Efficacy and safety of non-operative treatment for acute uncomplicated appendicitis: A Meta-Analysis

Roxani Georgiou MRCS[1], Simon Eaton PhD[2], Michael P Stanton MD[1], Agostino Pierro FRCS[3], Nigel J Hall PhD[1,4]

Affiliations:
1. Department of Paediatric Surgery and Urology, Southampton Children's Hospital, Southampton, UK
2. UCL Institute of Child Health, London, UK
3. The Hospital for Sick Children, Toronto, Canada
4. Faculty of Medicine, University of Southampton, Southampton, UK

Short title: Non-operative treatment for acute appendicitis

Funding source: No funding was secured for this study

Financial disclosure: None of the authors have any financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Registration: PROSPERO International prospective register of systematic reviews (registration number CRD42015026994); registered on October 12th 2015.

Corresponding author
Nigel J Hall
University Surgery Unit, Faculty of Medicine, University of Southampton, Mailpoint 816, Southampton General Hospital, Tremona Road, Southampton SO16 6YD UK
Tel: 023 8120 6146 / 6677; Email n.j.hall@soton.ac.uk

CONTRIBUTORSHIP STATEMENT

Roxani Georgiou performed the systematic review and data extraction, performed the analysis, wrote the draft of the manuscript and approved the final manuscript submitted.

Simon Eaton designed the study, performed the systematic review and data extraction, performed the analysis, revised the manuscript and approved the final manuscript submitted.

Michael Stanton designed the study, performed the analysis, revised the manuscript and approved the final manuscript submitted.

Agostino Pierro conceived and designed the study, revised the manuscript and approved the final manuscript submitted.

Nigel Hall conceived and designed the study, performed the systematic review and data extraction, performed the analysis, wrote the draft of the manuscript and approved the final manuscript submitted.

ABSTRACT

Context: Non-operative treatment (NOT) with antibiotics alone of acute uncomplicated appendicitis (AUA) in children has been proposed as an alternative to appendicectomy.

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 one RCT, compared NOT with appendicectomy. The remaining four reported outcomes of children receiving NOT without a comparison group. NOT was effective as the initial treatment in 97% of children (95%CI 96, 99). Initial length of hospital stay was shorter in children treated with appendectomy compared to NOT (mean difference 0.5 days [95%CI 0.2, 0.8]; p=0.002). At final reported follow-up (range 8 weeks – 4 years), NOT remained effective (no appendicectomy performed) in 79% of children (95%CI 73, 86%). Recurrent appendicitis occurred in 14% (95%CI 7, 21). Complications, and total length of hospital stay during follow-up were similar for NOT and appendicectomy. No serious adverse events related to NOT were reported.

Limitations: The lack of prospective randomised 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 to appendicectomy require further evaluation, preferably as large randomised trials to reliably inform decision making.

INTRODUCTION

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 since there is a peak in the incidence of appendicitis 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 more than 130 years ago[6], before the discovery of antibiotics. Consequently tens of thousands of appendicectomies 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 for acute appendicitis in adults [7-9] and more recently in children [10-12]. This non-operative treatment (NOT) of acute appendicitis in children remains controversial and unproven at present due to a lack of randomised controlled trials [13].

NOT may be extremely appealing to some children and their families and may have benefits over appendicectomy. Families of children with appendicitis frequently ask whether surgery is necessary or whether alternatives are available. Surgery requires general anaesthesia which, although a relatively safe intervention, does clearly carry some risks. Whilst appendicectomy for uncomplicated appendicitis is generally

considered a low risk procedure, complications following surgery occur in up to 7% of children[14, 15]. These risks of appendicectomy 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 in children in the reported literature.

METHODS

This study was conducted and reported in accordance with the PRISMA guidelines for systematic reviews [4] and was registered with the PROSPERO International prospective register of systematic reviews (registration number CRD42015026994) on October 12th 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 Appendix 1. The search was limited to articles published in English. Study selection was performed independently by two 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 scrutinised 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 non-operative treatment for acute uncomplicated appendicitis in children
2. *Types of participants:* children (<18 years of age)
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 acute uncomplicated appendicitis in children with or without a comparative group of children undergoing surgical treatment.

