Glycerin Enemas and Suppositories in Premature Infants: A Meta-analysis  
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**BACKGROUND AND OBJECTIVE:** Premature infants are often given glycerin enemas or suppositories to facilitate meconium evacuation and transition to enteral feeding. The purpose of this study was to assess the available evidence for this treatment strategy.

**METHODS:** We conducted a systematic search of Medline, Embase, Central, and trial registries for randomized controlled trials of premature infants treated with glycerin enemas or suppositories. Data were extracted in duplicate and meta-analyzed using a random effects model.

**RESULTS:** We identified 185 premature infants treated prophylactically with glycerin enemas in one trial (n = 81) and suppositories in two other trials (n = 104). All infants were less than 32 weeks gestation and had no congenital malformations. Treatment was associated with earlier initiation of stooling in one trial (2 vs 4 days, \( P = .02 \)) and a trend towards earlier meconium evacuation in another (6.5 vs 9 days, \( P = .11 \)). Meta-analysis demonstrated no effect on transition to enteral feeding (0.7 days faster, \( P = .43 \)) or mortality (\( P = 0.50 \)). There were no reports of rectal bleeding or perforation but there was a trend towards increased risk of necrotizing enterocolitis with glycerin enemas or suppositories (risk ratio = 2.72, \( P = .13 \)). These three trials are underpowered and affected by one or more major methodological issues. As a result, the quality of evidence is low to very low. Three other trials are underway.

**CONCLUSIONS:** The evidence for the use of glycerin enemas or suppositories in premature infants is inconclusive. Meta-analyzed data suggest that treatment may be associated with increased risk of necrotizing enterocolitis. Careful monitoring of ongoing trials is required.
Feeding and nutrition are significant challenges for premature infants in the NICU. These patients often receive glycerin enemas or suppositories to stimulate the passage of meconium and improve feeding tolerance. This practice is based on the observation that many premature infants experience significant delays in the passage of meconium, which is more viscous than normal stool. Delays in meconium evacuation seem to be associated with a delay in the transition to enteral feeding. If meconium evacuation could be expedited by using glycerin enemas or suppositories, this approach might lead to faster transition to enteral feeding, decreased reliance on parenteral nutrition, and better clinical outcomes. Unfortunately, there is little evidence to support this practice and to guide treatment decisions.

The objective of the present article was to assess the level of evidence regarding the use of glycerin enemas and suppositories in premature infants by updating the systematic review on this topic. We considered the results from randomized controlled trials of glycerin enemas or suppositories, and data underwent meta-analysis whenever possible. The gray literature and trial registries were also searched to identify trials that are underway or have not yet been published.

METHODS

Search Strategy
A systematic search was conducted of Medline, Embase, and the Cochrane Central Register of Controlled Trials for randomized controlled trials of infants treated with glycerin enemas or suppositories. An experienced medical librarian developed queries for each database to identify studies that mentioned "premature infants" and "glycerin laxatives." These concepts were expanded to ensure that no studies were missed due to variation in syntax and nomenclature. Appendices 1 through 3 present the search strategies and results.

We also performed manual searches of conference proceedings, theses and dissertations, and trial registries. We included all citations up until July 2014. No language limits were placed on the search.

Study Selection

Title and abstract screening was completed independently and in duplicate by the first 2 authors (M.H.L. and A.C.S.). The default approach for any disagreements was to automatically include the record. Inclusion criteria were: (1) participants who were premature infants <32 weeks' gestation and/or who had a birth weight <1500 g; (2) interventions that were glycerin enemas or suppositories used prophylactically or as rescue therapy for jaundice or feeding intolerance; and (3) studies that were randomized controlled trials. Glycerin enemas and glycerin suppositories were selected as important subgroups a priori. The review protocol is available from the authors upon request.

Data Extraction

Studies selected for full-text review underwent data extraction independently and in duplicate by the first 2 authors (M.H.L. and A.C.S.). To ensure consistency, we developed standardized data collection forms before use. Participant data included gestational age, birth weight, gender, presence of congenital anomalies, type of feeding (breastfeeding versus formula), age at start of enteral feeding, and calendar years of recruitment. Intervention characteristics included treatment type (glycerin enemas versus suppositories), type of placebo (no intervention versus sham procedure), dose, and treatment duration.

