Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

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abstract

CONTEXT: Nonoperative treatment (NOT) with antibiotics alone of acute uncomplicated appendicitis (AUA) in children has been proposed as an alternative to appendectomy.

OBJECTIVE: To determine safety and efficacy of NOT based on current literature.

DATA SOURCES: Three electronic databases.

STUDY SELECTION: All articles reporting NOT for AUA in children.

DATA EXTRACTION: Two reviewers independently verified study inclusion and extracted data.

RESULTS: Ten articles reporting 413 children receiving NOT were included. Six, including 1 randomized controlled trial, compared NOT with appendectomy. The remaining 4 reported outcomes of children receiving NOT without a comparison group. NOT was effective as the initial treatment in 97% of children (95% confidence interval [CI] 96% to 99%). Initial length of hospital stay was shorter in children treated with appendectomy compared with NOT (mean difference 0.5 days [95% CI 0.2 to 0.8]; $P = .002$). At final reported follow-up (range 8 weeks to 4 years), NOT remained effective (no appendectomy performed) in 82% of children (95% CI 77% to 87%). Recurrent appendicitis occurred in 14% (95% CI 7% to 21%). Complications and total length of hospital stay during follow-up were similar for NOT and appendectomy. No serious adverse events related to NOT were reported.

LIMITATIONS: The lack of prospective randomized studies limits definitive conclusions to influence clinical practice.

CONCLUSIONS: Current data suggest that NOT is safe. It appears effective as initial treatment in 97% of children with AUA, and the rate of recurrent appendicitis is 14%. Longer-term clinical outcomes and cost-effectiveness of NOT compared with appendicectomy require further evaluation, preferably in large randomized trials, to reliably inform decision-making.

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Dr Georgiou performed the systematic review and data extraction, performed the analysis, and wrote the draft of the manuscript; Dr Eaton designed the study, performed the systematic review and data extraction, performed the analysis, and revised the manuscript; Dr Stanton designed the study, performed the analysis, and revised the manuscript; Dr Pierro conceived and designed the study and revised the manuscript; Dr Hall conceived and designed the study, performed the systematic review and data extraction, performed the analysis, and wrote the draft of the manuscript; and all authors approved the final manuscript submitted.

This trial has been registered with the PROSPERO International prospective register of systematic reviews (registration CRD42015026994).

DOI: 10.1542/peds.2016-3003

Accepted for publication Nov 21, 2016

To cite: Georgiou R, Eaton S, Stanton MP, et al. Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis. *Pediatrics.* 2017;139(3):e20163003

Acute appendicitis is one of the most common general surgical emergencies worldwide, with an estimated lifetime risk between 7% and 8%.[1] The condition is of particular relevance to children because the peak in the incidence of appendicitis is in the second decade of life.[1,2] Overall, acute appendicitis is diagnosed in 1% to 8% of children presenting to the emergency department with acute abdominal pain.[3–5] The financial burden of treating appendicitis is huge.

The mainstay of treatment of acute appendicitis has been surgical ever since Fitz's report over 130 years ago[6] before the discovery of antibiotics. Consequently tens of thousands of appendectomies are performed in children worldwide every year. However, in recent years, the dogma that surgery is required has been challenged, and there is growing literature to suggest that antibiotics without surgery may be an effective treatment of acute appendicitis in adults[7–9] and more recently in children.[10–12] This nonoperative treatment (NOT) of acute appendicitis in children remains controversial and unproven at present due to a lack of randomized controlled trials (RCTs).[13]

NOT may be extremely appealing to some children and their families and may have benefits over appendectomy. Families of children with appendicitis frequently ask whether surgery is necessary or whether alternatives are available. Surgery requires general anesthesia, which, although a relatively safe intervention, clearly carries some risks. Appendectomy for uncomplicated appendicitis is generally considered a low-risk procedure, but complications after surgery occur in up to 7% of children.[14,15] These risks of appendectomy should be balanced against the risk of recurrent appendicitis in a child who receives NOT. The aim of this review is to determine the efficacy and safety of NOT for acute uncomplicated appendicitis (AUA) in children in the reported literature.

METHODS

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews[16] and was registered with the PROSPERO International prospective register of systematic reviews (registration CRD42015026994) on October 12, 2015.

