

## COCHRANE CAM REVIEW: SUMMARY OF FINDINGS

# THE EFFECT OF PROBIOTICS ON PREVENTING NECROTIZING ENTEROCOLITIS IN PREMATURE BABIES

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Up-to-date systematic reviews are of critical importance to healthcare providers and policy makers. Providers must keep current with research findings or they risk adverse consequences for patient care, including a delay in the uptake of treatments proven to be effective by randomized trials, as well as the continued recommendation and use of therapies proven ineffective or even harmful. Policy makers also increasingly rely on systematic reviews as a way of summarizing evidence and as a factor in decision making. Systematic reviews summarize research findings by using explicit, transparent, and reproducible methods to review existing randomized controlled trials (RCTs).

The Cochrane Collaboration is an international, nonprofit, and independent organization dedicated to making up-to-date, accurate systematic reviews of the effects of healthcare therapies available worldwide.<sup>1</sup> All reviews published under the Cochrane aegis adhere to a strict and meticulous methodology, undergo extensive peer review and quality checks at multiple stages, and require regular updating to account for new evidence. As a result, Cochrane reviews, considered to be among the most rigorous of all overviews, have been favorably compared with systematic reviews published in the most prestigious medical journals.<sup>2</sup> The 15 740 individuals who comprise the Cochrane Collaboration include researchers, clinicians, volunteers, and librarians,<sup>3</sup> all driven by enthusiasm and a desire to learn the truth about the value of different healthcare therapies. There are now more than 3737 completed Cochrane Reviews (as of Issue 2, 2009), 365 of which relate to complementary and alternative medicine (CAM) therapies. The Complementary Medicine Field is the designated group within the Cochrane Collaboration focused on facilitating the conduct of Cochrane systematic reviews of CAM therapies.

Systematic reviews, however, are sometimes not accessible because of their length and complexity. Shorter summaries of Cochrane reviews are necessary to bridge the gap in providers'

accessibility to evidence-based information about CAM. Over the past year, the Cochrane CAM Field has been working with the Norwegian branch of the Nordic Cochrane Center to produce Summary of Findings tables/Plain Language Summaries (SoF/PLS) of CAM-related Cochrane Reviews. In these SoF tables, we present the most important outcomes of each review (usually, but not always, the review's primary outcomes), the effect of the intervention on each outcome, and the quality of the evidence for each outcome. The preparation of each of these SoF/PLS is time- and labor-intensive and generally takes 3 to 4 days of an experienced methodologist's time. Some of the work involves deciding which outcomes to present for which time points and evaluating the strength and quality of the evidence for the outcomes. For each SoF, the authors of the Cochrane Review are also contacted to request clarification on any points that are not understood in the Cochrane Review and also to request their review of the SoF.

The development of such a vehicle for disseminating the bottom-line message of Cochrane Reviews in as simple a format as possible has been underway within the Cochrane Collaboration since 2000. The resulting SoF format, based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach for evaluating the strength and quality of evidence,<sup>4</sup> is the final summary format that has been decided upon by the Cochrane Collaboration. Several groups, including the *BMJ*, WHO, and many guidelines groups and professional societies, have already adopted the GRADE approach (and the accompanying SoFs) as the primary method of disseminating the bottom-line message of complex research findings to stakeholders, so CAM researchers and providers may also find it helpful to become familiar with this format.

Beginning with this issue, *Alternative Therapies in Health and Medicine* and the Cochrane Complementary Medicine Field introduce a series of columns called "Cochrane CAM Reviews: Summary of Findings." The column begins with the Consumer Summary, which provides a general introduction to the treatment, in this case probiotics, and the condition, necrotizing enterocolitis (NEC), as well as a narrative review of the effectiveness of probiotics for NEC. This is followed by a Summary of Findings table that documents in greater detail the number of babies diagnosed with NEC and other relevant outcomes in the probiotics group and the control group, the relative effect, the number of participants and studies, and a ranking of the quality of the evidence. The summary in this issue shows that an intervention as simple, inexpensive, and relatively safe as a probiotic has the potential to save the lives of thousands of babies.

