Annals of Internal Medicine | NIH Conference

Systematic Review: Effective Management Strategies for Lactose Intolerance

Aasma Shaukat, MD, MPH; Michael D. Levitt, MD; Brent C. Taylor, PhD, MPH; Roderick MacDonald, MS; Tatyana A. Shamliyan, MD; Robert L. Kane, MD; and Timothy J. Wilt, MD, MPH

Background: Lactose intolerance resulting in gastrointestinal symptoms is a common health concern. Diagnosis and management of this condition remain unclear.

Purpose: To assess the maximum tolerable dose of lactose and interventions for reducing symptoms of lactose intolerance among persons with lactose intolerance and malabsorption.

Data Sources: Multiple electronic databases, including MEDLINE and the Cochrane Library, for trials published in English from 1967 through November 2009.

Study Selection: Randomized, controlled trials of individuals with lactose intolerance or malabsorption.

Data Extraction: Three investigators independently reviewed articles, extracted data, and assessed study quality.

Data Synthesis: 36 unique randomized studies (26 on lactase- or lactose-hydrolyzed milk supplements, lactose-reduced milk, or tolerable doses of lactose; 7 on probiotics; 2 on incremental lactose administration for colonic adaptation; and 1 on another agent) met inclusion criteria. Moderate-quality evidence indicated that 12 to 15 g of lactose (approximately 1 cup of milk) is well tolerated by most adults. Evidence was insufficient that lactose-reduced solution or milk with a lactose content of 0 to 2 g, compared with greater than 12 g, is effective in reducing symptoms of lactose intolerance. Evidence for probiotics, colonic adaptation, and other agents was also insufficient.

Limitations: Most studies evaluated persons with lactose malabsorption rather than lactose intolerance. Variation in enrollment criteria, outcome reporting, and the composition and dosing of studied agents precluded pooling of results and limited interpretation.

Conclusion: Most individuals with presumed lactose intolerance or malabsorption can tolerate 12 to 15 g of lactose. Additional studies are needed to determine the effectiveness of lactose intolerance treatment.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2010;152:797-803. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 20 April 2010.

Lactose, the predominant carbohydrate in milk, is a disaccharide consisting of galactose bound to glucose. Intestinal absorption of lactose requires hydrolysis to its component monosaccharides by the brush-border enzyme lactase. In most of the world, the adult population undergoes a genetically programmed decrease in lactase synthesis after weaning, resulting in lactose malabsorption. If a sufficient amount of lactose is ingested, gastrointestinal symptoms may result, including diarrhea, bloating, flatulence, and abdominal discomfort.

Problems with lactose absorption can be described in several terms. *Lactase deficiency* is defined as brush-border lactase activity that is markedly reduced relative to the activity observed in infants. *Lactose malabsorption* occurs when a substantial amount of lactose is not absorbed in the intestine. Malabsorption is commonly assessed by hydrogen breath testing. Because lactose malabsorption nearly always is attributable to lactase deficiency, the existence of lactase deficiency usually is imputed from measurements of lactose malabsorption. The term *lactose intolerance* indicates that lactose malabsorption causes gastrointestinal symptoms. Whereas lactase deficiency and lactose malabsorption can be objectively verified, demonstration of lactose intolerance relies on self-reported symptoms after lactose ingestion. These symptoms are common in the absence of lactose ingestion and are highly susceptible to the placebo effect (1). Therefore, evidence of lactose intolerance and the benefit of treatment require blinded studies using an appropriate indistinguishable control group.

Severity of lactose-induced symptoms is a function of the dose of lactose ingested and malabsorbed. The prevalence of lactose malabsorption may exceed that of lactose intolerance, because study participants with lactose malabsorption who ingested limited quantities of lactose may not have had symptoms. Determining the amount of lactose that persons with lactose malabsorption can tolerate is crucial to understanding the health implications of lactose malabsorption.

One strategy to treat lactose intolerance is to restrict consumption of dairy foods containing lactose; however, such a diet usually contains less than the daily recommended intake of calcium. Commercial products devel-

See also:

Print
Related article 792

Web-Only
Appendix Tables
Appendix Figure
CME quiz
Conversion of graphics into slides

oped for lactose-intolerant persons include lactose-reduced milk and lactase supplements taken at the time of milk ingestion. Probiotics are live microorganisms that may be added to milk to produce yogurt or similar products, or they may be taken as supplements. Another approach to treatment of lactose intolerance is to steadily increase the dietary lactose load, allowing the colon to adapt over approximately 1 week (2, 3).

We aimed to assess the maximum tolerable dose of lactose for participants with lactose malabsorption and lactose intolerance and to determine which strategies are effective in managing persons with diagnosed lactose intolerance who wish to consume lactose in quantities greater than they can tolerate. This systematic review is a summary of a report that was commissioned by the Agency for Healthcare Research and Quality (AHRQ) as background material for the Eunice Kennedy Shriver National Institute of Child Health and Human Development and Office of Medical Applications of Research of the National Institutes of Health Consensus Development Conference on lactose intolerance and health (4).

Methods

We developed and followed a standard protocol for all steps of the review process. A full technical report provides the analytic framework; detailed methods, including the literature search strategies; and results for the 5 original key questions (4).

Key Questions

This evidence review addresses 2 of the 5 original key questions developed for the Consensus Development Conference on lactose intolerance and health.

1. What amount of daily lactose intake is tolerable in participants with diagnosed lactose intolerance?

2. What strategies are effective in managing individuals with diagnosed lactose intolerance?

Data Sources and Selection

We searched several databases, including MEDLINE via PubMed and Ovid, the Cochrane Central Register of Controlled Trials, BIOSIS Previews, Biological Abstracts, Global Health, Food Science and Technology Abstracts, and the Commonwealth Agricultural Bureau International database, to find studies published in English since 1967 through November 2009. Reference lists of retrieved articles were also searched.