Systematic Review and Search Strategy

We performed a systematic review of the literature via an electronic search in Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase in December 2015 to find relevant articles. We used the following search terms: "nonoperative," "non-operative," "conservative," "appendicitis," "child," "children." Full details of the search strategy for Medline are available in the Supplemental Information. The search was limited to articles published in English. Study selection was performed independently by 2 researchers with any disagreements resolved by a third. Studies that were unpublished or published in abstract form only were excluded at screening stage. The online systematic review management program Covidence (www.covidence.org) was used to coordinate the screening and data collection process. The reference lists of included articles were also scrutinized for additional articles meeting selection criteria that may have been missed in our initial search.

Study Selection Criteria

Studies were selected according to the following predefined criteria:

1. types of studies: any study design reporting NOT of AUA in children;
2. types of participants: children (<18 years of age); and
3. exclusion criteria: studies that reported NOT as treatment of complicated appendicitis (such as perforated appendicitis, ruptured appendicitis, appendicitis with an abscess, or appendix mass), studies that included a mixed population of adults and children, or studies that reported NOT as treatment of acute appendicitis only in children with malignancy.

We therefore included all relevant articles that reported any NOT regimen for AUA in children with or without a comparative group of children undergoing surgical treatment.

Quality Assessment

RCTs

We used the Jadad Scale[17] to assess the quality of the 1 RCT included in this review. This scale assesses risk of bias in RCTs and assigns a final score of 0 (highest risk of bias) to 5 (lowest).

Nonrandomized Studies

We used the methodological index for nonrandomized studies (MINORS) criteria to assess the quality of all eligible non-RCTs.[18] MINORS is a validated tool designed to assess the methodological quality of non-RCTs, whether comparative or noncomparative. It comprises 12 items, the first 8 being specifically for noncomparative studies, with all 12 items being relevant to comparative studies. The highest attainable score is 16 for noncomparative studies and 24 for comparative studies, with higher scores indicative of greater methodological quality.

Data Extraction

Data were extracted independently by 2 reviewers and differences resolved by consensus if necessary.

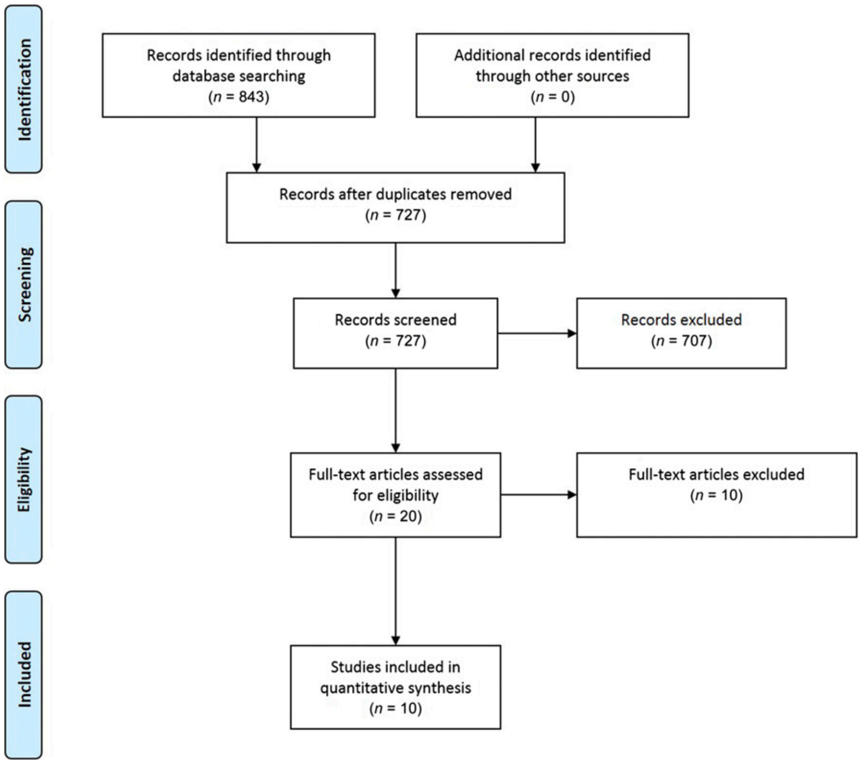

FIGURE 1
Article selection flowchart.