Quality assessment

Randomised controlled trials (RCTs)

We used the Jadad Scale[16] to assess the quality of the one RCT included in this review. This scale assesses risk of bias in RCTs and assigns a final score of zero (highest risk of bias) to five (lowest).

Non-randomised studies (non-RCTs)

We used the methodological index for non-randomised studies (MINORS) criteria to assess the quality of all eligible non-RCTs [17]. MINORS is a validated tool designed to assess the methodological quality of non-RCTs, whether comparative or non-comparative. It is comprised of 12 items, the first 8 being specifically for non-comparative studies, whereas all 12 items are relevant to comparative studies. The highest attainable score is 16 for non-comparative studies and 24 for comparative studies with higher scores indicative of greater methodological quality.

Data extraction

Data were extracted independently by two reviewers and differences resolved by consensus if necessary. The primary outcome was the efficacy of NOT, defined as discharge from hospital without appendicectomy 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 appendicectomy 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 one-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, Massachusetts, USA). Two-sided meta-analysis was used to compare outcomes between NOT and appendicectomy in comparative studies using random-effects models in Review Manager (v5.3, Cochrane Collaboration). Estimates of weighted mean difference for continuous variables and risk difference for categorical variables with 95% confidence intervals (95%CI) were generated. Proportions with adjusted 95%CI were generated for one-sided meta-analyses.

RESULTS

Search results and study selection

Figure 1 summarises the results of the search and selection of articles. A total of 11 studies met the selection criteria. One of these[18] was excluded since it reported interim results of a study that was subsequently reported in greater detail and this report was included [10]. Therefore 10 studies were included in the final quantitative analysis (Table 1).

Study characteristics

Among the 10 included studies, 7 were prospective and 3 were retrospective. Six studies compared children treated with either NOT or appendicectomy whilst 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 one 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 appendicectomy.

Study characteristics varied in terms of (i) the techniques used to diagnose AUA; (ii) antibiotic regime used as NOT (Table 2) and (iii) 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 acute uncomplicated appendicitis in most, if not all, children, with many also using either computed tomography (CT) scan or magnetic resonance imaging (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, four used NOT routinely in all patients meeting inclusion criteria [12, 19-21] whereas the remaining five studies all discussed both NOT and appendicectomy and allowed parents to make a choice either as part of a prospective evaluation of NOT [10, 22-24] or as part of routine practice [25].

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

Safety and initial efficacy of NOT

Four hundred and thirteen children were either randomised to, or selected for NOT. No study reported any adverse events related to NOT nor 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 95.5-98.7) of children during the initial hospital episode (Figure 2). Heterogeneity was low for this outcome measure (I^2=0%, p=0.7). NOT was unsuccessful as initial treatment in 17/413 children, all of whom underwent appendicectomy 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 two studies that were offered a second course of NOT for recurrence [23, 25]. The remaining 49 of these 68 children underwent appendicectomy for recurrent acute appendicitis and all had histologically confirmed recurrence. The adjusted incidence of recurrent appendicitis is 14% (95%CI 7, 21; Figure 3), however there was marked heterogeneity between these studies (I^2=80%, P<0.001).

During the reported follow-up period a further 11 who had successful initial NOT underwent appendicectomy 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 appendicectomy at final reported follow-up was 82% (95%CI 77, 87; Figure 4), with low heterogeneity between these studies (I^2=34%, p=0.14).

Comparative outcomes of NOT and appendicectomy

Six of the 10 included studies compared NOT with appendicectomy. These studies report outcomes in 658 children of whom 305 (46%) received NOT and 353 (54%) primary appendicectomy. Duration of initial hospital stay was reported in 4 studies (340 children) [10, 12, 23, 26] and was shorter by a mean of 0.5 days (95%CI 0.2, 0.8) in children undergoing appendicectomy than those treated with NOT (Figure 5). Total length of hospital stay at final reported follow-up, including for re-admissions, was reported in just two studies [12, 25]. 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 two studies was 5.3 months [12] and 54 months [25]. Total duration of hospital stay including during follow-up was similar between children treated initially with NOT and appendicectomy (weighted mean difference 1.1 days [95%CI -1.2, 3.5]; p=0.34; Figure 6) although heterogeneity between these two studies was very high (I^2=93%, p=0.0002). Total complications were reported in 5 of the 6 comparative studies (Table 3, Figure 7). Risk of complications was similar between children treated with either NOT or appendicectomy (risk difference 2% [95%CI 0, 5%]; p=0.1) with low heterogeneity (I^2=0.%, p=0.47).