Study Selection

Three investigators independently determined study eligibility on the basis of recommendations from our content expert. We included randomized trials that enrolled participants older than 4 years with presumed lactose intolerance or malabsorption. Most of the eligible studies that assessed treatment strategies were double-blind. In the few single-blind studies, the taste and texture of the test substance versus placebo were not masked, or it was unclear or not stated whether participants were adequately blinded to assignment. In such cases, we included studies in which the participants may have been able to distinguish among various agents but either did not know the study hypothesis or were masked to a sufficient number of formulations (if multiple agents were tested) that it would be unlikely to bias response.

We excluded studies of persons with the irritable bowel syndrome and other probable causes of acute gastrointestinal symptoms (for example, infectious agents, antibiotics, or inflammatory bowel disease). Studies that evaluated symptomatic response to single or multiple doses of lactose were included. Lactose-reduced milk and lactase supplements; probiotics; incremental lactose loads for colonic adaptation; and other dietary strategies were evaluated. Comparison groups could include placebo, usual care, no active treatment, or active control. We analyzed all eligible studies regardless of duration of follow-up.

Data Extraction and Assessment of the Methodological Quality of Individual Studies

Three investigators independently extracted data on study and population characteristics, interventions, and efficacy outcomes. Efficacy outcomes included the frequency and severity of specific gastrointestinal symptoms, such as abdominal pain, diarrhea, nausea, flatulence, and bloating. We rated study quality by using the following criteria: adequate allocation concealment, based on the approach by Schulz and Grimes (5); blinding methods (participant, investigator, or outcome assessor); analysis by the intention-to-treat principle; and losses to follow-up. The quality of the overall evidence was rated by the investigators according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) group criteria (6); on the basis of 4 domains (risk of bias, consistency, directness, and precision), the level of evidence was ranked as high, moderate, low, or insufficient.

Data Synthesis and Analysis

We synthesized the results by using the exact definitions that the authors used for lactose intolerance and malabsorption. Outcome reporting varied considerably across and within studies. For maximum tolerable doses of lactose, we devised a simple scoring system to summarize study results: – = no symptoms; ± = trivial symptoms (defined as 1 symptom reported that was ≤20% of the maximum score); + = minor symptoms (defined as ≥1 symptom that was 20% to 35% of the maximum score); and ++ = severe symptoms (≥2 symptoms reported, of which ≥1 was >35% of the maximum score). If studies did not report adequate detail on symptom scores, we estimated the summary symptom scores on the basis of the available data. Data could not be pooled because of heterogeneity in the inclusion criteria for intervention participants and control participants, means of delivering lactose, doses and formulations of lactose, timing of administration

and outcome measurement, and criteria for assessing symptoms.

Role of the Funding Source

The AHRQ suggested the initial questions and provided copyright release for this manuscript. The funding source had no role in the literature search, data analysis, conduct of the study, preparation of the review, or interpretation of the results. The AHRQ reviewed and approved the submitted manuscript without revisions.

Results

The details of our search strategy are presented in the Methods section and in the **Appendix Figure** (available at www.annals.org). Thirty-six unique randomized studies met our inclusion criteria (7–42); details of the individual studies are summarized in the full technical report (4). **Appendix Table 1** (available at www.annals.org) summarizes the overall characteristics of included studies.

Lactase- or Lactose-Hydrolyzed Milk Supplements or Lactose-Reduced Milk

Twenty-six studies evaluated lactase- or lactose-hydrolyzed milk supplements or lactose-reduced milk. The mean age of enrolled participants was 37 years. Six trials (8, 16, 20, 26, 27, 31) included children or adolescents. In the 19 studies that reported ethnicity (8, 10, 12, 14–16, 18, 20–22, 25–32), 40% of individuals were white, 30% were Hispanic, 20% were black, and 9% were Asian. Nineteen studies used commercial lactase products or hydrolyzed milk (7, 8, 10–12, 15–21, 23, 24, 28, 31, 32), 2 used milk products with lactose removed by ultrafiltration or chromatography (14, 22), and 5 assessed nonlactose solutions (9, 25–27, 29). Participants in 18 studies reported abdominal symptoms compatible with lactose malabsorption before study entry (7–17, 20, 22–25, 28, 32). In 10 studies (17–19, 21, 26, 27, 29–32), abdominal symptoms were not required for study participation (diagnosis was based solely on biochemical diagnosis) or participants were not reported to experience symptoms after ingestion of lactose. Lactose malabsorption was diagnosed by lactose tolerance testing with the hydrogen breath test in 11 studies (7, 8, 10, 12, 14–18, 29) and blood glucose testing in 13 studies (9, 11, 19, 20, 23–28, 30, 32).

Of the 18 studies that enrolled individuals with symptoms compatible with lactose intolerance, 14 (7, 10–13, 16, 17, 20, 22–25, 28, 32) used lactose doses greater than 12 g, similar to the lactose content of 1 cup of milk. Hydrolyzed lactose doses typically ranged from 0 to 2 g. In most studies, the lactose dose was consumed in a single serving. Lactose was administered over multiple intervals per day for at least part of the study in 6 trials (10, 12, 13, 19, 24, 28). One study encompassed 2 trials that tested the lactase supplements Lactodigest (Thompson Medical Company, New York, New York), DairyEase (Glenbrook Laboratories, New York, New York), and Lactaid (Lactaid, Pleasantville, New Jersey) (17), whereas the remaining 25 studies reported on milk that was lactose-reduced or hydrolyzed by adding a lactase enzyme, such as β-galactosidase.