The primary outcome was the efficacy of NOT, defined as discharge from hospital without appendectomy during the initial hospital episode. Secondary outcomes were concern over the safety or adverse effects of NOT, complications (no further definition was applied other than as defined in the source article, but this outcome did not include recurrent appendicitis), long-term efficacy of NOT (defined as remaining without appendectomy at final reported follow-up), recurrent appendicitis (confirmed by histology or treated with a second course of NOT), and length of hospital stay (both during the initial admission and total hospital stay required during follow-up).

Statistical Analysis

We used a 1-sided meta-analysis to estimate the overall efficacy of NOT for acute appendicitis across all studies using a random effects model in Meta-Analyst (Tufts University, Medford, MA).

Two-sided meta-analysis was used to compare outcomes between NOT and appendectomy in comparative studies by using random-effects models in Review Manager (v5.3, Cochrane Collaboration). Estimates of weighted mean difference for continuous variables (inverse variance method) and risk difference for categorical variables (Mantel-Haenszel method) with 95% confidence intervals (CIs) were generated. Proportions with adjusted 95% CIs were generated for 1-sided meta-analyses.

RESULTS

Search Results and Study Selection

Figure 1 summarizes the results of the search and selection of articles. Eleven studies met the selection criteria. One of these[19] was excluded because it reported interim results of a study that were subsequently reported in greater detail, and the latter report was included.[10] Therefore, 10 studies were included in the final quantitative analysis (Table 1).

Study Characteristics

Among the 10 studies included, 7 were prospective and 3 were retrospective. Six studies compared children treated with either NOT or appendectomy, and the remaining 4 reported outcomes of children receiving NOT without a comparison group. Outcomes of 766 children, of whom 413 were initially treated with NOT, were included. There was just 1 RCT,[11] which was a pilot RCT designed to inform a future larger efficacy study. As such it was not powered to provide definitive evidence of the efficacy of NOT versus appendectomy.

Study characteristics varied in terms of (1) the techniques used to diagnose AUA, (2) antibiotic regimen used as NOT (Table 2), and (3) the criteria used to select children for each treatment group. All studies used ultrasound in addition to clinical and laboratory parameters to confirm a diagnosis of AUA in most, if not all, children, with many also using either computed tomography or MRI. In terms of allocation to NOT, the RCT by Svensson et al[11] was the only study to randomly allocate children to treatment group. Of the other studies, 4 used NOT routinely in all patients meeting inclusion criteria,[12,20,23,25] whereas the remaining 5 studies all discussed both NOT and appendectomy and allowed parents to make a choice either as part of a prospective evaluation of NOT[10,21,22,27] or as part of routine practice.[24]

The methodological quality of the studies is summarized in Table 1. The single RCT had a Jadad score of 3 of 5 with 2 points deducted for a lack of blinding. The median MINORS score for comparative studies was 16 of 24 (range 13–22) and for noncomparative studies 10 of 16 (7–12).

TABLE 1 Characteristics of Included Studies

Study	Country	Study Interval	Publication Year	Study Design	Patients *n*		Follow-up for NOT Cases, mo	Jadad Score	MINORS Score
					NOT	Surgery			
Abes[20]	Turkey	2003–2006	2007	Retrospective, noncomparative	16	—	12 in all	—	7/16
Armstrong[12]	Canada	2012–2013	2014	Retrospective, comparative	12	12	Mean 6.5	—	16/24
Gorter[21]	Netherlands	2012–2014	2015	Prospective, noncomparative	25	—	2 in all	—	12/16
Hartwich[22]	United States	2012–2014	2015	Prospective, comparative	24	50	Mean 14	—	20/24
Kaneko[23]	Japan	1999–2001	2015	Prospective, noncomparative	22	—	Mean 36, range 24–45	—	9/16
Koike[24]	Japan	2004–2010	2014	Retrospective, comparative	130	114	Mean 30.6, minimum 18	—	13/24
Minneci[10]	United States	2012–2013	2015	Prospective, comparative	37	65	Median 21	—	22/24
Steiner[25]	Israel	2013–2014	2015	Prospective, noncomparative	45	—	Range 6–14	—	10/16
Svensson[26]	Sweden	2012–2013	2015	RCT	24	26	12 in all	3/5	—
Tanaka[27]	Japan	2007–2013	2015	Prospective, comparative	78	86	Mean 51	—	16/24

