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Systematic Review and Meta-analysis to Compare the Short- and Long-term Outcomes of Non-operative Management With Early Operative Management of Simple Appendicitis in Children After the COVID-19 Pandemic

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ABSTRACT

Background: Non-operative management (NOM) of simple appendicitis is becoming an increasingly researched treatment option. This systematic review aims to describe the short and long-term failure rates of NOM and the complication rate of appendicectomy in children with simple appendicitis.
Methods: The systematic review was registered a priori (CRD42022322149). Study inclusion criteria are: participants aged ≤ 18 years of age; groups undergoing both NOM and appendicectomy for simple appendicitis; outcomes including one or more of: NOM failure rate at 30 days or 1 year and beyond; study design: RCT or case control study. Four databases were searched and 3 reviewers determined study eligibility and data extraction. Risk of bias was assessed and meta-analysis was performed using Stata.
Results: The database search identified 2731 articles, 14 studies met the inclusion criteria; 4 RCTs and 10 case controlled studies. All studies had moderate-serious risk of bias. There were no deaths in either group in any study. Meta-analysis demonstrated a 30 day failure rate of 20 % (95 % CI 11–29 %) and 11 studies reported failure rate at 1 year or beyond at 32 % (95 % CI 25–38 %). Rates of significant complications of appendicectomy was 1 % (95 % CI 0–1 %).
Conclusions: Non-operative management of simple appendicitis in children is safe, with moderate early success. The failure rate increases over time, resulting in eventual appendicectomy in a third of the children diagnosed with appendicitis. These data will enable clinicians to have an informed discussion with children and their parents about their treatment options for simple appendicitis.
Level of evidence: II.

1. Introduction

Non-operative management (NOM) of simple appendicitis in children was an increasingly researched therapeutic option prior to the SARS-CoV-2 pandemic and with the advent of the pandemic became an increasingly used treatment modality for simple appendicitis [1]. A number of systematic reviews have considered the outcomes of NOM of simple appendicitis [2,3] but novel data have been published in the wake of the SARS-CoV-2 pandemic and completed clinical trials considering this question have recently been published, increasing both the magnitude and the quality of the evidence available.

A number of key issues around NOM for simple appendicitis require further evaluation specifically in children. In particular these include describing both the short and the long-term failure rate of NOM, the differentiation between simple (inflamed) and complex (gangrenous or perforated) appendicitis [4] and whether the presence of a faecolith influences the success of NOM [5]. The outcomes after appendicectomy for simple appendicitis, particularly those of post-operative complications and normal appendicectomy rate require quantification within the current era.

The primary aim of this systematic review is to describe the current literature in relation to early and late failure rate of simple

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appendicitis in children managed non-operatively. The secondary aims are to describe the complication rate after initial appendicectomy for simple appendicitis and to describe the outcomes of NOM in children with a faecolith.

2. Methods

The systematic review was developed according to the PRISMA statement [6] and registered on the PROSPERO database (CRD42022322149).

2.1. Definitions

Early appendicectomy: decision to perform appendicectomy as treatment for simple appendicitis at the time of diagnosis.

Non-operative management: decision to treat simple appendicitis with antibiotics at the time of diagnosis.

Failure of non-operative management for appendicitis: appendicectomy performed for clinical reasons including parental request due to ongoing symptoms or concern *after* a period of NOM (duration not defined). It does not include planned interval appendicectomy.

Early failure: Failure of NOM within 30 days.

Late failure: Failure of NOM (including early failure) until follow-up of at least 1 year.

2.2. Study eligibility criteria

Participants All participants within the study 18 years of age or below; all patients have a diagnosis of simple appendicitis either clinically or with imaging; reported at minimum 30 days of follow-up reported after treatment commenced for appendicitis.

Intervention Includes a group of patients who have undergone NOM for simple appendicitis.

Comparator Includes a group of patients who have undergone appendicectomy (either laparoscopic or open) for simple appendicitis.

Outcomes One or more of the following outcomes are described within the study.

1. Early failure rate of NOM of appendicitis at 30 days following initiation of NOM
2. Late failure rate of NOM of appendicitis at a minimum of 1 year following initiation of NOM
3. Overall complication rate of early appendicectomy
4. Rate of significant complication (Clavien Dindo III or IV) after early appendicectomy

Additional outcomes including the failure rate of NOM in the presence of a faecolith and the negative appendicectomy rate may be described.

Study design Included studies are either randomised control trials or case–control studies. Cohort, case series, case reports, abstracts, review articles and systematic reviews are not included.

2.3. Information sources and search strategies

Four databases were searched for publications: Medline, PubMed and Web of Science on the 4th April 2022 and Scopus on the 6th April 2022 without a date constraint for the beginning of the search period. No filters were used to limit the searches and the following broad search terms were used: “Appendix” OR “appendicitis” OR “appendi$” AND “Simple” OR “Non-complex” OR “non-perforated” OR “Uncomplicated” OR “unperforated” AND “Non-operative” OR “Conservative” OR “antibiotic” AND “child” OR “children” OR “paediatric” OR “pediatric” OR “adolescent”. Duplicated publications were removed and all papers were uploaded onto the systematic review aid Rayyan.ai.

