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Invited Review

Passive Protection Against Diarrheal Disease

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Diarrheal disease is a major health problem causing high mortality and morbidity in developing countries. In developed countries acute diarrheal disease is an important cause of hospitalization. Rotavirus is the major cause of infectious diarrhea in infants and young children globally (1). Other important enteric pathogens, particularly in developing countries, include enterotoxigenic and enteropathogenic *Escherichia coli*, *Shigella*, *Campylobacter* species, *Vibrio cholerae*, and *Cryptosporidium* (2).

Vaccines to immunize actively against these pathogens have reached various stages: licensure, controlled trials of efficacy, and clinical trials of safety and immunogenicity (3). Another approach to protection against diarrheal disease has been the use of passively acquired antibodies from either serum or colostrum. This review concentrates on studies in which bovine immunoglobulins, either in colostrum or as a bovine immunoglobulin concentrate, have been used to prevent or treat diarrheal disease.

There are a number of settings in which passive protection may be valuable to prevent diarrheal illness, particularly in the absence of active immunization. Rotavirus infection is responsible for nosocomial infection in ~20% of infants in the United States (3) and Australia (4). Passive protection could possibly lessen this high incidence of nosocomial rotavirus diarrhea (5,6). Specific settings in which passive protection may be of value in preventing infection include neonatal nurseries (7) and daycare centers, within families (8), and in immunocompromised people (9,10).

For many GI infections the most important protective factor is the presence of specific antibody in the lumen of the small intestine. This fact has certainly been proven for rotavirus infection (11), for which the antibody in humans is secretory IgA. Human milk has been shown to contain specific secretory IgA antibodies to many enteropathogens (12). For example, colostrum and breast milk have been shown to contain antibodies to the four major human rotavirus serotypes (13). Breastfed infants, however, still develop rotavirus diarrhea (14,15), which may be due to an overwhelming antigen load or to the absence of antibodies against the infecting serotype.

Many of the studies involving passive protection have been carried out using bovine colostrum or bovine milk immunoglobulin concentrates. The colostral product was taken from nonimmunized cows or from cows hyperimmunized against various pathogens (5–34). Some studies have used human γ-globulin or human serum immunoglobulin (7,9,10). In ruminants, the predominant milk antibody is IgG_1, which is mainly serum-derived and has specificity for enteric pathogens (34). IgG_1 has been shown passively to protect against infection by various enteric pathogens in animals and humans (Table 1). This finding lends support to the concept that ruminant IgG_1 may replace Secretory IgA in providing lactogenic immunity. Saif (40) reviewed the evidence supporting similarities and differences between ruminant IgG_1 and Secretory IgA, which includes resistance to proteolytic enzymes; the predominance of IgG_1 in milk and its specificity against enteric viruses; and the increase in IgG_1 but not IgA milk antibodies after intestinal administration of antigens in pregnant cows. In humans, bovine immunoglobulin IgG_1 has been shown to survive transit through the gut in colostrum (46), although there are conflicting reports regarding the survival of human immunoglobulin and bovine immunoglobulin concentrates (10,24,47).

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TABLE 1. *Human pathogens studied using passive protection*

Enteric pathogens (and references)	Study subjects
Campylobacter jejuni (35)	Calves
Clostridium difficile (36)	Hamsters
Cryptosporidium parvum (19,22,23,26–29,32,34,37,38)	Humans and mice
Enteropathogenic *E. coli* (17,30)	Humans
Enterotoxigenic *E. coli* (25)	Humans
Rotavirus (5–11,18,20,21,30,39–43)	Humans, lambs, calves, and pigs
Shigella flexneri 2a (33)	Humans
Vibrio cholerae (24,44,45)	Humans and rabbits

Losonsky et al. (10) showed that human serum immunoglobulin survived passage through the gut in immunocompromised children in an immunologically active form. The studies of Hilpert et al. (21) and McClead et al. (24) demonstrated partial recovery of functionally active bovine immunoglobulin preparations against rotavirus and cholera, respectively, following passage through the gut. Using an in vitro model of gut digestion, Petschow and Talbot (47) demonstrated a significant reduction in rotavirus-neutralizing titer in a bovine colostrum immunoglobulin concentrate by gastric acid, pepsin, and selected pancreatic enzymes. While comparative studies have not been carried out, it is possible that bovine IgG_1 survives passage through the gut more completely when given as a colostral product rather than as an immunoglobulin concentrate. The work of Ebina et al. (31) would support this concept, as they found whole colostrum but not specific immunoglobulins to be protective.

