

Best Evidence Statement (BEST)

April 15, 2011

Use of *Lactobacillus rhamnosus GG* in children with acute gastroenteritis

Clinical Question

P (population/problem) In children with acute gastroenteritis (AGE)
I (intervention) is the use of *Lactobacillus rhamnosus GG* in addition to oral rehydration solution (ORS)
C (comparison) compared to ORS alone
O (outcome) effective in reducing the duration of diarrhea?

Target Population:

Included: Overall healthy children aged 2 months to 18 years with acute gastroenteritis, with or without fever or vomiting

(AGE defined as a decrease in the consistency of stools and/or an increase in the frequency of evacuations (≥ 3 /day) lasting less than 7 days)

Excluded:

- children with underlying chronic diseases (mainly immunocompromised patients, and including debilitated state or malignancies and chronic conditions that can increase intestinal mucosal permeability)
- premature infants
(Boyle 2006 [5a])

Recommendation

It is recommended to administer *Lactobacillus rhamnosus GG* (LGG) to children with acute gastroenteritis to reduce the duration of diarrhea, risk of protracted diarrhea and duration of hospitalization (Szajewska 2007 [1a], Guarino 2008 [5a], Local Consensus [5]).

To obtain best efficacy:

- start LGG treatment as soon as possible
- at a dose of at least 10^{10} colony forming units per day (CFU/day)
- for 5 to 7 days

(Szajewska 2007 [1a], Guandalini 2008 [5a], Guarino 2008 [5a]).

Note: The criterion for efficacy of LGG for treatment of acute gastroenteritis is the presence of 10 billion CFU. It is important to determine that the product meets this criterion. One such product readily available locally is Culturelle capsules; Amerifit, Inc. (the product is gluten free but contains milk proteins). Culturelle for Kids contains only 1 billion CFU per dose, and other available probiotic products do not contain the LGG organism. Available in capsules; the contents of the capsules can be dissolved in water for oral administration.

Relevant Cincinnati Children's Hospital Medical Center (CCHMC) policies / procedures

CCHMC –Evidence-Based Clinical Care Guideline: Acute Gastroenteritis(2006) states that:

It is recommended that probiotics be considered as adjunctive therapy, as they have been shown to reduce the duration of diarrhea (Allen 2010 [1a]). Family preference may be central to the decision to use probiotics.

Parameters influencing the family's decision may include cost, degree of potential benefit, availability and unverified effectiveness of commercial products (CCHMC 2006[5a]).

Discussion/summary of evidence

The grade of the body of evidence supporting this recommendation is high. Although the standard treatment of acute diarrhea remains to be an oral rehydration solution (ORS), probiotics have gained an important role as adjuvant

therapy. A large number of trials, including randomized controlled trials (RCTs), and several well-designed meta-analyses reported that probiotics exert clinically significant antidiarrheal effects, particularly in children.

Though LGG has primarily been studied in preschool children, it has been tested in children older than 5 years and in adults, with similar results as that for younger children (*Szymanski 2006 [2a]*, *Khanna 2005 [2a]*). The management of acute gastroenteritis is the same for older as for younger children, although the prevalence of the condition is much lower among older children. Considering the available evidence and the safety profile of probiotics, the recommendation for use of LGG as treatment for acute diarrhea can be generalized to include older children (*Local Consensus [5a]*).

Clinical outcomes

Four meta-analyses have been published on the effect of probiotics in the treatment of acute infectious diarrhea (*Szajewska 2001 [1a]*, *Van Neil 2002 [1a]*, *Huang 2002 [1a]*, *Allen 2010 [1a]*). In all these papers, authors compared the effect of different probiotic strains to oral rehydration in children with AGE; one of the papers included in the analysis of results some RCTs performed on both pediatric and adults (*Allen 2010 [1a]*).

Despite the significant heterogeneity between the studies, all meta-analyses demonstrated that probiotics, and particularly lactobacilli, reduced the duration of an acute diarrheal episode by approximately 1 day. On the other hand, beneficial effects of probiotics seem to be strain-specific and pooling data on different strains may result in misleading conclusions.

A recent meta-analysis of RCTs involving 988 children with acute infectious diarrhea found that LGG is associated with a significant reduction in diarrhea duration (7 RCTs, 876 infants; weighted mean difference (WMD) -1.1 days, 95% Confidence Interval (CI): -1.9 to -0.3), particularly of Rotavirus diarrhea (WMD -2.1 days, 95% CI: -3.6 to -0.6), risk of diarrhea longer than 7 days (1 RCT, Relative Risk (RR): 0.25, 95% CI: 0.09 to 0.75), and duration of hospitalization (3 RCTs, number of participants =535; WMD -0.58, 95% CI: -0.8 to -0.4) (*Szajewska 2007 [1a]*).

