

Pedimune in Recurrent Respiratory Infection and Diarrhoea- The Indian Experience-The PRIDE Study

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ABSTRACT

Objective. To evaluate the efficacy and tolerability of bovine colostrum in preventing recurrent episodes of upper respiratory tract infections and diarrhoea in children

Methods. 605 children (1-8 yrs) having recurrent episodes of upper respiratory tract infections or diarrhea received Bovine Colostrum (Pedimune®) for 12 weeks. Total no of episodes of recurrent infections, hospitalization rate, overall well being and adverse events were assessed at every 4 weeks.

Results. Episodes of URTI and diarrhoea reduced significantly by 91.19 % and 86.60% at the end of therapy respectively. High to average improvement in overall well-being in 96 % of the patients were found by pediatrician while overall well-being stated by the patient/care taker was very good to good in 90.56 % of the patients.

Conclusion. Bovine colostrum was highly effective in the prophylactic treatment of recurrent URTIs and diarrhea in reducing not only the episodes but also the hospitalization due to them. [*Indian J Pediatr* 2006; 73 (7) : 585-591]

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Key words : Bovine colostrum; Respiratory infection; Diarrhoea

Respiratory diseases are a major cause of morbidity and mortality in developing countries. Data suggest that children could suffer from 7 to 8 upper respiratory infections per year until they are 5 years of age, when their immune status reaches adult level.¹ Acute upper respiratory tract infection (URTI) is a common disease in young children and contributes to approximately 20% of mortality in children younger than 5 years of age. It represents the most frequent problem in general pediatric practice and are responsible for more than a third of school absence.²

Diarrhea on the other hand is a major killer disease in children under five and recurrent diarrhea affects nearly 20% of the population, thus an important public health problem.³⁻⁶

The use of bovine colostrum as prophylaxis or treatment for infectious disease relates to the historical concept of "immune milk" being capable of transferring passive immunity. Bovine colostrum contains not only detectable levels of immunoglobulins far much higher (several hundred fold) than ordinary bovine milk^{7, 8}, but

also contains a series of physiologically bioactive constituents such as growth promoting factors that act as mediators of infantile growth and development⁹⁻¹¹ in addition to a series of antimicrobial fractions including lactoferrin : lactoperoxidase and lysozymes.¹²⁻¹⁴

Local protection in the form of immunosupplementation with bovine antibodies has been shown to be an effective means of providing local protection to the GI tract against disease.¹⁵ Colostrum from nonimmunized cows contains antibodies against many enteric pathogens and bovine immunoglobulin in the form of specific antibody has also been shown to be effective against various enteric diseases.¹⁵⁻¹⁷

Regular consumption of bovine colostrum has been reported as a protective role for infantile gastrointestinal immunity due to its direct effect on stimulation and development of infantile gut-associated lymphoid tissues which are responsible mainly for enhancing the infantile gut immunity.¹⁸⁻²⁰ The studies²¹⁻²⁴ in infants indicate the possible therapeutic role of orally ingested bovine colostrum against many bacterial and viral gastrointestinal infectious diseases.

In childhood, evaluation of immune system functions is necessary if these recurrent infections especially acute respiratory tract infection have an unexpectedly severe course. Bovine colostrum increases salivary IgA that

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primarily protects against respiratory tract infections.²⁵ Bovine colostrum contains high levels of oligosaccharides, which help prevent bacteria from attaching to the mucous membranes, which line the gut and the throat.²⁶ Clinical evidence suggests that bovine colostrum may prevent upper respiratory tract infection (URTI).²⁷

To date, local clinical trial data on use of bovine colostrum in recurrent infection in India is lacking. The present study was therefore conducted to evaluate the efficacy and tolerability of bovine colostrum in preventing recurrent episodes of upper respiratory tract infections and diarrhea in children.

MATERIALS AND METHODS

Patient Population

In this open, multi-centric, non-comparative, post-marketing study, a total of 605 children of either sex between 1 to 8 years of age were enrolled after obtaining informed written consent from parents, guardian or caretaker of the child. The study was conducted involving 133 pediatricians across the country. Children having recurrent episodes of upper respiratory tract infections (defined as >6 episodes of upper respiratory tract infections during the period 6 months prior to enrollment in the study) or having recurrent episodes of diarrhea (defined as >6 episodes of diarrhea not requiring hospitalization or >2 episodes of diarrhea requiring hospitalization during the period 6 months prior to enrollment in the study) were included in the study. Children, having any abnormalities of the respiratory tract, those having >3 episodes of lower respiratory tract and infections requiring hospitalization in the past 6 months or those children receiving corticosteroids (systemic or topical), immunomodulators or when parent/guardian did not give informed consent, were excluded. All children received Bovine Colostrum (Pedimune®, Mfg. by Merck India Ltd.) 3 gm (one teaspoonful) with a glass of water once daily for a period of 12 weeks. The selection and recruitment of patients in the trial commenced from 1 October 05 and study was completed by March 06.

