

## Effects of Lactoferrin-containing Formula in the Prevention of Enterovirus and Rotavirus Infection and Impact on Serum Cytokine Levels: A Randomized Trial

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**Background:** Lactoferrin has been shown to exhibit anti-enterovirus 71 (EV71) and anti-rotavirus properties. This trial was conducted to determine whether a formula containing bovine lactoferrin (bLF) exerts a protective effect against EV71 or rotavirus infection among children from 2 to 6 years old.

**Methods:** A prospective, randomized, single blind clinical trial of an oral supplement containing bLF (daily dose approximately 70 to 85 mg) was carried out with healthy children in a day care center from March 2002 to June 2003. The incidence of enterovirus or rotavirus infection and the serum level of interferon-gamma (IFN- $\gamma$ ) and interleukin-10 (IL-10) were compared between children receiving and not receiving bLF.

**Results:** A total of 172 children, 96 in group A, which received bLF, and 76 in group B which did not receive bLF, completed the trial. During the study period, no EV71 was isolated and seroconversion of EV71 antibodies was noted in only one child. Fourteen episodes of presumptive enterovirus infection and 12 episodes of presumptive viral enteritis were detected. No significant differences were observed between groups in the incidence of presumptive enterovirus infection or viral enteritis or the number of laboratory confirmed enterovirus or rotavirus infections. No significant differences were observed in the serum levels of IFN- $\gamma$  and IL-10 between groups either prior to or following the trial. In both groups, IFN- $\gamma$  levels increased, but IL-10 was unchanged following the trial.

**Conclusion:** An oral supplement of bLF at a dose of 70 mg/day did not show any benefits in the prevention of EV71 or rotavirus infection, or any impact on IFN- $\gamma$  or IL-10 serum levels in healthy children in this trial.

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**Key words:** bovine lactoferrin, kindergarten children, enterovirus 71, rotavirus, interferon- $\gamma$ , interleukin-10

Lactoferrin, a glycoprotein with a molecular weight of 80 KD, is present in mammalian exter-

nal secretions, particularly in milk and colostrum. Lactoferrin exhibits several biological functions,

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including antimicrobial activity toward bacteria, fungi, and viruses.<sup>(1,2)</sup> In terms of their anti-viral effects, human lactoferrin and bovine lactoferrin (bLF) have been recognized as potent inhibitors of several enveloped human pathogenic viruses (such as herpes simplex virus 1 and 2, human cytomegalovirus, human immunodeficiency virus and human hepatitis C virus) and naked pathogenic viruses (such as rotavirus, poliovirus type 1, and enterovirus type 71 [EV71]).<sup>(3-6)</sup> In most of these studies, the antiviral effects took place before, but not after, the virus had entered the cells.

As a natural compound, oral lactoferrin supplements for the treatment of infectious diseases and inflammation has been evaluated in animal studies in recent years. Several positive results have been noted in these studies, including anti-fungal properties,<sup>(7,8)</sup> anti-*E. coli* properties,<sup>(9)</sup> anti-*Helicobacter* properties,<sup>(10,11)</sup> and anti-inflammatory properties related to colitis.<sup>(12)</sup> Oral supplementation with lactoferrin also exhibits beneficial effect in promoting "Bifidus flora" in the intestines of newborns receiving formula containing lactoferrin.<sup>(13)</sup>

In 1998, a large outbreak of hand, foot and mouth disease caused by EV71 occurred in Taiwan. More than 80 children died of encephalomyelitis, which clinically manifested as shock syndrome and pulmonary edema.<sup>(14,15)</sup> Since that time, EV71 infection has become endemic in this area, and caused more than 40 deaths each year in 2000 and 2001.<sup>(6)</sup> Until recently, no effective vaccine or drug has been available to prevent or treat EV71 infection. In addition, rotavirus infection is a common problem for children in day care centers during the winter in Taiwan. No effective drugs are presently available. Having noted the ability of lactoferrin to inhibit EV71 and rotavirus in vitro, we conducted this clinical trial from March 2002 to June 2003 (when no rotavirus vaccines were available) to determine whether children would benefit from drinking a formula containing lactoferrin for the prevention of EV71 or rotavirus infection.

