Recurrence Rates After Intussusception Enema Reduction: A Meta-analysis

abstract

BACKGROUND AND OBJECTIVE: Reported rates of recurrence after enema reduction for intussusception are variable. Concerns for recurrence influence postreduction management. The objective of this study was to conduct a systematic review and meta-analysis to estimate overall, 24-hour, and 48-hour recurrence rates after enema reduction in children.

METHODS: PubMed, Cochrane Database, and OVID Medline were searched from 1946 through December 2011 using the search terms: intussusception, recurrence, and enema. Sixty-nine studies of patients age 0 to 18 years with radiographically proven intussusception reduced by enema that report the number of enema reductions and the number of recurrences were included. Extraction was done by the primary author (M.P.G.) with 10% of included studies independently audited to ensure concordance.

RESULTS: Overall recurrence rates were 12.7% (95% confidence interval [CI]: 11.1%–14.4%, I² = 28.8%) for contrast enema (CE), 7.5% (95% CI: 5.7%–9.8%, I² = 52.4%) for ultrasound-guided noncontrast enema (UGNCE), and 8.5% (95% CI: 6.9%–10.4%, I² = 50.1%) for fluoroscopy-guided air enema (FGAE). Recurrence rates within 24 hours were 3.9% (95% CI: 2.2%–6.7%, I² = 47.0%) for CE, 3.9% (95% CI: 1.5%–10.1%, I² = 0.0%) for UGNCE, and 2.2% (95% CI: 0.7%–6.5%, I² = 59.8%) for FGAE. Recurrence rates within 48 hours were 5.4% (95% CI 3.7%–7.8%, I² = 32.3%) for CE, 6.6% (95% CI: 4.0%–10.7%, I² = 0.0%) for UGNCE, and 2.7% (95% CI: 1.2%–6.5%, I² = 73.8%) for FGAE. Most included studies are retrospective and vary in quality of reporting. Few studies reported detailed patient characteristics including timing of recurrences.

CONCLUSIONS: The risk of early (within 48 hours) recurrence after enema reduction is low, suggesting outpatient management of well-appearing patients should be considered. Pediatrics 2014;134:110–119

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KEY WORDS intussusception, recurrence, enema

ABBREVIATIONS
CE—contrast enema
CI—confidence interval
FGAE—fluoroscopy-guided air enema
UGNCE—ultrasound-guided noncontrast enema

Dr Gray conceptualized and designed the study, conducted data collection, and drafted the initial manuscript; Dr Gorelick conceptualized and designed the study, aided in data collection, and revised and reviewed the initial manuscript; Drs Hoffmann and Li carried out the initial analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Please note that Dr Li is no longer employed at the Medical College of Wisconsin. She is now affiliated with United Healthcare Group. The change in affiliation occurred after analysis of the results was completed.

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Intussusception is a common cause of abdominal pain and intestinal obstruction in the pediatric population. Since 2000, annual hospitalization rates for intussusception in the United States have remained steady at approximately 35 cases per 100,000 infants, and are as high as 62 per 100,000 infants 26 to 29 weeks of age. Currently, the management of intussusception remains variable; however, there has been a significant trend away from surgical reduction toward enema reduction. Despite a growing body of literature supporting outpatient management of patients with successful enema reduction, it is still common practice to hospitalize patients for 24 to 48 hours of observation. This is based on historical recommendations founded on the concerns for recurrence and post-reduction complications. A body of evidence has emerged suggesting that the rate of significant complications, specifically perforation, post enema reduction is very low. As part of their review of intussusception management, Daneman and Navarro reported rates of perforation between 0% and 5.9%, with the vast majority of series reporting rates <1%. Reported recurrence rates, however, are highly variable, are not calculated in a standardized manner, and most are based on relatively small trials. In addition, many of the reported recurrences occurred >48 to 72 hours post-reduction. Consequently, management recommendations would be best based on a precise understanding of the risk of early (within 24–48 hours) recurrence for an individual patient.

The aim of our study was to perform a systematic review of the existing literature to estimate overall, 24-hour, and 48-hour recurrence rates post enema reduction in children with a radiographic diagnosis of ileocolic intussusception in an effort to pose suggested recommendations for clinical practice.

METHODS

Data Sources and Searches

We performed electronic searches of PubMed, the Cochrane Database, and OVID Medline from 1966 to the end of December 2011. The search included the following keywords: intussusception, recurrence, and enema (Supplemental Table 5). A prevalidated filter to limit the search to children was also used. The search was limited to human studies and publications in English. Hand searches of the bibliographies of all articles identified in the initial online search were completed to identify further articles for final inclusion. Authors were contacted if studies quoted a recurrence rate but did not define the numerator or denominator needed to calculate this rate.

