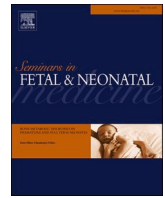




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Infection prevention for extremely low birth weight infants in the NICU

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ABSTRACT

Extremely preterm infants are particularly vulnerable to systemic infections secondary to their immature immune defenses, prolonged hospitalizations, delays in enteral feeding, early antibiotic exposure, and need for life-sustaining invasive interventions. There have been several evidence-based practices for infection prevention in this population, such as human milk feedings, utilization of “bundle checklists” and decolonization of pathogenic organisms. Other practices, such as the use of probiotics, human milk-derived fortifiers, and antifungal prophylaxis are more controversial and require further investigation regarding the risks and benefits of such interventions.

This chapter examines the susceptibility of the preterm newborn infant to invasive infections and describes several strategies for infection prevention, along with the associated limitations of such practices. It also addresses the various gaps in our understanding of preventing infections in this population, and the need for additional large multi-center randomized controlled trials. Additionally, the role of the SARs-CoV-2 global pandemic and associated strategies for infection prevention in the NICU are discussed.

1. Introduction

The Preterm Infant and Susceptibility to Infection:

Preterm infants are at a significant disadvantage when it comes to infection prevention [1,2]. Very low birthweight (VLBW) and extremely low birth weight (ELBW) neonates are particularly vulnerable to bacterial infections because of developmental immaturities in the immune system, need for prolonged hospitalizations and requirements for invasive monitoring, testing and treatments which bypass skin barrier defense mechanisms [1–5]. Moreover, the preterm skin lacks a well-formed stratum corneum (the outermost layer of the epidermis), as well as the vernix caseosa (a lipid-rich waxy coating containing active antimicrobial proteins and peptides), both of which are key for preventing pathogen entry [1,4–6].

Postnatal acquisition of the microbiome plays a critical role in immune development and response [7,8]. The preterm infant’s microbiome is largely driven by environmental exposures in the NICU [9]. Thus, repeated courses of antibiotics, the NICU ecological environment and choice of diet (formula or breast milk) are key regulators of the microbiome and may be important in the pathogenesis of late onset sepsis (LOS) [10–12]. In the setting of preterm rupture of membranes, the sterile or partially sterile uterine environment is compromised by

exposure to genital microbes. Even with preterm labor and intact membranes, the amniotic fluid (and secondarily the fetus) may become colonized. The mode of delivery greatly influences the kind of bacteria that colonize the newborn [13]. Caesarean-delivered infants bypass the vaginal canal secretions, which are rich in *Lactobacillus*, *Bacteroides* and *Bifidobacterium* species [8], and have a microbiota composition that is different from those infants born vaginally [14,15]. Several studies have investigated the practice of ‘vaginal seeding,’ through swabbing the mouths and skin of caesarean-born infants in an attempt to mimic the microbiota exposure during a vaginal birth [14]. This practice has a controversial reliability profile, as it does not take into account the potential exposure of preterm infants to unexpected pathogenic organisms, and therefore needs further investigation [16].

2. Infection prevention by disease process

2.1. Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is a multifactorial disease in which the susceptibility of the preterm intestine, immunodeficiencies associated with preterm delivery, nutritional practices and the intestinal microbiome play critical roles [17]. The gastrointestinal microbiota is

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mostly composed of bacteria from two major phyla, *Bacteroidetes* (gram negative bacteria) and *Firmicutes* (*Lactobacillus* and other gram-positive bacteria). Other important phyla, especially with regard to NEC development include *Proteobacteria* (pathogenic gram-negative bacteria) and *Actinobacteria* (*Bifidobacterium* and other gram-positive bacteria). Until fairly recently, culture-based methods were used to identify and define the microorganisms colonizing various body sites. Recent advances in molecular techniques (16S RNA sequencing and shotgun metagenomics) have allowed investigators to characterize the microbiome of the preterm infant with much greater precision and examine its role in the pathogenesis of diseases such as NEC [18].