## METHODS

This trial was approved by the ethical review committee of Chang Gung Memorial Hospital (CGMHIRB no: 90-214B) in accordance with the 1996 Declaration of Helsinki. Written informed con-

sent from parents was necessary for children to be enrolled.

### Patients

Healthy children 2 to 6 years old attending Chang Gung kindergarten were eligible for the trial. Children were not eligible to participate if they had particular underlying medical conditions including significant congenital diseases (such as congenital heart disease), or conditions associated with suppressed immunity (such as nephrotic syndrome), or were receiving immunosuppressive agents (such as systemic steroid therapy) within one month prior to the start of trial. Inhalation steroid therapy was not contraindicated for this study. Trials would be suspended for children with the following conditions during the study period: symptoms of lactose intolerance (such as diarrhea, abdominal distension, abdominal pain, skin allergy, or eczema), administration of immunosuppressive agents for more than one week, or the request from parents for any reason.

### Study design

Participants were randomly assigned to two groups (groups A and B). The study nurse, teachers, children, and parents were unaware which group would receive lactoferrin-containing formula. Children in group A took a commercially available lactoferrin-containing formula (Formula A, from ISIGNY Cooperation, Normandy, France) 200-240 ml (containing approximately 70 to 85 mg bLF; the concentration of bLF was 35 mg/100 gm formula) in the morning under the observation of teachers during the study period. Children in group B took a formula free of lactoferrin (Formula B, manufactured by ISIGNY and prepared specifically for this study) 200-240 ml in the morning. Both formulas provided the same composition of nutrients except for lactoferrin. During the study period in the morning, the study nurse went to the school and remained in close contact with the teachers and children. The activity, stool patterns, and body temperature were recorded on daily report cards. When necessary, children were referred to Chang Gung Children Hospital for evaluation and treatment.

### Laboratory tests

Throat swabs and/or rectal swabs were obtained by the nurse associated with the study and submitted

to the Clinical Pathological Department of Chang Gung Memorial Hospital for the isolation and typing of viruses when symptoms/signs suggestive of enterovirus infections (typical herpangina or hand, foot, and mouth disease) were noted, or when children complained of a sore throat without a significant cough or nasal secretions. When children were noted to have watery diarrhea and significant vomiting, stool specimens were collected and submitted for rotavirus antigen testing. Blood sampling for the determination of EV71 neutralizing antibody titer and serum levels of interferon (IFN)- $\gamma$  and interleukin (IL)-10 were done before and after the trial. EV71 neutralizing antibody titer was determined by standard protocol for the neutralization test on microtiter plates.<sup>(16,17)</sup> An EV71 neutralizing antibody titer greater than 1:8 was defined as seropositive. Serum IFN- $\gamma$  and IL-10 levels were determined by standard enzyme-linked immunosorbent assay with commercial kits purchased from R & D Systems (Human IFN- $\gamma$  Immunoassay, and Human IL-10

Immunoassay, Quantikine R&D System, Inc. Minneapolis, U.S.A.) All oral medications during the study period were recorded.

### Statistics

Chi square and Fisher's exact tests were used for categorical data including the incidence of enterovirus or rotavirus infection. The T-test and paired t-test were used for continuous data including age and the serum levels of cytokines in the participants.