Assessment Parameters

Primary outcome measure was reduction in the number of episodes of upper respiratory tract infections occurring during the study period (time from enrollment to 12 weeks of bovine colostrum therapy) as compared to the 6 months prior to enrollment in the study.

Secondary outcome measures were reduction in number of episodes of diarrhea and frequency of hospitalization required for RTI & diarrhea during study period as compared to 6 months prior to enrollment.

An overall well-being of patients and tolerability was evaluated by the patient/parent/guardian/caretaker on

a 5-point ranking scale of "1=Very Good, 2=Good, 3=Average, 4=Poor & 5=Very Poor". Physician evaluated global assessment of the patient's condition after 12 weeks of bovine colostrum therapy on a 5-point ranking scale of "1=High improvement, 2=Average improvement, 3=Poor improvement, 4=No improvement and 5=Worsening". Follow-up was done every 4 weeks for a period of 12 weeks and total no of episodes of recurrent infections; hospitalization rate, overall well-being and adverse events were assessed at every 4 weeks.

Statistical Analysis

The quantitative data is expressed as mean and standard deviation, whereas incidence is expressed as proportions. Ranking or categorical data was analyzed using Kruskal-Wallis test, Mann-Whitney 'U' test & Chi-Square test. Quantitative data is analyzed using the ANOVA & students t-test. For all tests, a 'p' value of <0.05 was considered significant at 95% C.I.

RESULTS

Of the 605 patients enrolled, 551 patients (341 males & 210 females) completed the study. 50 patients were lost to follow-up, 2 patients withdrew due to poor acceptability, 1 patient needed bronchodilator therapy for severe lower respiratory tract infection & was withdrawn, whereas 1 patient developed macular skin rash and was withdrawn. The results of 551 patients who completed the study were analyzed. Table 1 shows the demography and the baseline data of the patients enrolled in the study. Large number of children were between 2-4 & 4-6 years of age (38.29% & 29.04% respectively) as compared to <2 & >6 yrs of age (15.43% & 17.24% respectively) (Fig. 1).

TABLE 1. Demography of the Patients Enrolled in the Study

Parameter	Mean	S.D.	Range
Age (yr)	3.79	1.97	1 yr - 12 yrs
Height (cm)	92.03	17.59	19.00 - 152.00
Weight (Kg)	13.29	4.43	5.00 - 35.00
No. of Episodes in past 6 months			
URTI	5.94	3.83	0 - 20
Hospitalization for RTI	0.33	0.95	0 - 10
Diarrhea	1.08	2.03	0 - 12
Hospitalization for Diarrhea	0.18	0.75	0 - 10
Other Infections	0.20	0.58	0 - 4

As shown in table 2, the number of episodes [Mean \pm S.D.] of URITs occurring 6 months prior to bovine colostrum therapy was 5.94 ± 3.88 which decreased significantly to 1.60 ± 1.74 , 0.99 ± 1.20 and 0.52 ± 0.91 at the end of 4 wks, 8 wks and 12 wks of bovine colostrum therapy respectively ($p < 0.05$). The reduction in the mean number of episodes of URTI was similar in the children of

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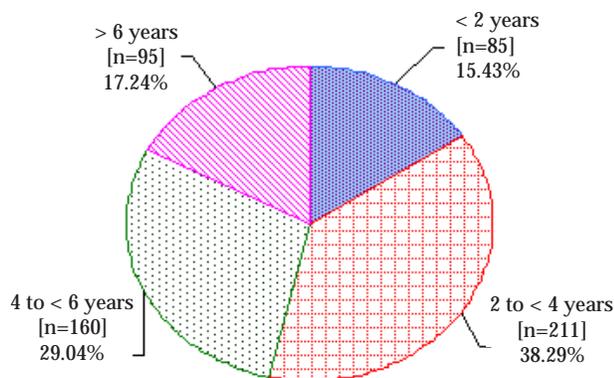


Fig. 1. Age distribution of the patients enrolled in the study [n=551]

all age groups ($p > 0.05$).