Use of drugs which suppress gastric acidity has been shown to alter the microbiome [19] and potentially increase the risk of LOS and NEC in very low birthweight infants [20,21]. Both proton pump inhibitors and H2-blockers have been correlated with increased abundance of colonization with *Proteobacteria*, *Actinobacteria* and *Bacteroidetes*. Antibiotics for early-onset sepsis decrease the numbers of *Firmicutes* and increase the abundance of *Proteobacteria* [22]. Intrapartum antibiotic prophylaxis has been shown to alter the microbiome for months postnatally, by increasing *Proteobacteria* and decreasing *Actinobacteria*, *Bifidobacterium* and *Bacteroides* [23]. Furthermore, prolonged treatment with antibiotics for early-onset sepsis has been associated with an increased risk of necrotizing enterocolitis and late onset sepsis [24,25]. In term infants, the abundance and diversity of bacteria is decreased at birth [26]. In comparison, bacterial diversity is further decreased in infants delivered preterm and is characterized by high numbers of *Firmicutes* and *Proteobacteria* (e.g., *Enterobacteriaceae*) and low levels of *Bifidobacterium*. This

abnormal pattern of colonization may alter the structural barrier of the intestine resulting in increased permeability and bacterial translocation, ultimately leading to NEC (Fig. 1).

No single bacterium has been causally linked to the development of NEC. However, NEC has been associated with a “bloom” in *Proteobacteria*, particularly *Enterobacteriaceae*, and a decrease in *Firmicutes* and *Bacteroidetes* [28]. This process termed dysbiosis is believed to precede the development of NEC. *Enterobacteriaceae* interact with toll like receptor-4, which is known to regulate the balance between healing and repair in the intestine [29] and is upregulated in infants with NEC [30]. However, it is unclear if the “bloom” of gram-negative bacteria actually causes NEC or that NEC results from the concurrent decrease of commensal bacteria (e.g., *Firmicutes*), which might be cytoprotective.

2.2. Probiotics and NEC prevention

Probiotics are live microbial supplements which provide benefit to the host beyond that of nutrition. Breast milk contains a variety of probiotics, but unfortunately is not always available to the preterm infant. Donor breast milk provides suboptimal nutrition unless fortified and does not contain viable bacteria once pasteurized. Probiotics have been shown to increase mucin and β -defensin production, decrease adherence of pathogens, enhance tight junctions, increase the number of IgA producing cells, kill pathogenic bacteria and dampen the inflammatory response [31].