## RESULTS

A total of 216 children (119 in Group A and 97 in Group B) were initially enrolled in this study (See Fig. 1). Forty-four children later quit for personal reasons other than milk intolerance or complications attributable to the formula, and a total of 172 children (96 in group A and 76 in group B) completed the trial. Age and gender were similar between group

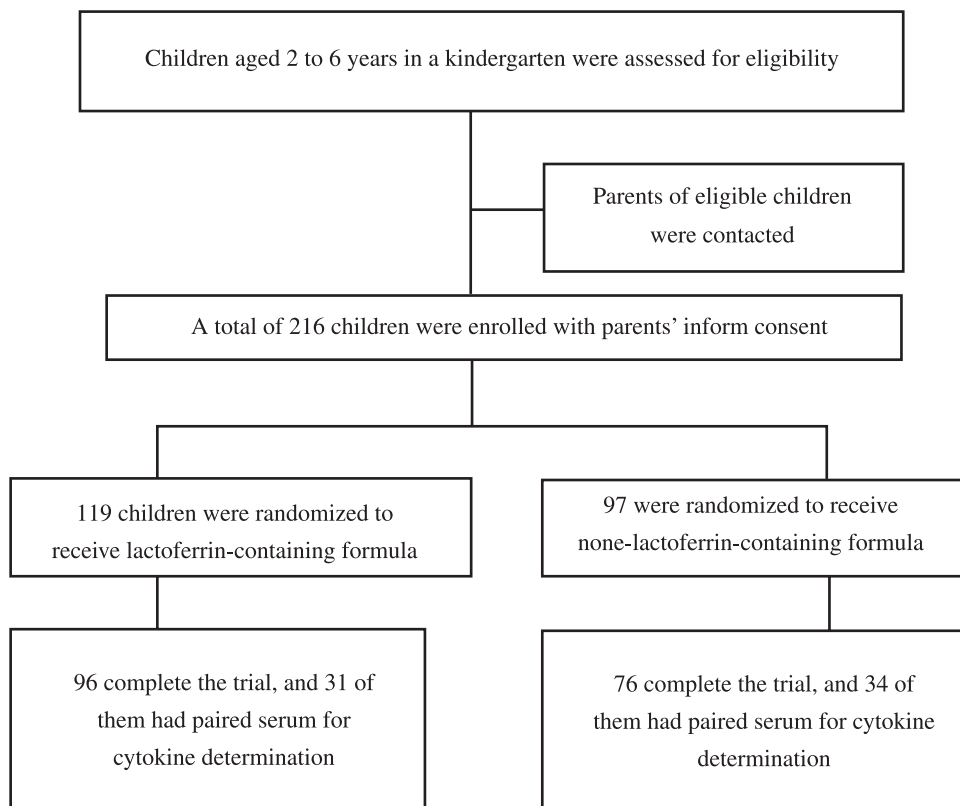


Fig. 1 Study flow

A and group B (Table 1).

Episodes of illness severe enough to warrant medical attention are summarized in Table 2. Two children (one in each group) were hospitalized for bronchopneumonia, and adenovirus was isolated from the nasopharyngeal swab of the patient in group B. There were a total of 40 episodes of suspected

**Table 1.** Gender and Age of Participants Receiving Formula with and without Lactoferrin

	Received formula containing lactoferrin	Received formula not containing lactoferrin	<i>p</i>
Participants completing trial	96	76	
2-3 years old	22	21	
3-4 years old	25	12	
4-5 years old	26	24	
5-6 years old	23	19	
Age (years)	4.70 ± 1.18*	4.68 ± 1.21	0.89
Boys	54 (56%)	43 (57%)	0.97

\*: mean ± standard deviation.

**Table 2.** Episodes of Illness Requiring Medical Help during Study

	Group A (n = 96)	Group B (n = 76)	<i>p</i>
Herpangina or HFM disease	9 (9)	5 (7)	0.74
Viral enteritis	6 (6)	6 (8)	0.93
Bronchopneumonia	1 (1)*	1 (1)†	0.58
Sinusitis	6 (6)	5 (7)	0.82
Chickenpox	2 (2)	0 (0)	0.59
Impetigo	1 (1)	0 (0)	0.90
GAS pharyngitis	2 (2)	0 (0)	0.59
Carbuncle	1 (1)	0 (0)	0.90
Febrile convulsion	1 (1)	0 (0)	0.90
Urticaria	1 (1)	0 (0)	0.90

