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Pediatrics 2006;118;746-752
DOI: 10.1542/peds.2005-2664

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Metoclopramide for the Treatment of Gastroesophageal Reflux Disease in Infants: A Systematic Review

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. Metoclopramide is a commonly used drug to treat gastroesophageal reflux disease in infants. Given its widespread use and growing concern about toxicity in this population, we conducted a systematic review of metoclopramide for the treatment of gastroesophageal reflux disease in infants.

METHODS. We performed a systematic search of PubMed and bibliographies of relevant review articles. We included cohort, case-control, and intervention studies of the efficacy, effectiveness, or toxicity of metoclopramide therapy for gastroesophageal reflux disease in infants. We excluded case reports, case series, review articles, and abstracts.

RESULTS. Twelve articles met our inclusion criteria. Of these, 11 were prospective trials, and 5 were randomized, blinded clinical trials. Study size ranged from 6 to 77 patients. Eight studies showed patient improvement with metoclopramide in at least 1 measured outcome; 1 study showed worsening symptoms with metoclopramide. Of the 5 randomized, blinded trials, 2 showed no effect of metoclopramide on any outcome, and 2 showed a significant placebo effect. Four studies commented on adverse effects of therapy, with irritability being the most frequently reported potential adverse effect of therapy. Other reported adverse effects included dystonic reactions, drowsiness, oculogyric crisis, emesis, and apnea. Among studies, there was marked heterogeneity in the patient populations, dosing, and outcomes studied. Therefore, a meta-analysis was not performed. We both agreed on a US Preventive Service Task Force rating of “poor” for the level of evidence, leading to an “inconclusive” recommendation for the safety and efficacy of metoclopramide in infants.

CONCLUSIONS. The current literature is insufficient to either support or oppose the use of metoclopramide for gastroesophageal reflux disease in infants. In the future, large blinded randomized clinical trials are needed to determine the efficacy and toxicity of metoclopramide in this population.
BOTH BENIGN AND pathologic gastroesophageal reflux disease (GERD) are extremely common in infancy. In a survey of outpatient pediatric practices, two thirds of 4-month-olds regurgitated at least daily. The incidence of GERD is higher in certain medically complicated subpopulations such as premature and neurologically impaired infants and those with congenital malformations. For example, estimates of the incidence of GERD in premature infants range from 40% to 85%. These fragile populations, however, may be at the highest risk from adverse effects of the therapy for GERD. Furthermore, although the North American Society of Pediatric Gastroenterology and Nutrition treatment guidelines emphasize the difference between gastroesophageal reflux (GER) and GERD (in which there are complications of GER), the complications of GER remain ill-defined in certain high-risk subgroups such as premature infants.

Metoclopramide has been used to treat GERD in infants for several decades. However, the recent impetus toward evidence-based prescribing in pediatric populations and reports of adverse drug reactions have spurred public discussion about the efficacy and safety profile of metoclopramide in infants and children.

In many practices, metoclopramide has become the standard of care without a rigorous approval process. Although the prevalence of metoclopramide use in infants across inpatient and outpatient settings is ill-defined, it is clear that it is commonly prescribed for infants and children. In the United States, >7 million prescriptions for metoclopramide were dispensed in 2004. In the same year, >30% of the annual outpatient visits in which metoclopramide was mentioned were in the pediatric population (aged 0–16 years). The practice patterns in the prescription of metoclopramide for GERD also vary widely. For instance, in a survey of 57 NICUs in England and Wales, 53% reported using dopamine antagonists such as metoclopramide to treat GERD in premature infants, whereas 47% did not.

Therefore, we conducted a systematic review of the literature of metoclopramide for GERD in infants aged 0 to 23 months as a supplement to the Cochrane systematic review of GERD therapies in children, which found both therapeutic benefit and increased adverse effects with metoclopramide treatment. Although the Cochrane review only included randomized trials and evaluated multiple therapies for GERD, we narrowed the scope of the research, focusing only on metoclopramide therapy for GERD, and broadened our search, accepting a broader variety of study designs in our inclusion criteria. This decision was spurred both by the paucity of randomized, controlled trials (RCTs) in infants and a desire to capture any additional reliable and valid evidence presented by cohort and case-control studies.