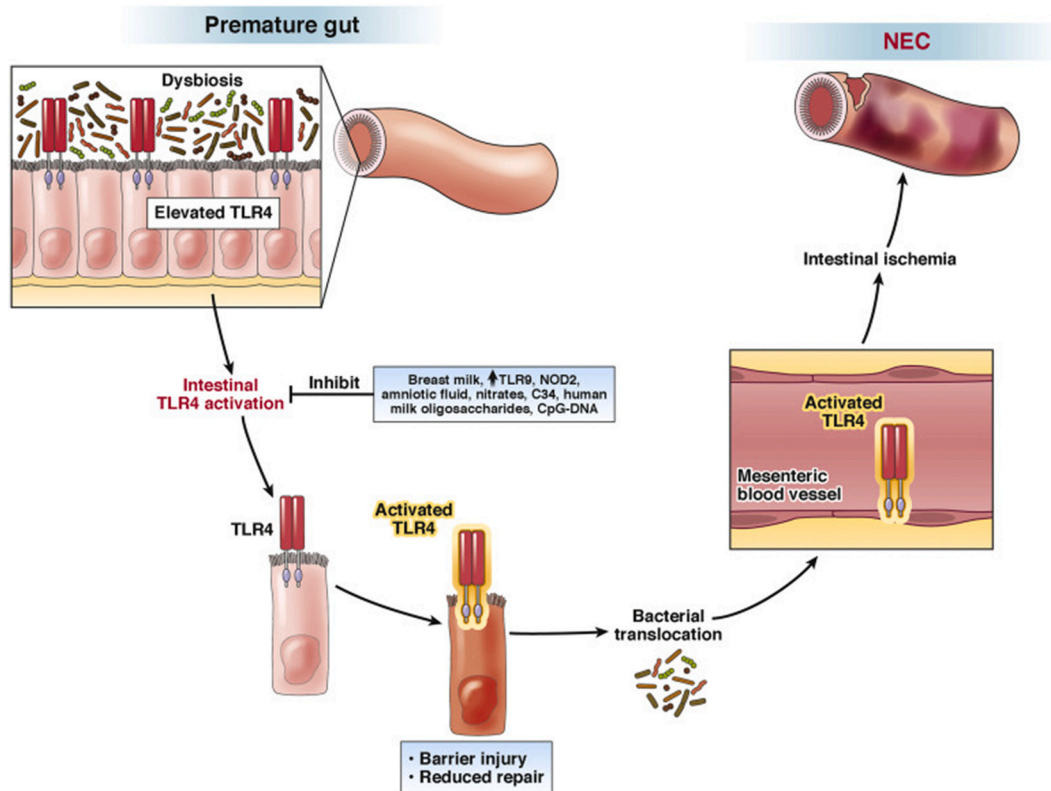
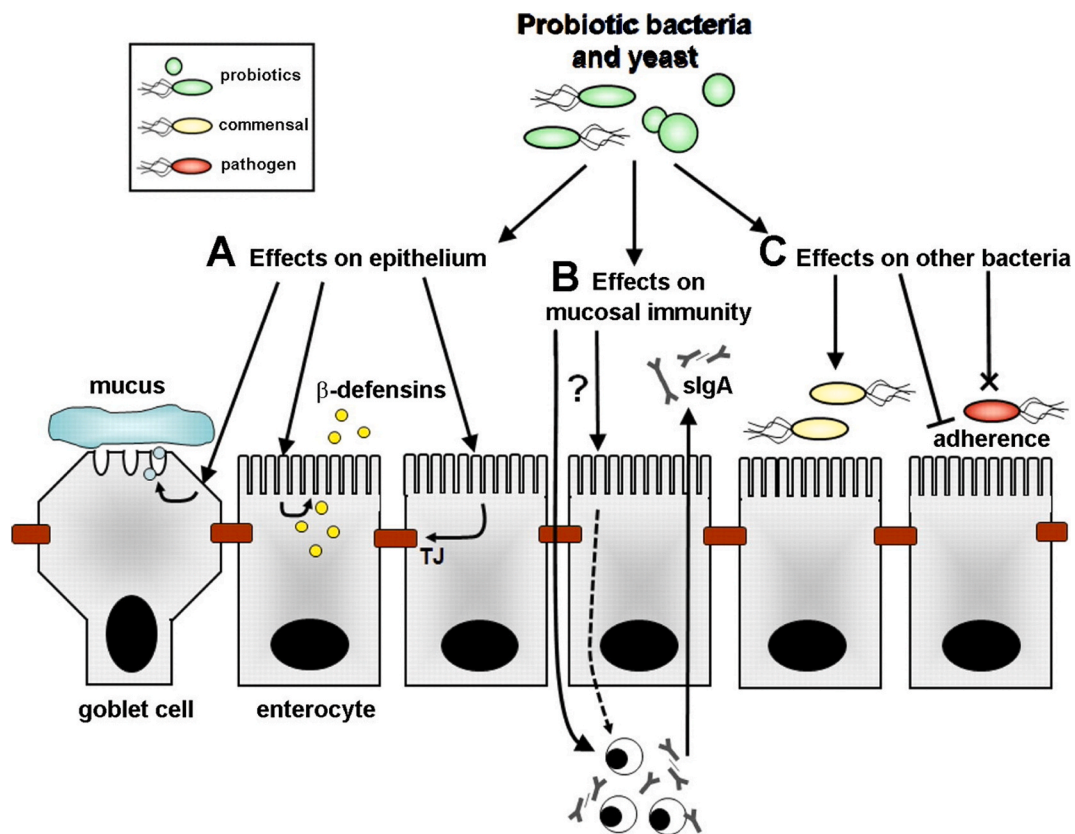


Fig. 1. Hackam, D. J. & Sodhi, C. P. *Cell Mol Gastroenterol Hepatol* (2018) [27].