DISCUSSION

We have systematically reviewed the existing literature reporting NOT of acute uncomplicated appendicitis in children and included 10 studies reporting 413 children treated with NOT. Given the frequency of acute appendicitis in the paediatric 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 in the last 10 years and are mainly cohort studies with or without a comparative group of children who were treated with appendicectomy. Of note there were none originating 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 for children with acute uncomplicated appendicitis. 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 following NOT. Complications following appendicectomy are rare, as are complications following NOT. In order to compare the risk of these rare events, it was decided *a priori* to use risk difference as an outcome measure, as this allows studies with no events in either arm to meaningfully contribute to the meta-analysis.[27] The data also suggest that in children with acute uncomplicated appendicitis NOT is highly effective – 97% of children were successfully discharged from their initial hospital admission following NOT. Together, these two facts support the further prospective evaluation of NOT compared to appendicectomy 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 analysed it, we noted a tendency for long term efficacy to be lower in studies with longer duration of follow-up. Whilst some surgeons may feel that this demonstrates inferiority of NOT to appendicectomy, a long term efficacy of 82% still equates to 4 out of every 5 children not having had surgery (and general anaesthesia).

When compared to the adult literature, the data synthesised 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 paediatric population is in part due to study design and in particular due to differing selection criteria between paediatric 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].

Whilst it is tempting to draw conclusions regarding comparative efficacy from our comparative analysis of NOT and appendicectomy, we consider that to do so would be misleading due to 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 appendicectomy, and apparent safety of NOT is consistent with there

being equipoise between these treatment modalities, this being a pre-requisite for any RCT. The only statistically significant difference in our comparative analysis was a shorter duration of initial hospital stay in children undergoing appendicectomy compared to 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 prior to initial hospital discharge that may have influenced this outcome. This and other limitations (discussed below) of study design, heterogeneity between studies, and methodology prevent more robust conclusions.

Limitations of study

There are limitations of this study and the source data which should be appreciated when considering how to apply the data synthesised here to clinical practice and research. These include the inclusion of data from retrospective studies, those from non-comparative studies and those from non-randomised 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 randomised 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 (Figures 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 (Figure 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.

There are a number of outcomes that are notably missing in the existing literature that are important when considering the role of NOT and appendicectomy 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 healthcare 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 employ 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 appendicectomy. 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 acute uncomplicated appendicitis in children. As far as we are aware it is the

first such review synthesise data specifically from children. The study highlights the lack of robust evidence comparing NOT with appendicectomy in children but provides data that supports and justifies ongoing and future endeavours[31, 32] to assimilate such evidence in order 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 acute uncomplicated appendicitis be reserved for those participating in carefully designed research studies.

.

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

TRANSPARENCY DECLARATION
Nigel J Hall affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figure legends

Figure 1: Article selection flowchart

Figure 2: Proportion of children with acute uncomplicated appendicitis who were successfully treated with non-operative treatment (NOT) during their initial hospital admission

Figure 3: Estimate of incidence of recurrent appendicitis during follow-up period in children with acute uncomplicated appendicitis that was initially successfully treated with NOT

Figure 4: Estimate of long term efficacy of NOT defined as no appendicectomy (any cause) at last reported follow-up

Figure 5: Forest plot comparing initial length of stay between NOT and appendicectomy

Figure 6: Forest plot comparing total length of stay (including readmissions) between NOT and appendicectomy

