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REVIEW

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Non-operative management of uncomplicated appendicitis in children, why not? A meta-analysis of randomized controlled trials

Francesco Brucchi[1†], Claudia Filisetti[2†], Ester Luconi[3], Paola Fugazzola[4,5*], Dario Cattaneo[7], Luca Ansaloni[4,5], Gianvincenzo Zuccotti[6,8], Simona Ferraro[6†], Piergiorgio Danelli[8,9†] and Gloria Pelizzo[2,8†]

Abstract

Background This study aims to provide a meta-analysis of randomized controlled trials (RCTs) comparing non-operative management (NOM) and operative management (OM) in a pediatric population with uncomplicated acute appendicitis.

Methods A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines. A comprehensive search was conducted in MEDLINE, Embase, and CENTRAL from inception to June 2024. Only randomized controlled trials (RCTs) were included, excluding studies involving adult patients and/or participants with complicated appendicitis. The variables considered were treatment complications, treatment efficacy during index admission and one-year follow-up, length of hospital stay (LOS), quality of life, and presence of appendicoliths.

Results Three RCTs involving 269 participants (134 antibiotics/135 appendectomy) were included. There was no statistically significant difference between the two treatments in terms of complication risk (combined RD = −0.03; 95% CI −0.11; 0.06, $p = 0.54$), even including complications related to NOM failure. The risk of complication-free treatment success rate in the antibiotic group is lower than in the surgery group (combined RD = −0.05; 95% CI −0.13; −0.04; $p = 0.29$). In patients without appendicolith, the combined risk difference of treatment success between NOM and OM was not statistically significant −0.01 (IC −0.17; 0.16; p value: 0.93). There is no statistical difference in terms of efficacy at 1 year, between NOM and OM (combined RD = −0.06; 95% CI −0.21; 0.09), $p = 0.44$). The LOS in the NOM group is significantly longer than in the OM group (difference of median = −19.90 h; 95% CI −29.27; −10.53, $p < .0001$).

†Francesco Brucchi and Claudia Filisetti: Share the first authorship.

†Simona Ferraro, Piergiorgio Danelli, and Gloria Pelizzo: Share the last authorship..

*Correspondence:
Paola Fugazzola
paola.fugazzola@gmail.com
Full list of author information is available at the end of the article

Conclusions This systematic review and meta-analysis provide evidence that NOM is safe and feasible for children with uncomplicated appendicitis and, in the group of patients without appendicolith, it is associated with a similar success rate to OM. However, more high-quality studies with adequate power and construction are still needed.

Introduction

Acute appendicitis is a common abdominal emergency requiring prompt diagnosis and treatment. Laparoscopic appendectomy (Operative Management, OM) has become the standard of care for uncomplicated appendicitis in adults and children 1. However, recent evidence, including a study by the CODA Collaborative, has explored non-operative management (NOM) using antibiotics as an alternative 2. This study showed that NOM allowed over 70% of adult patients to avoid surgery, many of whom were treated on an outpatient basis, resuming daily activities sooner 2. Conversely, NOM was associated with a higher rate of emergency visits and hospitalizations within 90 days 3.

Although more than 95% of patients with appendicitis currently undergo surgery 4, the COVID-19 pandemic prompted a re-evaluation of antibiotics for managing appendicitis 5. NOM presents potential benefits, such as avoiding surgical risks, reduced recovery time, and outpatient management. Despite these advantages, the efficacy and safety of NOM in children remain debated. Most evidence for NOM in pediatrics is derived from adult studies, which limits its direct applicability [6]. Additionally, small sample sizes and heterogeneity in design among trials have hampered definitive conclusions [7].

A recent meta-analysis by Kessler et al. evaluated NOM for uncomplicated appendicitis in children but faced methodological limitations and inconclusive findings [8]. Reported recurrence rates within one year range from 15 to 41%, yet many children remain recurrence-free long-term [9]. To address these gaps, this meta-analysis focuses exclusively on randomized controlled trials (RCTs) to assess the efficacy, hospital stay duration, quality of life (QoL), and complications of NOM versus OM in pediatric patients.

Material and methods

Data sources and searches

The peer-reviewed literature published from January 1959 to September 2024 was searched using Medline (PubMed), Embase, Scopus, and Cochrane Library databases with MeSH terms [appendicitis, appendectomy, appendicectomy, nonoperative, non-operative, conservative, OR antibiotic] AND [child, children, adolescent, infant, toddler, neonate, pediatric], and with limits "Title/Abstract, Human Subjects, English."

This meta-analysis was performed following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) Statement, Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines, and A MeaSurement Tool to Assess systematic Reviews (AMSTAR) guidelines [13–15]. The planned protocol of this meta-analysis was registered in PROSPERO (PROSPERO 2023: CRD42023413780). In addition, the reference lists of retrieved articles were screened to identify further studies. The final aim of the search was to identify RCTs comparing NOM vs. OM in pediatric patients to provide a synthesis of the scientific evidence by the meta-analysis process.