Dr. Angela Hoyos in Bogota Colombia was the first clinician to use probiotics in a NICU setting [32]. She treated every baby with Inflan containing *Bifidobacteria* and *Lactobacillus acidophilus*, which resulted in a marked decline in NEC and NEC related deaths. Similarly, Totsu et al. conducted a cluster-randomized double-blind, placebo-controlled trial including 19 hospitals across Japan, evaluating the benefit of administering the probiotic, *Bifidobacterium bifidum* to VLBW infants. The authors of this trial found that the probiotics group reached full enteral feeds earlier with a significantly decreased incidence of LOS compared to the placebo group [33].

Probiotics have been administered to thousands of newborn infants in randomized clinical trials and observational studies. The encouraging news is that the use of probiotics is relatively safe, except for the rare infant who develops sepsis with the probiotic organism or a contaminant. However, there are several controversies surrounding probiotic use. For example, the manufacturing processes for probiotics are not tightly regulated in the United States. The Food and Agriculture Organization/World Health Organization has issued recommendations on information that should be present on the product label, including; genus, species, strain designation, minimal viable number of each probiotic strain at the end of shelf life, the recommended effective dose of the probiotic, health claims, storage conditions and corporate contact details. That information is not generally available for commercial probiotic products used in the United States. There have been a number of studies testing the purity and content of commercial probiotic supplements. On the positive side, Shehata and Newmaster tested 182 probiotic “dietary supplements” from the United States and Canada [34] and found that only 8% of samples were non-compliant with labelling. However, several studies found both contamination (with potential pathogens) and missing species in a high percentage of probiotic supplements [35–42]. Other studies found that the number of viable counts were lower than indicated on the label [36,40,42–44]. It is important to note that most of the studies assessing viable bacterial counts were

conducted on samples from different countries on a limited number of specimens. In Europe, probiotic containing foods and supplements are carefully regulated. Over 3000 health claims for probiotics were rejected by the European commission except for better lactose digestion when used in yogurt cultures. In the United States, probiotics are considered dietary supplements and health claims are not regulated. The phrase “buyer beware” is appropriate when using off-the-shelf dietary supplements in preterm infants. There is a great need for pharmaceutical grade probiotic supplements.

The population of infants <28 week’s gestation is most susceptible to NEC. However, the majority of randomized trials examining effectiveness of probiotics have not included large numbers of infants in this gestational age stratum. Meta-analyses have been problematic because it is difficult to compare studies using different probiotic species. For example, Underwood et al. performed a dose escalation study comparing two microbial strains (*B. infantis* and *B. lactis*). Only *B. infantis* was able to colonize the gastrointestinal tract, *B. lactis* did not. Furthermore *B. lactis* is unable to utilize breast milk oligosaccharides [45]. In addition, the quality of the meta-analyses differed considerably and as of 2020 only one was rated as high quality based on AMSTAR criteria [46]. In a recent systematic analysis from the Cochrane library [47] Sharif et al. concluded that probiotics may reduce the incidence of NEC (conclusion rated as low certainty -number needed to benefit = 33). The evidence was assessed as low certainty because of limitations in trial design and publication bias. This meta-analysis also concluded that probiotics probably reduced mortality and infection. However, sensitivity meta-analyses of 16 trials at low risk of bias showed that probiotics reduced NEC but had no effect on mortality or infection rates. Importantly, there was no significant benefit of probiotics on the incidence of NEC in extremely low birth weight infants. These results should be cautiously interpreted as relatively few studies were included in these analyses and the authors warn that estimates might be imprecise [47].

In a strain specific meta-analysis by van den Akker et al. only a

minority of single strains or combination of strains reduced mortality or morbidity in clinical trials [48]. Importantly, most randomized clinical trials have not confirmed the purity of the product used in each study. Fungal sepsis has been reported from a NICU in which the commercial product contained the contaminating fungus [49]. Many manufacturers change the strains in the probiotic product without changing the label. Therefore, there is uncertainty what strain is actually being administered. Of the hundreds of probiotic trials, it is noteworthy that only two commercial probiotics studied in clinical trials have been shown to both increase colonization with the probiotic strain in the intestine and decrease colonization with *Enterobacteriaceae* [50]. Finally, most randomized trials have not considered cross contamination of the probiotic to the control group, which might benefit infants in the control group and dilute any potential benefit of probiotics.