Safety and Initial Efficacy of NOT

Four hundred and thirteen children were either randomized to or selected for NOT. No study reported any adverse events related to NOT or concern over the safety of NOT in children who underwent this course of treatment. Overall, NOT was successful as initial treatment in 97% (95% CI 95.5% to 98.7%) of children during the initial hospital episode (Fig 2). Heterogeneity was low for this outcome measure (I^2 = 0%, P = .7). NOT was unsuccessful as initial treatment in 17 of 413 children, all of whom underwent appendectomy during their initial hospital admission.

Recurrent Appendicitis and Long-term Efficacy of NOT

Duration of follow-up varied between included studies (Table 1). Sixty-eight children of the 396 who had initial successful NOT were diagnosed with recurrent appendicitis during the follow-up period. This includes 19 children from 2 studies that were offered a second course of NOT for recurrence.[24,27] The remaining 49 of these 68 children underwent appendectomy for recurrent acute appendicitis, and all had histologically confirmed recurrence. The adjusted incidence of recurrent appendicitis is 14% (95% CI 7% to 21%; Fig 3); however, there was marked heterogeneity between these studies (I^2 = 80%, P < .001).

During the reported follow-up period, an additional 11 who had successful initial NOT underwent appendectomy for a variety of reasons including recurrent acute appendicitis, ongoing abdominal pain, and parental choice. The long-term efficacy of NOT, defined as those children who have not had appendectomy at final reported follow-up, was 82% (95% CI 77% to 87%; Fig 4), with low heterogeneity between these studies (I^2 = 34%, P = .14).

Comparative Outcomes of NOT and Appendectomy

Six of the 10 included studies compared NOT with appendectomy. These studies report outcomes in 658 children of whom 305 (46%) received NOT and 353 (54%) primary appendectomy. Duration of initial hospital stay was reported in 4 studies (340 children)[10–12,27] and was shorter by a mean of 0.5 days (95% CI 0.2 to 0.8) in children undergoing appendectomy than those treated with NOT (Fig 5). Total length of hospital stay at final reported follow-up, including for readmissions, was reported in just 2 studies.[12,24] This outcome includes hospital admission for any complication related to disease or primary treatment including, for example, recurrence of appendicitis in children who had initially had NOT. Mean duration of follow-up in these 2 studies was 5.3 months[12] and 54 months.[24] Total duration of hospital stay including during follow-up was similar between children treated initially with NOT and appendectomy (weighted mean difference 1.1 days, 95% CI −1.2 to 3.5; P = .34; Fig 6) although heterogeneity between these 2 studies was high (I^2 = 93%, P = .0002). Total complications were reported in 5 of the 6 comparative studies (Table 3 and Fig 7). Risk of complications was similar between children treated with either NOT or appendectomy (risk difference 2%, 95% CI 0% to 5%; P = .1) with low heterogeneity (I^2 = 0%, P = .47).

DISCUSSION

We have systematically reviewed the existing literature reporting NOT of AUA in children and included 10 studies reporting 413 children treated with NOT. Given the frequency of acute appendicitis in the pediatric population, this suggests that NOT as a treatment modality remains in its infancy and is yet to become "mainstream." The included studies were all published