There is only one RCT that reports a head-to-head comparison of the efficacy of the following probiotic strains:

- A- LGG
- B- *Saccharomyces boulardii*
- C- *Bacillus clausii*
- D- a mixture including *L. bulgaricus*, *S. thermophiles*, *L. acidophilus* and *B. bifidum*
- E- *Enterococcus faecium* SF68

The authors demonstrated that only A (LGG) and D (the mixture) were effective in reducing duration and severity of diarrhea ($p < 0.001$) (*Canani 2007 [2a]*).

Dose-dependent efficacy

An early meta-analysis reported dose-related efficacy for lactobacilli preparations against gastroenteritis (*Van Neil 2002 [1a]*). A positive linear association between the load of the *Lactobacillus* dose and the reduction in diarrhea duration in days has been noted ($p < 0.01$).

This important concept emerged again from a recent review: probiotic efficacy was correlated in a linear fashion with bacterial load, the minimal effective dose being at least 10×10^9 CFU/day (*Guandalini 2008 [5a]*).

In addition, a dose-dependent effect of LGG on the rota viral shedding has been demonstrated. In an open-label RCT aimed to assess the effectiveness of different *Lactobacillus rhamnosus* doses on the fecal Rotavirus concentrations in children with diarrhea, authors compared three groups of patients receiving an high-dose (6×10^8 CFU), a low-dose (2×10^8 CFU) or no probiotic supplementation. After 3 days of treatment only the high-dose group showed a significant (more than 80%) reduction of fecal Rotavirus concentration from the baseline concentration ($p = 0.012$) (*Fang 2009 [2b]*).

In conclusion, LGG is effective in reducing duration of acute diarrhea in children, and its effect depends on the dose administered and the timing of initiation of the treatment (early treatment is better). The effect is highly significant among patients with watery diarrhea and viral gastroenteritis, but not among those with invasive bacterial diarrhea. The effect is more evident among children in developed countries compared with those in developing countries.

Health Benefits, Side Effects and Risks

Health benefits

The health benefits for LGG administration in adjunct to ORS consist of reduction of diarrhea duration, reduction in risk of having a protracted diarrhea and reduction of duration of hospitalization.

Indirectly, the use of LGG could lead to a reduction of AGE-related costs in term of work days lost by the family and days of hospitalization; and the routine use of LGG in inpatients and community children with acute diarrhea could reduce the exposure to nosocomial and daycare infection.

Side Effects

Probiotics are generally regarded as safe, and side effects in ambulatory care have rarely been reported. Bacterial translocation, sepsis, and the risk of carrying antibiotic resistance plasmids that may spread resistance to antibiotics have been reported (Egervan 2007 [4a] Kayser 2003 [4a]). The latter has been reported for some probiotics, such as *L. reuteri* ATCC 55730 and *Enterococcus faecium* but not for LGG.

Risks

The risk for bacteremia and sepsis after LGG ingestion has been reported in some case reports involving infants and children with severe underlying diseases like short-gut syndrome, prematurity, cerebral palsy or cardiac surgical diseases; all these children required parenteral nutrition through CVC or jejunostomy feeding. (Boyle 2006 [5a]). No risks have been reported by using LGG in cohorts of children with AGE involved in clinical trials.

References/citations (evidence grade in []; see Table of Evidence Levels following references)

- 1) Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003048[1a]
- 2) Besselink MG, van Santvoort HC, Buskens E et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2008;23:371:651-9. [2a]
- 3) Boyle RJ, Robins-Browne RM, Tang MLK. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006;83:1256-64. [5a]
- 4) Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ* 2007;340–6. 335. [2a]
- 5) Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for acute gastroenteritis (AGE) in children aged 2 months through 5 years. Guideline 5 pages 1-15 May 2006 <http://www.cincinnatichildrens.org/evidence>. [5a]
- 6) Egervan M, Danielsen M, Roos S, et al. Antibiotic susceptibility profiles of *Lactobacillus reuteri* and *Lactobacillus fermentum*. *J Food Prot* 2007;70:412–418. [4a]
- 7) Fang SB, Lee HC, Hu JJ. Dose-dependent effect of *Lactobacillus rhamnosus* on quantitative reduction of faecal rotavirus shedding in children. *J Trop Pediatr*. 2009;55:297-301. [2b]
- 8) Guandalini S. Probiotics for children with diarrhea: an update. *J Clin Gastroenterol* 2008; 42:S53–S57. [5a]
- 9) Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra J. H, Shamir^{1R}, Szajewska H. The ESPGHAN/ESPID Guidelines for the Management of Acute Gastroenteritis in Children in Europe: *J Pediatr Gastroenterol Nutr* 2008; 6:619-21.[5a]
- 10) Huang JS, Bousvaros A, Lee JW, et al. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. *Dig Dis Sci* 2002;47:2625–34. [1a]
- 11) Kayser FH. Safety aspects of enterococci from the medical point of view. *Int J Food Microbiol* 2003; 88:255–262. [4a]
- 12) Local Consensus. During Best Evidence Statement development timeframe. 2011, [5].
- 13) Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebocontrolled trials. *J Pediatr Gastroenterol Nutr* 2001;33:S17–S25. [1a]