As shown in the table, after bovine colostrum therapy, the percentage reduction in the number of episodes of URTI from baseline was, 73.01 %, 83.25 % and 91.19 % at 4, 8, and 12 weeks respectively.

The mean number of episodes of diarrhoea occurring 6 months prior to bovine colostrum therapy was 1.08 ± 2.03 . This decreased significantly to 0.33 ± 0.84 , 0.18 ± 0.66 and 0.14 ± 0.61 at the end of 4, and 12 weeks of bovine colostrum therapy respectively ($p < 0.05$).

Shown in Table 3 is the percentage reduction from baseline, in the number of patients reporting episodes of URTI and diarrhoea at 4, 8 and 12 weeks after bovine colostrum therapy. A significant reduction of 20.5%, 35.6% and 64.5% was observed at 4, 8 and 12 weeks of therapy, respectively, in the number of patients reporting episodes of URTI. A significant reduction of 35.6%, 64.3% and 71.3% was also observed at 4, 8 and 12 weeks of therapy, respectively, in the number of patients reporting episodes of diarrhoea. Fig 2 shows the percentage reduction in the number of episodes of URTI in the different age groups. After bovine colostrum therapy, the

percentage reduction in the number of episodes of URTI from baseline was 73.01 %, 83.25 % and 91.19 % at 4, 8, and 12 weeks respectively. There was a significant reduction in the number of episodes of URTI in all the age groups at the various observation intervals. The values shown in Fig 2 indicate that at 12 weeks, the decrease in percentage of patients reporting URTI episodes is significantly less in age group < 2yr as compared to the other three age groups. The decrease is similar in the other 3 age groups. As shown in Fig 3 among the age groups of

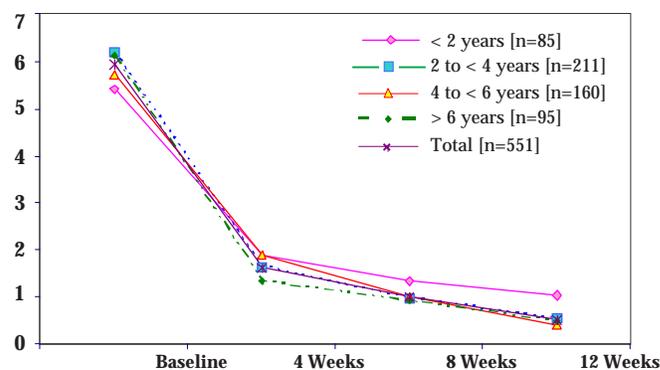


Fig. 2. No [Mean \pm S.D.] of episodes of URTI in the patients during the study period [n=551]

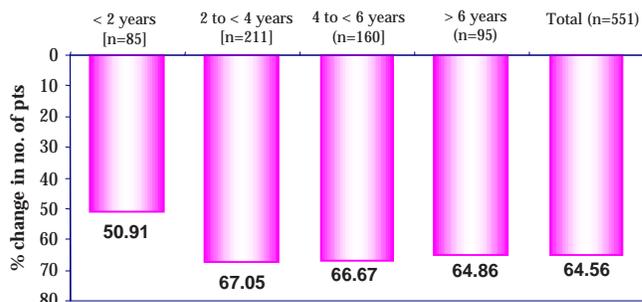


Fig. 3. Percent change in no. of patients reporting symptoms of URTI from baseline after 12 weeks of Pedimune therapy [n=551]

TABLE 2. Primary & Secondary Assessment Parameters at Baseline and Change at 4, 8 and 12 Weeks of Bovine Colostrum Therapy [n=551]

Parameter	Baseline Mean (SD)	Mean (%) change from baseline			'p' value
		4 wks.	8 wks.	12 wks.	
URTIs episodes	5.94 (3.88)	4.33 (73.01)	4.94 (83.25)	5.41 (91.19)	<0.001
Hospitalization for RTI	0.33 (0.95)	0.26 (77.74)	0.30 (90.87)	0.31 (94.22)	<0.05
Diarrhea episodes	1.08 (2.03)	0.75 (69.56)	0.89 (82.87)	0.93 (86.60)	<0.05
Hospitalization for diarrhoea	0.18 (0.75)	0.13 (75.95)	0.16 (89.05)	0.17 (92.32)	<0.05

TABLE 3. Number of Patients Reporting Episodes of URTI and Diarrhoea at Baseline and at 4, 8 & 12 Weeks of Bovine Colostrum Therapy [n=551]