The level of antibody present in colostrum and breast milk can be markedly increased by parenteral vaccination of the pregnant cow prior to delivery of the calf. While immunization of human mothers during pregnancy or immediately postpartum to boost rotavirus antibodies in breast milk has been considered, there are no published results of such studies (48). Brussow et al. (49) found that cows have elevated preimmunization titers in serum and colostrum to the four major human rotavirus serotypes (49), but this has not been a universal finding (50). Heterologous immunity is probably related to natural exposure to bovine rotavirus serotypes resembling human rotaviruses. Cows immunized with a single rotavirus serotype (SA11 serotype 3) produced an increase in neutralizing antibodies not only to serotype 3 but also serotypes 1, 2, 4, and 6. Similarly, cows immunized with SA11 produced colostral antibodies that protected piglets against challenge with two porcine rotavirus serotypes (42). Brussow et al. (49) also noted the induction of cross-neutralization antibodies by a single-serotype vaccination of cows with rotavirus. They suggest this response may be due to the recognition by the bovine immune system of a minor neutralizing antigen common to different rotavirus serotypes. There is also evidence that human rotaviruses of different serotypes may share immunodominant neutralization sites (51).

Heterotypic responses have also been noted in adult human volunteers following oral vaccination with a single-serotype rotavirus vaccine candidate (52). Young infants do not produce a heterotypic response, probably because of lack of prior exposure to rotavirus (52). The heterotypic response of the bovine immune system to a single rotavirus strain simplifies the commercial production of hyperimmune colostrum. The common human rotavirus serotypes are difficult to propagate, whereas SA11 is easily cultivated and can stimulate high-titer rotavirus antibodies that neutralize the four major human rotavirus serotypes (49).

PASSIVE PROTECTION STUDIES IN HUMANS

Rotavirus

Barnes et al. (7) were the first to show that oral immunoglobulin containing rotavirus antibody could modify the course of rotavirus infection. Low-birth-weight infants in a special-care nursery fed human γ-globulin, 5 ml four times daily, had a reduced incidence of rotavirus acquisition and reduced severity of rotavirus diarrhea.

Using hyperimmune bovine colostrum from cows immunized with human rotavirus Wa strain (serotype 1), Ebina et al. (18) were able to protect infants in an orphanage from acquiring rotavirus infection during a rotavirus outbreak. Infants fed commercial milk were not protected. Importantly, two of the infants fed rota-colostrum who remained asymptomatic showed rises in complement-fixing antibody. Thus, the rota-colostrum did not prevent immunological responses to natural rotavirus infection.

More recently, Ebina et al. (31) confirmed their earlier work in an animal model and in infants. They also showed that purified IgG, IgM, and IgA from rota-colostrum were not protective, possibly due to inactivation by GI proteolytic enzymes—which did not occur using the rota-colostrum. Petschow and

Talbot (47) showed that both acid and trypsin significantly reduce the biological activity of bovine milk immunoglobulins directed against rotavirus.

Some studies have provided evidence for the role of hyperimmune bovine colostrum in protecting against rotavirus cross-infection (5,6). Davidson et al. (5) fed hospitalized children aged 3–15 months with bovine colostrum containing high-titer antibodies to the four major human rotavirus serotypes. Nine of 65 control infants, but no treated infant, acquired symptomatic rotavirus infection during the treatment period. When diarrhea occurred, parents of children with symptomatic rotavirus infection were seven times more likely to seek medical attention than were parents of children with nonrotavirus diarrhea. A similar study was carried out in Hong Kong and India (6), confirming the earlier findings. In this study, the control group was fed colostrum containing no antibodies to rotavirus. No child in the treatment group developed symptomatic rotavirus infection versus 13 in the control group ($p < 0.01$). This result highlights that it was the presence of rotavirus antibody in colostrum rather than colostrum itself that provided protection against rotavirus infection. It is likely that the antibody titer is important, with higher antibody levels allowing for some intraluminal degradation of product while maintaining sufficient protective activity (43). The latter study (6) also showed that hyperimmune colostrum could protect against more than one rotavirus serotype.