Study Selection

Studies were included if they met all of the following criteria: (1) included patients age 0 to 18 years; (2) intussusception was radiographically proven and reduced by enema; and (3) the number of intussusceptions reduced by enema and the number of recurrences was provided or could be calculated. Two reviewers (M.P.G. and M.H.G.) independently evaluated titles and abstracts of articles retrieved from the initial search. A list of relevant articles was created, agreed on by both authors, and retrieved in full. Both authors (M.P.G. and M.H.G.) reviewed all full-text articles independently for final inclusion and disagreements were reconciled by consensus.

Data Extraction

Data were extracted onto a preformatted data sheet by the primary author (M.P.G.). The second author (M.H.G.) audited 10% of the articles included to ensure concordance. Outcome measures
TABLE 1 Characteristics of Studies Included in the Meta-analysis

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<th>Enema Type</th>
<th>Outcomes</th>
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included the number of successful reductions and the total number of recurrences. When data were available, the number of recurrences occurring <24 hours post reduction and <48 hours post reduction was recorded separately. For articles reporting both enema-reduced and operatively reduced intussusceptions, only data on those reduced by enema were included.

Factors that were believed to affect recurrence rates also were recorded. These included the type of enema performed (contrast enema [CE], fluoroscopy-guided air enema [FGAE], ultrasound-guided noncontrast enema [UGHCE]), year of publication, and country in which the study was conducted. Study location was stratified into “Developed” and “Developing” countries based on United Nations Children’s Fund definitions of industrialized countries, with “Developed” defined as the United States, England, Finland, France, Ireland, Israel, Germany, the Netherlands, Norway, Portugal, Scotland, Spain, the United Kingdom, Australia, Japan, and New Zealand.9

### Quality Assessment

It has been shown that the quality of reporting is associated with the methodological quality of clinical trials; however, there are currently no validated scales to assess the quality of observational studies.10,11 Most studies included in our meta-analysis are observational; therefore, we chose to evaluate the methodological quality of the studies included in this review and meta-analysis using a scale we developed. Studies were assigned a score of 0 to 2 for each of the following criteria (the criteria for assigning 0, 1, or 2 points are indicated respectively in parentheses):

1. **Enrollment** (not specified, non-consecutive, consecutive);
2. **Design** (not specified, retrospective, prospective).

Studies were then assigned a score of 1 to 3 for each of the following criteria (the criteria for assigning 1, 2, or 3 points are indicated respectively in parentheses):

1. **Definition of data source** (not specified, specific but general mention of data source, eg, “medical records were reviewed,” specifically defined, eg, “inpatient and radiology records were reviewed”);
2. **Data abstraction** (not specified, specific mention of data to be extracted but not method of abstraction, specific mention of what data and how it was abstracted).

We made note of follow-up (retrospective versus prospective) when possible, and found little variance. Most studies had retrospective follow-up. As such, we did not include “follow-up” in our

### Table 1

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<tr>
<th>Study (Year)</th>
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<th>Quality Score</th>
<th>Age, mo</th>
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<td>Tangi et al (1991)17</td>
<td>Wales</td>
<td>11</td>
<td>5</td>
<td>Undefined</td>
<td>62</td>
<td>FGAE</td>
<td>TotR</td>
<td>8.7</td>
</tr>
<tr>
<td>Tareen et al 201115</td>
<td>Ireland</td>
<td>295</td>
<td>5</td>
<td>0–144</td>
<td>70</td>
<td>FGAE</td>
<td>TotR</td>
<td>15.8</td>
</tr>
<tr>
<td>Todani et al (1990)61</td>
<td>Japan</td>
<td>137</td>
<td>5</td>
<td>Undefined</td>
<td>62</td>
<td>FGAE</td>
<td>TotR</td>
<td>8.7</td>
</tr>
<tr>
<td>Wang et al (1993)12</td>
<td>China</td>
<td>224</td>
<td>5</td>
<td>1.5–48</td>
<td>72</td>
<td>FGAE</td>
<td>24 h, 48 h, TotR</td>
<td>1.4</td>
</tr>
<tr>
<td>Yoon et al (2001)15</td>
<td>South Korea</td>
<td>49</td>
<td>9</td>
<td>2–84</td>
<td>73</td>
<td>FGAE</td>
<td>24 h, 48 h, TotR</td>
<td>6.7</td>
</tr>
</tbody>
</table>

24 h, 24-hour recurrence rate; 48 h, 48-hour recurrence rate; TotR, total recurrence rate.