**Abbreviations:** HFM: hand, foot, mouth; GAS: group A streptococcal; \*: Admitted in June 2002 but no definite pathogen was identified; †: Admitted in May 2002, due to adenoviral infection. Values are given as the frequency (%) in each cell.

viral throat infections including 14 episodes of presumptive enterovirus infections during the study (Table 2). All 14 children with presumptive enterovirus infection experienced mild symptoms (either no fever or fever subsided within 2 days) and enterovirus was isolated in 10 of them. The specific virus types isolated included coxsackieviruses A4, A10, and B2, echovirus 6, and pan-enterovirus (Table 3). A total of 12 episodes of presumptive viral enteritis were noted during the study and stool rotavirus antigen tests were performed in 8 children with diarrhea and significant vomiting. Positive results were noted in 4 of them (Table 3). All 12 patients with viral enteritis experienced improvement in two to four days, and the duration of vomiting and diarrhea was not different between group A and B (3.1 ± 1.3 vs. 3.5 ± 1 days, *p* = 0.53). No medical event was noted in any participant in the final month of the trial.

One hundred and twenty two patients had blood samples taken prior to the trial, and EV71 neutralizing antibody titers higher than 1:8 were noted in 37 (30%) of the subjects (19 children in group A and 18 in group B). Following the trial, seroconversion of EV71 antibodies was noted only in one child in Group A, who had not experienced clinically evident enterovirus infection during the study.

A total of 65 children (31 in group A and 34 in group B) had paired serum taken for cytokine level determination and the results are shown in Fig. 2.

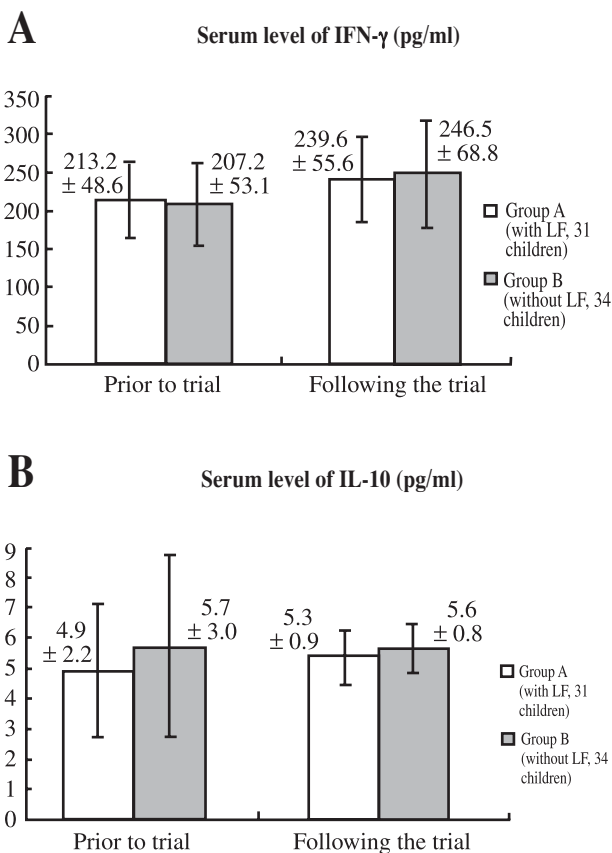
**Table 3.** Virus Isolation and Positive Rotavirus Antigen Detection during Study (March 2002- June 2003)

	Group A (n = 96)	Group B (n = 76)	<i>p</i>
Enterovirus	7 (7)*	3 (4)†	0.52
Rotavirus	2 (2)	2 (3)	1.0
Adenovirus	1 (1)	1 (1)	1.0
HSV-1	0 (0)	1 (1)	0.44
Influenza B	0 (0)	1 (1)	0.44

**Abbreviations:** HSV: herpes simplex virus; \*: subtypes includes Coxsackievirus A4 (1 child), Coxsackievirus B2 (2 children), Echovirus 6 (1 child), and pan-enterovirus (3 children); †: subtypes includes Coxsackievirus A10 (1 child) and pan-enterovirus (2 children).