2.4. Selection strategy

Two authors (AN and RH) reviewed the titles and abstracts of all articles resulting from the search independently from each other using the systematic review tool Rayyan. Publications which clearly did not meet the inclusion criteria were excluded. When it was unclear whether the inclusion criteria were met and when it appeared that they were met the full publication was reviewed. After all publications had a decision by both reviewers the findings were unblinded. Discrepancies between the two reviewers were resolved by a third reviewer (ED).

2.5. Data collection

Data were extracted from studies eligible for inclusion by one author (RH) and checked by a second author (ED). Study investigators were not contacted for missing data so only published data are presented. Information was recorded on the design of the studies including the age of eligibility. Data items extracted from studies are available in the supplementary information.

2.6. Study of risk of bias

Two authors (RH and ED) independently examined the risk of bias of the eligible studies. The risk of bias 2 [7] score was used for randomised control trials and the ROBINS-I tool [8] for case controlled studies. In cases of disagreement the reviewers met and discussed the reasons for this and came to a decision about the score to apply.

2.7. Effect measures and synthesis of the data

Meta-analysis of the pre-determined outcome measures was performed using Stata v18. Population proportions were calculated along with 95 % confidence intervals. A weight random effects model was employed to determine the summary proportion and heterogeneity described using the I^2 statistic. Sub-analysis of only randomised control trials was undertaken using the same methodology.

3. Results

The literature search yielded 2731 articles. Of this, a total of 14 studies met eligibility criteria and were included in final analysis (Fig. 1) [4,9–21]. These articles represented 5048 patients managed non-operatively and 66,988 managed with early appendicectomy (total: 72,036). Agreement about the risk of bias was present in 11/14 studies. The three studies where disagreement was present were attributed a ‘Moderate’ grade after discussion, having being attributed ‘Serious’ by one reviewer and ‘Moderate’ by the second. Moderate to serious risk of bias was seen in all studies eligible for inclusion in this systematic review (Table 1). A summary of included studies is shown in Table 2.

There was no minimum age in 4 studies, and a lower exclusion criteria of 3–7 years in the rest. Upper age limits were 15 years for 4 studies, 16 years for one, 17 years for 7 and 18 years for 2 studies.

Study design comprised of 5 randomised controlled trials, 2 of which were multicentre, 2 non-randomised studies, 6 case controlled studies, of which 4 were prospective and one prospective patient choice study. Two studies were feasibility studies [4,10].

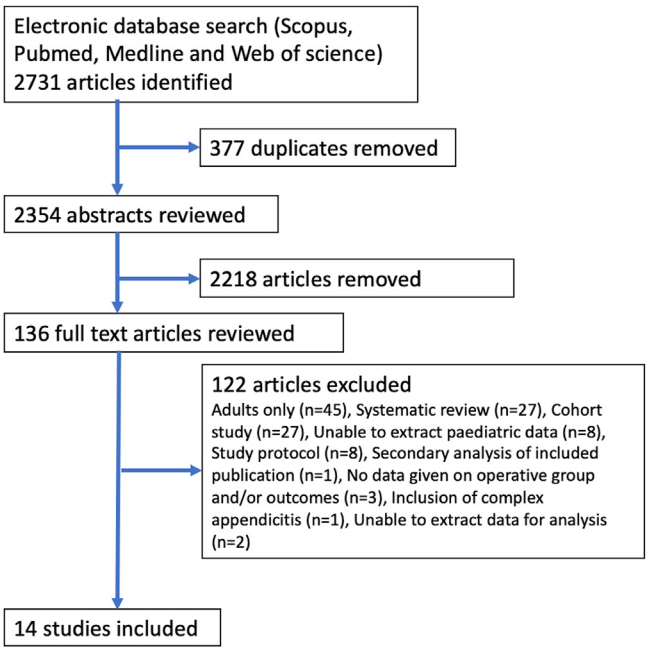


Fig. 1. PRISMA flow diagram describing study selection process.

Two studies specifically excluded patients if a faecolith was present [9,22]. All apart from 3 studies reporting early failure rates [4,11,13] required radiological confirmation of appendicitis in the non-operative group. One study was stopped early due to high failure rate of non-operative management in children who had a confirmed faecolith [20].

Table 1
Risk of Bias assessment.