Maximum Tolerable Dose of Lactose

Among the 21 studies that specifically evaluated tolerance to varying doses of lactose, we found moderate evidence that increasing doses of lactose produce symptoms among persons with diagnosed lactose malabsorption, with or without self-reported symptoms, and the tolerable dose may differ if lactose is consumed with versus without other nutrients (**Appendix Tables 2** and **3**, available at www.annals.org). Most studies indicated that persons with lactose intolerance or malabsorption could ingest 12 g of lactose as a single dose with no or minor symptoms when lactose or milk was administered as a single test dose without other nutrients (**Appendix Table 3**), and doses of 15 to 18 g seemed to be well tolerated when given as a single test dose with other nutrients. As the dose was increased above 18 g, intolerance became more prominent, with single doses of 24 g usually yielding substantial symptoms. Consumption of 50 g of lactose induced symptoms in most individuals.

Efficacy of Lactose-Reduced and Hydrolyzed Formulations and Lactase

We examined the strategy of consuming lactose-reduced and hydrolyzed formulations in an attempt to provide data that will inform persons who wish to consume milk and milk products that contain more lactose than they can usually tolerate. Among 26 articles representing 28 unique trials (7–32), we found insufficient evidence that use of lactase- or lactose-reduced milk was effective in reducing symptoms of lactose intolerance compared with control participants given lactose (**Table**). The quality of the studies was low, with very few studies reporting adequate allocation concealment. Studies were typically small, and reporting of symptoms was variable or not done: composite scores of 4 to 5 symptoms or individual symptoms, such as abdominal pain, diarrhea, bloating, and flatulence, were reported, either as means or proportions and without validated assessment of a minimal clinically important difference.

Seven studies, representing 9 comparisons that enrolled individuals with symptoms compatible with lactose intolerance (7, 9, 14, 16, 22, 25, 32), had inconsistent results in reduced overall symptom scores with lactose-reduced preparations compared with control preparations. None of the 4 studies with control administration of up to 12 g of lactose (9, 14, 22, 25) reported a significant improvement in overall symptoms. As reported earlier, lactose doses of 12 g or less were well tolerated and produced minimal or no symptoms. Only 2 of 5 trials (7, 22) reported significant reductions in overall symptoms with

Table. **Evidence of the Effectiveness of Clinical Interventions for the Treatment of Lactose Intolerance**

Clinical Intervention	RCTs (Participants With Lactose Intolerance), *n (n)**	Level of Evidence	Conclusions
Lactose-reduced or hydrolyzed milk	26 (741)	Insufficient	*Overall symptom scores:* Lactose-reduced or hydrolyzed milk did not consistently reduce gastrointestinal symptoms (abdominal pain, diarrhea, and flatulence) associated with lactose intolerance compared with control participants who were given lactose. Only 2 of 5 trials with participants who self-reported symptoms before study enrollment reported statistically significant reductions in overall symptoms with lactose-reduced or hydrolyzed milk compared with control participants given more than 12 g of lactose. The clinical significance of any reported changes is not known. *Abdominal discomfort:* Lactose-reduced or hydrolyzed milk did not consistently reduce abdominal discomfort. Five of 9 trials in which participants self-reported symptoms before study enrollment reported statistically significant reductions in abdominal discomfort with lactose-reduced or hydrolyzed milk compared with control participants given more than 12 g of lactose. The clinical significance of any reported changes is not known. *Diarrhea:* Lactose-reduced or hydrolyzed milk did not consistently reduce diarrhea. Only 2 of 8 trials with participants who self-reported symptoms before study enrollment reported statistically significant reductions in diarrhea or loose stools with lactose-reduced or hydrolyzed milk compared with control participants given more than 12 g of lactose. The clinical significance of any reported changes is not known.
Lactase supplements taken with milk	2 (31)	Insufficient	Lactase supplements were no more effective than placebo in reducing gastrointestinal symptoms in 1 small trial of individuals who self-reported symptoms before enrollment. Lactase supplements were more effective than placebo in reducing symptoms in 1 small trial of individuals without self-reported symptoms before study enrollment.
Probiotics	7 (105)	Insufficient	Probiotics, including yogurts, did not consistently reduce gastrointestinal symptoms compared with control participants given lactose. Milk containing *Lactobacillus acidophilus* was no more effective than regular milk in reducing symptoms in the only trial of individuals with self-reported symptoms before study enrollment.
Colonic adaptation	2 (66)	Insufficient	Colonic adaptation was no more effective in reducing gastrointestinal symptoms compared with control participants given lactose. One trial reported improvement in flatulence after lactose feeding compared with dextrose feeding, but reduction in abdominal pain and diarrhea did not differ between groups. The second trial reported that the overall clinical score and individual symptom scores were not different between the lactose and sucrose groups.
Rifaximin	1 (32)	Insufficient	Rifaximin statistically significantly reduced gastrointestinal symptoms compared with baseline levels, but no direct comparison with placebo was reported and the study did not use intention-to-treat analysis. The clinical significance of any reported changes is not known.

RCT = randomized, controlled trial.
* Some trials also contained lactose-tolerant control participants.

lactose-reduced or hydrolyzed milk compared with control participants given more than 12 g of lactose (**Table**).