### Table 2

<table>
<thead>
<tr>
<th>Enema Modality</th>
<th>Overall Recurrence Rate, % (95% CI)</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>48-h</td>
</tr>
<tr>
<td>CE</td>
<td>12.7 (11.1–14.4)</td>
<td>5.4 (3.7–7.8)</td>
</tr>
<tr>
<td>UGNCE</td>
<td>7.5 (5.7–9.8)</td>
<td>6.6 (4.0–10.7)</td>
</tr>
<tr>
<td>FGAE</td>
<td>8.5 (6.9–10.4)</td>
<td>2.7 (1.2–6.5)</td>
</tr>
</tbody>
</table>
quality score. Total net scores could range from 2 to 10, with higher scores indicating higher quality. Both authors (M.P.G. and M.H.G.) independently assigned the quality scores for each study and differences were reconciled by mutual agreement. $\kappa$ for interrater agreement was calculated.

**Data Analysis**

Recurrence rates were calculated in a standardized manner for each study by dividing the total number of patients with recurrence by the total number of patients with a successful reduction. Patients with $>1$ recurrence were counted only once. Heterogeneity between studies was identified by using a $\chi^2$ test and quantified with the I$^2$ statistic. Meta-analysis was performed by using a random effects model based on the method of DerSimonian and Laird. To account for the number of zero proportions in this study, the log-transformed proportion was used to calculate confidence intervals that would be non-negative. The analysis was stratified based on enema type. Meta-regression was performed to identify potential sources of heterogeneity. We planned a priori to assess for sources of heterogeneity, including quality score, the year of study completion, and study location. In post hoc analysis, estimated median age was included in the meta-regression. The vast majority of studies reported only an age range. As such, median age was estimated by the midpoint and square-root transformation of the midpoint. Both variables were tested in the regression analysis. For the primary outcome, recurrence rates by enema modalities, a $P$ value of .05 was used. For the secondary analyses comparing different time frames and covariates, a $P < .01$ was used to account for multiple testing of the secondary outcomes.

R 2.13 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 11.2 (Stata Corp, College Station, TX) were used for this analysis.

**RESULTS**

**Description of Articles**

The described search strategies identified 325 articles and abstracts (Fig 1). Of these, 154 were excluded based on their title or abstract, and 167 were retrieved in full. Sixty-nine articles met full inclusion criteria and were included in the meta-analysis (Table 1). Ninety-eight articles were excluded after review of the full text (Supplemental Table 4).

The studies included were drawn from a wide body of literature including general pediatric, emergency medicine, and radiology journals. The quality scores for the 69 included studies were widely variable and ranged from 2 to 10; however, interrater reliability for quality scores was excellent ($\kappa = 0.93$). Fifty-five of these articles were retrospective...
studies and 49 of them had consecutive enrollment. One study was a randomized controlled study. The studies included were conducted in 28 different countries, with 13 studies conducted in the United States. The ages of study participants ranged from <1 month to 22 years.

**Recurrence Rates**

When estimating pooled recurrence rates across all studies, independent of enema modality, we found that the results were highly heterogeneous signifying that effect sizes varied between studies and enema modality. The overall results were heavily biased toward contrast enema reduction, largely due to the substantial difference in the number of studies included for each enema modality (46 CE, 9 UGNCE, 24 FGAE). Although to some extent the number of subjects adjusts for this (5362 subjects with CE vs 10,013 subjects with FGAE or UGNCE), it is not enough to fully account for the bias. Because the results for individual enema modalities are not subject to this bias, subsequent analyses were stratified by modality.

Recurrence rates are reported by modality in Table 2. Overall recurrence rates were 12.7% (95% confidence interval [CI] 11.1%–14.4%, I² = 28.8%) for CE, 7.5% (95% CI 5.7%–9.8%, I² = 52.4%) for UGNCE, and 8.5% (95% CI 6.9%–10.4%, I² = 50.1%) for FGAE (Fig 2). The recurrence rates at 24 hours and 48 hours were low. Recurrence rates within 24 hours post reduction were 3.9% (95% CI 2.2%–6.7%, I² = 47.0%) for CE, 3.9% (95% CI 1.5%–10.1%, I² = 0.0%) for UGNCE, and 2.2% (95% CI 0.7%–6.5%, I² = 59.8%) for FGAE (Fig 3). Recurrence rates within 48 hours post reduction were 5.4% (95% CI 3.7%–7.8%, I² = 52.3%) for CE, 6.6% (95% CI 4.0%–10.7%, I² = 0.0%) for UGNCE, and 2.7% (95% CI 1.2%–6.5%, I² = 73.8%) for FGAE (Fig 4).