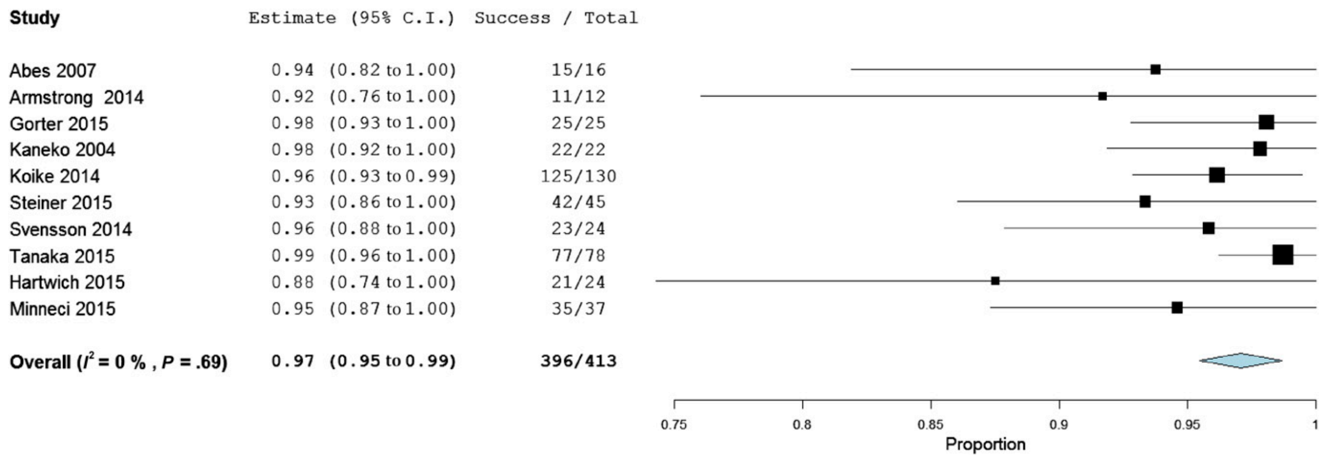

FIGURE 2
Proportion of children with AUA who were successfully treated with NOT during their initial hospital admission.

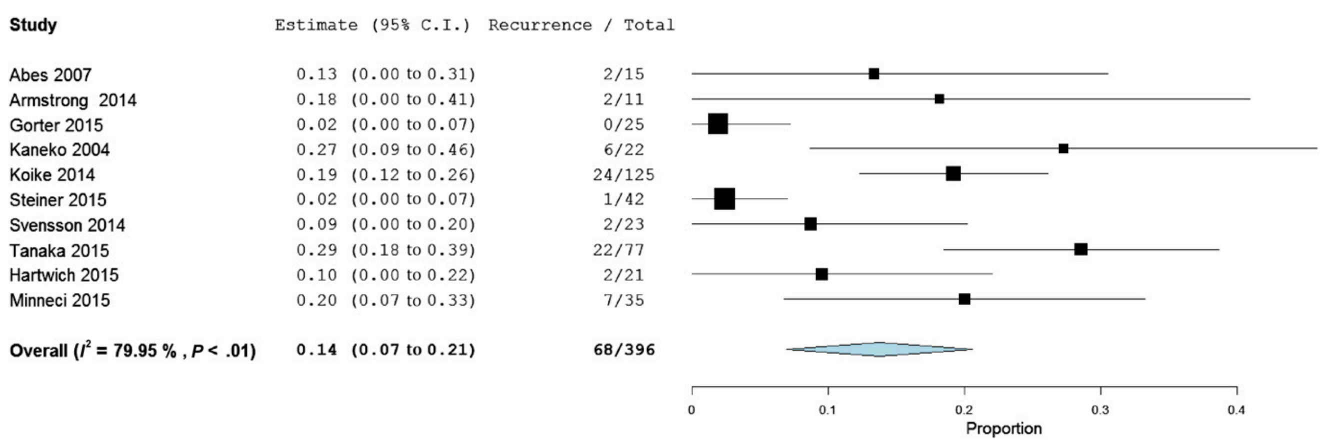

FIGURE 3
Estimate of incidence of recurrent appendicitis during follow-up period in children with AUA that was initially successfully treated with NOT.