METHODS
We performed a PubMed search using the search terms “Reglan neonate,” “Reglan infant,” “metoclopramide neonate,” “metoclopramide infant,” “gastroesophageal reflux medication,” and “gastroesophageal reflux treatment.” The search limits included English language, humans, age group “birth to 23 months,” and publication dates 1980 to August 2005. Of the review articles identified by this search, the bibliographies of those from 1995–2005 with full-text available online were searched for additional articles that were missed by the PubMed search described above. Review articles were used only to screen for articles meeting the inclusion criteria for the study that were not identified by the PubMed search; reviews were not included in the analysis of the data.

We included only published articles in the systematic review. Study designs that met inclusion criteria were cohort studies, case-control studies, and controlled trials. We considered controls to be either a separate group of randomly assigned or nonrandomly assigned patients not receiving metoclopramide or individual patients acting as their own controls. Both blinded and nonblinded studies were included in the review. Abstracts, case reports, case series, and review articles were excluded from this analysis.

Outcomes included in the systematic review were limited to the efficacy, effectiveness, or toxicity of metoclopramide for reflux in infants. We defined efficacy as the therapeutic effect of the drug in a clinical trial and effectiveness as the benefit of the drug outside of a controlled research setting. We defined a toxicity of drug treatment as any unintended adverse consequence of the drug’s use, such as dystonic reactions and irritability. Given the difficulty of quantifying GERD in a clinically and physiologically meaningful way, we accepted studies with outcomes that included clinical symptoms, pH-probe results, gastrointestinal motility, growth, or tolerance of feeding. In trials with treatment arms that included pharmacologic interventions other than metoclopramide, such as cisapride or bethanachol, we only considered the analyses comparing metoclopramide to nonintervention or placebo therapy.

We graded the level of evidence according to the scale for strength of overall evidence used by the US Preventive Services Task Force (USPSTF). The quality and homogeneity of studies were assessed for suitability in a meta-analysis.

RESULTS
The PubMed search yielded 1284 articles. A search of 9 review article bibliographies yielded 1 additional article. By our consensus, 12 articles met the inclusion criteria. Of these, 11 were intervention trials and 1 was a cohort study.

The study sizes ranged from 6 to 77 patients, with the
Results of Blinded RCTs

Only 5 blinded randomized trials were identified by our search.\textsuperscript{11,12,18,32,34} In 1985, Hymann et al\textsuperscript{11} showed an improvement in the gastric fractional emptying rate in 10 infants during a metoclopramide period compared with a placebo period. In 1988, Hymann et al\textsuperscript{12} found a similar improvement in gastric fractional emptying rate in term and postoperative infants but not in premature infants. Tolia et al\textsuperscript{18} found no difference in the symptom scores or scintigraphy of 30 infants assessed during metoclopramide and placebo periods. In addition, these infants showed significant improvement during their placebo period compared with their baseline scores. A subgroup analysis of infants >3 months of age suggested improved weight gain during the metoclopramide period when compared with their placebo period. Tolia et al also reported pH-monitoring results; they found a significant improvement in the percent time that esophageal pH was <4 but not in the other pH parameters studied. Two randomized trials used pH-probe monitoring as their primary outcomes.\textsuperscript{32,34} Pons et al\textsuperscript{34} found no improvement in pH measurements between a metoclopramide and placebo group; because of a significant placebo effect, both the metoclopramide and placebo groups had significant improvements in several pH-probe measurements compared with their baseline studies. Bellissant et al\textsuperscript{12} also found no difference in any pH-probe parameters in separate groups of infants treated with either placebo or metoclopramide. This was the only study that reported a power calculation.

Toxicity

None of the studies that met our inclusion criteria used toxicity as a primary end point. Furthermore, the methods for surveillance of unintended effects of treatment were not described in any of the studies. Adverse effects were reported in 4 of the 12 studies.\textsuperscript{10,14,15,32} The events reported included dystonic reactions, oculogyric crisis, irritability, drowsiness, emesis, and apnea.