Author, year	Bias tool	Overall bias risk
Minneci, 2020	Robins -I	Moderate
Patkova, 2020	ROB-2	High
Sajjad, 2021	ROB-2	High
Hall, 2021	ROB-2	Unclear
Miyano, 2018	Robins -I	Moderate
Bachur, 2017	Robins -I	Serious
Tanaka, 2015	Robins -I	Moderate
Minneci, 2019	Robins -I	Moderate
Armstrong, 2014	Robins -I	Moderate
Lee, 2017	Robins -I	Moderate
Hartwich, 2016	Robins -I	Moderate
Mudri, 2017	Robins -I	Serious
Mahida, 2016	Robins -I	Moderate
Perez-Otero, 2021	ROB-2	High

3.1. Primary outcome

3.1.1. Early failure

Twelve studies reported the 30 day failure rate in 834 children who underwent NOM, which ranged between 1.3 and 53.4 % (Fig. 2a). Meta-analysis revealed a failure rate of 20 % (95 % CI 11–29 %). Two studies that have not been included in this early analysis reported "early success" as 100 % at a time point that was not described. Three randomised control trials reported early failure (Sajjad, Minneci and Perez-Otero). Meta-analysis revealed a failure rate of 14 % (95 % CI 3–25 %). Both analyses revealed a high degree of heterogeneity between studies; the I^2 was 94 % in the complete analysis and 75 % in the analysis of randomised control trials.

3.1.2. Late failure

Late failure was described in 4951 children who underwent non-operative management. Length of follow up was 1 year for 9 studies, 3 years for one study and 5 years for another and ranged from 16.5 to 60 % (Fig. 2B). Meta-analysis revealed an overall failure rate of 32 % (95 % CI 25–38 %) in these children but a high level of heterogeneity between studies (I^2 83 %). Sub-analysis of the randomised control trials revealed a failure rate of 29 % (95 % CI 17–42 %) with a high level of heterogeneity (I^2 70 %).

3.2. Secondary outcomes

3.2.1. Complication rate – overall

Complications rates in early appendicectomy groups were reported in 8 studies. The rates of all reported complications was 0–29.6 % (Fig. 3a) and at meta-analysis the overall rate of reported complications was 9 % (95 % CI 2–16 %). There was significant variability reported between studies (I^2 95 %).

3.2.2. Complication rate – significant complications

Significant complications, categorised as Clavien Dindo III or IV, were reported by 7 studies. The rate of reported significant complications were 0–7.4 % (Fig. 3b) with an overall significant complication rate of 1 % (0–1%). This includes two studies that reported zero complications overall and two studies that reported no serious complications of early appendicectomy. This analysis revealed minimal heterogeneity between studies (I^2 0.1 %)

3.3. Faecalith

Children where a faecalith was present were included in 9 studies, excluded in two and it was not discussed in 3 studies. In the studies where children with a faecolith were included, one reported that all early failures had an appendicolith [11]. Two studies found a high rate of failure (approximately 50 %) of NOM when a faecolith was present [14,17]. Armstrong states one of 2 patients with failure of NOM had a faecalith [16]. One study looking at exclusively children with faecoliths was stopped early as the failure rate of NOM was 60 % [20].