Based on a careful review of all available evidence, the Committee on Fetus and Newborn of the American Academy of Pediatrics concluded that “Given the lack of FDA-regulated pharmaceutical grade products in the United States, conflicting data on safety and efficacy, and potential for harm in a highly vulnerable population, current evidence does not support the universal administration of probiotics to preterm infants, particularly those with birthweights <1000 g” [51]. Importantly, there are still several NICUs in the United States and globally that routinely choose to administer probiotics to their VLBW infants, despite the AAP recommendations, based on results from various studies as well as from anecdotal experiences. Additional large randomized clinical trials using pharmaceutical grade product are still necessary and in progress.

2.3. Human milk feedings for prevention of NEC

Human milk contains a variety of antimicrobial factors and immunomodulating agents and has a unique microbiome that may serve as a source of commensal bacteria (*Bifidobacterium* and *Lactobacillus*) [52, 53]. However, unpasteurized breast milk may contain a variety of species, some of which may be pathogenic for the neonate. In preterm infants, use of human milk is considered an evidenced based strategy to reduce the incidence of NEC. However, in mothers delivering very preterm infants, the supply of human milk may initially be inadequate and require supplementation (donor breast milk or formula), or calorically inadequate and require milk fortifiers (bovine or human). Observational studies of feeding infants with mother’s own milk demonstrate a reduction in the incidence of NEC. Randomized clinical trials, by necessity, have only included donor breast milk that was supplemented with human-milk derived or bovine-derived fortifiers. Donor breast milk is pasteurized which alters some of the immunological benefits, without significantly affecting the nutritional composition. Furthermore, donor breast milk is usually collected from women delivering infants at term, in whom the nutrient supply is very different from that found in milk from women delivering preterm infants. As with the systematic reviews of probiotics, the meta-analyses of human breast milk vs formula are very heterogeneous and include studies of infants fed an exclusively human diet vs. those receiving varying amounts of bovine fortified donor milk or formula. Furthermore, the meta-analyses include studies conducted over a number of years. However, a few generalizations are still possible.

- All meta-analyses demonstrated a reduction in the incidence of NEC with donor milk compared with preterm formula.
- There is no difference in all-cause mortality in infants fed formula vs. donor milk.

- There is no difference in tolerance of feedings with donor milk or formula.
- Formula fed infants exhibited significantly better weight gain and linear growth. In the systematic review of Quigley et al., growth in head circumference was also faster with formula, but not when donor breast milk was fortified [54].
- No long-term differences in neurodevelopment or growth have been demonstrated
- There is no evidence that human milk (donor or maternal) decreases the risk of late onset sepsis.

Although controversial, there is no evidence that human milk-based fortifiers decrease the risk of NEC vs. fortifiers prepared from bovine sources. The recent meta-analysis of Grace et al., which concluded that human milk derived fortifiers resulted in a lower incidence of NEC included only two studies and is too small to make meaningful conclusions [55].

3. Late onset sepsis (LOS)

LOS, or sepsis occurring after 72 h of life, is a major contributor of neonatal morbidity and mortality, with an incidence of 1–2 per 1000 live born newborns and a high overall mortality rate [56–58]. Gram positive organisms, specifically *Staphylococcus aureus*, account for the majority of LOS infections. Coagulase negative *Staphylococcus* (CoNS) is often cited as a leading cause of LOS in the NICU [56,57,59]. However, based on more recent definitions of true bacteremia, as opposed to blood sample contamination with CoNS, the prevalence of CoNS LOS is likely less than previously reported [60,61]. Gram negative bacteria, such as *Escherichia coli*, *Enterobacter*, and *Klebsiella*, as well as fungal species, primarily *Candida albicans*, are also responsible for LOS and have an overall higher mortality rate than gram positive infections [56,57].