Figure 7: Forest plot comparing complications between NOT and appendicectomy

Tables

Table 1 – Characteristics of included studies

Study	Country	Study Interval	Publication Year	Study Design	No of patients		Follow up for NOT cases (months)	Jadad Score	MINORS score
					NOT	Surgery			
Abes [20]	Turkey	2003-2006	2007	Retrospective, non-comparative	16		12 in all		7/16
Armstrong[12]	Canada	2012-2013	2014	Retrospective, comparative	12	12	mean 6.5		16/24
Gorter[24]	Netherlands	2012-2014	2015	Prospective, non-comparative	25		2 in all		12/16
Hartwich [22]	USA	2012-2014	2015	Prospective, comparative	24	50	mean 14		20/24
Kaneko [21]	Japan	1999-2001	2015	Prospective, non-comparative	22		mean 36, range 24-45		9/16
Koike [25]	Japan	2004-2010	2014	Retrospective, comparative	130	114	mean 30.6, minimum 18		13/24
Minneci [10]	USA	2012-2013	2015	Prospective, comparative	37	65	median 21		22/24
Steiner [19]	Israel	2013-2014	2015	Prospective, non-comparative	45		range 6-14		10/16
Svensson [26]	Sweden	2012-2013	2015	RCT	24	26	12 in all	3/5	
Tanaka [23]	Japan	2007-2013	2015	Prospective, comparative	78	86	mean 51		16/24

RCT – randomised controlled trial; NOT – non-operative treatment

Table 2: Antibiotic protocol for each study

Study	Intravenous antibiotic regime		Oral antibiotic regime	
	Antibiotic	**Duration**	**Antibiotic**	**Duration**
Abes [20]	sulbactam and ornidasole	48 hrs minimum	Not specified	
Armstrong [12]	ciprofloxacin and metronidazole or ampicillin, gentamicin and metronidazole	24 hrs minimum	co-amoxiclav	To complete 7 day total course
Gorter [24]	co-amoxiclav and gentamicin	48 hrs minimum	co-amoxiclav	5 days
Hartwich [22]	piperacillin-tazobactam	2 doses	co-amoxiclav	7 days
Kaneko [21]	flomoxef	Until abdominal tenderness resolved	Not specified	
Koike [25]	cefoperazone	48 hrs minimum	cefcapene pivoxil	3 days
Minneci [10]	piperacillin-tazobactam or ciprofloxacin and metronidazole	24 hrs minimum	co-amoxiclav or ciprofloxacin and metronidaxole	To complete 10 day total course
Steiner [19]	ceftriaxone and metronidazole	72-120 hrs	co-amoxiclav	5 days
Svensson [11]	meropenem and metronidazole	48 hrs minimum	ciprofloxacin and metronidazole	8 days
Tanaka [23]	First line: cefmetazole: Second line: sulbactam/ampicillin and ceftazidime Third line: meropenem or imipene/cilastatin and gentamicin	Until CRP<).5 mg/dL	Not specified	

Table 3: Complications as reported in source articles

NOT (n=175)	Appendicectomy (n=239)
Surgical site infection (1)*	Surgical site infection (2)
	Prolonged ileus (2)
	Readmission (1)
	Re-operation (1)
	Other (not further specified, 3)

Only data from articles reporting complications are included; *in a child who failed initial NOT and underwent appendicectomy

Appendix A

Search strategy in Medline

nonoperative[All Fields] OR non-operative[All Fields] OR conservative[All Fields] AND ("appendicitis"[MeSH Terms] OR "appendicitis"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol*. 1990;132(5):910-925.
2. Al-Omran M, Mamdani M, McLeod RS. Epidemiologic features of acute appendicitis in Ontario, Canada. *Can J Surg*. 2003;46(4):263-268.
3. Reynolds SL, Jaffe DM. Children with abdominal pain: evaluation in the pediatric emergency department. *Pediatr Emerg Care*. 1990;6(1):8-12.
4. Reynolds SL, Jaffe DM. Diagnosing abdominal pain in a pediatric emergency department. *Pediatr Emerg Care*. 1992;8(3):126-128.
5. Scholer SJ, Pituch K, Orr DP, Dittus RS. Clinical outcomes of children with acute abdominal pain. *Pediatrics*. 1996;98(4 Pt 1):680-685.
6. Fitz RH. Perforating inflammation of the vermiform appendix with special reference to its early diagnosis and treatment. *Trans Assoc Am Physicians*. 1886;1:107-144.
7. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg*. 2006;30(6):1033-1037.
8. Svensson JF, Hall NJ, Eaton S, Pierro A, Wester T. A review of conservative treatment of acute appendicitis. *Eur J Pediatr Surg*. 2012;22(3):185-194.
9. Hansson J, Korner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg*. 2009;96(5):473-481.
10. Minneci PC, Mahida JB, Lodwick DL, et al. Effectiveness of Patient Choice in Nonoperative vs Surgical Management of Pediatric Uncomplicated Acute Appendicitis. *JAMA Surg*. 2015:1-8.
11. Svensson JF, Patkova B, Almstrom M, et al. Nonoperative Treatment With Antibiotics Versus Surgery for Acute Nonperforated Appendicitis in Children: A Pilot Randomized Controlled Trial. *Ann Surg*. 2014.
12. Armstrong J, Merritt N, Jones S, Scott L, Butter A. Non-operative management of early, acute appendicitis in children: is it safe and effective? *J Pediatr Surg*. 2014;49(5):782-785.
13. Wilms IM, de Hoog DE, de Visser DC, Janzing HM. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database Syst Rev*. 2011(11):CD008359.
14. Go DY, Boo YJ, Lee JS, Jung CW. Transumbilical laparoscopic-assisted appendectomy is a useful surgical option for pediatric uncomplicated appendicitis: a comparison with conventional 3-port laparoscopic appendectomy. *Ann Surg Treat Res*. 2016;91(2):80-84.
15. Cundy TP, Sierakowski K, Manna A, Cooper CM, Burgoyne LL, Khurana S. Fast-track surgery for uncomplicated appendicitis in children: a matched case-control study. *ANZ J Surg*. 2016.
16. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
17. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73(9):712-716.
18. Minneci PC, Sulkowski JP, Nacion KM, et al. Feasibility of a nonoperative management strategy for uncomplicated acute appendicitis in children. *J Am Coll Surg*. 2014;219(2):272-279.