3.4. Negative appendicectomy rate

The negative appendicectomy rate was reported by 9 studies. It was reported as zero by 6 studies, 3.1 % and 3.8 % in two studies with a maximum of 7 % in one UK study where imaging was not used prior to diagnosis of appendicitis. Meta-analysis demonstrated an overall negative appendicectomy rate of 1 % (95 % CI 0–2 %) with an I^2 of 3 %.

Table 2
Summary of studies.

Author, year	Study type	Country	Age	NOM of simple appendicitis					Early appendicectomy for simple appendicitis					Early failure	Late failure
				(n)	Age (y)	Symptom dur (hr)	Imaging Diagnosis	Faecolith	(n)	Age	Symptom dur (hr)	Imaging Diagnosis	Neg app		
Minneci, 2020	Multi-centre non-randomised control trial	USA	7–17 years	370	12.3 (2.8)	18.6 (11.2)	370 (100 %)	0	698	12.6 (2.8)	18.4 (10.8)	698 (100 %)	u/k	Y	Y
Patkova, 2020	Single centre feasibility RCT	Sweden	5–15 years	24	12.2 (5.9–15.0)	20	24 (100 %)	u/k	26	11.1 (6.2–14.8)	23	26 (100 %)	0 (0 %)	X	Y
Sajjad, 2021	Single centre RCT	Pakistan	5–15 years	90	9.56 (1.8)	21.7 (10.6)	u/k	u/k	90	10.1 (1.8)	18.98 (11.8)	u/k	u/k	Y	Y
Hall, 2021	Multi-centre feasibility randomised control trial	UK	4–15 years	27	10.3	34	8 (30 %)	u/k	27	10.6	32	8 (30 %)	2 (7 %)	Y	X
Miyano, 2018	Single centre case −control study	Japan	0–15 years	58	u/k	u/k	u/k	u/k	34	u/k	u/k	u/k	u/k	Y	X
Bachur, 2017	Retrospective multi-centre case-controlled study	USA	0–18 years	4190	11.4 (8.8–14.3)	u/k	3406 (81 %)	u/k	65,712	11.4 (8.8–14.2)	u/k	42,414 (65 %)	u/k	X	Y
Tanaka, 2015	Prospective case-controlled study	Japan	0–16 years	78	10.1 (2)	22 (15.5)	78 (100 %)	19	86	10.4 (2.3)	21 (12.3)	86 (100 %)	u/k	Y	Y
Minneci, 2019	Case-controlled study	USA	7–17 years	73	u/k	u/k	73 (100 %)	0	127	u/k	u/k	u/k	0	Y	Y
Armstrong, 2014	Retrospective single-centre case-controlled study	Canada	0–17 years	12	12.2 (4.2)	27.3 (9.5)	12 (100 %)	u/k	12	12 (3.2)	27.5 (12.8)	12 (100 %)	0	Y	X
Lee, 2017	Prospective patient choice study	USA	3–17 years	51	10 (7–13)	24 (24–48)	u/k	14	32	11 (8–15)	24 (24–48)	u/k	1 (3 %)	Y	Y
Hartwich, 2016	Prospective case-controlled study	USA	5–18 years	24	12.6 (0.6)	20.9 (1.9)	24 (100 %)	4	50	12.1 (0.5)	21.7 (2.8)	50 (100 %)	0	Y	Y
Mudri, 2017	Retrospective case-controlled study	Canada	6–17 years	26	12	u/k	26 (100 %)	3	26	11	u/k	26 (100 %)	1 (4 %)	Y	Y
Mahida, 2016	Prospective case-controlled study	USA	7–17 years	5	14 (13–14)	18 (10–24)	5 (100 %)	u/k	9	11 (9–15)	13 (12–24)	9 (100 %)	0	Y	Y
Perez-Otero, 2021	Multicentre randomised control study	USA	6–17 years	20	10.2 (8.5–11.1)	23 (14–24)	20 (100 %)	5	19	9.7 (7.3–14.4)	24 (24–36)	19 (100 %)	0	Y	Y