TABLE 2 Antibiotic Protocol for Each Study

Study	Intravenous Antibiotic Regimen		Oral Antibiotic Regimen	
	Antibiotic	Duration	Antibiotic	Duration
Abes[20]	Sulbactam and ornidasole	48-h minimum	Not specified	
Armstrong[12]	Ciprofloxacin and metronidazole or ampicillin, gentamicin, and metronidazole	24-h minimum	Co-amoxiclav	To complete 7-d total course
Gorter[21]	Co-amoxiclav and gentamicin	48-h minimum	Co-amoxiclav	5 d
Hartwich[22]	Piperacillin-tazobactam	2 doses	Co-amoxiclav	7 d
Kaneko[23]	Flomoxef	Until abdominal tenderness resolved	Not specified	
Koike[24]	Cefoperazone	48-h minimum	Cefcapene pivoxil	3 d
Minneci[10]	Piperacillin-tazobactam or ciprofloxacin and metronidazole	24-h minimum	Co-amoxiclav or ciprofloxacin and metronidaxole	To complete 10-d total course
Steiner[25]	Ceftriaxone and metronidazole	72–120 h	Co-amoxiclav	5 d
Svensson[11]	Meropenem and metronidazole	48-h minimum	Ciprofloxacin and metronidazole	8 d
Tanaka[27]	First line: cefmetazole; second line: sulbactam/ampicillin and ceftazidime; third line: meropenem or imipenem/cilastatin and gentamicin	Until CRP <.5 mg/dL	Not specified	

CRP, C-reactive protein.

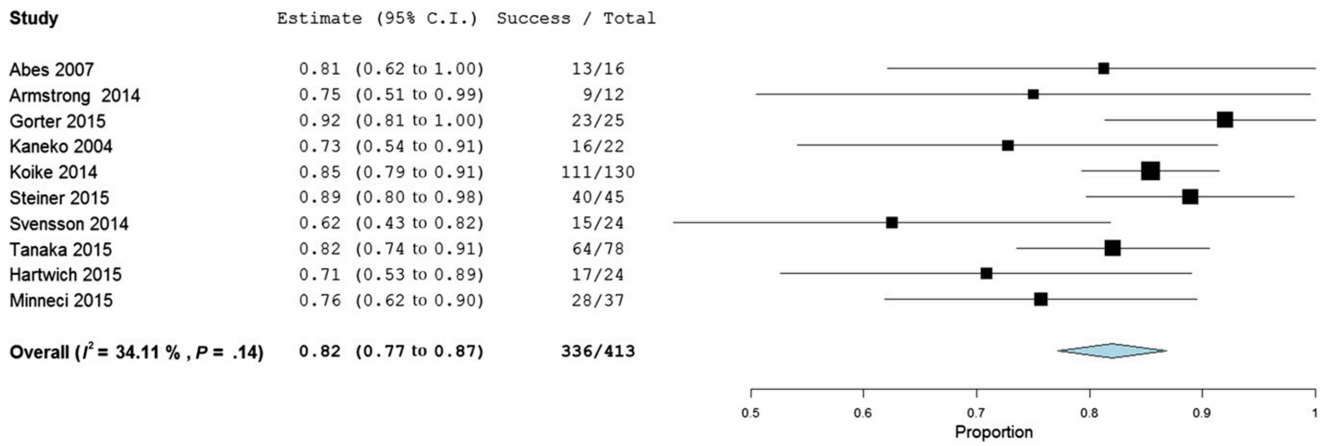

FIGURE 4
Estimate of long-term efficacy of NOT defined as no appendectomy (any cause) at last reported follow-up.

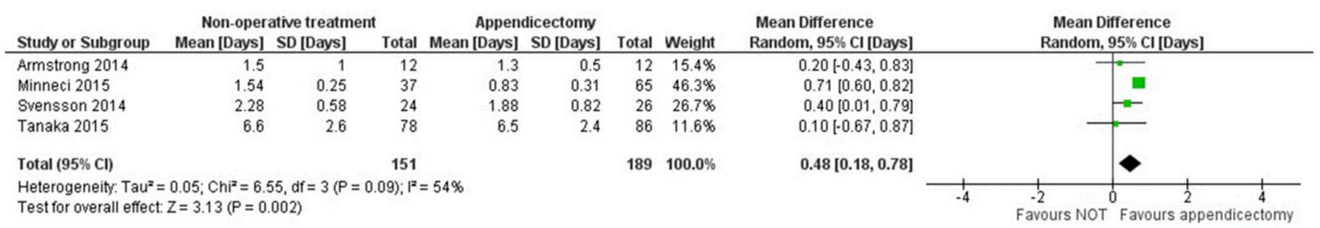

FIGURE 5
Forest plot comparing initial length of stay between NOT and appendectomy.