Probiotics

Six crossover (34–39) and 1 parallel-group (33) randomized trials were included (**Appendix Table 1**). The inclusion criteria and the type, source, and concentration of yogurt and probiotics studied varied, and no 2 studies studied the same agent. The trials were small, enrolling 9 to 28 persons. Four trials assessed strains of *Lactobacillus acidophilus*, *L. bulgaricus*, or *Bifidobacterium longum* added to milk before consumption (34, 36, 38, 39). Three studies evaluated yogurts (33, 37, 38). Lactose malabsorption was diagnosed by hydrogen breath testing in all studies.

We found insufficient evidence to determine the effectiveness of yogurt or probiotics to improve symptoms of lactose intolerance (**Table**). Only 1 study (39) noted that the enrolled participants reported symptoms compatible with lactose malabsorption before study entry. The investigators reported no difference in symptom score in groups given milk or milk containing unfermented *L. acidophilus*. In the remaining studies, study entry was based solely on results of hydrogen breath tests, and participants were not reported to experience symptoms after ingestion of lactose, severely limiting applicability of the findings to treatment of participants with symptoms of lactose intolerance.

Incremental Lactose for Colonic Adaptation

Two studies, a U.S. crossover trial (41) and a French parallel trial (42), met our inclusion criteria (**Appendix Table 1**). We found insufficient evidence to support the role of incremental doses of lactose to treat symptoms of lactose intolerance (**Table**). Hertzler and Savaiano (41) enrolled 20 volunteers with lactose intolerance and randomly assigned them to receive either dextrose or lactose in a blinded manner for 10 days; participants then crossed over for days 12 through 21. The daily dose of lactose and dextrose was 0.6 g/kg of body weight, which was increased by 0.2 g/kg daily to a maximum of 1 g/kg daily (approximately 42 to 70 g of lactose daily for an average 70-kg adult). Participants were given a lactose challenge on days 11 and 22. Improvement in flatulence was reported after lactose feeding compared with dextrose feeding, whereas occurrence of abdominal pain and diarrhea did not differ.

Participants were unique in that although they experienced lactose malabsorption, average symptom scores were low (1 on a scale of 0 to 5) even with the highest doses of lactose (70 g—an amount greater than that in 1 quart of milk) and were very similar to scores seen with dextrose. In a study of 46 Asian persons with lactose intolerance, Briet and colleagues (42) evaluated colonic adaptation to 15 days of lactose administration compared with 15 days of sucrose administration. The end-of-study overall clinical score and individual symptom scores did not differ between the lactose and sucrose groups. When the investigators compared end-of-study results with baseline values, overall clinical scores and mean scores for abdominal pain and other symptoms improved to a similar extent between the lactose and sucrose groups, suggesting a placebo response.

Other Strategies

We found insufficient evidence regarding the antibiotic rifaximin for treatment of lactose intolerance. One small study (40) evaluated 40 Italian persons. Participants were not required to have symptoms compatible with lactose intolerance before enrollment. Sixteen participants were randomly assigned to 10 days of treatment with rifaximin, 800 mg/d; 16 were assigned to a 40-day lactose-free diet; and 8 were given placebo for 10 days. The study showed statistically significant reductions in total symptom scores after rifaximin treatment and lactose-free diet (but not placebo) compared with baseline. No direct comparisons between groups were reported, and analysis of results was provided for only 14 rifaximin recipients, 13 lactose-free diet recipients, and 5 placebo recipients. The entry criteria, lack of comparison with placebo, lack of intention-to-treat analysis, and unclear clinical significance of the change in score severely limit the interpretation of the findings.

Discussion

Because tolerance to lactose is enhanced when lactose is ingested with other nutrients, we divided data into studies in which lactose or milk was ingested in the fasting state versus with other nutrients. When lactose or milk was ingested with other foods, symptoms did not increase significantly compared with control participants if the lactose dose was less than 15 g (the quantity in 10 ounces of milk). A significant increase in symptoms was noted with doses greater than 20 g, and substantial symptoms occurred in most studies testing 50 g. When lactose or milk was given to fasting participants, a statistically significant but minor increase in symptoms was reported for lactose doses as low as 12 g, with greater symptoms noted with increasing lactose doses. A few studies suggested that lactose is better tolerated when consumed multiple times during the day as opposed to a single dosage (10, 41).

We found no significant reduction in symptoms with lactose-hydrolyzed products for lactose doses of 12 g or less, as would be predicted from the failure to observe symptoms with 12-g doses. At lactose doses greater than 12 g, studies showed inconsistent benefit of lactose-hydrolyzed products. Evidence on yogurt, probiotics, rifaximin, and colonic adaptation as interventions was insufficient to reliably assess their efficacy. It seems axiomatic that lactose-exclusion diets should be beneficial in terms of symptoms of lactose intolerance. However, we identified no studies addressing the long-term effect (>1 month) of lactose-exclusion diets on gastrointestinal symptoms in the general population, vegans, or persons with diagnosed lactose malabsorption or lactose intolerance.

The most important limitation of these studies was enrollment criteria. Meaningful assessment of the influence of an intervention on lactose-induced symptoms requires that the test participants actually have lactose-induced symptoms—that is, they have lactose intolerance. For most studies, the enrollment criterion was a positive result on testing for lactose malabsorption. Therefore, most of the data we evaluated are applicable to participants with lactose malabsorption rather than lactose intolerance, as the latter diagnosis requires blinded studies showing that a given person has greater symptoms with lactose than with an indistinguishable control. Additional limitations included that most studies evaluated individuals over a single 8-hour recording period and fed participants a test dose, typically in the absence of other nutrients. As a result, it is difficult to generalize findings to persons with chronic relapsing–remitting problems and a constellation of symptoms who ingest a wide variety of lactose-containing products in the presence of other nutrients. Studies were small, heterogeneous in population and setting, disparate in reporting of overall and individual symptoms, and generally of low quality. Results could not be pooled, and generalized estimates of clinically relevant treatment effects could not be determined.