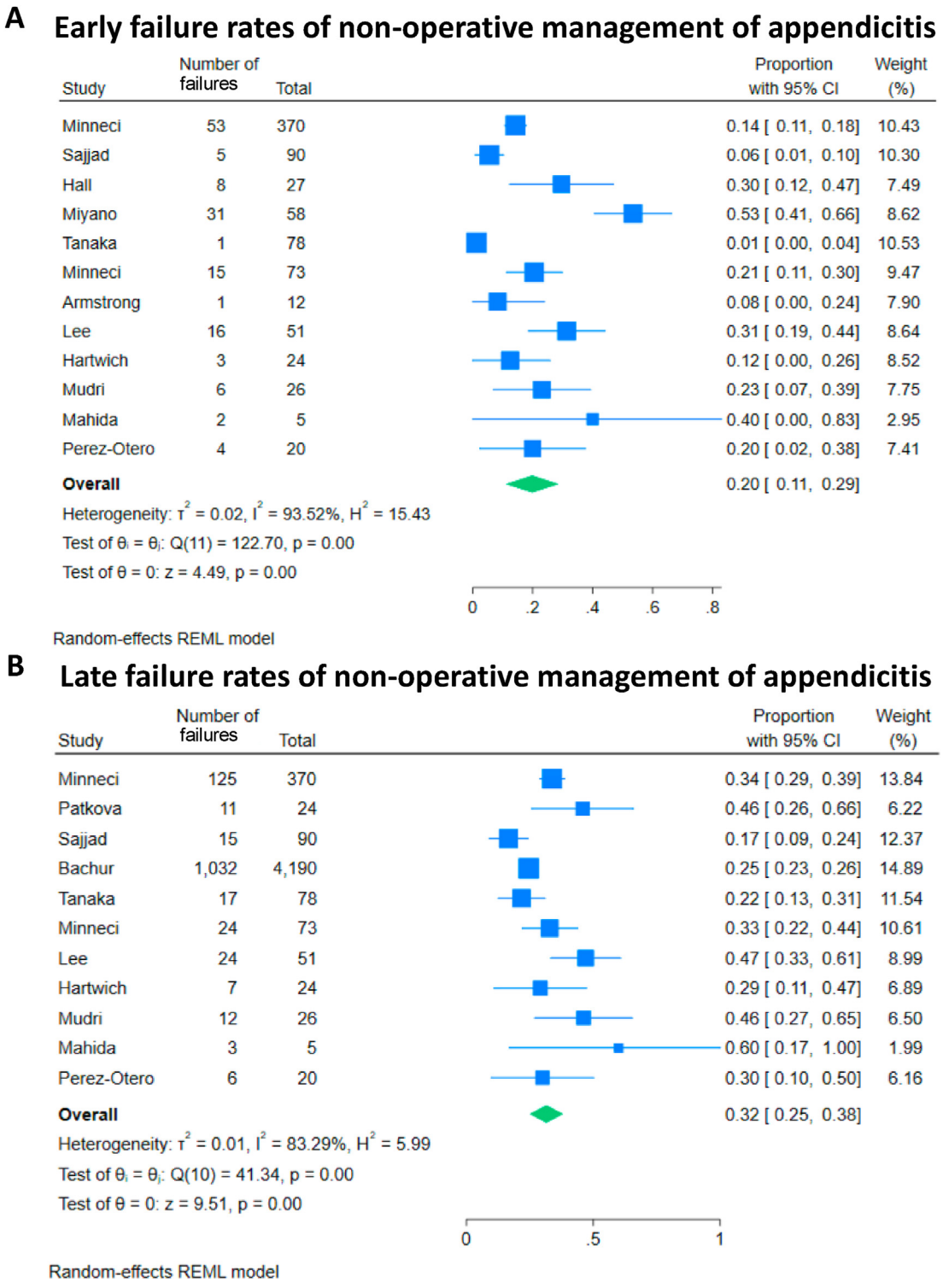
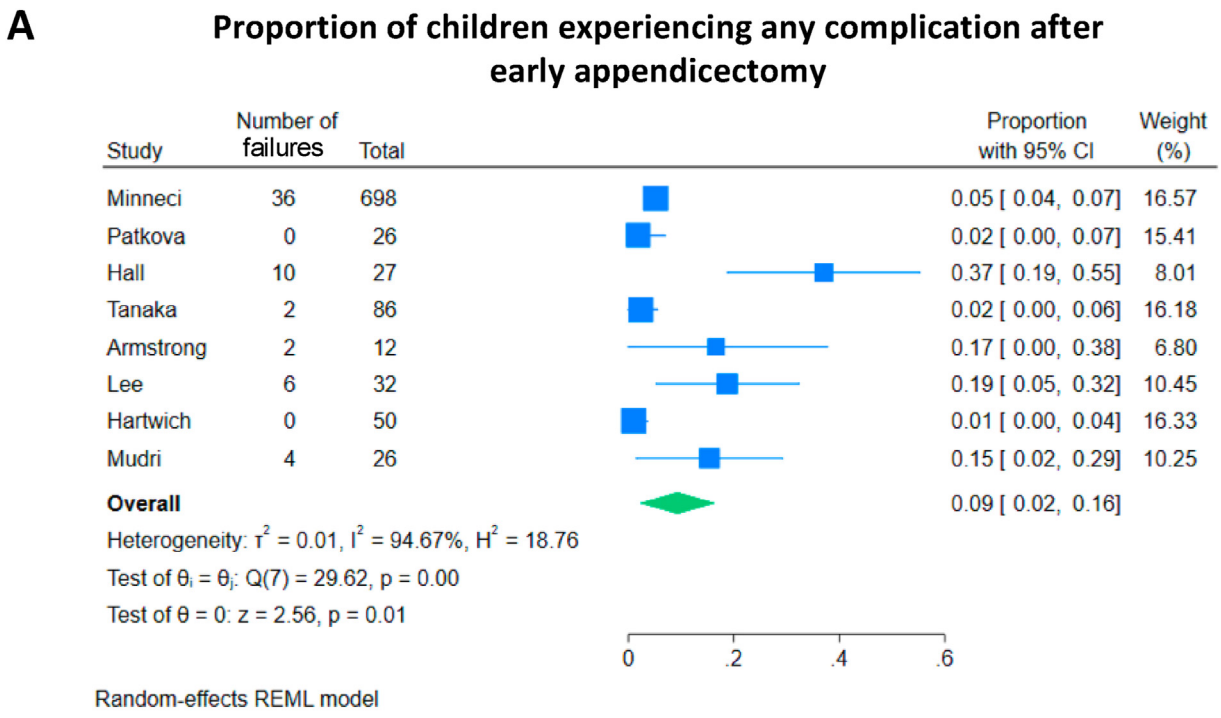