**Sensitivity Analyses**

Heterogeneity was found when combining studies by enema modality (Table 2). A study by Higgins et al suggests that I² values from 0% to 50% represent a low to moderate amount of heterogeneity. Meta-regression was conducted to identify potential sources of heterogeneity. Enema modality was a significant source of heterogeneity (P = .002 FGAE, P = .028 UGNCE, P = .151 CE) for overall recurrence rates. Enema modality, however, was not a significant source of heterogeneity for 48-hour (P = .461 CE, P = .706 UGNCE, P = .515 FGAE) or 24-hour recurrence rates (P = .471 CE, P = .702 UGNCE, P = .661 FGAE). Study quality, year of study publication, and country of origin were not found to be significant sources of heterogeneity for overall, 48-hour, or 24-hour recurrence rates. In post hoc regression analysis, estimated median age was not found to be significant for overall, 24-hour, or 48-hour recurrence rates.

Because the study by Bai et al accounted for nearly one-third of the
patients included in the overall recurrence rate data for UGNCE, we conducted a weighted meta-regression to estimate the effect of each method. Pooled estimates including the study by Bai et al\textsuperscript{63} were compared with pooled estimates excluding this study (Table 3). Inclusion of the study by Bai et al\textsuperscript{63} had minimal effect on the pooled estimate.

Learning effect was assessed by examining results by year. A significant trend was identified for quality score. Quality scores showed a significant trend (even using the multiple testing adjustment) with year (Spearman $r = 0.504$, $P = .0004$) for CE only. If studies are restricted to 1980 and later, there is no correlation between quality scores and year of publication (Supplemental Table 6). Of note, all studies of noncontrast reductions were published after 1980. The Begg test for publication bias was used and did not demonstrate bias for any of the outcome variables.

**DISCUSSION**

This meta-analysis of published studies demonstrates that an individual's risk of having an early (within 24 to 48 hours) recurrent intussusception after a successful enema reduction is low. In addition, the risk of recurrence is independent of enema type, study location, year of study completion, and study quality. The risk of recurrence in the first 24 hours post reduction is 2.2% to 3.9% and 2.7% to 6.6% in the first 48 hours. Assuming a 24-hour recurrence risk of 3.9%, it would require hospitalizing 26 patients for 24 hours to identify a single recurrence. This suggests that the vast majority of recurrences will not be identified by overnight hospitalization. In addition, recurrent intussusceptions can be safely and successfully reduced via repeat enema, and significant complications associated with enema reduction are rare. Multiple studies supporting outpatient management after successful enema reduction have demonstrated high rates of success with repeat enema reduction without delayed complications.\textsuperscript{16–20} In their series of 1340 patients, Nirmis et al\textsuperscript{20} reported success rates as high as 96% with barium enema and 92% with air enema.
There are several limitations to our study. First, because of the relative infrequency with which intussusception occurs, most of the studies included in this meta-analysis are retrospective studies. Many are small, and they vary widely in quality. As such, we attempted to measure and control for the quality of reporting for each study. Second, the studies differ in both known features, such as enema reduction technique or setting, and possibly unknown features that we were unable to measure. As these differences were expected, we used random effects modeling in our analyses, adjusting for the suspected confounders and providing more conservative estimates of confidence limits. Finally, the number of studies reporting the specific timing of recurrences was limited.

Despite these limitations, our study improves the understanding of the risk of early (within 24 to 48 hours) recurrence for an individual patient, and strongly suggests that that risk is low. In combination with the knowledge that serious postreduction complications are rare and that recurrences can be safely and successfully managed nonoperatively, it is reasonable to suggest that outpatient management in an appropriately selected population of well-appearing patients would be appropriate. In addition to the risk of recurrence, providers need to consider clinical factors, such as ease of reduction, number of reduction attempts, and a patient’s hemodynamic status pre- and postreduction when making disposition decisions. Consistent with other recently published studies, our results support the development of multidisciplinary guidelines for the appropriate outpatient management of those asymptomatic patients who have had successful enema reduction.