Our findings may aid clinicians in the diagnosis and management of patients presenting with symptoms suggesting lactose intolerance. The patient's daily ingestion of lactose should be assessed. Lactose intolerance is excluded as the cause of symptoms in persons who ingest less than 15 g of lactose with meals. A hydrogen breath test may be useful in participants who ingest (or wish to ingest) multiple servings of lactose-containing products per day. A negative breath test result excludes lactose malabsorption as the cause of symptoms, and a positive result indicates that symptoms may be attributable to lactose. The next step is to determine whether symptoms improve with a dairy-free diet, while keeping in mind that dietary manipulation has a strong placebo effect. Patients whose symptoms improve on a lactose-free diet can be instructed to ingest limited quantities (1 serving daily) of lactose-containing products, gradually increasing lactose intake until symptoms develop. In the absence of large amounts of milk consumption (for example, 1 quart of milk in a single dose), such symptoms as severe diarrhea or abdominal pain are very unlikely to be attributable solely to lactose intolerance.

We recommend conducting rigorous double-blind, placebo-controlled studies to evaluate treatment effectiveness in persons with well-documented lactose intolerance. Studies should use standardized diagnostic measures, interventions, and outcome reporting, with emphasis on clinically important differences. Rigorous long-term safety data on these interventions, such as probiotics, are also needed.

From University of Minnesota and Minneapolis Veterans Affairs Medical Center; Center for Chronic Disease Outcomes Research, Minneapolis Veterans Affairs Medical Center; Minnesota Evidence-based Practice Center; and University of Minnesota School of Public Health, Minneapolis, Minnesota.

Disclaimer: The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ or the Department of Veterans Affairs. No statement in this report should be construed as an official position of AHRQ, the U.S. Department of Health and Human Services, or the Department of Veterans Affairs.

Grant Support: This research was conducted by the Minnesota Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality, Rockville, Maryland (contract HHSA 290-2007-10064-I).

Potential Conflicts of Interest: Dr. Shaukat: *Grants received/pending (money to institution) and support for travel to meetings for the study or otherwise:* AHRQ. Dr. Levitt: *Grants received/pending, consulting fee or honorarium, support for travel to meetings for the study or otherwise, and payment for writing or reviewing the manuscript:* NIH. Dr. Taylor: *Grants received/pending:* AHRQ. Dr. Kane: *Grants received/pending (money to institution):* AHRQ; *Consultancy:* United Healthgroup, SCAN Health Plan, Cleveland Clinic, Medtronic. Dr. Wilt: *Grants received/pending:* AHRQ; *Support for travel to meetings for the study or otherwise and travel/accommodation expenses covered or reimbursed:* Reimbursement for travel and per diem for consensus conference meetings in Washington, DC. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-0181.

Requests for Single Reprints: Timothy J. Wilt, MD, MPH, Center for Chronic Disease Outcomes Research (111-0), Minneapolis Veterans Affairs Medical Center, One Veterans Drive, Minneapolis, MN 55417; e-mail, tim.wilt@med.va.gov.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Wampold BE, Imel ZE, Minami T.** The story of placebo effects in medicine: evidence in context. J Clin Psychol. 2007;63:379-90; discussion 405-8. [PMID: 17279527]

2. **Scrimshaw NS, Murray EB.** The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. Am J Clin Nutr. 1988; 48:1079-159. [PMID: 3140651]

3. **Perman JA, Modler S, Olson AC.** Role of pH in production of hydrogen from carbohydrates by colonic bacterial flora. Studies in vivo and in vitro. J Clin Invest. 1981;67:643-50. [PMID: 7193687]

4. **Wilt TJ, Shaukat A, Shamliyan T, Taylor BC, MacDonald R, Tacklind J, et al.** Lactose intolerance and health. Evidence Report/Technology Assessment no. 192. (Prepared by the Minnesota Evidence-based Practice Center under contract HHSA 290-2007-10064-I.) Rockville, MD: Agency for Healthcare Research and Quality; February 2010. AHRQ publication no. 10-E004. Accessed at www.ahrq.gov/downloads/pub/evidence/pdf/lactoseint/lactint.pdf on 10 May 2010.

5. **Schulz KF, Grimes DA.** Allocation concealment in randomised trials: defending against deciphering. Lancet. 2002;359:614-8. [PMID: 11867132]

6. **Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al; GRADE Working Group.** Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490. [PMID: 15205295]

7. **Montalto M, Nucera G, Santoro L, Curigliano V, Vastola M, Covino M, et al.** Effect of exogenous beta-galactosidase in patients with lactose malabsorption and intolerance: a crossover double-blind placebo-controlled study. Eur J Clin Nutr. 2005;59:489-93. [PMID: 15674309]

8. **Gremse DA, Greer AS, Vacik J, DiPalma JA.** Abdominal pain associated with lactose ingestion in children with lactose intolerance. Clin Pediatr (Phila). 2003; 42:341-5. [PMID: 12800728]

9. **Järvinen RM, Loukaskorpi M, Uusitupa MI.** Tolerance of symptomatic lactose malabsorbers to lactose in milk chocolate. Eur J Clin Nutr. 2003;57:701-5. [PMID: 12771971]

10. **Suarez FL, Adshead J, Furne JK, Levitt MD.** Lactose maldigestion is not an impediment to the intake of 1500 mg calcium daily as dairy products. Am J Clin Nutr. 1998;68:1118-22. [PMID: 9808231]