Outcomes of interest were selected a priori. These included (in order of decreasing importance): mortality, necrotizing enterocolitis (NEC), rectal perforation, rectal bleeding, feeding intolerance, jaundice, transition to enteral feeding, and meconium evacuation. These outcomes were selected because they are clinically relevant and/or likely to be affected by the use of glycerin enemas or suppositories. Mortality, NEC, and rectal perforation were specified a priori as critical outcomes.

Statistical Analysis

Outcome data were pooled whenever possible in Review Manager version 5.2. We decided a priori to use a random effects model because moderate heterogeneity was anticipated between studies due to variation in the participants and types of interventions. Summary statistics were reported as risk ratios (RRs) for dichotomous outcomes and mean differences for continuous outcomes. We also reported 95% confidence intervals (CIs) and P values.

Heterogeneity was reported quantitatively by using the I² statistic: 0% to 40% might not be important (ie, low heterogeneity), 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% represents considerable heterogeneity. The importance of the observed value (eg, "low" versus "moderate") depends on: (1) magnitude and direction of effects; and (2) strength of evidence for heterogeneity (eg, P value from the χ² test).

For the purposes of meta-analysis, SDs were estimated whenever they were not reported explicitly by using the following approach: range/4 (when n = 15–70) and range/6 (when n >70). Given the low number of studies meeting our inclusion criteria, we decided not to produce a funnel plot for any of the pooled outcomes.

Risk of Bias Assessment for Individual Trials

Risk of bias for individual trials was assessed independently and in
duplicate by using the Cochrane Collaboration’s tool for assessing risk of bias.24 This instrument consists of 6 domains that classify risk of bias as low, unclear, or high. Differences between reviewers were resolved through discussion and consensus.

Quality of Evidence Across Studies
The quality of evidence for each outcome was reported by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system26 with GRADEpro version 3.6.27 This system takes into account findings from multiple studies and grades the quality of evidence for each outcome as high (4 of 4 points), moderate (3 of 4), low (2 of 4), or very low (1 of 4). By default, the quality of evidence is high for results from randomized controlled trials and is low for results from observational studies. Ratings can be downgraded due to risk of bias, inconsistency, indirectness, imprecision, or publication bias and upgraded due to the presence of a large effect (RR < 0.5 or > 2), if attempts to control for confounding would change the observed effect, and the presence of a dose–response gradient.

RESULTS
Search Results
Our systematic search of Medline, Embase, and the Cochrane Central Register of Controlled Trials yielded 68 titles and abstracts, which was reduced to 45 records after duplicates were removed. Titles and abstracts were screened independently and in duplicate.

Six records were selected for full-text review. Two of these were excluded because they were not randomized controlled trials.13,28 Another study was excluded because the intervention comprised glycerin enemas as well as oral probiotics 3 times a day for 7 days.29 Because probiotics have been shown to decrease the risk of NEC and all-cause mortality in preterm infants, combined treatment likely has different effects than using glycerin suppositories alone.30 Our selection review resulted in 3 randomized controlled trials of glycerin enemas (1 trial) or suppositories (2 trials).14,31,32 An overview of the study selection procedure is shown in Fig 1.

Participants
The 3 randomized controlled trials included 185 premature infants with a gestational age < 32 weeks and/or birth weight < 1500 g. One trial included infants between 28 and 32 weeks’ gestational age only.32 All 3 trials specifically excluded infants with major congenital malformations or structural gastrointestinal anomalies. One of the glycerin suppository trials also excluded premature infants with hypoxic-ischemic encephalopathy stage ≥ 2.31 The other trial excluded those with any signs of hemodynamic instability.32

Interventions
Study interventions consisted of prophylactic glycerin enemas or suppositories administered once daily for several days. Each trial established slightly different dosing, treatment start date, and duration characteristics (Table 1). In the trial of glycerin enemas, study treatments started at 12 hours of life and continued until meconium evacuation was complete (defined as 2 normal stools free of meconium staining).14 No maximum treatment duration was reported. In the 2 trials of glycerin suppositories, study interventions started at 24 (or 48) hours of life and continued for a total of 10 (or 13) days of treatment, regardless of stooling or meconium evacuation.31,32

FIGURE 1
Search results and study selection procedures according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.49
Participants in the control group in 2 of the trials were assigned to no intervention. In Shinde et al, participants in the control group were treated with a sham procedure, which involved opening the diaper and closing it again (K. Nandkishor, MD, MSc, personal communication, 2015).