3.1. Central line associated bloodstream infections

Episodes of LOS are often viewed as preventable hospital acquired infections (HAI). Central line associated bloodstream infections (CLABSI) are the most common HAI in the NICU, due to sustained need for vascular access and a lengthy hospital stay. A peripherally inserted central catheter (PICC) is most commonly used in neonates and several evidence-based practices have been implemented for CLABSI prevention [62–65]. Over the last decade, there has been a considerable shift in perception of CLABSI, from an unavoidable complication of a life-saving intervention to a preventable and reportable medical error that requires intervention [64].

The Institute for Healthcare Improvement (IHI) together with the Centers for Disease Control and Prevention (CDC) and other national scientific organizations have issued evidence-based guidelines that promote using central line bundles to improve CLABSI rates in the healthcare setting [66,67]. Care bundles are an “all-or-nothing” approach of evidence-based practices, that when implemented simultaneously, improve outcomes. In the case of CLABSI prevention bundles, there are 5 key best practices that require full compliance:

- 1) Focus on sterile barrier precautions during PICC insertion (mask, sterile gown, sterile gloves and large sterile drapes)
- 2) Hand hygiene
- 3) Skin preparation with an antiseptic

- 4) Dressing changes when dressing becomes bloody, soiled or no longer occlusive
- 5) Daily review of line necessity with immediate removal of unwarranted lines

Additionally, frequent hands-on education of staff members and unannounced audit regarding adherence to these care bundles, are recommended [68,69]. Statewide collaboratives using CLABSI prevention bundles have been highly effective in reducing the incidence of infection [70–72].

3.2. MRSA/MSSA colonization and infection prevention

Methicillin-sensitive *Staphylococci aureus* (MSSA) and Methicillin-resistant *Staphylococci aureus* (MRSA) are common causes of LOS in preterm infants, and significant contributors of morbidity and mortality in the NICU [73–75]. A meta-analysis of MRSA colonization in neonates during NICU admission described a pooled prevalence of 1.9% (95% CI 1.3%–2.6%) for MRSA colonization, with a relative risk to develop MRSA bloodstream infection (BSI) of 24.2 (95% CI 8.9–66) in colonized infants [76]. Colonization with *Staphylococci aureus* (SA) is a well-known risk factor for subsequent development of a BSI in the NICU population, and several prevention strategies have been developed to mitigate spread [76–79]. Weekly surveillance of admitted neonates, effective hand hygiene, environmental and equipment decontamination, cohorting of colonized infants, and implementing strict contact precautions have all been shown to reduce endemic SA across NICUs [79–82].

Identifying MRSA and MSSA colonized neonates through weekly nasal swabs has led to decolonization efforts using topical antimicrobial agents. Mupirocin applied to the nares combined with the use of chlorhexidine baths (relevant to gestational, >36^{0/7} weeks and chronological age, > 4 weeks old) have shown promising reductions in MRSA [83,84], as well as MSSA colonization and infections [85]. Both parents and care providers can contribute to the spread of SA. Recently, Milstone et al., conducted a clinical trial randomizing parents of MRSA colonized neonates to either receive mupirocin and chlorhexidine cloths or placebo [86]. These authors report that 14.6% of neonates with parents in the treatment group acquired a concordant SA strain compared with 28.7% of neonates with parents in the placebo group (risk difference –14.1%, and hazard ratio of 0.43). This study opens the door for future research examining decolonization of healthcare workers and care-takers of colonized neonates, with potential to reduce subsequent nosocomial infections. It is important to mention, that the increased use of mupirocin ointment in critically ill preterm neonates has led to the emergence of mupirocin resistant *Staphylococci aureus* strains. While the prevalence of these resistant strains remains low, this can have future implications for infection prevention and eradication [87,88].

4. Fungal infections

VLBW and ELBW neonates are at increased risk for invasive fungal disease, which is associated with increased morbidity mortality and neurodevelopmental impairments [57,89]. The incidence of invasive fungal disease in these birth weight populations ranges widely with an average of 16% (range 4–43%) [90]. The majority of cases are caused by *Candida* species, specifically *Candida albicans* and *Candida parapsilosis*,

and typically cause late-onset sepsis [57]. However, a few cases occur through vertical transmission and may cause early-onset sepsis. Attempting to prevent invasive fungal disease in high-risk patients is imperative to avoid mortality and long-term sequelae.