Values are given as the frequency (%) in each cell.

Prior to the trial, the serum level of IFN- $\gamma$  was similar between group A and B ( $p = 0.63$ , Fig. 2A). Following the trial, the serum level of IFN- $\gamma$  increased in both groups A and B ( $p = 0.04$  and  $0.01$  respectively), and the serum level of IFN- $\gamma$  remained similar between groups ( $p = 0.66$ ). The serum level of IL-10 was similar between group A and B prior to the trial ( $p = 0.24$ , Fig. 2B). Following the trial, the serum level of IL-10 in both groups was similar to their pre-trial levels ( $p = 0.15$  and  $0.98$  respectively) and the serum IL-10 level remained similar between groups ( $p = 0.21$ ).



**Fig. 2** Serum levels of IFN- $\gamma$  and IL-10 in 65 participants. A total of 65 participants had paired serum taken for serum cytokine level determination. The serum levels of IFN- $\gamma$  and IL-10 were similar between participants in the two groups both before and after the trial (A and B). All 65 children were symptom free before the trial and during the last month of the trial. IFN: interferon; IL: interleukin; LF: lactoferrin.

## DISCUSSION

Beneficial effects from the oral supplementation with bLF or bLF-containing preparations have been shown in previous human studies. Oral supplements of lactoferrin inhibited viremia and had an impact in serum cytokine levels in patients with chronic hepatitis C infection.<sup>(18,19)</sup> Oral supplements of lactoferrin-containing products (tablets or yoghurt) ameliorated the frequency and duration of vomiting and diarrhea in children with rotavirus enteritis, although they did not decrease the incidence of this disease.<sup>(20)</sup> In a recent report, oral supplementation with bLF (100 mg/day) was noted to protect very low-birth-body-weight neonates from late onset sepsis.<sup>(21)</sup> However, in the present trial no difference in the incidence or severity of enterovirus or rotavirus infection was observed between the two groups.

Several factors probably contributed to this result. First, this trial was not carried out in a period of high EV71 disease burden. EV71 disease burden was high from 1998 to 2001 but then decreased. Coxsackievirus A16 (CA16) was the most predominant strain (44%), while EV71 accounted for only approximately 14% of the typeable enteroviruses isolated at Chang Gung Memorial Hospital in 2002 and 2003. During the study period, no EV71 was isolated from participants, and seroconversion of EV71 antibodies was noted in only one child. In terms of rotavirus infection, the disease burden was also low in this kindergarten; only four episodes of rotavirus infection were diagnosed by stool rotavirus antigen tests. Low disease burden for both EV71 and rotavirus infection made it more difficult to evaluate the preventive effect of lactoferrin. Another factor in this study was that the dose of lactoferrin was about 70 mg/day, which was less than that in other studies, particularly when judged by body weight. Also, the strict sanitary policies of this kindergarten, particularly during the last three months of the trial when the severe acute respiratory syndrome outbreak occurred, made disease transmission more difficult.

Oral supplementation with bLF has been reported to influence the serum levels and production of cytokines, but the results vary considerably among studies. It appears that oral supplementation with bLF is able to produce a Th1-cytokine dominant environment in individuals with viral infections. An increase in the serum level of IL-18 and the number