### Mortality
Mortality rates between treatment groups were similar in all 3 trials and ranged from 5% to 17% (N. Haiden, MD, MSc, personal communication, 2015). Mortality data in the glycerin enema trial were confirmed after communication with the principal investigator (N. Haiden, personal communication, MD, MSc, 2015). Meta-analysis of data from all 3 trials revealed no difference between treatment groups (RR: 1.34 [95% CI: 0.58–3.11]; I² = 0%, P = .50) (Fig 2).

### Necrotizing Enterocolitis
The rates of NEC between treatment groups were similar in all 3 trials and ranged from 5% to 17% (N. Haiden, MD, MSc, personal communication, 2015). Meta-analysis of data from all 3 trials revealed no difference between treatment groups (RR: 1.34 [95% CI: 0.58–3.11]; I² = 0%, P = .50) (Fig 2).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>N</th>
<th>Years Recruited</th>
<th>Country</th>
<th>Intervention</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiden et al14</td>
<td>Inclusion criteria:</td>
<td>81</td>
<td>2000–2001a</td>
<td>Austria</td>
<td>1. Daily glycerin enema (n = 42); 10 mL/kg (0.8 g of glycerin in 10 mL of normal saline)</td>
<td>Not registereda</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td></td>
<td>2. No intervention (n = 39)</td>
<td></td>
</tr>
<tr>
<td>Khadr et al31</td>
<td>Inclusion criteria:</td>
<td>54</td>
<td>2006–2008</td>
<td>United Kingdom</td>
<td>1. Daily glycerin suppository (n = 29); 250 mg (24–28 wk) 500 mg (28–32 wk)</td>
<td>International Standard Randomized Controlled Trial Number 4706576434</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td></td>
<td>2. No intervention (n = 25)</td>
<td></td>
</tr>
<tr>
<td>Shinde et al32</td>
<td>Inclusion criteria:</td>
<td>50</td>
<td>2010–2011</td>
<td>India</td>
<td>1. Daily glycerin suppository (n = 25); 1000 mg (28–32 wk) Open and closing diaperb</td>
<td>Not registeredb</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td></td>
<td>2. Sham procedure (n = 25)</td>
<td></td>
</tr>
</tbody>
</table>

a N. Haiden, personal communication, MD, MSc, 2015.
b K. Nandkishor, personal communication, MD, MSc, 2015.

df = 9, P = .13 [Fig 3].

df = 6, P = .09 [Fig 3].
trials\textsuperscript{14,31} and was confirmed in the other trial after communication with its principal investigator (N. Haiden, personal communication, MD, MSc, 2015).

There were no cases of rectal bleeding. Absence of rectal bleeding was reported explicitly in 1 of the glycerin suppository trials\textsuperscript{31} and was confirmed in the other 2 studies (K. Nandkishor, MD, MSc, personal communication, 2015; N. Haiden, MD, MSc, personal communication, 2015).

**Feeding Intolerance**

There were no differences between treatment groups in terms of feeding intolerance. This outcome was reported in the 2 glycerin suppository trials but was variably defined.\textsuperscript{7,31,32}

In Khadr et al,\textsuperscript{31} there were no differences between groups in terms of incidence of abdominal distension >2 cm, number of bilious residuals, number of feedings withheld, number of feedings reduced or not increased, and percentage of gastric residuals compared with total enteral feeding volume. These outcomes were all measured within the first 10 days of life.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>No Treatment Events</th>
<th>Weight</th>
<th>RR M-H, Random, 95% CI Year</th>
<th>RR M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Glycerin Enemas</td>
<td>Haiden,\textsuperscript{14} 2007</td>
<td>6</td>
<td>42</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>42</td>
<td>39</td>
<td>41.1%</td>
<td>1.86 [0.50 to 6.92]</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Test for overall effect: $Z = 0.92$ ($P = .36$)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**FIGURE 2**