Minimizing risk factors for fungal sepsis is an important way to minimize the risk of disease. Modifiable risk factors include: prolonged exposure to empiric antibiotics, exposure to 3rd generation cephalosporins and other broad-spectrum antibiotics, and use of foreign bodies (such as endotracheal tubes, central venous or arterial catheters and other hardware) [91,92]. Other risk factors for invasive fungal disease include positive pressure ventilation and intubation, gastrointestinal pathology, previous blood stream infection, parenteral nutrition and intravenous lipids [92]. In a matched case-control study, multivariate analyses showed that candidemia was associated with prolonged catheter use, which had an odds ratio of 1.06 per day of use (95% CI of 1.02–1.10) and with previous blood stream infection, with an odds ratio of 8.02 (95% CI of 2.76–23.30) [92]. It is well established that reducing exposure to these risk factors is associated with a reduction in risk of systemic fungal disease [91].

4.1. Antifungal prophylaxis and infection prevention

Antifungal prophylaxis is used to reduce the risk of invasive fungal disease; however, variations in this practice exist worldwide. Fluconazole seems to be emerging as the drug of choice for prophylaxis. It has a long half-life, is excreted renally, and has a good safety profile, although more studies in neonates are needed [93]. Side effects reported include transaminitis [94] and cholestasis in ELBW neonates who received fluconazole prophylaxis [95].

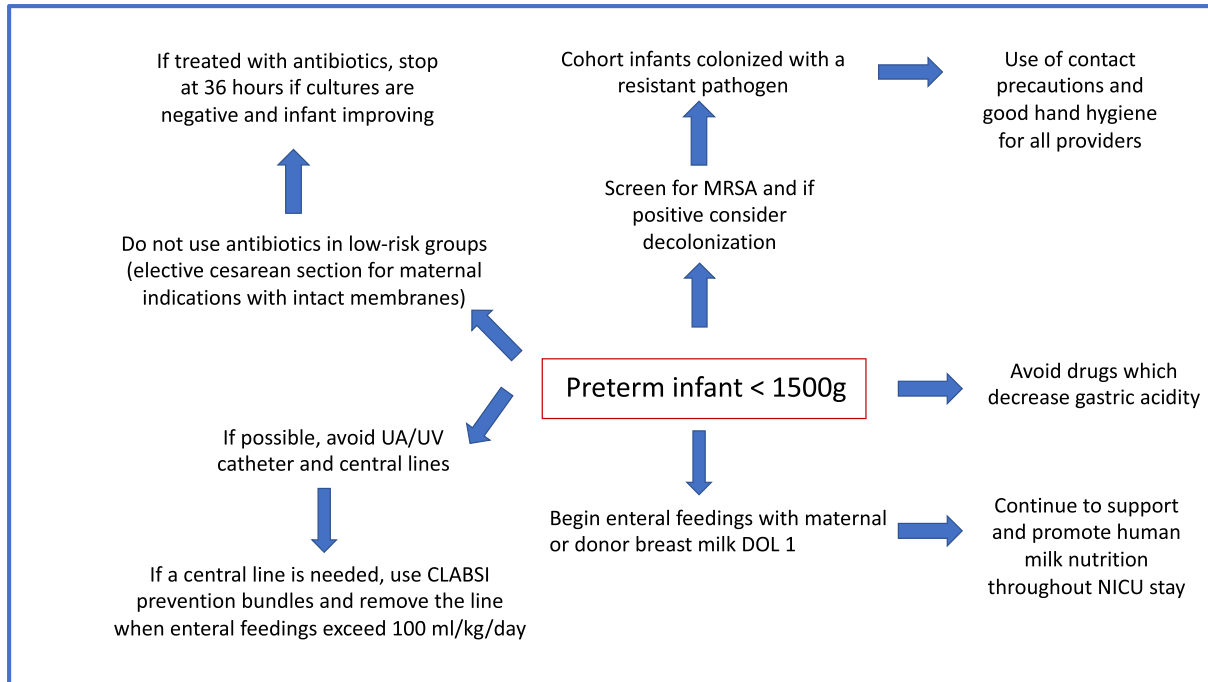
In the first large, prospective, randomized, double-blinded clinical trial examining the efficacy of fluconazole prophylaxis in preventing invasive fungal infection, 10 ELBW neonates developed invasive fungal infection in the placebo group compared to 0 in the fluconazole prophylaxis group (P = 0.0008) [96]. In a more recent large multicenter study, Benjamin et al. concluded that prophylactic fluconazole reduced the incidence of invasive fungal infection in infants <750 g, but did not reduce neurodevelopmental impairments at 18–22 months postnatally [97]. In addition to fluconazole, other agents including topical antifungal medications and liposomal amphotericin B have been used to reduce the incidence of fungal infections. Neither of these agents have been adequately studied in neonates. In a randomized control trial comparing prophylaxis with nystatin, fluconazole and placebo, the incidence of fungal infections was 4.3% in nystatin group, 3.2% in fluconazole group and 16.5% in placebo group [98]. A 2015 Cochrane Review concluded that prophylactic systemic antifungal therapy may reduce the incidence of invasive fungal infection in very low birth weight infants, however, there was considerable heterogeneity in the reported studies [99].