19. Steiner Z, Buklan G, Stackievicz R, Gutermacher M, Erez I. A role for conservative antibiotic treatment in early appendicitis in children. *J Pediatr Surg*. 2015.
20. Abes M, Petik B, Kazil S. Nonoperative treatment of acute appendicitis in children. *J Pediatr Surg*. 2007;42(8):1439-1442.
21. Kaneko K, Tsuda M. Ultrasound-based decision making in the treatment of acute appendicitis in children. *J Pediatr Surg*. 2004;39(9):1316-1320.
22. Hartwich J, Luks FI, Watson-Smith D, et al. Nonoperative treatment of acute appendicitis in children: A feasibility study. *J Pediatr Surg*. 2016;51(1):111-116.
23. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg*. 2015;50(11):1893-1897.
24. Gorter RR, van der Lee JH, Cense HA, et al. Initial antibiotic treatment for acute simple appendicitis in children is safe: Short-term results from a multicenter, prospective cohort study. *Surgery*. 2015;157(5):916-923.
25. Koike Y, Uchida K, Matsushita K, et al. Intraluminal appendiceal fluid is a predictive factor for recurrent appendicitis after initial successful non-operative management of uncomplicated appendicitis in pediatric patients. *J Pediatr Surg*. 2014;49(7):1116-1121.
26. Svensson JF, Patkova B, Almstrom M, et al. Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children: a pilot randomized controlled trial. *Ann Surg*. 2015;261(1):67-71.
27. Eaton S, Hall NJ, Pierro A. Zero-total event trials and incomplete pyloromyotomy. *J Pediatr Surg*. 2009;44(12):2434-2435.
28. Rollins KE, Varadhan KK, Neal KR, Lobo DN. Antibiotics Versus Appendicectomy for the Treatment of Uncomplicated Acute Appendicitis: An Updated Meta-Analysis of Randomised Controlled Trials. *World J Surg*. 2016.
29. Di SS, Sibilio A, Giorgini E, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Ann Surg*. 2014;260(1):109-117.
30. Hall NJ, Kapadia MZ, Eaton S, et al. Outcome reporting in randomised controlled trials and meta-analyses of appendicitis treatments in children: a systematic review. *Trials*. 2015;16:275.
31. HTA - 14/192/90: CONservative TReatment of Appendicitis in Children a randomised controlled Trial CONTRACT (Feasibility study). http://www.nets.nihr.ac.uk/projects/hta/1419290. Accessed 18/08/2016, 2016.
32. A Collaborative Multicenter open-label, non-inferiority, randomized controlled trial comparing appendectomy versus non-operative treatment for acute uncomplicated appendicitis in children (APPY Trial). https://clinicaltrials.gov/show/NCT02687464. Published 2016. Accessed 3/6/2016.