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>No Treatment Events</th>
<th>Weight</th>
<th>RR M-H, Random, 95% CI Year</th>
<th>RR M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Glycerin Enemas</td>
<td>Haiden et al,\textsuperscript{14} 2007</td>
<td>3</td>
<td>42</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>42</td>
<td>39</td>
<td>33.3%</td>
<td>2.79 [0.30 to 26.67]</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Test for overall effect: $Z = 0.90$ ($P = .37$)</td>
<td></td>
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</tbody>
</table>

**FIGURE 3**

In Shinde et al,\textsuperscript{32} there was no difference between treatment groups in terms of the number of participants who had feedings withheld: 7 of 21 versus 4 of 21 (RR: 1.75 [95% CI: 0.60–5.10]; \textit{P} value not reported). Differences in how feeding intolerance was reported in these 2 trials resulted in data that could not undergo meta-analysis.

**Jaundice**

None of the trials reported outcomes related to jaundice, such as or serum bilirubin level or need for phototherapy.

**Transition to Enteral Feeding**

There were no differences between treatment groups in transition to enteral feeding in any of the 3 trials. Each trial defined full enteral feeding differently: in Haiden et al,\textsuperscript{14,15} 150 mL/kg per day; in Shinde et al,\textsuperscript{32} maintenance of 180 mL/kg per day for 24 hours; and in Khadr et al,\textsuperscript{31} tolerance of full enteral feedings (prespecified volume not defined) and discontinuation of parenteral nutrition for >48 hours without feedings being reduced or withheld.

There were also differences in feeding regimens, with feeding initiated on median day 1 (range: 1–1.8 days),\textsuperscript{31} median day 2 (range: 0–9 days),\textsuperscript{14} or mean day 5.5 (SD: 2.5).\textsuperscript{32}

The 2 glycerin suppository trials also reported the type of feeding used. In the trial by Khadr et al,\textsuperscript{31} which included premature infants 24 to 32 weeks’ gestation, expressed breast milk was used exclusively in 10 (19%) of 54 infants. In Shinde et al,\textsuperscript{32} which included premature infants 28 to 32 weeks’ gestation only, 37 (74%) of 50 received expressed breast milk exclusively. Communication with the principal investigator of the glycerin enema trial indicated that the use of expressed breast milk when the study was conducted was ∼70% to 80% (N. Haiden, MD, MSc, personal communication, 2015).

For the purposes of meta-analysis, transition to enteral feeding was calculated as the difference (in number of days) between the mean or median start of enteral feeding and full enteral feeding. Across all 3 trials, there was no statistically significant difference between treatment groups (0.7 day faster with glycerin enemas or suppositories; 95% CI of 2.4 days faster to 1.0 day slower, \textit{P} = .49) (Fig 4). Heterogeneity was substantial (\textit{I}^2 = 51%), but there was no statistically significant subgroup difference between glycerin enemas and suppositories (\textit{P} = .89).

**Completion and Initiation of Meconium Evacuation**

The trial of glycerin enemas reported a nonsignificant trend toward earlier completion of meconium evacuation with active treatment (median: 6.5 vs 9 days; \textit{P} = .11).\textsuperscript{14} The other 2 trials did not report this outcome.\textsuperscript{31,32}

Initiation of meconium evacuation was not affected by the use of glycerin enemas starting at 12 hours of life (median: 1 vs 1 day; \textit{P} = .68), but a statistically significant effect was observed for the use of glycerin suppositories starting at 24 hours of life (median: 2 vs 4 days; \textit{P} = .016).\textsuperscript{31}