Leung and Lai\textsuperscript{14} reported 5 adverse events among the 32 infants in the metoclopramide group in their nonblinded trial. Two infants experienced increased drowsiness, 2 demonstrated increased irritability, and 1 infant had an acute oculogyric crisis after an accidental fourfold overdose. The intended dosing in this study was 0.125 mg/kg per dose every 6 hours. Hyams et al\textsuperscript{10} reported 4 adverse events during treatment with metoclopramide among their population of 42 infants who served as their own controls in a nonblinded trial: 3 infants in this study experienced increased irritability on metoclopramide, and 1 had dystonia. The irritability started 15 minutes after drug injection, lasted for ~2 hours, and occurred in 1 infant in each of the 3 dosing groups (0.1, 0.2, and 0.3 mg/kg per dose). A dystonic reaction occurred in 1 of the 21 infants in the 0.3 mg/kg per dose group.
### Summary of Studies Meeting Inclusion Criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MCP Dose</th>
<th>Population</th>
<th>Design</th>
<th>Outcomes: Significant Effect</th>
<th>Outcomes: No Effect Seen</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sankaran et al (1982)</td>
<td>6</td>
<td>0.1 mg/kg per d – TID</td>
<td>Preterm infants; GA 26–35 wk, postnatal age 25–70 d; history: feeding intolerance</td>
<td>Clinical trial; not randomized, not blinded; infant as own control; before and after MCP; feeding tolerance and intestinal transit studied</td>
<td>Gastric aspirate (ml/d), weight gain (g/d); intestinal transit time (h), feed volume (ml/kg per d)</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Leung and Lai (1984)</td>
<td>41</td>
<td>0.5 mg/kg per d – QID</td>
<td>Age 21–125 d (mean: 160); weight 2.73–17.2 kg (mean: 6.35); history: regurgitation, FTT, and/or apnea; several infants with prematurity, cardiac, gastrointestinal, and neurologic anomalies included</td>
<td>Clinical trial: randomized (9 in control group, 32 in treatment group); not blinded; symptoms recorded</td>
<td>None reported</td>
<td>None reported</td>
<td>2 drowsiness; 2 irritability; 1 oculogyric crisis</td>
</tr>
<tr>
<td>Hyman et al (1985)</td>
<td>10</td>
<td>1 mg/kg, single dose</td>
<td>Age 3–16 mo (mean: 6); weight 2.2–9.4 kg (mean: 5.6); history: recurrent vomiting, postoperative ileus, gastroparesis of prematurity, or intestinal pseudo obstruction; 2 patients on parental nutrition, GA not reported</td>
<td>Clinical trial; randomized, blinded; infant as own control; before MCP; pH probe study</td>
<td>Gastric fractional emptying rate (ml/min); gastric fluid output (ml/min)</td>
<td>Gastric acid secretion</td>
<td>None reported</td>
</tr>
<tr>
<td>Hyams et al (1986)</td>
<td>42</td>
<td>0.1 mg/kg per dose</td>
<td>(n = 10), 0.2 mg/kg per dose (n = 11), or 0.3 mg/kg per dose (n = 21) every 4 h × 3 doses</td>
<td>Clinical trial; not randomized, not blinded; infant as own control before MCP; pH probe study</td>
<td>0–2 h post–dextrose meal in 0.3 mg/kg per dose group; % time esophageal pH &lt;4 and mean acid clearance time (min/episode)</td>
<td>All pH-probe results at 0.1 and 0.2 mg/kg per dose; at 0.3 mg/kg all pH-probe parameters postformula and 2–4 h post–glucose meal</td>
<td>3 instability; 1 dystonic reaction</td>
</tr>
<tr>
<td>Rode et al (1987)</td>
<td>18</td>
<td>0.2 mg/kg per dose every 6 h</td>
<td>Mean age 6.5 mo (SD: ±4.02); mean weight 5.9 kg (SD: ±2.2); history: did not respond to medical therapy or admitted for complications of GER; GA not reported</td>
<td>Clinical trial; not randomized, not blinded; infant as own control before MCP; pH probe study</td>