It is re-assuring that of the studies done, there seems to be a lack of emergence of resistant fungal species for neonates who have received antifungal agents (IDSA) and there does not seem to be an emergence of inherently resistant fluconazole fungal species [100]. Continued surveillance and monitoring of the fungal ecology in NICUs where fluconazole or nystatin prophylaxis is adopted is warranted to exclude these unwanted shifts in sensitivity to these agents.

5. Infection prevention during COVID

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has dramatically changed the way we deliver healthcare globally. While SARS-CoV-2 has not had major clinical implications for preterm infants in the NICU [101,102], it has led to more rigid infection prevention strategies (i.e., visitor restrictions, hand hygiene, environmental disinfection, and donning of personal protective equipment). Maternal breastmilk has been more closely examined as a potential protective mechanism for infants of women who were previously infected with SARS-CoV-2 or immunized with the vaccine. Multiple studies have shown that maternal spike specific IgA targeting SARS-CoV-2 is found in breastmilk of mothers previously infected or vaccinated [103–105] without evidence of SARS-CoV-2 transmission

neonates due to transplacental transfer of SARS-CoV-2 antibodies after covid19 vaccination during pregnancy, it is important to understand the safety of covid19 vaccine administration and promote its use in pregnant and lactating women. Preliminary results for safety of mRNA covid19 vaccine in pregnant women concluded that there were no obvious safety concerns [109]. Injection-site pain was the most commonly reported side effect; headache, myalgia, chills and fever were also reported. No neonatal deaths were reported. Only data from December 14, 2020 to February 29, 2021 were available for analysis, indicating that more longitudinal studies are needed for better assessment of safety during and after pregnancy. Preliminary data suggests that it is safe to administer mRNA covid19 vaccine to lactating individuals [110].



Flow Diagram: Infection Prevention in the Very Low BirthWeight Infant:

[106]. Similarly, breastfed infants have been shown to have salivary IgA specific for SARS-CoV-2, which is important for stimulating the mucosal immune response [105]. While very premature infants are not capable of initiating breastfeeding until much later in their NICU stay, expressed maternal breastmilk has been encouraged and should be used whenever possible.

While risk factors for maternal to neonatal transmission of SARS-CoV-2 are not fully understood, several precautions and management strategies for mother-infant dyads have been proposed. In an observational cohort study of 120 neonates born to SARS-CoV-2 infected mothers, 68% completed follow up, and all tested negative for the virus at 5–7 days of life as well as 14 days of life [107]. The American Academy of Pediatrics recommends that all SARS-CoV-2 positive mothers and newborns room-in after delivery, per hospital standard practice, while taking precautions such as hand hygiene and use of surgical mask during breastfeeding and hands-on care [108]. While the preterm population is not rooming-in with an infected mother, the Academy of Pediatrics guidelines recommends cohorting the infant in a negative pressure room and having the medical staff take precautions (N95, eye protection, don gown and gloves) until the infant tests negative within the first 72 h of age. Additionally, visitation restrictions are in place for a mother with SARS-CoV-2.

Given the emerging data that vaccine provides some protection to

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