In the glycerin suppository trial, treatment was also associated with lower frequency of delayed initiation of meconium evacuation (24% vs 64%; \textit{P} = .003). Meta-analysis of data for initiation of meconium evacuation demonstrated no significant treatment effect (1 day faster with treatment, 95% CI of 3.0 days faster to 0.9 day slower; \textit{I}^2 = 89\%, \textit{P} = .30) (Fig 5). The CIs from the 2 trials did not overlap, and the test for subgroup differences was significant (\textit{P} = .002).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Mean</th>
<th>SD</th>
<th>Total</th>
<th>No Treatment Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 Glycerin Enemas</td>
<td>Haiden,\textsuperscript{14} 2007</td>
<td>24</td>
<td>12.5</td>
<td>42</td>
<td>25</td>
<td>11.6</td>
<td>39</td>
<td>9.1%</td>
<td>-1.00 [–6.25 to 4.25]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>42</td>
<td></td>
<td></td>
<td>39</td>
<td></td>
<td></td>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: \textbf{Z} = 0.37 (\textit{P} = .71)</td>
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<tr>
<td>1.3.2 Glycerin Suppositories</td>
<td>Khadr et al,\textsuperscript{31} 2011</td>
<td>6.4</td>
<td>2.2</td>
<td>29</td>
<td>8</td>
<td>2.2</td>
<td>25</td>
<td>51.9%</td>
<td>-1.60 [–2.78 to –0.42]</td>
</tr>
<tr>
<td>Shinde et al,\textsuperscript{32} 2014</td>
<td>6.4</td>
<td>2.7</td>
<td>21</td>
<td>5.8</td>
<td>3.2</td>
<td>21</td>
<td>39.1%</td>
<td>0.60 [–1.19 to 2.39]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>46</td>
<td>90.9%</td>
<td>-0.61 [–2.75 to 1.54]</td>
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<tr>
<td>Heterogeneity: \textit{\chi}^2 = 1.82; \textit{\chi}^2 = 4.05, df = 1 (\textit{P} = .04); \textit{I}^2 = 75%</td>
<td>Test for overall effect: \textbf{Z} = 0.56 (\textit{P} = .56)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>92</td>
<td>100.0%</td>
<td>-0.69 [–2.38 to 1.01]</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: \textit{\chi}^2 = 1.09; \textit{\chi}^2 = 4.05, df = 2 (\textit{P} = .13); \textit{I}^2 = 51%</td>
<td>Test for overall effect: \textbf{Z} = 0.79 (\textit{P} = .43)</td>
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<tr>
<td>Test for subgroup differences: \textit{\chi}^2 = 0.02, df = 1 (\textit{P} = .89); \textit{I}^2 = 0%</td>
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</table>

**FIGURE 4**

Transition to enteral feeding (mean difference in days to full enteral feeding) in premature infants treated with glycerin enemas or suppositories versus no treatment. IV, inverse variance.
Other Outcomes

There were no differences between treatment groups in terms of intraventricular hemorrhage, retinopathy of prematurity, patent ductus arteriosus, sepsis based on positive culture results, or oxygen requirements (Table 2) (N. Haiden, personal communication, MD, MSc, 2015). There were no differences reported between groups for weight gain or length of hospital stay in any of the 3 trials.14,31,32

Risk of Bias of Individual Studies

All 3 trials were at high risk of bias in ≥2 of 6 domains (Table 3). Sequence generation was created by using random number software in 2 of the trials (K. Nandkishor, MD, MSc, personal communication, 2015; N. Haiden, MD, MSc, personal communication, 2015) and shuffling of sealed envelopes in Khadr et al.31 Allocation concealment was maintained in all 3 studies by using opaque envelopes (K. Nandkishor, MD, MSc, personal communication, 2015; N. Haiden, MD, MSc, personal communication, 2015).32 Two of the 3 trials were open-label studies with no blinding.14,31 Shinde et al32 relied on a research nurse to administer study interventions, and all other clinicians, study personnel, and outcome assessors were blinded to treatment allocation (K. Nandkishor, personal communication, 2015).

Incomplete outcomes were discussed in all 3 trials. In the most recent glycerin suppository trial, 3 participants in each group (≥10% of the total sample size) were transferred to another hospital before complete outcomes could be obtained.31 A sensitivity analysis was performed for this situation by imputing missing data for mortality and NEC by using the approach of "best- and worst-case scenario."24 This method did not affect the meta-analysis for mortality. For NEC, however, the worst-case scenario (ie, 3 of 3 infants in the treatment group developing NEC versus 0 of 3 in the control group) would have made our meta-analysis statistically significant (RR: 3.68 [95% CI: 1.07–12.65]; P = .04). As a result, we concluded that the lack of complete outcome data for this trial resulted in a high risk of bias.