Study selection

Two investigators (FB and CF) independently performed the literature search and data extraction using Rayyan systematic review software 16. They independently assessed the eligibility of all preliminary identified records based on the title first and then the abstract. After this initial selection, the complete manuscript of the relevant studies was carefully read to confirm the eligibility and extract useful information. Any disagreement regarding the eligibility of an article was settled by consensus with a third reviewer (LC).

The inclusion criteria of selected studies were:

Population: children/adolescents (< 18 years) presenting with uncomplicated acute appendicitis diagnosed either clinically or radiologically (patients with appendicolith were included);

Intervention: antibiotic treatment;

Comparator: appendectomy,

Outcomes: treatment efficacy, length of primary hospital stay (LOS), post-treatment complications, quality of life.

Only RCTs were included in this review and meta-analysis to reduce selection bias.

No geographic or language restrictions were applied. Papers were excluded if they reported duplicative results from the same authors' group.

Data extraction and quality assessment

Two authors examined the main features of each retrieved article, reporting the following data: year of publication, country where the study was performed and population source, total number of individuals, gender and age, outcomes, biochemical blood tests, Alvarado score, length of primary hospital stay (LOS), recurrence at 1 year, length of follow-up, efficacy of the treatment performed, statistical analysis.

Outcome measures

The primary outcome was post-treatment complications: In the OM group, complications were specifically defined as intraoperative and postoperative complications including negative appendectomies as well, whereas in the NOM group, they encompassed adverse events necessitating hospitalization (e.g. Clostridium infection, allergic reactions, abscesses) and the 30-day complication rate of appendectomy performed in patients initially considered for NOM and in whom NOM failed (including negative appendectomies).

Secondary outcome measures:

1. Complication-free treatment success (treatment efficacy) during the index admission (with a subgroup analysis in patients with and without appendicolith). The efficacy of NOM was defined as the absence of the following: failure of antibiotic therapy or recurrence of appendicitis necessitating appendectomy in the first 48 h, abscess or complex abdominal fluid collection formation, and recurrence within 6 months. If a secondary appendectomy was conducted based on parental preference or due to clinical suspicion of recurrence in instances where the appendix appeared normal in the absence of abdominal symptoms, conservative treatment was considered successful.
2. Complication-free treatment success (treatment efficacy) at 1-year follow-up
3. Length of primary hospital stay (LOS), defined according to the number of days (or hours) of inpatient admission during the initial hospitalization.
4. Quality of life assessed in patients after NOM or OM
5. In the NOM population, treatment efficacy differences in the presence or absence of appendicoliths.
6. In the OM group, a negative appendectomy rate

Data synthesis and analysis

The random effect model was considered for the meta-analysis of all the outcomes. Length of primary hospital stay was expressed in hours of inpatient admission during the initial hospitalization. In the meta-analysis, the effect size was described as the median difference between the length of stay for antibiotic treatment and surgery. The combined results were obtained. A 95% confidence interval accompanies all the estimations. The quantile matching estimation method was used 17. We performed an intention-to-treat analysis for the rest of the outcomes. The primary and secondary outcomes about the treatment efficacy based on 1-year follow-up, appendicolith (only for antibiotics treatment), and the complications the effect sizes (and the 95% CI) were expressed as the Risk Difference because of the presence of 100% events in one or two arms. The inverse variance method was used because it is the only option in the case of a random effect model. A continuity correction of 0.5 in studies with zero cell frequencies was performed to calculate the confidence limit and standard error. The differences were expressed as the risk in the case of antibiotic treatment and surgery.

Q and I2 statistics were used to test the heterogeneity among ES results. The low, moderate, and high degrees of heterogeneity correspond to I2 values of 25%, 50%, and 75%, respectively 18 .

All the analyses were performed with R software (R Core Team 2021) 19. The package "metamedian" was used to calculate the difference between the medians 17. The package "meta" was used for the risk difference 20.

Assessment of risk of bias

To assess any potential bias in the studies included in the analysis, the researchers utilized the risk of bias tool developed by the Cochrane Collaboration 18. The studies were evaluated concerning the presence of selection bias, performance bias, detection bias, and attrition bias. A total risk of bias score was then determined based on these domains, with the levels categorized as low risk of bias, high risk of bias, or unclear risk of bias.

Results

Features of the retrieved studies

Figure 1 displays the PRISMA flowchart. The search strategy retrieved 10,488 potentially eligible papers, restricted to 3439 after removing duplicate records. After evaluating titles and abstracts, 3320 records were excluded, leaving 119 original articles preliminarily considered eligible for full-text examination. Among these, 116 papers were excluded due to differing designs and outcomes. Ultimately, 3 RCTs met the inclusion criteria and were included in the meta-analysis (publication dates 2015–2022), involving 269 patients allocated to NOM (n = 134) and OM (n = 135). Table 1 provides an overview of the general characteristics of the studies and the investigated groups.