**TABLE** Summary of Findings: Probiotics for Prevention of Necrotizing Enterocolitis in Preterm Infants

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)†	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Probiotics			
<b>Severe NEC (necrotizing enterocolitis)</b> Stage II or more by Bell's criteria, diagnosed prior to discharge	59 per 1000	19 per 1000 (10 to 35)	RR 0.32 (0.17 to 0.60)	1264 (5)	⊕⊕⊕O moderate <sup>1</sup>
<b>Nosocomial sepsis</b> Positive blood or cerebrospinal fluid cultures taken beyond 5 days of age	152 per 1000	141 per 1000 (111 to 181)	RR 0.93 (0.73 to 1.19)	1284 (6)	⊕⊕⊕O moderate <sup>2</sup>
<b>All cause neonatal mortality</b>	64 per 1000	28 per 1000 (16 to 48)	RR 0.43 (0.25 to 0.75)	1207 (5)	⊕⊕⊕O moderate <sup>3</sup>
<b>Duration of total parenteral nutrition</b>	The mean duration of total parenteral nutrition ranged across control groups from 13.9 to 14.7 days	The mean duration of total parenteral nutrition in the intervention groups was lower (4.6 lower to 1.9 higher)		952 (2)	⊕OOO very low <sup>4,6</sup>
<b>Duration of hospitalization</b>	The mean duration of hospitalization ranged across control groups from 39 to 47 days	The mean duration of hospitalization in the intervention groups was lower (12 lower to 53 higher)		397 (2)	⊕OOO very low <sup>5,7</sup>

\*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†CI indicates confidence interval; RR, risk ratio.

GRADE Working group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

<sup>1</sup> 3/5 unclear randomization procedure, 3/5 unclear allocation concealment, 2/5 unclear blinding, 1 study unclear losses to follow up

<sup>2</sup> 4/6 unclear randomization procedure, 4/6 unclear allocation concealment, 3/6 unclear blinding, 1 study unclear losses to follow up

<sup>3</sup> 2 unclear and 1 inadequate randomization procedure, 2 unclear and 1 inadequate allocation concealment, 1 unclear blinding and 1 unclear losses to follow-up

<sup>4</sup> Unclear allocation concealment in 1 of the 2 studies

<sup>5</sup> The 2 studies are so heterogeneous in results that review authors did not combine in meta-analysis

<sup>6</sup> Wide confidence intervals

<sup>7</sup> Inadequate randomization procedure and allocation concealment in 1 of the 2 studies

## CONSUMER SUMMARY

### The Effect of Probiotics on Preventing NEC in Premature Babies

A review of the effect of probiotics on NEC in premature babies was conducted by researchers in The Cochrane Collaboration. After searching for all relevant studies, they found 9 studies done by other researchers. Their findings are summarized here.

### What Is NEC and Why Probiotics?

NEC is a serious bowel disease that occurs when the bowel (intestine) becomes infected and parts of the bowel die. It affects mostly premature babies, particularly those who are of very low weight (less than 1500 g). Up to 10 of 100 babies of very low birth weight may develop NEC.

It is not entirely clear what causes NEC. In premature babies, the bowels are not fully developed and are more likely to become infected. It is also possible that the use of infant formula plays a part, as babies who are breast-fed are less likely to suffer from NEC.

Babies with NEC may have the same symptoms as babies with other digestive diseases, such as feeding problems, vomiting, and bloated and tender stomachs. NEC is usually diagnosed with x-rays and blood tests. If a baby is suspected of having NEC, antibiotics are given, feedings are stopped, and the baby is fed only intravenously until the bowel heals.

In about one-third of affected babies, the damage to the bowel is so serious that it perforates (tears). If this happens, bacteria from the bowel can leak into the stomach and cause an infection. At

worst, the baby could die. If the bowel perforates, surgery is performed, and the damaged parts of the bowel are removed.

Probiotics are dietary supplements that contain potentially "good" bacteria. The most common type of probiotic supplements are yogurt and other dairy products in which these bacteria already exist or where they are added.

The most frequently used probiotics are *Lactobacillus* and *Bifidobacterium*. These bacteria already live in the stomach and bowel, but premature babies may not have enough of them. The idea behind feeding the babies probiotics before they become ill is that it may help decrease the amount of harmful bacteria in the bowel.

### What Does the Research Say?

Not all research provides the same quality of evidence. The higher the quality, the more certain we are about what the research says about an effect. The words *will* (high-quality evidence), *probably* (moderate-quality evidence), and *may* (low-quality evidence) describe how certain we are about the effect.

The studies showed that giving premature babies probiotics

- probably prevents severe NEC,
- probably makes little or no difference to the number of babies who develop severe blood infections, and
- probably leads to fewer babies dying during their first month.

In general, side effects are poorly documented, and it is difficult to provide precise information. There is a fear that probiotics

may cause infections. In these studies, this side effect was not seen.

The babies in these studies all weighed less than 2500 g. Some of the babies weighed less than 1500 g, and some weighed less than 1000 g. The studies do not show if the treatment was equally effective for all of these groups.