The protocol for Khadr et al31 was registered and available online,24 and there was no evidence of selective reporting. The other 2 trials were not registered, and the risk of bias due to selective reporting was therefore unclear (K. Nandkishor, MD, MSc, personal communication, 2015; N. Haiden, MD, MSc, personal communication, 2015).

All 3 trials were at high risk of bias due to low power. The glycerin enema trial was powered to detect a "30% difference" in days to complete meconium evacuation.14 The glycerin suppository trials were powered to detect a reduction in days to full enteral feeding of 3.63 and 3 days, respectively.31,32 These effect sizes are substantially larger than the magnitude of the true effect size (if it actually exists). Powering these trials for a more moderate effect size would have required substantially larger sample sizes. The glycerin enema trial was also at high risk of bias due to the number of protocol violations: 15 of 42 infants in the intervention group missed a scheduled glycerin enema, and 8 of 39 in the control group received at least 1 enema despite being assigned to no treatment.14 Outcomes were reported on the basis of intention-to-treat and per-protocol analyses, but there were no significant differences between these approaches. The other 2 trials also examined the results on the basis of an intention-to-treat analysis (K. Nandkishor, MD, MSc, personal communication, 2015).31
Quality of Evidence

The quality of evidence across all 3 trials for mortality, NEC, transition to enteral feeding, and completion of meconium evacuation was low (2 of 4 points). Using the GRADE approach, the quality of evidence was downgraded for all outcomes due to risk of bias (−1 point) (Table 3).\(^{35,36}\) Ratings were also downgraded for imprecision by 1 point for low number of events (for mortality and NEC) and/or 1 point for CIs that crossed 1 (for NEC, transition to enteral feeding, and completion of meconium evacuation).\(^ {37}\) The quality of evidence for NEC was upgraded due to the presence of a large effect (+1 point).\(^ {30}\)

The quality of evidence for rectal bleeding, rectal perforation, and initiation of meconium evacuation was very low (1 of 4 points) (Table 4). This outcome was due to risk of bias (−1 point) and imprecision due to low number of events (−1 point) and/or CIs that crossed 1 (−1 point).\(^ {36,37}\) The quality of evidence for initiation of meconium evacuation was also downgraded due to inconsistency because the CIs from the 2 trials did not overlap.\(^ {39}\) The other possible explanation for this lack of overlap is that glycerin enemas and glycerin suppositories may have truly different effects on initiation of meconium evacuation.

### TABLE 3 Risk of Bias of Individual Studies According to the Cochrane Collaboration Risk of Bias Tool\(^ {24}\)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Haiden et al,(^ {14}) 2007</th>
<th>Khadr et al,(^ {31}) 2011</th>
<th>Shinde et al,(^ {32}) 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Blinding of patients and personnel</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Incomplete outcomes addressed</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>No selective reporting</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>No other bias</td>
<td>High(^ {a,b})</td>
<td>High(^ a)</td>
<td>High(^ a)</td>
</tr>
</tbody>
</table>

\(^ a\) Low statistical power

\(^ b\) Frequent protocol violations.

### Ongoing Trials

Our systematic search of the gray literature and trial registries resulted in 77 records. Three of these records were protocols for ongoing randomized controlled trials of premature infants treated prophylactically with glycerin suppositories. The first trial recruited 79 premature infants from 30 to 35 weeks’ gestation who required phototherapy for physiologic hyperbilirubinemia.\(^ {40}\) The primary outcome was total duration of phototherapy; secondary outcomes included duration of initial phototherapy, need to restart phototherapy, peak serum bilirubin, mean serum bilirubin, rate of decline of serum bilirubin, and use of stool softeners after completion of phototherapy. Recruitment was completed in 2013, and the results are pending.

We also identified a 2-center trial of glycerin suppositories from Saudi Arabia with plans to recruit 220 premature infants with a birth weight <1250 g.\(^ {41}\) The primary outcome is days to full enteral feeding; recruitment began in 2013. In January 2015, our center started recruitment for a pilot, randomized controlled trial of 30 premature infants of 24 to 32 weeks’ gestation and/or birth weight 500 to 1500 g.\(^ {42}\) The purpose of this study is to further assess the feasibility and safety of glycerin suppositories before embarking on a larger, multicenter trial.