11. **Xenos K, Kyroudis S, Anagnostidis A, Papastathopoulos P.** Treatment of lactose intolerance with exogenous beta-D-galactosidase in pellet form. Eur J Drug Metab Pharmacokinet. 1998;23:350-5. [PMID: 9725505]

12. **Suarez FL, Savaiano D, Arbisi P, Levitt MD.** Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. Am J Clin Nutr. 1997;65:1502-6. [PMID: 9129483]

13. **Vesa TH, Lember M, Korpela R.** Milk fat does not affect the symptoms of lactose intolerance. Eur J Clin Nutr. 1997;51:633-6. [PMID: 9306091]

14. **Vesa TH, Korpela RA, Sahi T.** Tolerance to small amounts of lactose in lactose maldigesters. Am J Clin Nutr. 1996;64:197-201. [PMID: 8694020]

15. **Suarez FL, Savaiano DA, Levitt MD.** A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. N Engl J Med. 1995;333:1-4. [PMID: 7776987]

16. **Johnson AO, Semenya JG, Buchowski MS, Enwonwu CO, Scrimshaw NS.** Correlation of lactose maldigestion, lactose intolerance, and milk intolerance. Am J Clin Nutr. 1993;57:399-401. [PMID: 8438774]

17. **Lin MY, Dipalma JA, Martini MC, Gross CJ, Harlander SK, Savaiano DA.** Comparative effects of exogenous lactase (beta-galactosidase) preparations on in vivo lactose digestion. Dig Dis Sci. 1993;38:2022-7. [PMID: 8223076]

18. **Brand JC, Holt S.** Relative effectiveness of milks with reduced amounts of lactose in alleviating milk intolerance. Am J Clin Nutr. 1991;54:148-51. [PMID: 2058576]

19. **Cavalli-Sforza LT, Strata A.** Double-blind study on the tolerance of four types of milk in lactose malabsorbers and absorbers. Hum Nutr Clin Nutr. 1987; 41:19-30. [PMID: 3570859]

20. **Nielsen OH, Schiøtz PO, Rasmussen SN, Krasilnikoff PA.** Calcium absorption and acceptance of low-lactose milk among children with primary lactase deficiency. J Pediatr Gastroenterol Nutr. 1984;3:219-23. [PMID: 6368790]

21. **Rosado JL, Solomons NW, Lisker R, Bourges H.** Enzyme replacement therapy for primary adult lactase deficiency. Effective reduction of lactose malabsorption and milk intolerance by direct addition of beta-galactosidase to milk at mealtime. Gastroenterology. 1984;87:1072-82. [PMID: 6434367]

22. **Lybeck Sørensen K, Vergara Meersohn M, Sonne J, Larsen L, Edelsten D, Gudmand-Høyer E.** A new type of low-lactose milk. Tolerance by lactose malabsorbers and evaluation of protein nutritional value. Scand J Gastroenterol. 1983;18:1063-8. [PMID: 6424228]

23. **Rask Pedersen E, Jensen BH, Jensen HJ, Keldsbo IL, Hylander Møller E, Nørby Rasmussen S.** Lactose malabsorption and tolerance of lactose-hydrolyzed milk. A double-blind controlled crossover study. Scand J Gastroenterol. 1982;17: 861-4. [PMID: 6818684]

24. **Reasoner J, Maculan TP, Rand AG, Thayer WR Jr.** Clinical studies with low-lactose milk. Am J Clin Nutr. 1981;34:54-60. [PMID: 6893787]

25. **Unger M, Scrimshaw NS.** Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. I. Initial experience with a double-blind procedure. Nutr Res. 1981;1:227-33.

26. **Haverberg L, Kwon PH, Scrimshaw NS.** Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. I. Initial experience with a double-blind procedure. Am J Clin Nutr. 1980;33:17-21. [PMID: 7188826]

27. **Kwon PH Jr, Rorick MH, Scrimshaw NS.** Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. II. Improvement of a double-blind test. Am J Clin Nutr. 1980;33:22-6. [PMID: 7188827]
28. **Cheng AH, Brunser O, Espinoza J, Fones HL, Monckeberg F, Chichester CO, et al.** Long-term acceptance of low-lactose milk. Am J Clin Nutr. 1979;32:1989-93. [PMID: 114042]
29. **Rorick MH, Scrimshaw NS.** Comparative tolerance of elderly from differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks: a double-blind study. J Gerontol. 1979;34:191-6. [PMID: 374454]
30. **Lisker R, Aguilar L.** Double blind study of milk lactose intolerance. Gastroenterology. 1978;74:1283-5. [PMID: 348553]
31. **Paige DM, Bayless TM, Huang SS, Wexler R.** Lactose hydrolyzed milk. Am J Clin Nutr. 1975;28:818-22. [PMID: 1173737]
32. **Jones DV, Latham MC, Kosikowski FV, Woodward G.** Symptom response to lactose-reduced milk in lactose-intolerant adults. Am J Clin Nutr. 1976;29:633-8. [PMID: 946937]
33. **Lerebours E, N'Djitoyap Ndam C, Lavoine A, Hellot MF, Antoine JM, Colin R.** Yogurt and fermented-then-pasteurized milk: effects of short-term and long-term ingestion on lactose absorption and mucosal lactase activity in lactase-deficient subjects. Am J Clin Nutr. 1989;49:823-7. [PMID: 2497632]
34. **Lin MY, Yen CL, Chen SH.** Management of lactose maldigestion by consuming milk containing lactobacilli. Dig Dis Sci. 1998;43:133-7. [PMID: 9508514]
35. **Mustapha A, Jiang T, Savaiano DA.** Improvement of lactose digestion by humans following ingestion of unfermented acidophilus milk: influence of bile sensitivity, lactose transport, and acid tolerance of *Lactobacillus acidophilus.* J Dairy Sci. 1997;80:1537-45. [PMID: 9276791]
36. **Jiang T, Mustapha A, Savaiano DA.** Improvement of lactose digestion in humans by ingestion of unfermented milk containing *Bifidobacterium longum.* J Dairy Sci. 1996;79:750-7. [PMID: 8792277]
37. **Martini MC, Smith DE, Savaiano DA.** Lactose digestion from flavored and frozen yogurts, ice milk, and ice cream by lactase-deficient persons. Am J Clin Nutr. 1987;46:636-40. [PMID: 3116836]
38. **Savaiano DA, AbouElAnouar A, Smith DE, Levitt MD.** Lactose malabsorption from yogurt, pasteurized yogurt, sweet acidophilus milk, and cultured milk in lactase-deficient individuals. Am J Clin Nutr. 1984;40:1219-23. [PMID: 6439026]
39. **Newcomer AD, Park HS, O'Brien PC, McGill DB.** Response of patients with irritable bowel syndrome and lactase deficiency using unfermented acidophilus milk. Am J Clin Nutr. 1983;38:257-63. [PMID: 6410897]
40. **Cappello G, Marzio L.** Rifaximin in patients with lactose intolerance. Dig Liver Dis. 2005;37:316-9. [PMID: 15843080]
41. **Hertzler SR, Savaiano DA.** Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. Am J Clin Nutr. 1996;64:232-6. [PMID: 8694025]
42. **Briet F, Pochart P, Marteau P, Flourie B, Arrigoni E, Rambaud JC.** Improved clinical tolerance to chronic lactose ingestion in subjects with lactose intolerance: a placebo effect? Gut. 1997;41:632-5. [PMID: 9414969]