<td>No of reflux events; % time pH &lt;4; No of refluxes &gt;5 min</td>
<td>Longest reflux (min); esophageal clearance time (min); ambient pH of lower esophagus</td>
<td>None reported</td>
</tr>
<tr>
<td>Machida et al (1988)</td>
<td>28</td>
<td>0.125 mg/kg per dose QID</td>
<td>Mean 9 mo old (SD: ±11 mo); history: regurgitation, apnea, FTT, GA not reported</td>
<td>Clinical trial; not randomized, not blinded; infant as own control before MCP; pH probe study</td>
<td>No reflux events in 24 h (more frequent with Reglan)</td>
<td>% time pH &lt;4; No of episodes &gt;5 min; longest episode</td>
<td>3 instability</td>
</tr>
<tr>
<td>Hyman et al (1988)</td>
<td>22</td>
<td>1 mg/kg, single dose</td>
<td>Age ≥12 mo; weight 1.5–8.0 kg; history: postoperative (n = 6), regurgitation (n = 9), prematurity (n = 7); GA ≥26–36</td>
<td>Clinical trial; randomized, blinded; infant as own control; gastric-emptying study</td>
<td>Term infant groups: gastric fractional emptying rate (%/min)</td>
<td>Premature infant group: gastric fractional emptying rate (%/min); all pH-probe parameters postformula and 2–4 h post–glucose meal</td>
<td>None reported</td>
</tr>
<tr>
<td>Keams et al (1988)</td>
<td>6</td>
<td>0.15 mg/kg per dose every 6 h</td>
<td>Age 1–5.5 mo; history: referred for GERD</td>
<td>Clinical trial; not randomized, not blinded; infant as own control before MCP; pH probe study</td>
<td>Tenth dose vs baseline. No of reflux events &gt;5 min; longest episode pH &lt;4 (min)</td>
<td>First dose vs baseline: all parameters; tenth dose vs baseline; % time pH &lt;4; acid clearance (min/episode)</td>
<td>None reported</td>
</tr>
<tr>
<td>Tolia et al (1989)</td>
<td>30</td>
<td>0.1 mg/kg per dose QID</td>
<td>Age 1–9 mo (median: 2); term; no underlying medical conditions, GER diagnosed by pH probe</td>
<td>Clinical trial; randomized, blinded; infant as own control; baseline, placebo, and MCP periods; pH probe, scintigraphy; symptom score</td>
<td>% time pH &lt;4 (placebo effect: symptom scores on placebo were significantly improved from baseline)</td>
<td>Symptom score; daily weight change; gastric emptying; No. of episodes pH &lt;4, No. of episodes &gt;5 min</td>
<td>None reported</td>
</tr>
<tr>
<td>Pons et al (1993)</td>
<td>24</td>
<td>0.1, 0.2, or 0.4 mg/kg per dose, single dose</td>
<td>Age 1–18 mo; history: GER diagnosed by pH study; underlying medical conditions excluded</td>
<td>Clinical trial; randomized, blinded; infant randomly assigned to receive placebo or MCP after baseline measurement; pH probe study</td>
<td>None (placebo effect: several pH-probe parameters improved from baseline in the placebo group)</td>
<td>All pH-probe parameters</td>
<td>None reported</td>
</tr>
<tr>
<td>Bellissant et al (1997)</td>
<td>39</td>
<td>0.2 mg/kg per dose TID</td>
<td>Mean age 105 d (SD: ±74); mean weight 5.6 kg (SD: ±19); history: GER diagnosed by pH study; underlying medical conditions excluded</td>
<td>Clinical trial; randomized, blinded; infant randomly assigned to receive placebo or MCP after baseline measurement; pH probe study</td>
<td>None</td>
<td>All pH-probe parameters; weight</td>
<td>1 apnea; 1 emesis; 1 irritability</td>
</tr>
<tr>
<td>Kimball and Carlton (2001)</td>
<td>77</td>
<td>Mean dose: 0.4 mg/kg per d Premature GA 23–36 wk (mean: 30); birth weight 1.9–3.0 kg (mean: 1300); treated in NICUs</td>
<td>Retrospective cohort; chart review; infant own control; apnea frequency before and after treatment with cisapride or MCP</td>
<td>Clinical trial; analysis of methylxanthine treatment showed significantly decreased apnea</td>
<td>None</td>
<td>Apnea frequency</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