### DISCUSSION

The quality of evidence for the use of glycerin enemas and suppositories in premature infants is low to very low. Three single-center, randomized controlled trials have been conducted and published to date.\(^ {14,31,32}\) These studies are underpowered and at risk for bias due to a variety of methodologic issues, including problems with blinding, outcome assessment, incomplete follow-up,
<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Studies (n - participants)</th>
<th>Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>No. of Participants</th>
<th>Effect</th>
<th>No. of Participants</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
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<tr>
<td>Mortality</td>
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<td>Serious²</td>
<td>None</td>
<td>None</td>
<td>Serious⁵</td>
<td>None</td>
<td>12/93 (13%)</td>
<td>RR: 1.34 (0.58–3.11)</td>
<td>32 more per 1000</td>
<td>196 more</td>
<td>Low</td>
<td>Critical</td>
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<tr>
<td>NEC</td>
<td>3 (n = 179)</td>
<td>Randomized trials</td>
<td>Serious²</td>
<td>None</td>
<td>None</td>
<td>Very serious³,⁶</td>
<td>Large effect⁷</td>
<td>9/93 (10%)</td>
<td>RR 2.72 (0.76–9.81)</td>
<td>60 more per 1000</td>
<td>8 fewer to 307 more</td>
<td>Low</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>Rectal perforation</td>
<td>3 (n = 185)</td>
<td>Randomized trials</td>
<td>Serious²</td>
<td>None</td>
<td>None</td>
<td>Very serious³,⁶</td>
<td>None</td>
<td>0/96 (0%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Very low</td>
<td>Critical</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>3 (n = 185)</td>
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<td>None</td>
<td>None</td>
<td>Very serious³,⁶</td>
<td>None</td>
<td>0/96 (0%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td>Jaundice</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<td>—</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td>Transition to enteral feeding</td>
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<td>None</td>
<td>Serious⁵</td>
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<td>92</td>
<td>0.7 d faster (2.4 faster to 1.0 slower)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Completion of meconium evacuation</td>
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<td>Serious²</td>
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<td>None</td>
<td>Serious⁵</td>
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<td>42</td>
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<td>—</td>
<td>Important</td>
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<td></td>
</tr>
<tr>
<td>Initiation of meconium evacuation</td>
<td>2 (n = 135)</td>
<td>Randomized trials</td>
<td>Serious²</td>
<td>None</td>
<td>None</td>
<td>Serious⁵</td>
<td>None</td>
<td>71</td>
<td>1 d faster (3.0 faster to 0.9 slower)</td>
<td>—</td>
<td>—</td>
<td>Important</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* See Table 3.
⁻⁵ 95% CIs for relative risk include 1 or P > .05.
⁻³ Small number of events (<300).
⁻⁶ RR > 2.00
⁻⁷ No overlap between CIs from different studies.
and/or the possibility of selective reporting.24

The published data from these 3 trials suggest that the use of glycerin enemas and suppositories has no effect on transition to enteral feeding or mortality. One trial reported earlier initiation of meconium evacuation with glycerin suppositories31 and another reported a trend toward earlier completion of meconium evacuation with glycerin enemas.14 Although there were no reports of rectal bleeding or perforation in these 3 trials, our meta-analysis found a trend toward increased risk of NEC with the use of glycerin enemas or suppositories compared with no treatment. The total number of events in each group was small (9 of 92 vs 3 of 85), and although the risk ratio was 2.72, the accuracy of this estimate remains uncertain.

Given the methodologic limitations of randomized trials published to date, we believe that the evidence for the use of glycerin enemas or suppositories in premature infants is inconclusive. Meta-analysis of the data suggests that treatment is not associated with any consistent benefits and may result in harm. These conclusions are similar to those of previous systematic reviews but include an additional message of caution given the concerning but nonsignificant trends found by our meta-analysis.