### Where Does This Information Come From?

The Cochrane Collaboration is an independent global network of volunteers, dedicated to summarizing research about healthcare. This information is taken from this Cochrane Review: Al Faleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev.* 2008;1:CD005496.

### Acknowledgments

This summary was prepared by Claire Glenton and Gunn Vist, the Nordic Cochrane Centre's Norwegian branch, Norwegian Knowledge Centre for Health Services, on behalf of the Cochrane Complementary and Alternative Medicine Field and with funding from the US National Center for Complementary and Alternative Medicine (NCCAM) of the US National Institutes of Health (grants number R24 AT001293).

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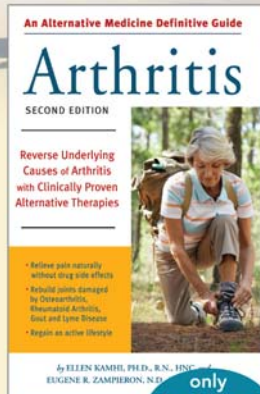
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more (and it might), so let's begin with those who already have chronic disease. Integrated healthcare teams led by physicians practicing lifestyle medicine can save our healthcare system. Presently, however, physicians lack training and financial incentives to help people learn how to eat a healthy diet, exercise, stop smoking, manage their weight, or address the effects of environmental toxins. So they continue to do what they know how to do: prescribe medication and perform surgery.

Personalized lifestyle medicine is a high-science, high-touch, low-tech, low-cost treatment that is more effective for the top 5 chronic diseases than our current approaches. Yet is it not taught in medical schools, practiced by physicians, or delivered in hospitals or healthcare settings. In fact, this treatment, if applied to all the patients with cardiovascular disease, diabetes, metabolic syndrome (obesity), prostate cancer, and breast cancer could reduce net health care expenditures \$930 billion over 5 years and result in dramatically better health and quality of life.\*

#### OPPORTUNITIES FOR CHANGE

On August 6, 2009, Senator Ron Wyden (D, Oregon) introduced new legislation, the Take Back Your Health Act (S. 1640) that includes payment for intensive lifestyle medicine as treatments, not just prevention. This legislation has bipartisan co-sponsorship by Senators John Cornyn (R, Texas) and Tom Harkin (D, Iowa). We worked closely with these senators to help craft this initiative. This pending legislation, or changes in Medicare policy, can make it feasible for intensive lifestyle treatments to take hold in medical care. It will reinvigorate primary care medicine and drive the transformation of existing healthcare institutions, medical schools, postgraduate education, and insurers to meet the demand for interventional lifestyle treatment of chronic disease. It will induce doctors to learn and practice lifestyle medicine both because it works better for their patients and physicians will be paid to do it. It will support the development of a wellness- and health-based economy rather than one based on sickness and chronic disease.

If lifestyle medicine becomes central to the practice of medicine, our sick care system will be transformed into a healthcare system.

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\*According to Cleveland Clinic estimates for the Take Back Your Health Act of 2009. Data were prepared by the clinic and presented to Congress by Drs Mark Hyman, Dean Ornish, and Michael Roizen.

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#### ERRATA

##### North American Research Conference Abstracts

In each of the following abstracts that were published in our May/June issue in partnership with the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM), an author was mistakenly excluded from the listing. The corrected listings appear below.

##### 3156

Poznanski A, Lapides J, Hsu M, Gracely R, Clauw D, Harris R. Differences in central neural pain processing following acupuncture and sham acupuncture therapy in fibromyalgia (FM). University of Michigan Medical School, 24 Frank Lloyd Wright Drive, Ann Arbor, MI 48106  
apozna@umich.edu  
*Altern Ther Health Med*. 2009;15(3):S120.

##### 2975

Shin S, Tsutomu K, Sei S. Anti-obesity effect by a newly developed Chinese Qi-gong meridian therapy. Japan Chinese Medical Qigong Diet Association, Tokyo 150-0002, Japan  
saisei@nirs.go.jp  
*Altern Ther Health Med*. 2009;15(3):S122.

CAHCIM regrets the errors.

##### Probiotics for Preventing Necrotizing Enterocolitis

The byline for the article, "The effect of probiotics on preventing necrotizing enterocolitis in premature babies," which appeared on page 18 of our Jul/Aug issue (*Altern Ther Health Med*. 2009;15(4):18-20) should have read "Eric Manheimer, MS; Brian Berman, MD; Gunn Vist, PhD; Claire Glenton, PhD."

The authors regret the oversight.