CME Credit

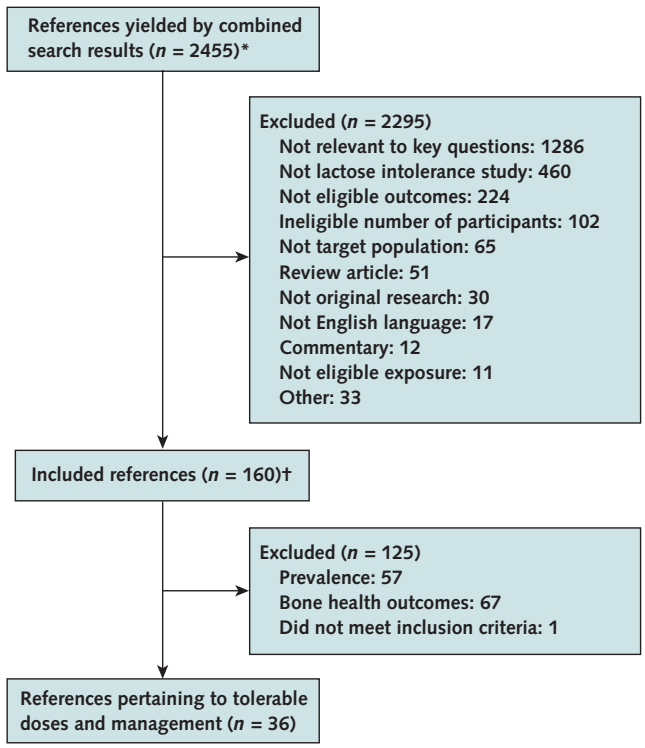
Readers can get CME credit for the following: 1) questions from the ACP's Medical Knowledge Self-Assessment Program (MKSAP) related to In the Clinic articles that are published in the first issue of every month, and 2) designated articles in each issue. To access CME questions, click on the CME option under an article's title on the table of contents at www.annals.org. Subscribers may take the tests free of charge. For a nominal fee, nonsubscribers can purchase tokens electronically that enable them to take the CME quizzes.

Reviewers who provide timely, high-quality reviews also may get CME credit.

Current Author Addresses: Dr. Shaukat: Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota Medical School, 420 Delaware Street SE (MMC 36), Minneapolis, MN 55455.
Dr. Levitt: Department of Medicine, University of Minnesota and Veterans Affairs Medical Center, One Veterans Drive, Minneapolis, MN 55417.
Drs. Taylor and Wilt and Mr. MacDonald: Center for Chronic Disease Outcomes Research, Minneapolis Veterans Affairs Medical Center (111-0), One Veterans Drive, Minneapolis, MN 55417.
Drs. Shamliyan and Kane: Division of Health Policy and Management, University of Minnesota School of Public Health, D351 Mayo (MMC 197), 420 Delaware Street SE, Minneapolis, MN 55455.

Author Contributions: Conception and design: A. Shaukat, M.D. Levitt, T.A. Shamliyan, R.L. Kane, T.J. Wilt.
Analysis and interpretation of the data: A. Shaukat, M.D. Levitt, B.C. Taylor, R. MacDonald, R.L. Kane, T.J. Wilt.
Drafting of the article: A. Shaukat, M.D. Levitt, R. MacDonald.
Critical revision of the article for important intellectual content: A. Shaukat, M.D. Levitt, B.C. Taylor, T.A. Shamliyan, R.L. Kane, T.J. Wilt.
Final approval of the article: A. Shaukat, M.D. Levitt, B.C. Taylor, R. MacDonald, T.A. Shamliyan, R.L. Kane, T.J. Wilt.
Provision of study materials or patients: R. MacDonald.
Statistical expertise: B.C. Taylor, T.J. Wilt.
Obtaining of funding: R.L. Kane, T.J. Wilt.
Administrative, technical, or logistic support: R. MacDonald, R.L. Kane.
Collection and assembly of data: A. Shaukat, M.D. Levitt, B.C. Taylor, R. MacDonald, T.A. Shamliyan.