Figure 1

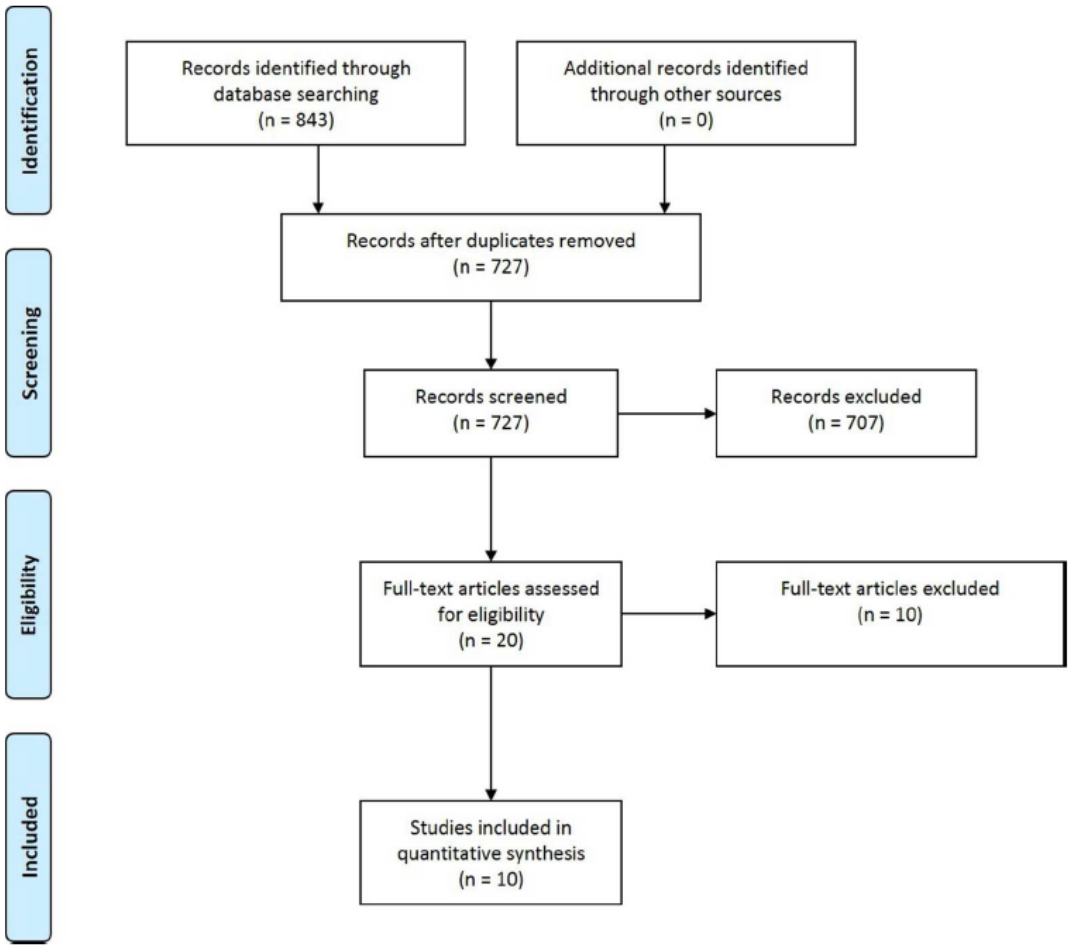
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 843)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 727)
Records screened (n = 727)
Records excluded (n = 707)
Full-text articles assessed for eligibility (n = 20)
Full-text articles excluded (n = 10)
Studies included in quantitative synthesis (n = 10)

