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Immunotherapy in Neonatal Sepsis: Advances in Treatment and Prophylaxis

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Abstract

Purpose of review—Systemic infections in premature and term infants cause significant morbidity and mortality in spite of appropriate antimicrobial therapy. Consequently, immunotherapy has emerged as a potential adjuvant therapeutic modality to reduce the incidence and mortality associated with neonatal sepsis.

Recent findings—The most recent findings during the review period include systematic reviews of previously published trials evaluating the use of intravenous immunoglobulin and colony stimulating factors in neonatal sepsis. In addition, the most recent trials describing the use of anti-staphylococcal antibodies, probiotics, glutamine supplementation, recombinant human protein C, and lactoferrin in the prevention and treatment of neonatal sepsis have been reviewed.

Summary—Immunotherapy used as an adjuvant for the prevention and treatment of neonatal sepsis holds promise. Clinical trials specifically designed towards the neonatal population and appropriately powered to detect treatment differences are necessary prior to universal recommendation of these therapies in the nursery.

Keywords

newborn; prematurity; systemic infection; immune system

Introduction

Approximately 20% of very low birth weight (VLBW, <1,500 g) infants suffer from culture-proven sepsis and 10–20% die from sepsis in spite of antimicrobial therapy.[1, 2] Investigators have examined the use of immunotherapies as preventive and adjuvant treatments of neonatal sepsis. An array of products has been evaluated including intravenous immunoglobulin, myeloid colony stimulating factors, probiotics, glutamine supplementation, recombinant human protein C, and lactoferrin. This review will provide concise and up to date (2003–2008) information from the National Medical Library Medline database; studies are summarized in Table 1.[3–19]

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Intravenous immunoglobulin

Endogenous immunoglobulin synthesis does not begin until 24 weeks of life: thus, young infants rely on in-utero maternally acquired immunoglobulins for protection against systemic infection.[6] The placental transfer of these protective antibodies, however, does not occur until week 32 of gestation[6] and post-natally IgG levels decrease due to reduced production in newborns. Therefore, investigators have proposed the use of intravenous immunoglobulins (IVIG) to prevent and treat neonatal sepsis in this population.

Antibody prophylaxis and adjuvant therapy

In 1994, The National Institute of Child Health and Human Development Neonatal Research Network published the largest randomized clinical trial (n=2,416) assessing the role of IVIG in the reduction of premature neonatal sepsis.[20] The prophylactic administration of IVIG in this study did not reduce the incidence of nosocomial infections, morbidity and mortality in premature infants.[20] A multicenter (20 sites), randomized, double blinded, placebo controlled study evaluated the safety and efficacy of 2 infusions (14 days apart, dose = 1000 mg/Kg) of an anti-staphylococcal IVIG (Altastaph) in VLBW infants. The product was determined to be safe among the intervention group (n=104); however, when compared to placebo (n=102) no change was observed in the cumulative incidence of invasive staphylococcal infections.[4]

Another multicenter, randomized clinical study involving 95 sites in the US and Canada evaluated the effect of up to 4 infusions of INH-A21 (Veronate, dose = 750 mg/Kg dosed on days 1, 3, 8 and 15), an anti-staphylococcal IVIG (anti-clumping Factor A and anti-Ser-Asp dipeptide repeat G), on the prevention of Staphylococcal late-onset sepsis among 1,983 infants with birth weights <1,250 g who received at least one infusion of study drug or placebo (989 vs. 994, respectively). In this study, no difference was observed between treatment groups in frequency of *Staphylococcus aureus* infections, 5% for INH-A21 vs 6% for placebo.[3]

Pagibaximab, an anti-staphylococcal monoclonal antibody (anti-lipoteichoic acid) administered in 3 doses (7 days apart, 60 to 90 mg/kg/dose), was evaluated in a randomized, placebo controlled phase II study in infants with birth weight <1,300 g (n= 88). A trend was observed in the reduction of Staphylococcal bloodstream infections; none of the subjects in the 90 mg/kg group had confirmed staphylococcal sepsis compared to 20% and 13% in the 60 mg/kg and placebo groups, respectively (P<0.11). In this study, the pharmacokinetics of pagibaximab were linear and the product was well tolerated.[5]

Immunoglobulin G preparations targeted towards specific Staphylococcal antigens (Altastaph and Veronate) have not proven successful in the reduction of Staphylococcal neonatal systemic infections. A new product, pagibaximab, has been evaluated in a small number of patients; phase II/III studies will be conducted to assess the efficacy of this product.