A systematic review published in 2011 assessed whether glycerin enemas and suppositories decrease feeding intolerance in premature infants.9 The authors considered the results from the trial on glycerin enemas by Haiden et al14 and a historical cohort study of 83 very low birth weight infants from a single hospital in South Korea.13 In the cohort study, full enteral feeding was achieved within 16 days during the treatment period and 22.9 days for the control period (P < .001). Significant improvements were also reported for days to passage of first meconium, duration of central catheter usage, sepsis after 7 days of life, and positive results of catheter culture. The authors of the systematic review reported that the historical cohort study was of fair quality and reported positive results, whereas the randomized controlled trial by Haiden et al was of good quality but reported negative results. The authors of the review concluded: “The evidence regarding the effectiveness of glycerin [enemas or suppositories] for improving feeding intolerance in very low birth weight infants is inconclusive.”29

In 2014, an unpublished Cochrane Review was conducted that considered the results from the trials by Haiden et al and Shinde et al.14,31,43 The authors concluded that the available evidence does not support the use of glycerin enemas or suppositories in clinical practice and that further studies are needed.43 Previous trials and systematic reviews have not assessed the effect of glycerin enemas or suppositories on jaundice in premature infants. Results are pending from a recently completed trial of 79 premature infants treated with glycerin suppositories to reduce jaundice.40 Three other randomized controlled trials have also been conducted in healthy term infants.44–46 A systematic review of these 3 studies was published in 2011 and concluded that early meconium evacuation with the use of glycerin suppositories was not associated with any clinical benefit in healthy term infants.47

Our search strategy identified 3 trials on the use of glycerin suppositories in premature infants that are underway or have not yet been published. One of these was recently completed, and the results are pending.11,40 This trial did not specify NEC as a primary or secondary outcome a priori, but communication with the principal investigator confirmed that none of the 79 infants was diagnosed with NEC (C.T. D'Angio, MD, personal communication, 2015). This outcome was likely because the trial enrolled late preterm (30 to 35 weeks' gestation) rather than early preterm (<32 weeks' gestation) infants, who are at higher risk for developing NEC.

The other 2 ongoing trials of glycerin suppositories in premature infants have started recruiting participants and are ongoing. These trials should be closely monitored for increased risk of NEC. The nature of the association between glycerin medications and NEC will become clearer as additional data become available. One possibility is that the apparent relationship is nothing more than a spurious correlation that will disappear with the inclusion of more data. The other explanation is that there is a real effect that has not yet become statistically significant. Our center has elected to proceed with a trial as a pilot study limited to 30 premature infants.42,40 This trial and others like it should be discontinued if it becomes clear that glycerin suppositories are associated with increased harm.

**CONCLUSIONS**

The quality of evidence for the use of glycerin enemas and suppositories in premature infants is low to very low. Previous randomized controlled trials are underpowered and at risk for bias due to a variety of methodologic issues. As a result, the evidence for this treatment is inconclusive. Meta-analysis of the data suggests that glycerin enemas and suppositories have no consistent effect on meconium evacuation, transition to full enteral feeding, or mortality. Previous trials have assessed the effect of these medications on jaundice in term infants but not in premature infants. No cases of rectal bleeding or perforation were reported in any of the trials published to date, but these data indicate a nonsignificant trend toward increased risk of NEC when glycerin enemas or suppositories are
used on a daily basis. We recommend that ongoing trials be monitored carefully because treatment may be associated with increased harm.

**ACKNOWLEDGMENTS**

We thank Alla Lansavichene, BSc, MLIS, for helping us to develop and execute the search strategy. We also acknowledge Nathan Evaniew, MD, and Moin Khan, MD, for their review and constructive feedback.

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the use of glycerine suppositories. International Standard Randomised Controlled Trial Number Registry. Available at: www.isrctn.com/ISRCTN47065764. Accessed August 1, 2014


## APPENDIX 1  Medline Search Strategy and Results

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<thead>
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<th>No.</th>
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<th>Results</th>
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<td>11 995</td>
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<td>3 and (6 or 9)</td>
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<td>11</td>
<td>exp Infant/</td>
<td>942 470</td>
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## APPENDIX 2  Embase Search Strategy and Results

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<td>17 341</td>
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<tr>
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DOI: 10.1542/peds.2015-0143 originally published online May 18, 2015;

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