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**THE NEW LIBRARY:** A few weeks ago, my wife and I went downtown to the Public
Library to hear a talk. Amazingly, the place was packed. I have been in libraries of
various sizes over the past year: the small Charlotte, VT library, the huge New York
City Library, and the medium sized Burlington Library. All were humming with
activity. A few years ago, many predicted the demise of the public library citing
the rise of the internet, e-readers, and social media. However, libraries have been
busy re-inventing themselves and not only have staved off extinction but are
thriving. As reported in *The New York Times* (U.S.: March 7, 2014), physical visits to
libraries are off the charts. For example, the Boston Public Library had an almost
50% increase in the number of visitors in 2012 to more than 1.7 million. My son
can borrow movies, physical books, and electronic books from the Burlington
Library. Some libraries offer access to 3-D printers, laser cutters, and milling
machines, while others lend out musical instruments or plots of land on which to
practice organic farming. Many are trying to lure visitors with wide open spaces,
lobbies, and even food courts. I see people eating in libraries all the time — which
when I was a child would have led to automatic dismissal and revocation of my
library card.

Librarians too have different jobs. Rather than answering single questions, they
may act as information navigators to help customers sift through many, many
answers. While some libraries have gone completely digital — meaning that no
books are present at all — all-digital libraries have not been entirely successful
and have often brought back books. The reason is that while almost a third of
Americans read e-books, in 2012 less than 5% read e-books only. I for one am
thrilled with the change. I like the fact there are still large tables and comfy
chairs, but now there are food courts, computers, internet access, and all kinds
of activities that appeal to not only my parents and I, but my children as well.

*Noted by WVR, MD*
**ERRATA**

**Freed et al. Specialty Specific Comparisons Regarding Perspectives on Fellowship Training. Pediatrics. 2014;133(suppl 2):S76–S77**

An error occurred in the print edition of the supplement article by Freed et al, titled “Specialty Specific Comparisons Regarding Perspectives on Fellowship Training” published in the May 2014 supplement issue of Pediatrics (2014;133[suppl 2]:S76–S77; doi: 10.1542/peds.2013-3861F). On page S77, Reference 1, the link reads: “www.abp.org/links/sctc.html”. This should have read: “http://pediatrics.aappublications.org/content/133/Supplement_2/S76/suppl/DCSupplemental”.

doi:10.1542/peds.2014-1365


An error occurred in the article by Gray et al, titled “Recurrence Rates After Intussusception Enema Reduction: A Meta-analysis” published in the July 2014 issue of Pediatrics (2014;134(1):110–119; doi:10.1542/peds.2013-3102). On page 110, under the Results heading of the Abstract, this reads: “Overall recurrence rates were 11.6% (95% confidence interval [CI] 10.0%–13.3%) for contrast enema (CE), 6.9% (95% CI 5.1%–9.0%) for ultrasound-guided noncontrast enema (UGNCE), and 7.7% (95% CI 5.6%–10.0%) for fluoroscopy-guided air enema (FGAE). Recurrence rates within 24 hours were 2.7% (95% CI 1.2%–4.8%) for CE, 0.9% (95% CI 0.1%–4.8%) for UGNCE, and 1.5% (95% CI 0.0%–6.2%) for FGAE. Recurrence rates within 48 hours were 3.6% (95% CI 1.9%–5.9%) for CE, 3.1% (95% CI 0.1%–10.4%) for UGNCE, and 1.9% (95% CI 0.1%–5.6%) for FGAE.”

This should have read: “Overall recurrence rates were 12.7% (95% confidence interval [CI]: 11.1%–14.4%, I² = 28.8%) for contrast enema (CE), 7.5% (95% CI: 5.7%–9.8%, I² = 52.4%) for ultrasound-guided noncontrast enema (UGNCE), and 8.5% (95% CI: 6.9%–10.4%, I² = 50.1%) for fluoroscopy-guided air enema (FGAE). Recurrence rates within 24 hours were 3.9% (95% CI: 2.2%–6.7%, I² = 47.0%) for CE, 3.9% (95% CI: 1.5%–10.1%, I² = 0.0%) for UGNCE, and 2.2% (95% CI: 0.7%–6.5%, I² = 59.8%) for FGAE. Recurrence rates within 48 hours were 5.4% (95% CI 3.7%–7.8%, I² = 32.3%) for CE, 6.6% (95% CI: 4.0%–10.7%, I² = 0.0%) for UGNCE, and 2.7% (95% CI: 1.2%–6.5%, I² = 73.8%) for FGAE.” The correct values were reflected in the body of the manuscript.

doi:10.1542/peds.2014-2089
Recurrence Rates After Intussusception Enema Reduction: A Meta-analysis
Matthew P. Gray, Shun-Hwa Li, Raymond G. Hoffmann and Marc H. Gorelick
*Pediatrics* 2014;134;110; originally published online June 16, 2014;
DOI: 10.1542/peds.2013-3102

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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