Parameter	Baseline No. (%)	% reduction from baseline			'p' value
		4 wks.	8 wks.	12 wks.	
URTIs episodes	443 (80.40)	20.54	35.67	64.56	<0.01
Hospitalization for RTI	91 (16.52)	74.73	90.11	90.11	<0.001
Diarrhea episodes	157 (28.49)	35.67	64.33	71.34	<0.05
Hospitalization for diarrhoea	39 (07.08)	66.67	84.62	84.62	<0.01

<2 yrs, 2-4 yr, 4-6 yr and 6-8 yr, percentage change in patients reporting symptoms of URTI was significantly reduced upto 50.91 %, 67.05 %, 66.67 % & 64.86 % at the end of bovine colostrum therapy respectively.

From Fig 4 it is also evident that the number of episodes of diarrhoea was higher in the age group between 2-<4 yr, as compared to the other age groups. Percentage reduction in number of patients reporting episodes of diarrhoea was significantly less in age group 4-6 yrs compared to the other three age groups when comparison was done among the four age groups to find out maximum percentage reduction in number of diarrhoea episodes.

As shown in Fig 5 among the age groups of <2 yr, 2-4 yr, 4-6 yr and 6-8 yr, percentage change in no of pts having diarrhea was significantly reduced upto 77.14 %, 76.47%, 55.88% & 70.00% at the end of bovine colostrum therapy respectively.

Fewer patients required hospitalization due to diarrhea. The mean number of episodes of hospitalization occurring 6 months prior was 0.18 ± 0.75 decreased significantly to 0.04 ± 0.29 , 0.02 ± 0.17 and 0.01 ± 0.12 at the end of 4 wk, 8 wk and 12wk respectively after taking bovine colostrum therapy ($p < 0.05$). Number of episodes of hospitalization due to diarrhea was significantly reduced ($p < 0.05$) by 75.95 %, 89. 05 % and 92.32 % at 4 weeks, 8 weeks and 12 weeks of bovine colostrum

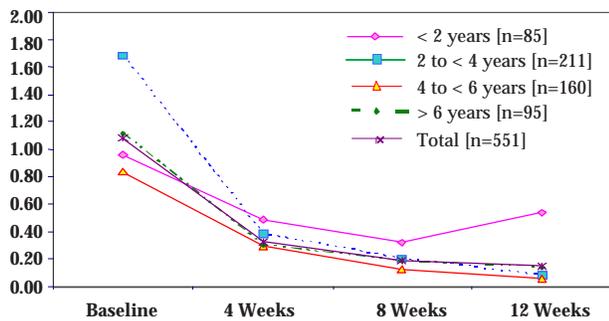


Fig. 4. No. [Mean ± S.D.] of episodes of diarrhea in the patients during the study period [n=551]

therapy respectively compared to baseline data. Total incidence of adverse events was found to be 2.97 % shown in table 4. All of them were mild to moderate in nature. One patient was withdrawn from the study due to skin rash.

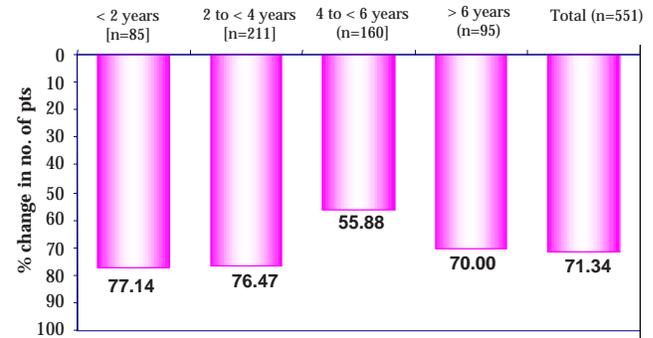


Fig. 5. % change in no. of pts. having diarrhea from baseline after 12 wks of Pedimune therapy [n=551]

96% of the pediatrician reported a high to average improvement in the overall well-being of the patients receiving bovine colostrum (Fig. 6). Overall well-being stated by the patient or parent or guardian or caretaker

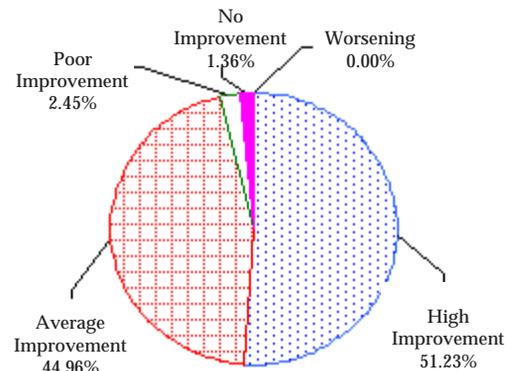


Fig. 6. Overall well-being assessed by the physicians after 12 weeks of Pedimune therapy on a 5-point ranking scale [n=551]

TABLE 4. Adverse Events Reported by the Patients During the Study Period [n=605].

