Biochem Cell Biol.* **2021**, 99, 1-6. <https://doi.org/10.1139/bcb-2020-0073>. PMID: 32830532.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.