- 14) Szajewska H, Skorka A, Ruszczynski M, et al. Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. *Aliment Pharmacol Ther* 2007;25:871–881. [1a]
- 15) Van Niel CW, Feudtner C, Garrison MM, et al. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; 109:678-684. [1a]

Guidelines that include LGG as a treatment for acute gastroenteritis in children

- A. Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for acute gastroenteritis (AGE) in children aged 2 months through 5 years. [5a] <http://www.cincinnatichildrens.org/evidence>. Guideline 5 pages 1-15 May 2006 [5a]
- B. Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra J. H, Shamir^{1R}, Szajewska H. The ESPGHAN/ESPID Guidelines for the Management of Acute Gastroenteritis in Children in Europe: *J Pediatr Gastroenterol Nutr* 2008; 6:619-21.[5a]
- C. Harris C, Wilkinson F, Mazza D et al. Evidence-based guidelines for the management of diarrhea with or without vomiting in children. *Aust Fam Physician*. 2008;37:22-9. Full text at <http://www.mihsr.monash.org/hfk/pdf/diarrhoea-sh-infect-cont-20051122.pdf> [5a]

Other references

Largest RCT on the use of LGG in children (included in cited meta-analysis)

Guandalini S, Pensabene L, Zikri MA, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. *J Pediatr Gastroenterol Nutr* 2000;30:54–60[2a]

Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life

Supporting information

Introductory/background information

Acute gastroenteritis is an extremely common problem in childhood, particularly in the first three years of life. In developed countries it is usually a mild disease, however, AGE is associated with a substantial number of hospitalizations and high costs. Dehydration is the main clinical feature and generally reflects disease severity. Rehydration is the key treatment and drugs are generally not necessary, but could help to reduce duration of diarrhea, number of evacuations and, consequently dehydration and severity of the disease (*Guarino [5a]*).

A number of drugs have been proposed as an adjunct to rehydration. A number of probiotic strains have been tested to date, but proof of efficacy is compelling only for a few. The rationale for the use of probiotics to treat and prevent diarrheal diseases is based on the assumption that they modify the composition of the colonic microflora and act against enteric pathogens (*Guarino [5a]*).

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Search strategy

- 1) **Databases:** MEDLINE, Cochrane Database of Systematic Reviews
Search Terms: gastroenteritis/tw, gastroenteritis/MeSH
 acute diarrhea/MeSH, acute diarrhea/tw
 probiotic/tw, probiotics/MeSH
 Lactobacillus/tw, Lactobacillus/MeSH
 child*
Filters: Publication date: 1980 to present
 humans
 English language
 "all child (0 to 18 years)"
- 2) Additional articles identified by the author and ad hoc reviewers
- 3) Additional articles identified from reference lists of reviewed articles

Applicability issues

The recommendations suggested in this BEST have a good applicability in daily clinical practice due to:

- similarity between the population included in the studies and the target population of this BEST
- feasibility of the treatment in the CCHMC clinical setting
- likelihood for a positive cost-benefit ratio for probiotic use in AGE when including hospitalization and emergency department (ED) readmission rates.

Process measures may include the percentage of hospitalized children with AGE who were administered *Lactobacillus rhamnosus GG* (LGG).

Outcome measures may include inpatient length of stay and the number of readmissions to the ED for AGE.

At CCHMC we will use a rapid **Quality Improvement** strategy aimed to increase the rate of administration of LGG in hospitalized preschool children with AGE, with the final objective to reduce the duration of hospitalization and the rate of readmission to the ED in children with AGE by reducing the duration of diarrhea.

The primary intervention will be education of medical and non-medical personnel working in selected units and involved in the management of children with AGE (attending physicians, fellows, residents, nurses, and pharmacists, families).

The intervention will be focused on the following points:

- education of physicians and nurses to improve the knowledge of evidence for probiotic use in AGE
- interaction with the pharmacy service to ensure availability of LGG in the appropriate formulation for inpatients
- standardization of LGG administration (time, dose, frequency and duration of the therapy)
- education of the family to ensure correct home therapy.

As the baseline value we will use the percentage of children, aged 2 months to 5 years, receiving LGG for treatment of AGE in the previous 13 months, in the same inpatient units as are used for the intervention. We will assess, with a weekly measurement during the next 6 months, the variation of the percentage of preschool children receiving LGG during hospitalization.

Copies of this Best Evidence Statement (BEST) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm>

Examples of approved uses of the BEST include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence-based care;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the BEST may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any BEST adopted, adapted, implemented or hyperlinked by the organization is appreciated.

For more information about CCHMC Best Evidence Statements and the development process, contact the Anderson Center at: 513-636-2501 or HPCEInfo@cchmc.org.

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed by two independent reviewers against established criteria.