Fig. 2. A and B. Early (within 30 days) and late (at 12 months and beyond) failure rate on non-operative management of appendicitis.

4. Discussion

This systematic review compares non-operative and operative management of simple appendicitis in children. During the COVID-19 pandemic the proportion of children managed non-operatively for appendicitis rose to 28 % in the UK [23] but treatment strategies rapidly returned to almost pre-pandemic levels of operative management and international studies did not demonstrate the same shift towards NOM [24]. Non-operative management (NOM) of simple appendicitis has become an increasingly researched topic in adult practice, with recent trials demonstrating a 72 % success rate at 1 year [25], that oral antibiotic therapy is non-inferior to intravenous antibiotic therapy [26] and most recently that antibiotic therapy is not superior to no therapy at all [27]. However,



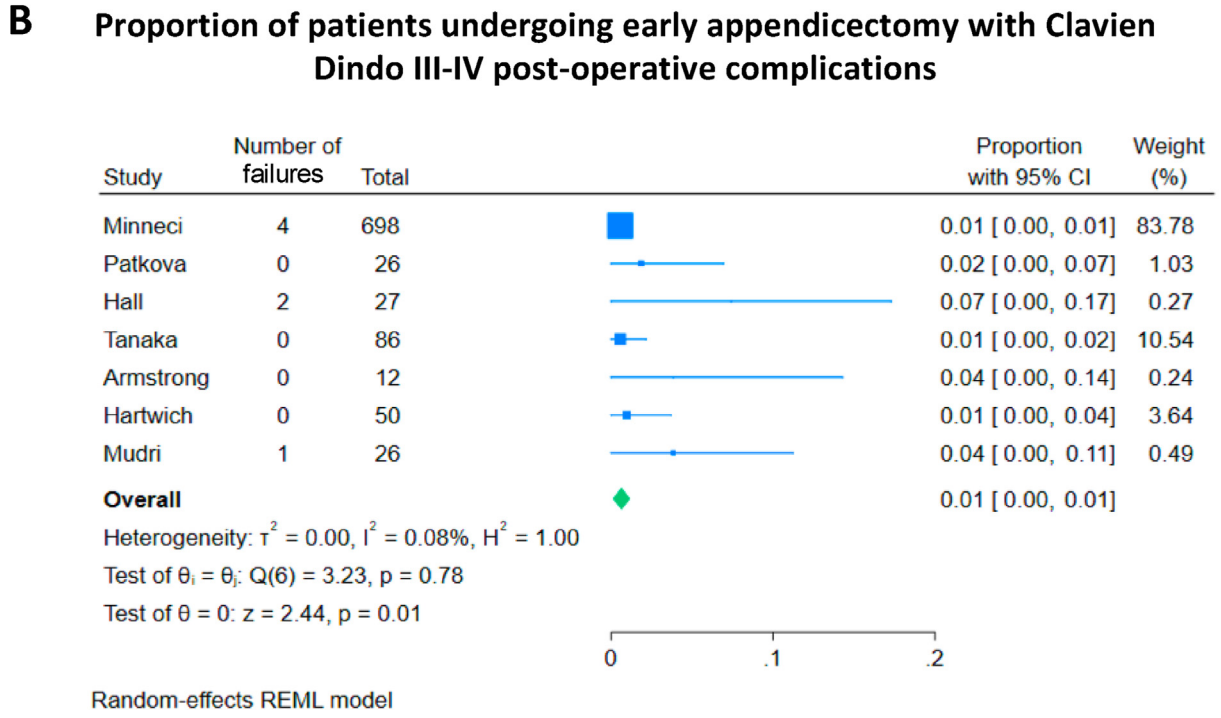


Fig. 3. A. Proportion of patients with any reported post-operative complication after early appendicectomy. B. Proportion of patients with Clavien Dindo III or IV complication after early appendicectomy.

adults are more likely to have simple appendicitis than children [28], suggesting that the progression of the disease may differ in children and necessitating child-specific research. The studies within this review demonstrate that both operative management and NOM of simple appendicitis in children is safe, with no reported deaths in any of the included studies.

A range of study designs are included within this systematic review. Four randomised controlled trials (RCTs) successfully recruited 161 children to non-operative management. The remaining studies used either clinician or patient determined treatment (or both) which may significantly bias the outcome of NOM. Taking this into account, the summary early failure rate of

NOM at 30 days was lower in RCTs (14 %) compared to the overall failure rate (20 %) and the overall long-term failure rate was essentially equivalent in the RCT trials (29 %) compared to all the studies (32 %). The high level of heterogeneity demonstrated between these studies may be an indication of the influence of bias on these findings, along with the influence of other factors which have not been controlled for including the age of patients, presence of faecolith and laboratory and imaging findings. Despite this high level of heterogeneity, the long-term failure rate is equivalent to that found in previous systematic reviews [3,29], including an umbrella review which combines outcomes in adults and children [30], all of which demonstrate an higher failure rate than was found in early systematic reviews [31].

When considering complications of appendicectomy, one study had a particularly high complication rate of 29.6 % [4] although 30 % of children in this study had complex appendicitis at the time of operation, which is known to have a higher complication rate. Additionally, this study captured complications that were managed in primary care as well as the primary hospital. The largest study to report complication rates reported an overall complication rate of 5 % [9] however primary care contact was not taken into consideration.

These studies demonstrate ongoing controversy in the diagnosis of simple appendicitis, with most undertaking imaging to confirm the diagnosis. Four studies did not require radiological diagnosis of appendicitis prior to embarking on conservative management [4,11,13,17]. Negative appendicectomy rates were not described in all studies but had an overall rate of 1 %. This is low compared to other published literature [32,33] and is likely to reflect that imaging was required for the majority of enrolled children. The highest negative appendicectomy rate occurred in a study where imaging was not mandated prior to enrolment [4], leading to the potential for bias when considering the efficacy of non-operative management. It may positively bias the study by enrolling children who do not actually have appendicitis or negatively bias the study as imaging indicators of complex appendicitis will not be detected. This makes it more difficult to draw conclusions on the findings of studies when imaging was not employed prior to embarking on conservative management.

The presence of a faecalith and whether it predicts failure of non-operative management is another area of uncertainty. Nine papers stated how many children were included that had a faecalith on ultrasound. The risk of failure was higher in those who had a faecalith compared to those without and this reached statistical significance in 2 studies.