MCP indicates metoclopramide; TID, 3 times per day; QID, 4 times per day; GA, gestational age; FTT, failure to thrive. In studies of metoclopramide and another drug, only results comparing metoclopramide to a nondrug control are reported.

a The number of infants receiving metoclopramide was not specified.
In 28 infants serving as their own nonblinded controls, Machida et al found an increase in the number of reflux episodes when the patients were treated with metoclopramide, from a mean of 41 (SD: 29.7) during the placebo period versus a mean of 54 (SD: 44.9) episodes per 24 hours during the metoclopramide period. Three infants were so irritable after their metoclopramide infusions that manometry could not be repeated. The authors then attempted to perform a small double-blinded placebo-controlled trial in which parents kept weekly records documenting the frequency and amount of emesis. Fifteen families refused to participate in this study because of worsening of symptoms or irritability during the drug phase of the original trial. Of the 8 patients who participated, 5 received placebo and 3 received metoclopramide. All 3 of the infants who participated in the metoclopramide arm dropped out of the study because of increased irritability and vomiting. No families who participated in the placebo arm stopped therapy. Dosing in both the pH-probe and outpatient phases of this study was 0.125 mg/kg per dose every 6 hours.

Summary Statistics
Because of the heterogeneity of the studied patient populations, the variable dosing, and the different outcome measures used in the 12 studies, both reviewers deemed a meta-analysis inappropriate. Thus, no pooled estimates of effect or risk of therapy are reported. Similarly, combined estimates of dose response were not considered appropriate in light of the wide variability in patient populations and outcome measures in the literature. This heterogeneity, the mixture of study designs, and the nature of the outcomes made a funnel plot to assess for publication bias infeasible.

Level of Evidence
We graded the level of evidence according to the scale for strength of overall evidence used by the USPSTF. We both classified the quality of the literature as “poor” on the basis of the limited number of studies, small sample sizes, quality of study designs, and lack of consistency of the literature. This corresponds to a recommendation grade of “I,” meaning that the level of evidence for both benefit and harm was insufficient to recommend for or against routine use of metoclopramide (see Appendices 1 and 2).

DISCUSSION
Despite the long history of use of metoclopramide in infants, only 12 articles met our inclusion criteria for this systematic review. The literature is marked by small study sizes, a paucity of randomized and blinded studies, and heterogeneity of patient characteristics, dosing, and outcome measures. Therefore, the available evidence substantiates neither clinically significant benefit nor harm from metoclopramide in the treatment of GERD in infants. However, these studies highlight both the clinical questions and the potential methodologic issues that remain to be addressed by future studies.

In this systematic review we reached a different conclusion than that of the Cochrane review of therapies for GERD in infants, which stated that, “Overall, there is evidence that suggests that metoclopramide will reduce the clinical symptoms and reflux index when compared with placebo in infants with GERD.” Our methodology differed from the Cochrane study in several key ways. Our study focused only on the evidence for this pharmacologic therapy for GERD. We accepted a wider range of study designs than the Cochrane review, including case-control, cohort, and RCTs. Unlike the Cochrane review, we limited our criteria to full-length published articles and did not include abstracts in our search. We both felt that quality and heterogeneity of the studies made combining studies in a meta-analysis for an overall estimate of effect inappropriate. These concerns about the body of literature, as well as the small sample sizes of the published studies, led to our rating the quality of evidence “poor”; therefore, our recommendation is “inconclusive” (see Appendices 1 and 2).

The heterogeneity of the patient populations in the 12 identified studies raises important biological questions about the effect and toxicity of metoclopramide. It is likely that different populations, such as preterm, neurologically impaired, or postoperative patients, may have different efficacy and toxicity profiles than otherwise healthy term infants. In addition, given that the natural history of GERD in the majority of infants is improvement and resolution over time, particular attention must be given to the age of patients and the duration of the studies. However, there are no data to determine the effect of metoclopramide on these different patient populations.