The approaches discussed so far used the hyperimmune colostrum as a food additive. Several recent studies have used infant formula supplemented with hyperimmune bovine immunoglobulin, with conflicting results (8,30). A study by Brunser et al. (30) in Chile using formula containing anti–rotavirus antibodies and anti–enteropathogenic *E. coli* antibodies was unsuccessful, most likely related to the low level of antibody (43). A trial from Charleston, SC, U.S.A. (8), was successful in reducing symptomatic rotavirus infection in healthy infants in the community but had no effect on the actual incidence of rotavirus infection. This failure to prevent infection while reducing symptoms almost certainly relates to the level of antibody given. Schaller et al. (43) showed in a gnotobiotic piglet model that at very high levels of antibody administration, both symptoms and rotavirus excretion could be abolished. However, it may not be economically feasible to use this approach in infant formula. Similarly, while the addition of colostral antibodies to infant formula may be helpful in young infants, it does not provide protection once infants are weaned, which usually happens around 12 months of age when infants are still at risk of severe rotavirus illness. The use of a food supplement would be more practical for older infants.

Several studies have reported on the efficacy of human milk or human serum immunoglobulin in managing the immunocompromised child with chronic rotavirus infection (9,10). Other experimental approaches to the provision of passive prophylaxis have used egg yolk immunoglobulin (53,54), human milk (55), and human intestinal mucins (56), but these approaches have yet to be tested in humans. Saavedra et al. (57) found that infant formula supplemented with *Bifidobacterium bifidum* and *Streptococcus thermophilus* can reduce the incidence of acute diarrhea and rotavirus shedding in infants admitted to the hospital.

Hyperimmune bovine colostral concentrate (21) and oral human serum immunoglobulin have also been used in the treatment of acute and chronic rotavirus diarrhea (59,60). Mitra et al. (58) have recently shown therapeutic efficacy of hyperimmune bovine colostrum in the treatment of rotavirus gastroenteritis in children aged six to 24 months. The treatment group received 100 ml of hyperimmune colostrum three times daily and showed a significant reduction in duration and severity of the diarrhea. Hilpert et al. (21) fed hyperimmune bovine immunoglobulin concentrate in a daily dose of 2 g/kg body weight for 5 days to 75 infants hospitalized with acute rotavirus gastroenteritis. A 10-kg child thus received 20 g/day of bovine immunoglobulin; no side effects were seen. Hilpert et al. noted a decrease in duration of rotavirus excretion but no effect on clinical symptoms. More recently, Guarino et al. (58) fed a single dose of human serum immunoglobulin (300 mg/kg) to hospitalized children with acute rotavirus diarrhea in a double-blind placebo-controlled trial. They found a significant decrease in the duration of diarrhea, viral excretion, and hospital stay in the treated group. The cost of treatment was high, at $200 per 10-kg infant, but this expense may be offset by the decreased length of hospital stay.

Escherichia coli

Lyophilized immunoglobulins obtained from colostrum of cows immunized with several enterotoxigenic *E. coli* serotypes, fimbria types, *E. coli* heat-labile enterotoxin, and cholera toxin were shown to provide complete protection against enterotoxigenic *E. coli* infection in 10 adult volunteers (25). This approach shows that bovine milk immunoglobulins may have a role in the prevention of travelers' diarrhea.

Brunser et al. (30), however, were unable to show any protective benefit of supplementing infant formula with bovine milk immunoglobulin concentrate against the major enteropathogenic *E. coli* serogroups in a small-scale field trial in Chile. This failure probably relates to the low level of antibody in the formula.

Sixty children aged 10 days to 18 months with diarrhea due to enteropathogenic *E. coli* were treated daily for 10 days with 1 g/kg hyperimmune anti–enteropathogenic *E. coli* immunoglobulin (17). The treatment was effective in eliminating the *E. coli* in 43 of 51 children infected with strains present in the vaccine but in only one of nine infected with strains not incorporated in the vaccine. These results suggest that specific milk immunoglobulin may be an effective treatment for *E. coli* infections.