A systematic review evaluated the relationship between IVIG therapy and all-cause mortality during hospitalization in premature and term infants. Combining the results of 7 studies (n=262), treatment with IVIG in cases of culture-proven infection resulted in a reduction in all-cause mortality (RR 0.55; 95% CI 0.31, 0.98).[6] The authors did not observe between-study heterogeneity; however, the formal testing of heterogeneity is underpowered (especially in a setting when fewer than 20 studies are analyzed), and the studies were different in the variety of IVIG products, different dosing regimens, and patient populations. Larger, randomized studies are necessary to answer this question.

Granulocyte and granulocyte-macrophage colony stimulating factors

Myeloid colony stimulating factors (CSFs) including granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) are cytokines that stimulate the production of bone marrow neutrophils. Because premature infants often suffer from limited number and function of neutrophils, investigators have evaluated the use of these factors in the prevention and adjuvant treatment of neonatal sepsis.

A systematic review examined the effect of adjuvant G-CSF or GM-CSF on 14 and 28-day overall mortality in neonates with suspected or documented sepsis. Combination of five studies (n=194) in the 28-day mortality analysis showed a reduction in all-cause mortality in treated infants (RR 0.51; 95% CI 0.27, 0.98).[7] When results from 3 studies (n=97) limited to neutropenic infants with systemic infection were analyzed, 14 and 28-day overall mortality was reduced by CSF therapy (RR 0.34; 95% CI 0.12, 0.92).[7]

Colony stimulating factors are a safe treatment modality in older patients; however, the current evidence suggests a multi-center randomized clinical trial demonstrating clinical efficacy of CSF is needed prior to universal recommendation of this therapy in the nursery.

Probiotics

Lactobacillus and *Bi dobacterium sp*., the most frequently used probiotic supplements, are live microbial species that under physiologic conditions colonize the gastrointestinal tract of healthy individuals. Investigators have hypothesized that probiotic supplements may protect high-risk infants in the nursery from developing necrotizing enterocolitis (NEC) and sepsis. [13] Most of the available literature on the use of probiotics among infants has been related to the prevention of NEC and allergies. Some reports, however, have included infants with culture proven sepsis, which will be discussed in this section.

A randomized controlled trial in VLBW infants of a mixed probiotic supplement (*Lactobacillus acidophilus* and *Bifidobacterium infantis*) to prevent NEC and mortality was conducted. The probiotic preparation was given twice daily (125 mg/kg/dose) to breast-fed infants until NICU discharge. Although the study was not powered to detect differences in sepsis rates, culture-proven systemic infection was lower among infants in the study group than controls [12.2% (22/180) vs. 19.3% (36/187) p=0.03].[8] A subsequent prospective, randomized, controlled study by the same investigators used a different probiotic combination, *Bifidobacterium bifidum* and *Lactobacillus acidophilus*. Two hundred seventeen VLBW infants were administered the probiotic, 125 mg/kg twice daily, with breast milk or formula for 6 weeks. NEC or death occurred in 1.8% (4/217) of infants in the probiotic group compared with 9.2% (20/217) in the control group (P=0.002). In contrast to their earlier study, the rate of sepsis tended to be higher in the probiotic group.[9]

Honeycutt et al., conducted a prospective, double-blinded, randomized, placebo-controlled trial in 61 patients (12 neonates, 6 in the treatment arm) admitted to a pediatric intensive care unit. They evaluated the use of one capsule of *Lactobacillus rhamnosus* strain *GG* (10×10^9 cells/capsule) administered daily for the duration of hospitalization in the reduction of the incidence of nosocomial infections; the product did not reduce the incidence of nosocomial infections.[10]

A study from Finland evaluated the use of probiotics and synbiotics in the prevention of infections among term infants in a randomized, placebo-controlled trial. For 6 months after birth, infants (n=939) born to mothers who received prenatal probiotics, received 1 capsule of *Lactobacillus rhamnosus GG* and LC705, *Bi dobacterium breve* Bb99,

Propionibacterium freudenreichii ssp *shermanii* JS ($8–9 \times 10^9$ colony-forming units in each capsule) and 0.8 g of galactooligosaccharides (synbiotic of bovine origin) (n=468) or placebo (n=471). During the intervention period (0–6 months) no difference was observed between the synbiotic and placebo groups in the occurrence of respiratory infections (66 vs 68%), middle ear infections (15 vs 19%), or gastroenteritis (13 vs 14%).[11] During the follow-up period from 6–24 months there was a modest reduction in respiratory infections OR 0.49 (95% CI 0.27, 0.97) in the symbiotic group.

