Synbiotics prevent neonatal sepsis in rural India

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Neonatal sepsis is one of the primary causes of 2.7 million neonatal deaths every year followed by preterm birth. Although large-scale statistics is not available, India contributes to a major portion of this disease burden. Sepsis refers to culture-confirmed bacterial infections; however, in developing countries it primarily refers to possible severe bacterial infection (pSBI). Several conditions are clubbed together as 'bacterial infection' and treated with antibiotics. While preterm birth is the most common cause of death (41%) during early neonatal period (0–6 days), sepsis (37%) is the most common cause during late neonatal period (7–27 days)[1]. The source of early onset neonatal sepsis is maternal blood, skin or genital tract, while late-onset sepsis is hospital- or community-acquired during or after delivery. Causative organisms for early-onset sepsis include *Streptococcus agalactiae* and *Escherichia coli*, while implicated organisms in the late-onset sepsis include *Staphylococcus aureus*, *E. coli*, and *Klebsiella* sp.[2,3]. Low birth weight, premature birth, invasive procedures and admission in the intensive care unit can predispose an infant to sepsis.

Management of neonatal sepsis involves targeting endogenous mediators of adult sepsis to reduce inflammation, intravenous immunoglobulin injection or vitamin A treatment. Several clinical trials have targeted the mediators of host response, including interleukin 8 (IL-8) and tumour necrosis factor (TNF). However, a network analysis of systemic inflammation in humans shows the huge complexity of this response[4]. Thus, targeting single or few molecules during clinical trials has low effect on the morbidity of sepsis. Another strategy is the use of immunoglobulin G (IgG) therapy. Infants and preterm infants have low levels of serum IgG. Thus, it was speculated that intravenous polyvalent IgG immune globulins may prevent or help treat neonatal sepsis. However, no difference in mortality, major disabilities and secondary outcomes was observed in the test group[5]. Neonatal immunization is another way of reducing neonatal infections; however, it is also beset with many pitfalls. Neonates have an immature immune system with extremely low levels of immunoglobulins (IgG), except for IgG specific to maternal antigens which are transferred across the placenta during the third trimester. Maternal antibodies persist in the infant for 6–12 months during which they protect the neonates and infants from infectious diseases. However, maternal IgG antibodies also suppress vaccine-induced immune response which results in reduced or no effect of vaccines against neonatal diseases[6]. Studies have shown that both *S. agalactiae* and *Streptococcus pneumoniae* vaccines are ineffective in neonates[7]. The two interventions that have actually proved to be helpful in developing countries are breast-feeding and cleaning of the vagina, neonatal skin and umbilical chord using antiseptics[8–10]. A study also examined a dose–response relationship where the odds of sepsis decreased by 19% for every 10 ml kg^{-1} day^{-1} increase in the dose of human milk[11]. Thus, most of the management strategies employed till now have not shown promising results to prevent neonatal sepsis.

A study performed a double-blind, placebo-controlled, randomized trial to examine the effect of synbiotics on neonatal sepsis in India[12]. The study was performed in 149 villages of Odisha, which has the highest infant and neonatal mortality rate in India. The synbiotic, a combination of *Lactobacillus plantarum* and fructooligosaccharide, was administered orally to infants from day-2 to day-5 for seven days. The study registered 7089 pregnant women, and 2506 newborns were excluded due to several reasons, such as birth weight below 2 kg, gestational age <35 weeks, infant not able to tolerate oral feeds, mother had fever or infection, congenital abnormalities in the infant, or the infant was on antibiotics. Finally, 4556 newborns were selected for the study and divided into placebo ($N = 2278$) and synbiotic ($N = 2278$) groups. In total, there were 319 confirmed cases of sepsis, and blood culture was performed for 182 of those infants. Only 5% of sepsis was found in the first week after birth, while 72% of sepsis cases were found in weeks 3–8 after birth, suggesting that bulk of the neonatal sepsis occurs after the first two weeks of life. The primary outcome was a combination of sepsis and death, while secondary outcomes included infections, such as diarrhoea, omphalitis and skin infection. Although the bacterial burden of neonatal sepsis was not high (1.2% in control population), the predominant cause of culture-positive neonatal sepsis were Gram-negative bacteria. This is supported by a previous study which also found that neonatal sepsis in India is primarily contributed by Gram-negative bacteria[13].

The study[12] observed 40% reduction in the primary outcome (sepsis and death) in the synbiotic group. All three components of sepsis–culture-positive sepsis, culture-negative sepsis and lower respiratory tract infections were lower in the treatment group. The use of synbiotics led to 82% reduction in the risk for Gram-positive infections and 75% reduction in the risk for Gram-negative infections. Secondary infections were also reduced by 52% and lower respiratory tract infections were reduced by 31% in the synbiotic group. Gastrointestinal adverse events, including abdominal distention were low and the synbiotic preparation was well-tolerated by the neonates. The effect on lower respiratory tract infection is interesting, as it suggests that the host–probiotic interaction could also improve systemic host immunity. Previous studies have shown that *Lactobacillus rhamnosus* can improve immune response in a mouse model of *Pseudomonas aeruginosa* by inducing the recruitment of regulatory T-cells[14].

Previous studies on the effect of synbiotics on neonatal sepsis have been conflicting. Two studies in Turkey showed that the inclusion of synbiotics in breast milk reduced the incidence of sepsis and enterocolitis[15,16]; however, another study conducted in a tertiary care teaching hospital in South India on enterally fed neonates showed only a modest reduction in the risk of sepsis[17]. One of the key differences between this study and previous studies is the choice of probiotic. Jacobs *et al.*[18] used a mixture of *Streptococcus thermophilus*, *Bifidobacterium*

infantis and *Bifidobacterium lactis*; Costeloe *et al.*[19] used *Bifidobacterium breve* and Sinha *et al.*[20] a combination of eight probiotics (VSL-3)[19]. None of these studies used prebiotics along with the probiotics. Thus, the addition of prebiotic and choice of probiotic is critical to prevent sepsis and may have to be tailored based on the study population.

One of the drawbacks of this study is that it was conducted in near-term and normal weight babies, while the previous studies focused on low birth weight or pre-term babies which are more prone to lethal sepsis. Also several factors, including, status of vitamins A and D, vaccination, access to sanitized water and hygienic conditions, exposure to smoke and maternal body-mass index have not been documented, which also influence neonatal infections.

This study is critical towards treating and understanding neonatal sepsis in India. It shows that a single synbiotic preparation could prevent sepsis in term or late-preterm infants in the country. Additionally, it also depicts that only a fraction of cases identified as pSBI are bacterial in origin. Thus, the study shows that a paradigm shift in the current treatment of neonatal sepsis is required if the rest of neonatal sepsis is of viral origin. South Asia accounts for 3.5 million cases of neonatal sepsis every year with India carrying a major portion of this disease burden. Thus this study provides a strategy to effectively prevent neonatal sepsis in rural India.

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