Cryptosporidium

A number of small studies using either hyperimmune bovine colostrum containing cryptosporidial antibodies (19,23,27,29,34) or nonspecific bovine immunoglobulin concentrate (32) or colostrum (22,26) have been reported with variable but encouraging results. Most patients were immunosuppressed due to HIV infection, congenital hypogammaglobulinemia, or leukemia. The failures in this approach occurred mainly in patients given nonspecific bovine immunoglobulin or colostrum, again highlighting the importance of specific antibody. At present, there is no specific therapy for *Cryptosporidium*, but the results of the reported studies suggest that further double-blind controlled studies of a hyperimmune anticryptosporidial product are indicated.

Shigella

Tacket et al. (33) demonstrated the efficacy of a hyperimmune bovine colostrum against *Shigella flexneri* 2a in preventing infection in challenged volunteers. The duration of shedding of the organism was also decreased in the treatment group.

NONSPECIFIC DIARRHEA

In 1973, Fernandez et al. (16) reported the positive benefits of treating children with prolonged infantile diarrhea with lyophilized bovine colostrum. A study reported from Prague (61) suggested that partly purified bovine colostrum with high volumes of antibodies against certain strains of enteropathogenic *E. coli* was beneficial in treating preterm and full-term infants hospitalized with diarrhea.

Stephan et al. (28) reported that 22 of 33 treatment cycles in 29 patients with AIDS receiving 10 g/day of bovine colostral immunoglobulin from nonimmunized cows for 10 days produced a significant decrease in nonspecific diarrhea. In a similar open and uncontrolled study, Rump et al. (32), using the same preparation in patients with AIDS with chronic diarrhea, found a significant clinical benefit, free of side effects, for the duration of therapy.

CONCLUSIONS

The results from the use of colostrum-derived bovine immunoglobulins in humans suggest that these immunoglobulins may have an important place in the prevention of many diarrheal disease. They have already been shown to be of value in preventing hospital-acquired symptomatic rotavirus infection (5, 6) and also in causing a reduction in rotavirus diarrhea in the community (8). *Clostridium difficile*, another important cause of hospital-acquired infection, particularly in adults and AIDS-infected patients, is also a candidate for passive prevention, as suggested by recent animal studies (36). This passive approach would also seem to be potentially useful in daycare centers where rotavirus, *Campylobacter*, *Shigella*, and *Cryptosporidium* are important pathogens (62).

The immunosuppressed patient, whether immunosuppressed due to a congenital defect or secondary to chemotherapy or infections such as AIDS, is particularly susceptible to a number of life-threatening enteric infections. Often no other therapy is available, and hyperimmune bovine colostrum has shown promise, particularly against *Cryptosporidium* (23,27,29,32) and rotavirus (9,10).

Another important possibility for the passive approach is in the prevention of travelers' diarrhea, which affects about half of all travelers to developing countries (63). Hyperimmune bovine immunoglobulin has been shown to be safe and effective in prevention of the major causes of travelers' diarrhea, including enterotoxigenic *E. coli* (25), *Shigella* (33), rotavirus (5–10,18,20), and *Campylobacter* (35). The current use of antibiotic prophylaxis, while effective, has side effects and is already leading to the development of significant drug resistance (64).

The possibility of the development of allergic reactions to bovine immunoglobulin, which has the potential to limit its usefulness, has been raised (64), and studies were carried out in known milk-and/or egg-allergic children. However, studies to date have not reported allergic reactions or any other adverse reaction. In several studies, children known to be allergic to cow milk were excluded (5,6), which would seem to be a sensible approach at present. The possibility of later development of atopic disease in young infants fed bovine immunoglobulin requires further study.

Hyperimmune bovine colostrum or immunoglobulin is relatively cheap and easy to produce, is straightforward to use, appears to be safe except possibly in allergic children, and may provide a simple approach to the prevention and possibly also treatment of many enteric pathogens. These facts are particularly important, since active vaccines for many pathogens seem to be a long way off. Even when active vaccines do become available, the use of passive protection will still be important in young infants and in children and adults who are unable to mount their own immune response. Active immunization of all children is difficult to achieve with current immunization programs, and passive protection in settings where children are at risk for cross-infection may remain beneficial.

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