The effects of probiotics on the incidence of bacterial sepsis and invasive fungal infections were examined as secondary outcomes in a *Candida sp.* gastrointestinal colonization study. Infants (n=80, birth weight <1,500 g) admitted to the NICU were randomized to receive *Lactobacillus rhamnosus* (6×10^9 CFU/day) daily oral supplementation for 6 weeks versus no intervention. There was no difference between the 2 groups in the incidence of sepsis.[12] A systematic review of 5 randomized clinical trials (n=1,284) in preterm infants (<37 weeks) evaluating the effect of probiotics in the prevention of necrotizing enterocolitis showed reduction in NEC (RR 0.32; 95% CI 0.17, 0.60) and moratlity (RR 0.43; 95% CI 0.25, 0.75) but no difference between groups in the rate of systemic infection (RR 0.93; 95% CI 0.73, 1.19).[13]

It is frequently speculated that probiotics are a safe therapeutic tool, however, *Lactobacillus GG* sepsis has been documented in the immunocompromised host. The clinical significance of heterogeneity in probiotic products and the likely differences in probiotic responses among infant sub-population need to be defined. Therefore, until larger randomized controlled-trials are conducted, the routine use of probiotics to prevent invasive bacterial and fungal infections in neonates is not recommended. These products should be evaluated under the standards applied to drugs (e.g., PK, safety, pivotal efficacy trials, good manufacturing practices, good clinical practices, etc.) rather than simply provided as a food supplement.

Glutamine

Glutamine is the most abundant amino acid in plasma and human milk. Studies in animals and immunocompromised adults have suggested that intravenous parenteral nutrition supplemented with glutamine decreases the risk of sepsis and mortality.[14] To this end, investigators collaborating in the National Institute of Health and Child Development Neonatal Research Network evaluated the effect of glutamine supplementation among extremely low birth weight infants (n=1,433) on the incidence of late-onset sepsis and overall mortality in a multicenter, randomized, double-blinded, clinical trial. Infants were randomized within 72 hours of birth to receive either TrophAmine (control) or an isonitrogenous study amino acid solution with 20% glutamine whenever they received parenteral nutrition up to 120 days of age, death, or discharge. Glutamine supplementation increased plasma glutamine concentrations by 30% by 10 days of study. Glutamine also increased serum urea nitrogen but did not increase the frequency of levels > 40 mg/dL. Fifty one percent (350/721) of infants who received glutamine supplementation died or developed late-onset sepsis, compared to 48% (343/712) of control infants (RR: 1.07; 95% CI 0.97, 1.17; P=0.18). Glutamine had no effect on mortality or incidence of late-onset sepsis.[14]

A smaller randomized study of 35 very low birth weight infants also failed to show a difference in the number of episodes of culture-positive sepsis or hospital stay between infants exposed and those not exposed to glutamine.[15] A double-blinded, randomized controlled trial in the Netherlands evaluated the effects of enteral glutamine supplementation (maximum 0.3 g per kg per day) versus control on infectious morbidity (secondary outcome) among very low birth weight infants between days 3 and 30 of life. Glutamine supplementation was added to breast milk or preterm formula. The study was designed to

assess the impact of glutamine supplementation on time to reach full enteral feeding; which was not hastened with therapy. The study also found that in the glutamine-supplemented group (n=52), 50% (26/52) of infants had 1 serious infection (including nosocomial pneumonia) compared with 76% (38/50) in the control group (n=50) (adjusted OR: 0.33; 95% CI: 0.13, 0.86; P=0.023).[21] These data should be interpreted with caution because the study was not powered to evaluate differences in number of infection episodes.

A recently published Cochrane systematic review examined the effect of enteral or parenteral glutamine supplementation on the incidence of culture-proven invasive infection from 5 clinical trials (n= 2,240). The meta-analysis did not reveal a statistically signi cant difference between the glutamine supplemented and control groups (RR 1.01; 95% CI 0.91, 1.13).[17]

Glutamine should not be routinely used to decrease the incidence of sepsis in young infants.

Lactoferrin

Lactoferrin is an iron-binding glycoprotein. Its role in the immune host response towards infections has been suggested by its substantial secretion on mucosal surfaces and by its release at inflammatory sites.[22] Lactoferrin has broad-spectrum antimicrobial activity resulting from its iron sequestering ability and its iron-independent killing by direct interaction with the microbial surface resulting in cell lysis.[22] Clinical data of lactoferrin therapy is lacking, but recently, investigators in Italy provided preliminary data of its use in the prevention of late-onset neonatal sepsis. Preliminary results from this multicenter, randomized, placebo controlled trial involving VLBW infants who received daily orally administered Bovine lactoferrin alone (n=99, dose = 100 mg/day), in combination with *Lactobacillus GG* (n=99, dose = 106 CFU/day), or placebo (n=104) for 30–45 days show that the incidence of culture-proven sepsis was lower in the groups that received lactoferrin. [18] Final and complete results from this study are pending. Additional efforts focused on drug safety, pharmacokinetics, and efficacy are necessary prior to regulatory approval and recommendation of lactoferrin use in neonatal sepsis.