of Th1 cells (positive IFN- $\gamma$  and negative IL-4) in peripheral blood was noted after oral supplementation with lactoferrin in patients with chronic hepatitis C infection.<sup>(18)</sup> In mice infected with Type 1 herpes simplex virus, drinking water containing 1.5% lactoferrin increased serum levels of IL-18 and the production of IFN- $\gamma$  from splenocytes.<sup>(22)</sup> In addition, oral supplementation with lactoferrin increased the production of anti-inflammatory cytokines in rats with colitis; a significant induction of IL-4 and IL-10, and a significant reduction in TNF- $\alpha$  and IL-6 were noted in the colonic tissue derived from mice with chemical colitis under experimental conditions.<sup>(12,23)</sup> However, few studies have investigated the impact of oral supplementation with bLF-containing preparations on the serum cytokines in healthy children. In the present trial, IFN- $\gamma$  and IL-10 were selected as markers for pro-inflammatory and anti-inflammatory cytokines respectively; however, no significant difference was observed in the serum level of either cytokine between children in either group following the trial. These results are in agreement with a recent report (involving 8 healthy men) in which oral supplementation with bLF (200 mg/day) was not associated with significant changes in the serum levels of any of the identified cytokines, including tumor necrosis factor- $\alpha$ , IFN- $\gamma$ , IL-2, IL-4, IL-6, and IL-10.<sup>(24)</sup> It appears that the impact of oral supplementation of lactoferrin on the serum level of cytokines is not the same among healthy individuals and those with viral infections. Our results indicate that oral supplementation with 70 mg bLF per day would not have a significant impact on the serum level of IFN- $\gamma$  and IL-10 in children 2 to 6 years old.

In conclusion, for children 2 to 6 years old, no preventive effect on EV71 or rotavirus infection was shown with a nutritional preparation containing lactoferrin in this trial. In addition, for children 2 to 6 years old, oral supplementation with bLF at a dose of 70 mg/day did not have an impact on the serum level of IFN- $\gamma$  or IL-10. To our knowledge, this is the first report evaluating the preventive effects of lactoferrin-containing formula on enterovirus infection and its impact in serum cytokines in healthy children. Further studies are required to evaluate the preventive effect of oral supplementation with bLF on viral infection. These studies ought to be carried out when diseases are endemic, using higher doses of lactoferrin.

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# 含乳鐵蛋白之幼兒奶粉於預防腸病毒及輪狀病毒感染之效用： 臨床研究

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- 背景：**於體外試驗中已知乳鐵蛋白有抗腸病毒 71 型及輪狀病毒之作用。本臨床研究在觀察含乳鐵蛋白成分之配方奶粉對於幼稚園孩童是否有預防腸病毒 71 型及輪狀病毒感染的效果。
- 方法：**本研究於 2002 年三月至 2003 年六月間針對一所幼稚園健康孩童以飲用含乳鐵蛋白的配方奶粉(每日接受的乳鐵蛋白約 70 至 85 mg)進行前瞻性，隨機分配，單盲的臨床研究。分析比較在研究期間，兩組孩童於腸病毒 71 型及輪狀病毒感染的次數及研究前後血清中丙型干擾素(interferon gamma, IFN- $\gamma$ )及第十型介白素(IL-10)之血清濃度。
- 結果：**共有 172 位小朋友完整地完成本次研究，其中 A 組有 96 位，B 組有 76 位。於研究期間未檢出 EV71 病毒且只有一位小朋友於研究期間呈現 EV71 抗體陽轉。試驗期間共發現 14 例疑似腸病毒感染及 12 例疑似病毒性腸炎感染的案例。兩組小朋友在腸病毒感染次數及病毒性腸炎感染次數，培養出的腸病毒數目，及陽性輪狀病毒抗原數目上，沒有顯著性的差異。無論研究前後血中丙型干擾素及第十型介白素的濃度於兩組小朋友之間並無明顯差異。於研究完成後兩組小朋友之丙型干擾素濃度較一年前均有上升，然而第十型介白素的血中濃度均與研究前無明顯變化。
- 結論：**本研究未能顯示經腸道補充乳鐵蛋白具有預防腸病毒 71 型或輪狀病毒感染的功效。此外，本研究顯示每日口服補充 70 mg 的牛乳鐵蛋白不會影響年齡 2 至 6 歲的健康幼童血中的丙型干擾素及第十型介白素的濃度。  
(長庚醫誌 2011;34:395-402)

**關鍵詞：**乳鐵蛋白，幼稚園孩童，腸病毒 71 型，輪狀病毒，丙型干擾素，第十型介白素