4.1. Strengths and limitations

A good number of prospective studies were included, however most were not randomised. The protocols, including diagnostic criteria for simple appendicitis, varied significantly between studies. There were also differing protocols with treatment of non-operative management, including specific antibiotic use, duration and intravenous versus parenteral administration. Half of the studies had a moderate to severe risk of bias, however a significant aspect of this was blinding which is ethically and practically challenging to enforce when comparing surgical and non-surgical management techniques. Additional outcomes including the length of stay and the influence of management on quality of life, patient reported outcome measures and time off school were not sufficiently reported to be included in this meta-analysis but an ongoing study by N Hall et al. will describe these important outcomes [34].

This meta-analysis is limited by the lack of availability of individual patient data which may help to determine the influence of factors including age and presence of faecolith on outcomes, addressing the significant heterogeneity seen between studies.

5. Conclusion

This systematic review comparing non-operative management of simple appendicitis with operative management in children demonstrates that both are safe treatment options. Non-operative management has a 30 day success rate of 80 % and a success rate of 68 % at a year or beyond. The presence of a faecalith significantly increases the risk of failure of non-operative management. By comparison, early appendectomy complication rates are 10 % with a severe complication rate of 1 %. These figures can be used to discuss the options of operative and non-operative management of simple appendicitis with children and their families prior to embarking on a treatment strategy.

The heterogeneity of studies within this meta-analysis indicates that more in-depth research considering the influence of age, laboratory and imaging findings on success of NOM is called for. This will enable clinicians to identify children who are most likely to have a successful outcome of NOM and to support families in making a truly informed decision about the treatment strategy for a child with simple appendicitis.

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Conflict of interest

No competing interests from any authors.

Data availability

All data available on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2023.12.021.

References

[1] Bethell GS, Rees CM, Sutcliffe JR, et al. Management and early outcomes of children with appendicitis in the UK and Ireland during the COVID-19 pandemic: a survey of surgeons and observational study. BMJ Paediatr Open 2020;4:e000831. https://doi.org/10.1136/bmjpo-2020-000831.
[2] Kessler U, Mosbahi S, Walker B, et al. Conservative treatment versus surgery for uncomplicated appendicitis in children: a systematic review and meta-analysis. Arch Dis Child 2017;102:1118–24. https://doi.org/10.1136/archdischild-2017-313127.
[3] Maita S, Andersson B, Svensson JF, et al. Nonoperative treatment for nonperforated appendicitis in children: a systematic review and meta-analysis. Pediatr Surg Int 2020;36:261–9. https://doi.org/10.1007/s00383-019-04610-1.
[4] Hall NJ, Eaton S, Sherratt FC, et al. CONservative TReatment of Appendicitis in Children: a randomised controlled feasibility Trial (CONTRACT). Arch Dis Child 2021. https://doi.org/10.1136/archdischild-2020-320746.
[5] Chong S, Kaur M, Palmer C, et al. Non-operative management of acute appendicitis at a major trauma centre – a retrospective case series. Br J Surg 2021;108. https://doi.org/10.1093/bjs/znab259.534.
[6] Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. https://doi.org/10.1136/bmj.n160.
[7] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.