Recombinant human protein C

Activated protein C is an endogenous compound that promotes anticoagulation and modulates the inflammatory response. During severe systemic infections, the levels and degree of protein C activation are decreased; in one study, decreased activity of activated protein C was associated with increase mortality among neonates with sepsis.[22] Investigators have therefore proposed the use of recombinant human activated protein C (drotrecogin alfa) in septic patients in order to attenuate the amplified inflammatory response. A phase III clinical trial in adults (n=1,690) showed that the use of activated protein C in patients with severe sepsis, when compared to placebo, was associated with an absolute reduction in the risk of death of 6.1%.[23] In this study, the incidence of serious bleeding was higher in the treatment group (3.5 percent vs. 2.0 percent, P=0.06). The largest randomized controlled-trial of recombinant activated protein C in children (n=477; approximately 6% young infants) failed to show an improvement in the clinical score used at the primary outcome and in the 28-day mortality when the drug was compared to placebo. [19]

Randomized clinical trials specifically designed for the neonatal population should be conducted before recommendations are issued on its use for the adjuvant treatment neonatal sepsis. Careful consideration of potential side effects, specially the risk of intraventricular bleeding among treated neonates, should be taken into account before treating individual patients with this therapeutic modality.

Conclusion

Immunotherapy used as an adjuvant for the prevention and treatment of neonatal sepsis holds promise; however, for most of these therapies tested to date, clinical trials have failed to demonstrate a significant effect in neonatal outcomes. Some of these studies are limited by the study design, sample size, and outcome evaluation and therefore, trials specifically designed towards the neonatal population and appropriately powered to detect treatment differences are necessary prior to universal recommendation of these therapies in the nursery. Systematic reviews on the use of IVIG to treat neonatal systemic infections suggest potential benefit; and targeted antibody therapy warrants further study. Probiotic therapy and nutritionally additives warrant product standardization and future rigorous study for regulatory approval as a drug (rather than the less robust hurdle as a food additive). Other therapeutic options, such as colony stimulating factors and lactoferrin, may benefit patients meeting specific criteria, but require further testing in young infants with clear benefit prior to widespread use.

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Table 1

Immunotherapies for treatment of neonatal sepsis.

	Author	Year	Study design	N	Population	Outcome	Effect/comnents
IVIG							
	DeJonge et al.[3]	2007	RCT	1,983	Infants <1,250 g	Prevention of Staphylococcal late-onset sepsis	NS
	Benjamin et al.[4]	2006	RCT	206	Infants <1,500 g	Prevention of Staphylococcal late-onset sepsis	NS
	Trackray et al.[5]	2006	RCT	88	Infants <1,300 g	Prevention of Staphylococcal late-onset sepsis	NS
	Ohlsson et al.[6]	2004	Systematic review	262	Premature and term infants	All-cause mortality	P<0.05
CSF							
	Carr et al.[7]	2003	Systematic review	451	Premature and term infants	All-cause mortality	P<0.05 (28-day mortality)
Probiotics							
	Lin et al.[8]	2005	RCT	367	Infants <1,500 g	Incidence of culture proven sepsis	P=0.03
	Lin et al.[9]	2008	RCT	434	Infants <1,500 g	Incidence of culture proven sepsis	NS
	Honeycutt et al.[10]	2007	RCT	12	Infants in the Pediatric Intensive Care Unit	Incidence of nosocomial infections	NS
	Kukkonen et al.[11]	2008	RCT	939	Full term infants	Post-natal infections	NS
	Manzoni et al.[12]	2006	RCT	80	Infants <1,500 g	Incidence of bacterial sepsis or invasive fungal infections	NS
	Alfaleh et al.[13]	2008	Systematic review	1,284	Premature infants (<37 weeks)	Incidence of sepsis	NS
Glutamine supplementation							
	Poindexter et al.[14]	2004	RCT	1,433	Infants <1,000 g	Incidence of late-onset sepsis and overall mortality	NS
	Thompson et al.[15]	2003	RCT	85	Infants <1,500 g	Incidence of culture proven sepsis	NS
	van den Berg et al.[16]	2005	RCT	102	Infants <1,500 g	Incidence of nosocomial infections	P=0.023
	Tubman et al.[17]	2008	Systematic review	2,240	Premature infants (<37 weeks)	Incidence of culture proven sepsis	NS
Lactoferrin							
	Manzoni et al.[18]	2008	RCT	302	Infants <1,500 g	Incidence of culture proven late-onset sepsis	Incidence reduction, preliminary data

	Author	Year	Study design	N	Population	Outcome	Effect/comnents
Recombinant human protein C							
	Nadel et al.[19]	2007	RCT	477	Pediatric patients, 6% neonates	Time to organ failure resolution and 28-day mortality	NS

IVIG: Intravenous Immunoglobulin; CSF: Colony Stimulating Factors; RCT: Randomized Controlled Trial; GA: Gestational Age; NS: not significant.