The heterogeneity of the types of end points reported in the literature highlights the difficulty in choosing meaningful and reliable outcome measures for GERD therapy in infants. Inconsistent measurement strategies and case definitions of pathologic reflux and adverse events have been applied in these 12 studies. For instance, small reported changes in pH-probe parameters may or may not correlate with clinically meaningful changes in patient status. This issue is particularly relevant, because no studies in our systematic review reported a normalization of pH-probe results with the use of metoclopramide. Similar concerns exist with changes in the rate of gastric emptying. Although clinical symptoms would seem to be the ideal outcome of interest, the measurement and quantification of reflux symptoms are fraught with difficulties. For example, simple quantification of emesis frequency or amount seems appealing at first glance. However, many pediatricians consider emesis resulting from reflux in an otherwise healthy
child to be benign GER and not GERD. Irritability may be meaningful to parents and doctors, but because this qualitative outcome is also a reported adverse effect of metoclopramide itself, blinding and the development of validated measurement scales would be of utmost importance. In premature infants, a subpopulation frequently treated with metoclopramide, the task of separating benign from pathologic reflux and identifying which symptoms are caused by reflux is particularly difficult. For instance, although GERD is often implicated by clinicians and researchers in the pathogenesis of apnea, this connection has been challenged in the literature. Similarly, feeding intolerance in premature infants is likely multifactorial, making the relative contribution of GERD difficult to ascertain. Failure to thrive because of reflux may be one of the most concrete potential study outcomes, but it is rare and also likely to coincide with, and be confounded by, other disease states. Finally, there is a paucity of data on the impact of metoclopramide on the respiratory manifestations of GERD, such as wheezing and aspiration risk. This lack of a well-defined clinical end point for studies of GERD makes the evaluation of therapy difficult.

The Cochrane review concluded that there were increased adverse effects with metoclopramide therapy. However, given the small study sizes, the frequency of nonblinded designs, the lack of systematic criteria to define or identify adverse outcomes, and the heterogeneity of both the patient populations and metoclopramide dosing in all 12 studies, we could make no firm conclusions about the incidence of adverse events, the patient populations most at risk, or the doses at which adverse effects are most likely to occur. No studies that met the inclusion criteria for our systematic review addressed potential adverse effects on long-term developmental outcome.

No studies reported measures of effect sizes, such as relative risk or risk difference, and only 1 study reported a power calculation. The absence of estimates of effect size, either from the individual articles or a meta-analysis, makes it difficult to assess the clinical significance of any statistically significant results.

Furthermore, because all the studies published were relatively small, it is possible that the negative studies in the literature were underpowered to detect an effect. The results of our systematic review are limited by the availability of studies in the public domain and, specifically, on PubMed. Because of the heterogeneity of studies and the types of outcomes reported, we were unable to formally assess for publication bias, although it does seem likely that many small negative studies remain unpublished.

There remains a lack of definitive evidence regarding either the efficacy or the toxicity of metoclopramide for the treatment of GERD in infants. Under such conditions, clinicians cannot adequately assess the risk-benefit profile of the drug when treating infants with GERD. Additional work is needed to clarify the subpopulations most likely to be harmed or benefited by metoclopramide therapy, the optimal dosing for these subgroups, and the most valid and clinically significant outcome measures in these populations. Ultimately, a large randomized placebo-controlled clinical trial of metoclopramide will be necessary. Until such a study is completed, clinicians can only continue to judiciously treat and monitor the infants with GERD under their care.

APPENDIX 1 USPSTF Standard Recommendation Language

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>USPSTF Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.)</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.)</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.)</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)</td>
</tr>
<tr>
<td>I</td>
<td>The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.)</td>
</tr>
</tbody>
</table>

APPENDIX 2 US Preventive Service Task Force Recommendations Grid Based on Levels of Evidence

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Substantial</th>
<th>Moderate</th>
<th>Small</th>
<th>Zero/Negative</th>
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<tbody>
<tr>
<td>Good</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Fair</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Poor</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
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REFERENCES
3. Kohelet D, Boaz M, Serour F, Cohen-Adad N, Arbel E, Gorenstein A. Esophageal pH study and symptomatology of gastro-