Figure 2

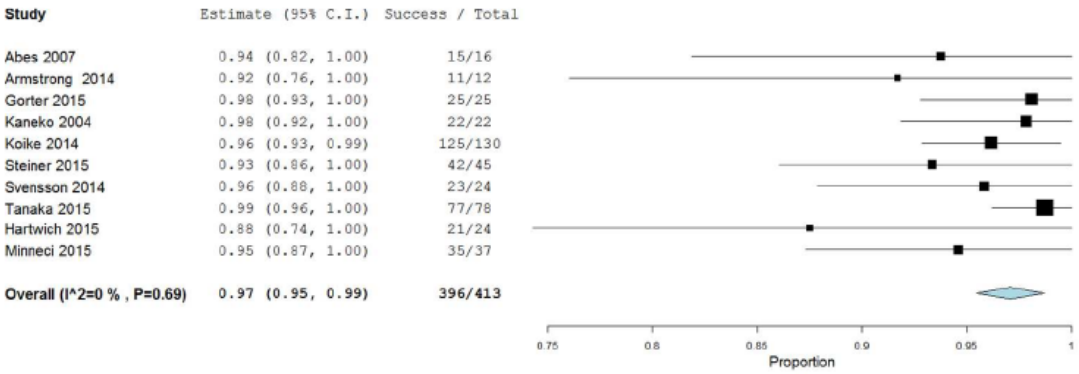

Figure 3

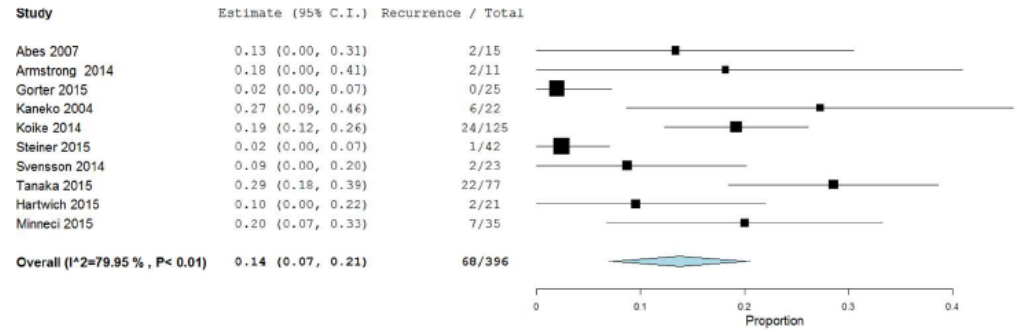

Figure 4

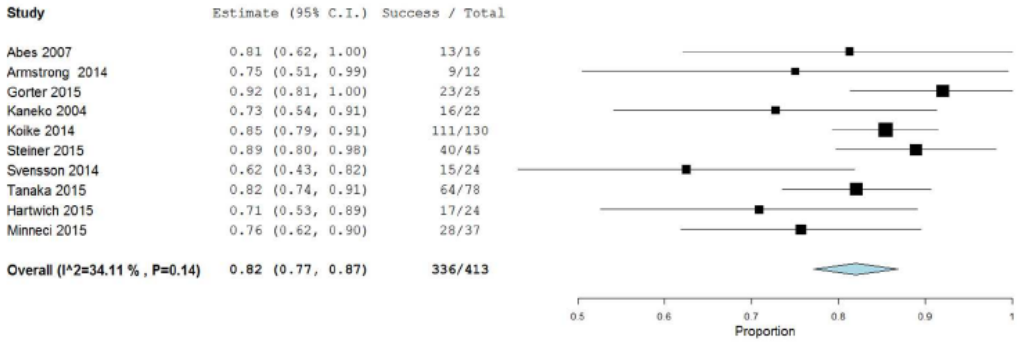

Figure 5

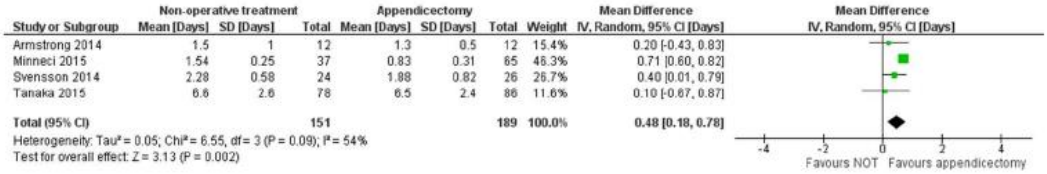

Figure 6

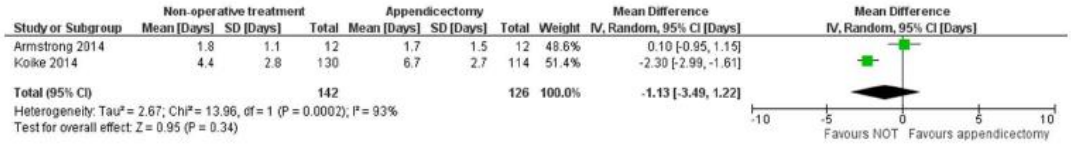

Figure 7