Appendix Figure. **Study flow diagram.**



* Searches of MEDLINE via PubMed and Ovid and the Cochrane Central Register of Controlled Trials were combined, and duplicate listings were removed.
† The total number of included references is not a sum of eligible references for each question because of overlapping eligibility.

Appendix Table 1. Summary of Study Characteristics

Characteristic	Value	Studies Reporting, *n*
Commercially available lactase- or lactose-hydrolyzed milk or nonlactose solutions		
All studies, *n*	6–150	28 (26 publications)
Lactose-tolerant control participants, *n*	5–64	14
Studies in which participants were not noted to be symptomatic at baseline, symptoms were not required for study inclusion, or unclear, *n*	6–150	10
Studies with children, *n*	9–150	6 (4 exclusive)*
Mean age (range of means), *y*	37 (10–77)	19
Mean proportion of women (range), %	56 (0–93)	23
Mean race/ethnicity proportions (range), %		
White	40 (0–100)	19 (1 exclusive)*
Hispanic†	30 (0–100)	19 (3 exclusive)*
Black	20 (0–100)	19 (2 exclusive)*
Asian	9 (0–100)	19 (1 exclusive)*
Studies conducted in the United States, *n*	11–110	15
Method of diagnosis, *n*		
Hydrogen breath test	11	
Blood sugar test	13	
Urine galactose test	1	
Double-blind study, *n*‡	24	
Single-blind study, *n*	4	
Multiple-dose studies§	6	
Prebiotics or probiotics		
All studies, *n*	9–28	7
Lactose-tolerant control participants, *n*	10	1
Studies in which participants were not noted to be symptomatic at baseline, symptoms were not required for study inclusion, or unclear, *n*	9–28	6
Mean age (range of means), *y*	1 trial reported mean age; for 6 studies, age ranged from 18 to 50 y	7
Mean proportion of women (range), %	24 (0–53; 2 men only)	4
Mean race/ethnicity proportions (range), %		
White	45 (0–100)	4 (2 exclusive)*
Black	24 (0–100)	4 (1 exclusive)*
Asian	30 (0–100)	4 (1 exclusive)*
Studies conducted in the United States, *n*	9–28	5
Method of diagnosis: hydrogen breath test	28	
Double-blind study, *n*‡	5	
Single-blind or blinding status unclear, *n*	2	
Colonic adaptation studies		
All studies, *n*	20–46	2
Studies in which participants were not noted to be symptomatic at baseline, symptoms were not required for study inclusion, or unclear, *n*	1	
Mean age (range of means), *y*	32 (30–33)	2
Mean proportion of women (range), %	45 (25–54)	2
Mean race/ethnicity proportions (range), %		
Asian	91 (70–100)	2
Other	9 (0–30)	2
Studies conducted in the United States, *n*	1	
Method of diagnosis: hydrogen breath test	46	
Double-blind study, *n*‡	46	

* The number in parentheses reflects studies whose samples comprised only the age or ethnic group indicated in the row heading.
† Participants could be of any race.
‡ Some studies noted that it may not be possible to mask flavors of tests.
§ Test products were administered more than once daily.

Appendix Table 2. **Symptomatic Response of Adults With Lactose Malabsorption to Lactose Ingested With Nutrients Other Than Milk**

Study, Year (Reference)	Participants With Lactose Malabsorption, *n*	Severity of Symptoms, by Approximate Daily Lactose Dose*											
		7 g	9 g	12 g	15 g	18 g	22 g	30 g	34 g	42 g	49 g	56 g	63 g	70 g
Cheng et al, 1979 (28)	15						++							
Suarez et al, 1998 (10)	31								+					
Vesa et al, 1997 (13)	30					–								
Jones et al, 1976 (32)	16	–			–			++						
Rorick and Scrimshaw, 1979 (29)	23			–										
Suarez et al, 1997 (12)	19						–							
Suarez et al, 1995 (15)	21			–										
Hertzler and Savaiano, 1996 (41)	18									–	–	–	–	–

* – = no symptoms; + = minor symptoms; ++ = severe symptoms.

Appendix Table 3. **Symptomatic Response of Adults With Lactose Malabsorption to Lactose Ingested Without Nutrients Other Than Milk**

Study, Year (Reference)	Participants With Lactose Malabsorption, *n*	Severity of Symptoms, by Approximate Daily Lactose Dose*																		
		0 g	2 g	3 g	6 g	8 g	10 g	12 g	13 g	14 g	16 g	17 g	19 g	20 g	23 g	24 g	25 g	29 g	30 g	49 g	50 g	100 g
Rosado et al, 1984 (21)	25												+									
Kwon et al, 1980 (27)	45									–								+				
Cavalli-Sforza and Strata, 1986 (19)	40					±			±							+						
Reasoner et al, 1981 (24)	9																		+	++		
Rask Pedersen et al, 1982 (23)	17														+							
Lybeck Sørensen et al, 1983 (22)	35		–	–				–							–	+					++	
Johnson et al, 1993 (16)	45											+										
Jones et al, 1976 (32)	17						–										+				++	
Xenos et al, 1998 (11)	8																					++
Montalto et al, 2005 (7)	20													++								
Brand and Holt, 1991 (18)	26										+											
Hertzler and Savaiano, 1996 (41)	13	–	–		–			+						++								

* – = no symptoms; ± = trivial symptoms; + = minor symptoms; ++ = severe symptoms.