Event	No. of patients & Severity				Outcome
	Mild	Moderate	Severe	Total	
Cough	01	00	00	01	Resolved
Skin Rash	00	01	00	01	Pt. withdrawn from study
Stomatitis	01	00	00	01	Resolved
Abdominal Pain	01	01	01	03	Resolved
Nausea	01	01	00	02	Resolved
Sneezing	01	00	00	01	-
Diarrhea	01	02	00	03	Resolved
GI Upset	00	02	00	02	Persisted in 1 pt.
Vomiting	00	01	00	01	Resolved
Bad taste	00	01	00	01	1 pt. Discontinued
Wheeze attack	00	01	00	01	Single episode, causality not established
Constipation	00	01	00	01	Resolved, Therapy continued
Total	06	11	01	18	Total Incidence = 2.97 %

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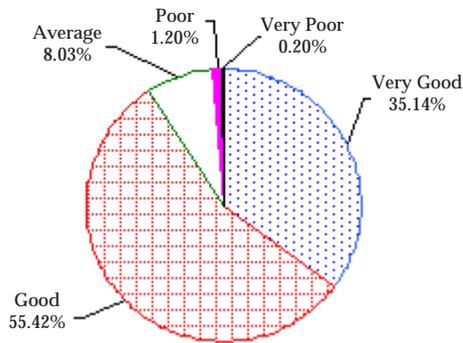


Fig. 6a. Overall well-being assessed by the patients after 12 weeks of Pedimune therapy on a 5-point ranking scale [n=551]

was very good to good in 90.56 % of the patient receiving bovine colostrum (Fig. 6a).

DISCUSSION

Children with a history of recurrent infections present a diagnostic challenge to their pediatricians because of the expectations of the parents for an explanation regarding the increase in the frequency of infections.²⁸ A wide spectrum of diseases influences the respiratory tract directly or indirectly, by causing recurrent infections. The immune system is not at its full maturity at birth and may not be totally developed until school going age. The most common serological abnormality reported in children with recurrent infections is partial IgA deficiency or IgG subclass deficiency. Humoral immunodeficiency diseases such as transient hypogammaglobulinemia of infancy and IgG subclass deficiency are also a common problem that increases susceptibility to recurrent infections.²⁸ Most children with recurrent respiratory infections do not have an immunodeficiency, however they often have deficient antibodies.²⁹ IgA and/or IgG subclass deficient children may be asymptomatic, may be associated with recurrent infections, allergic disorders, autoimmune disorders, malignancies or recurrent sinopulmonary infections.³⁰⁻³² In humans the protective antibody in the intestinal lumen has always been assumed to be secretory IgA.³³

Lack of Indian experience and looking into above facts, we used bovine colostrum concentrate containing immunoglobulin dry powder bovine colostrum for children (1-8 yr) having recurrent episodes of upper respiratory tract infections. The choice for 3 months duration was based on the author's knowledge of frequency of URTI.

In the present study the number of episodes of URTI reduced significantly by 91.19 % at the end of 12 weeks of bovine colostrum therapy. The number of patients reporting URTI episodes was also significantly reduced by 67.05% at the end of 12 weeks of bovine colostrum therapy. Another noteworthy finding of the present study was 86.60% reduction in number of episodes of diarrhea

and 92.00% reduction in hospitalization due to diarrhea after 12 weeks of bovine colostrum therapy, across the all age groups.

Out of the 605 patients, only 54 were not able to complete the study as many of them were lost to follow up. 2 patients discontinued treatment, out of which one discontinued due to skin rash and the other discontinued due to poor acceptability of taste. Total incidence of adverse effect was found to be 2.97%, and was mild to moderate in nature and resolved after appropriate therapy. No treatment discontinuation was reported.

After 12 weeks of bovine colostrum therapy, pediatrician reported high to average improvement in an overall well-being in 96% of the patients while an overall well-being stated by the patient or parent or guardian or caretaker was very good to good in 90.56 % of the patients. Overall, Pedimune[®] was very well tolerated in almost all the patients across all the age groups.