[8] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
[9] Minneci PC, Hade EM, Lawrence AE, et al. Association of nonoperative management using antibiotic therapy vs laparoscopic appendectomy with treatment success and disability days in children with uncomplicated appendicitis. JAMA 2020;324:581–93. https://doi.org/10.1001/jama.2020.10888.
[10] Patkova B, Svenningsson A, Almstrom M, et al. Nonoperative treatment versus appendectomy for acute nonperforated appendicitis in children: five-year follow up of a randomized controlled pilot trial. Ann Surg 2020;271:1030–5. https://doi.org/10.1097/SLA.0000000000003646.
[11] Sajjad MN, Naumeri F, Hina S. Non-operative treatment versus appendectomy for acute uncomplicated appendicitis: a randomized controlled trial. Pakistan J Med Sci 2021;37:1276–81. https://doi.org/10.12669/pjms.37.5.4016.
[12] Miyano G, Ochi T, Seo S, et al. Factors affecting non-operative management of uncomplicated appendicitis in children: should laparoscopic appendectomy be immediate, interval, or emergency? Asian J Endosc Surg 2019;12:434–8. https://doi.org/10.1111/ases.12677.
[13] Bachur RG, Lipsett SC, Monuteaux MC. Outcomes of nonoperative management of uncomplicated appendicitis. Pediatrics 2017;140. https://doi.org/10.1542/peds.2017-0048.
[14] Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. J Pediatr Surg 2015;50:1893–7. https://doi.org/10.1016/j.jpedsurg.2015.07.008.
[15] Minneci PC, Cooper JN, Leonhart K, et al. Effects of a patient activation tool on decision making between surgery and nonoperative management for pediatric appendicitis: a randomized clinical trial. JAMA Netw Open 2019;2:e195009. https://doi.org/10.1001/jamanetworkopen.2019.5009.
[16] Armstrong J, Merritt N, Jones S, et al. Non-operative management of early, acute appendicitis in children: is it safe and effective? J Pediatr Surg 2014;49:782–5. https://doi.org/10.1016/j.jpedsurg.2014.02.071.
[17] Lee SL, Spence L, Mock K, et al. Expanding the inclusion criteria for nonoperative management of uncomplicated appendicitis: outcomes and cost. J Pediatr Surg 2017. https://doi.org/10.1016/j.jpedsurg.2017.10.014.
[18] Hartwich J, Luks FI, Watson-Smith D, et al. Nonoperative treatment of acute appendicitis in children: a feasibility study. J Pediatr Surg 2016;51:111–6. https://doi.org/10.1016/j.jpedsurg.2015.10.024.
[19] Mudri M, Coriolano K, Butter A. Cost analysis of nonoperative management of acute appendicitis in children. J Pediatr Surg 2017;52:791–4. https://doi.org/10.1016/j.jpedsurg.2017.01.050.
[20] Mahida JB, Lodwick DL, Nacion KM, et al. High failure rate of nonoperative management of acute appendicitis with an appendicolith in children. J Pediatr Surg 2016;51:908–11. https://doi.org/10.1016/j.jpedsurg.2016.02.056.
[21] Perez Otero S, Metzger JW, Choi BH, et al. It's time to deconstruct treatment-failure: a randomized controlled trial of nonoperative management of uncomplicated pediatric appendicitis with antibiotics alone. J Pediatr Surg 2022;57:56–62. https://doi.org/10.1016/j.jpedsurg.2021.09.024.
[22] Minneci PC, Mahida JB, Lodwick DL, et al. Effectiveness of patient choice in nonoperative vs surgical management of pediatric uncomplicated acute appendicitis. JAMA Surg 2016;151:408–15. https://doi.org/10.1001/jamasurg.2015.4534.
[23] Bethell GS, Gosling T, Rees CM, et al. Impact of the COVID-19 pandemic on management and outcomes of children with appendicitis: the children with AppendicitiS during the CoronAvirus panDEmic (CASCADE) study. J Pediatr Surg 2022;57:380–5. https://doi.org/10.1016/j.jpedsurg.2022.03.029.
[24] van Amstel P, El Ghazzaoui A, Hall NJ, et al. Paediatric appendicitis: international study of management in the COVID-19 pandemic. Br J Surg 2022;109:1044–8. https://doi.org/10.1093/bjs/znac239.
[25] Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340–8. https://doi.org/10.1001/jama.2015.6154.
[26] Sippola S, Haijanen J, Gronroos J, et al. Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: the APPAC II randomized clinical trial. JAMA 2021;325:353–62. https://doi.org/10.1001/jama.2020.23525.
[27] Salminen P, Sippola S, Haijanen J, et al. Antibiotics versus placebo in adults with CT-confirmed uncomplicated acute appendicitis (APPAC III): randomized double-blind superiority trial. Br J Surg 2022;109:503–9. https://doi.org/10.1093/bjs/znac086.
[28] Armagan HH, Duman L, Cesur O, et al. Comparative analysis of epidemiological and clinical characteristics of appendicitis among children and adults. Ulus Travma Acil Cerrahi Derg 2021;27:526–33. https://doi.org/10.14744/tjtes.2020.47880.
[29] Xu J, Adams S, Liu YC, et al. Nonoperative management in children with early acute appendicitis: a systematic review. J Pediatr Surg 2017;52:1409–15. https://doi.org/10.1016/j.jpedsurg.2017.05.003.
[30] Emile SH, Sakr A, Shalaby M, et al. Efficacy and safety of non-operative management of uncomplicated acute appendicitis compared to appendectomy: an umbrella review of systematic reviews and meta-analyses. World J Surg 2022;46:1022–38. https://doi.org/10.1007/s00268-022-06446-8.
[31] Gorter RR, The SML, Gorter-Stam MAW, et al. Systematic review of nonoperative versus operative treatment of uncomplicated appendicitis. J Pediatr Surg 2017;52:1219–27. https://doi.org/10.1016/j.jpedsurg.2017.04.005.
[32] Tiboni S, Bhangu A, Hall NJ, et al. Outcome of appendicectomy in children performed in paediatric surgery units compared with general surgery units. Br J Surg 2014;101:707–14. https://doi.org/10.1002/bjs.9455.
[33] Collaborative RSGobotWMR. Appendicitis risk prediction models in children presenting with right iliac fossa pain (RIFT study): a prospective, multicentre validation study. Lancet Child Adolesc Health 2020;4:271–80. https://doi.org/10.1016/S2352-4642(20)30006-7.
[34] Hall NJ, Eaton S, Abbo O, et al. Appendectomy versus non-operative treatment for acute uncomplicated appendicitis in children: study protocol for a multicentre, open-label, non-inferiority, randomised controlled trial. BMJ Paediatr Open 2017;1. https://doi.org/10.1136/bmjpo-2017-000028.