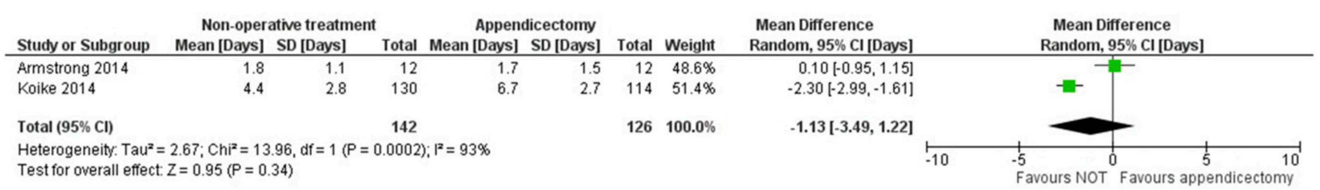

FIGURE 6
Forest plot comparing total length of stay (including readmissions) between NOT and appendectomy.

in the past 10 years and are mainly cohort studies with or without a comparative group of children who were treated with appendectomy. Of note none originated from the United Kingdom. The lack of large high-quality RCTs and prospective evaluations confirms that NOT is a treatment yet to be formally evaluated in children.

Importantly, we have not identified any evidence to suggest that NOT is an unsafe treatment of children with AUA. No study reported any safety concern related to the use of NOT, and no study reported any specific adverse events related to NOT. No studies reported perforated appendicitis after NOT. Complications after appendectomy are rare, as are complications after NOT. To compare the risk of these rare events, it was decided a priori to use risk difference as an outcome measure, because this allows studies with no events in either arm to meaningfully contribute to the meta-analysis.[26] The data also suggest that in children with AUA, NOT is highly effective; 97% of children were

TABLE 3 Complications as Reported in Source Articles

NOT (*n* = 175)	Appendectomy (*n* = 239)
Surgical site infection (1)[a]	Surgical site infection (2)
	Prolonged ileus (2)
	Readmission (1)
	Reoperation (1)
	Other (not further specified, 3)

Only data from articles reporting complications are included.
[a] In a child who failed initial NOT and underwent appendectomy.

Study or Subgroup	Non-operative treatment Events	Total	Appendicectomy Events	Total	Weight	Risk Difference Random, 95% CI
Armstrong 2014	1	12	2	12	1.1%	-0.08 [-0.35, 0.18]
Hartwich 2015	0	24	0	50	20.8%	0.00 [-0.06, 0.06]
Minneci 2015	0	37	5	65	13.5%	-0.08 [-0.15, -0.00]
Svensson 2014	0	24	0	26	13.9%	0.00 [-0.07, 0.07]
Tanaka 2015	0	78	2	86	50.6%	-0.02 [-0.06, 0.02]
Total (95% CI)		**175**		**239**	**100.0%**	**-0.02 [-0.05, 0.00]**
Total events	1		9			

Heterogeneity: Tau² = 0.00; Chi² = 3.52, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.62 (P = 0.10)

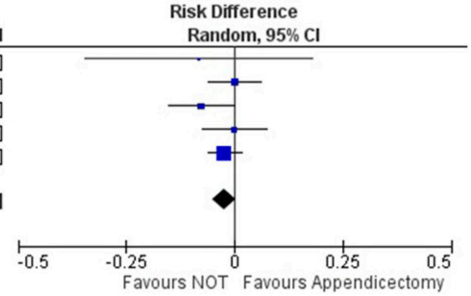

FIGURE 7
Forest plot comparing complications between NOT and appendectomy.

successfully discharged from their initial hospital admission after NOT. Together, these 2 facts support the further prospective evaluation of NOT compared with appendectomy in this population of children.

As may be anticipated, the long-term efficacy of NOT (as we have defined it) is lower than this initial 97%. During the follow-up reported, it is 82%. Although we have not formally analyzed it, we noted a tendency for long-term efficacy to be lower in studies with longer duration of follow-up. Although some surgeons may feel that this demonstrates inferiority of NOT to appendectomy, a long-term efficacy of 82% still equates to 4 of every 5 children not having had surgery (and general anesthesia).