Bogstedt *et al*³⁴ demonstrated sufficient prophylactic activity of a daily dose of 500 mg bovine immunoglobulins against rotavirus diarrhea. Similarly, 200 - 400 mg lozenges of bovine colostrum was found to be effective by Sherif S *et al*³⁵ in improvement and modulation of humoral and cell mediated immune indices during the feeding (2 weeks) and post-feeding (2 weeks) period in human volunteers. Also, a direct positive correlation between the daily colostrum dose and titers of measured immunity indices are found. Many studies²¹⁻²⁴ suggest the possible therapeutic and prophylactic role of oral bovine colostrum in infants against many bacterial and viral infections of gastrointestinal tract and upper respiratory tract. The dosage of bovine oral immunoglobulins needed to obtain therapeutic efficacy is still to be determined and the ideal duration of treatment with bovine colostrum in an "at risk" population is not known. In previous studies, dried bovine colostrum is studied in doses between 200 mg to 40 gm daily orally for 10 days to 3 months.

Similarly, Brinkworth and colleagues had reported in their study, a 48% significant reduction in the number of subjects reporting symptoms of URTI in the bovine colostrum treatment arm as compared to the whey protein treatment arm²⁷. The reduction in the number of episodes of URTIs in the present study is consistent with an earlier observation by Brinkworth GD *et al*, however, there were certain important differences in the duration and dosage of the bovine colostrum in the studies.

Shafiqul A *et al*²² found antirotavirus immunoglobulins of bovine colostrum origin effective in the management of children aged 4 to 24 months with acute rotavirus diarrhea. Another study³³ also reported 100 % protection against symptomatic rotavirus infection with the efficacy of bovine colostrum in rotavirus diarrhea in children aged 3 to 15 months. The present study has also demonstrated significant reduction in number of episodes of diarrhea, no of patients suffering from diarrhea and also hospitalization due to it.

The defense of mucosal surfaces against pathogenic microorganisms is provided by a variety of mechanisms, among which the predominant role of IgA is well-established.³⁶ IgA antibodies are the major mediators of resistance to viral infection of the respiratory mucosa.³⁷ The quantity of secretory IgA in the nasopharynx appears to be age-dependent: it is lowest in young children and increases thereafter gradually with age.³⁸ Previous studies have shown that there is a direct relationship between salivary IgA levels and resistance to URTI²⁷, as such that higher salivary IgA levels reduce the incidence of URTI and vice versa. Mero *et al*²⁵ reported that salivary IgA concentration increases after 2 weeks of bovine colostrum supplementation. Colostral induced increase in IgA may be a probable mechanism for building respiratory tract immunity and thus decrease in episodes of URTI as reported in the present study.

Regular consumption of bovine colostrum has been reported as a protective role for infantile gastrointestinal immunity due to its direct effect on promoting and development of infantile gut-associated lymphoid tissues which are responsible mainly for pronouncing the infantile gut immunity.³⁵ Colostrum from nonimmunized cows contains antibodies against many enteric pathogens and bovine immunoglobulin in the form of specific antibody has also been shown to be effective against various enteric diseases.¹⁵⁻¹⁷ Thus, immunoglobulins in Pedimune and its competitive inhibition of the binding of luminal toxins could be a plausible mechanism of reduced episodes of diarrhea seen with bovine colostrum therapy.

The present study has some limitations. It is unblinded observational study and there is further need for randomized control trial. There may be a problem of recall bias with parents, as the outcome variables were decreased in ARI and diarrhea. Due to short follow up period, incidence of ARI may vary with seasonal changes, which may effect the end results of the study as outcomes were compared with preceding 6 months baseline data of the patients.

The results of the present study clearly demonstrated that bovine colostrum protects children against recurrent upper respiratory tract infection and diarrhea. Pedimune® (bovine colostrum) provides a simple way of preventing episodes of recurrent upper respiratory tract infection and diarrhea in susceptible children and thus may be useful in preventing recurrent infections in immunocompromised children or adults.

CONCLUSION

In conclusion, bovine colostrum was highly effective in the prophylactic treatment of recurrent URTIs and diarrhea in reducing not only the episodes but also the hospitalization due to them. These results suggest that clinical application of bovine colostrum might soon provide a therapeutic option for a condition affecting

millions of children worldwide. Although the present findings are based on self-reported symptoms, hence considered only of preliminary nature. Future studies should attempt to confirm these findings and simultaneously measure markers of immune function in order to identify the possible correlation by which this supplement elicits this effect.

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