When compared with the adult literature, the data synthesized here suggest that antibiotic treatment of acute appendicitis is at least as effective in children as in adults. The most recent systematic review of adult RCTs found that antibiotics were initially effective in 84%, and of these 79% had no further problem during 1 year of follow-up.[28] It is possible that the higher efficacy we have identified in the pediatric population is in part due to study design and in particular to differing selection criteria between pediatric observational studies and adult RCTs. In a recent adult observational study, success rate of NOT was 88% at 7 days and 83% at 1 year.[29]

Although it is tempting to draw conclusions regarding comparative efficacy from our comparative analysis of NOT and appendectomy, we consider that to do so would be misleading because of the nature of the underlying studies. We believe the best use of these data is to act as justification for the future investigation of NOT and to guide sample size calculations in such studies where appropriate. The lack of major differences in outcomes between NOT and appendectomy and apparent safety of NOT is consistent with there being equipoise between these treatment modalities, this being a prerequisite for any RCT. The only statistically significant difference in our comparative analysis was a shorter duration of initial hospital stay in children undergoing appendectomy compared with those treated with NOT. A similar finding is reported in adult RCTs.[28] We note that the majority of these early-phase studies evaluating NOT prescribed a minimum duration of antibiotics and/or hospital stay before initial hospital discharge that may have influenced this outcome. This and other limitations (discussed next) of study design, heterogeneity between studies, and methodology prevent more robust conclusions.

There are limitations of this study and the source data that should be appreciated when considering how to apply the data synthesized here to clinical practice and research. These include the inclusion of data from retrospective studies, those from noncomparative studies, and those from nonrandomized studies. All these features increase the possibility that bias, from a number of possible sources, has influenced our results. We therefore caution against the use of these data as definitive comparative evidence and await future randomized studies. We also acknowledge differences in selection criteria, diagnostic techniques, and antibiotic regimes between studies in children treated with NOT. Accordingly, we have used a random effects model for all meta-analyses. Despite these differences between studies there was minimal heterogeneity between the outcomes of short- and long-term efficacy of NOT (Figs 2 and 4). However, for the outcome of recurrent appendicitis, there was significant heterogeneity between studies related, we suspect in part, to duration of follow-up (Fig 3). Future studies should ensure adequate duration and completeness of follow-up for the detection of recurrence. Although the time span during which recurrent appendicitis may occur is clearly much longer in children than in adults, a minimum of 1 year for all participants would seem appropriate and feasible in a research context.

A number of outcomes that are notably missing in the existing literature are important when considering the role of NOT and appendectomy in the treatment of acute appendicitis in children. These include cost, cost-effectiveness, and patient and family quality of life. Future prospective research should include a comparison of these outcomes to enable a wider comparison not just at the level of the individual patient but for the health care system and society as a whole.

Although we have used initial discharge from hospital as the primary outcome for our study, we acknowledge that the overall decision of which treatment strategy to use may be based on more than this alone. It is quite likely that treatment decisions will be based on a combination of several outcomes including initial efficacy of treatment, incidence of complications, rate of recurrent appendicitis, and possibly incidence of negative appendectomy. Future studies should ensure adequate reporting of all these outcomes. Further work is underway to determine which of these outcomes should be included in the development of a Core Outcome Set for appendicitis in children.[30,31]

This study has provided a comprehensive review of the existing literature pertaining to NOT for AUA in children. As far as we are aware, it is the first such review to synthesize data specifically from children. The study highlights the lack of robust evidence comparing NOT with appendectomy in children but provides data that support and justify ongoing and future endeavors[31,32] to assimilate such evidence so that we can best serve the huge number of children who develop appendicitis every year. This review also confirms a position of equipoise between treatment approaches in such trials. Until such studies are completed, we would recommend that NOT of children with AUA be reserved for those participating in carefully designed research studies.

ACKNOWLEDGMENTS

Dr Hall is supported by the Southampton NIHR Biomedical Research Centre in nutrition. Dr Eaton is supported by Great Ormond Street Hospital NIHR Biomedical Research Centre and by Great Ormond Street Children's Charity. Dr Pierro is supported by the Robert M. Filler Chair of Paediatric Surgery, University of Toronto, Canada.

ABBREVIATIONS

AUA: acute uncomplicated appendicitis
CI: confidence interval
MINORS: methodological index for nonrandomized studies
NOT: nonoperative treatment
RCT: randomized controlled trial

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2017;139;
DOI: 10.1542/peds.2016-3003 originally published online February 17, 2017;

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