Significant heterogeneity was observed among the studies, particularly in the diagnostic criteria used to define uncomplicated appendicitis, the type and duration of antibiotics administered, and the outcomes evaluated. To ensure transparency, the Risk of Bias analysis

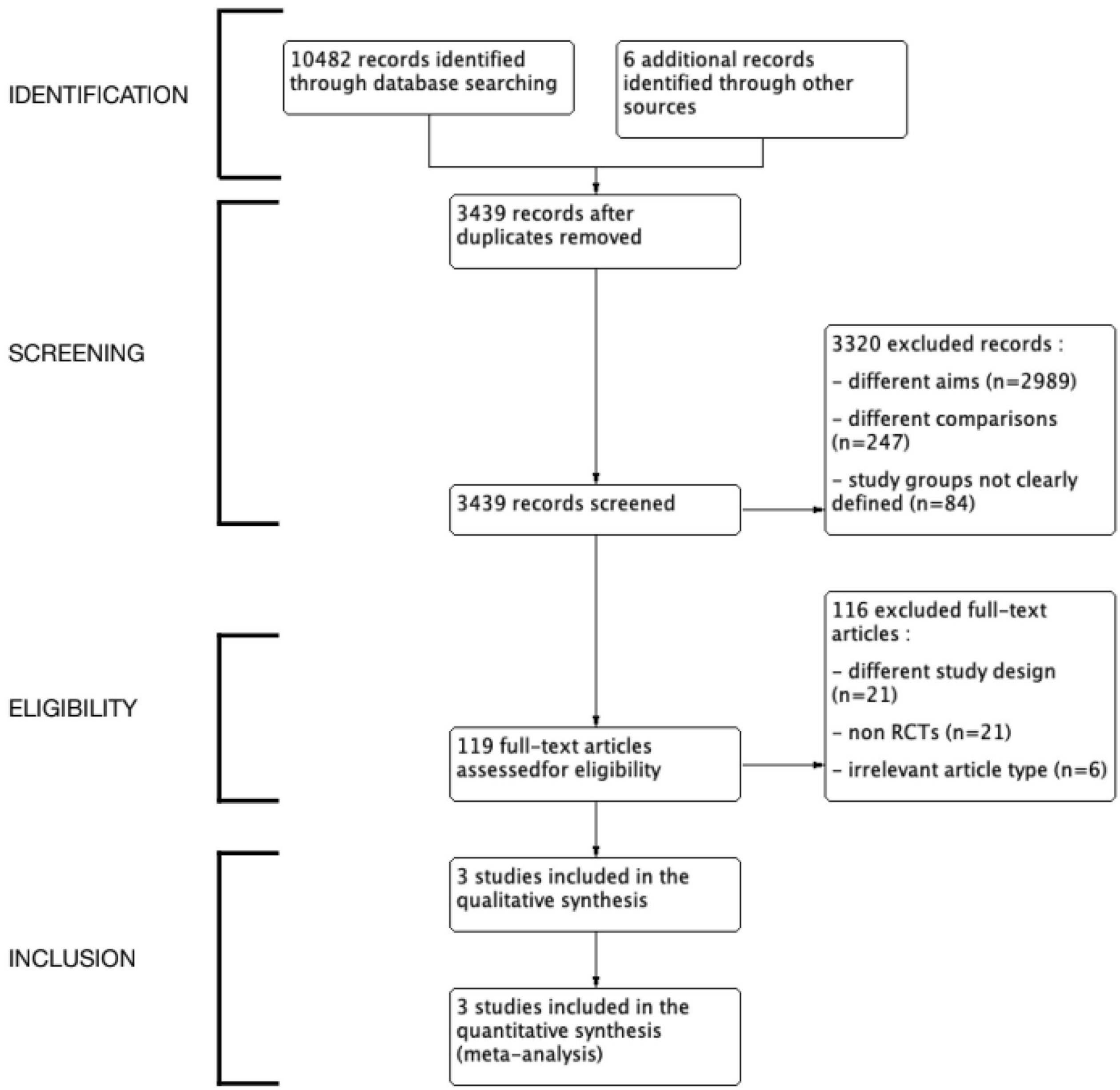

Fig. 1 Preferred reporting items for systematic reviews and meta-analysis flow diagram of included randomized control trials in the systematic review and meta-analysis

is provided in the supplementary materials (Fig. 1S). Regarding study quality, 2 of the 3 RCTs exhibited a low risk of selection bias due to adequate random sequence generation and allocation concealment. However, the risk of selection bias remained unclear in one study due to insufficient information. Notably, the risk of attrition and reporting bias was consistently low across all included studies.

Meta-analysis

Post-treatment complications (Fig. 2)

Two studies 21, 22 reported post-treatment complications; they showed different results regarding risk difference. The combined risk difference is −0.03 (95% CI −0.11; 0.06, p value = 0.54). Heterogeneity between studies was not significant (I2 = 0%).

Table 1 Main features of the included RCTS

Study	Study design	Participants	Outcomes	Diagnostic method
Sajjad [4]	RCT, single center, 180 patients	All children between 5 and15 years of age of both genders admitted in the pediatric surgery emergency and having pediatric appendicitis score (PAS ≥ 7)	Primary outcome: Failure of NOM	PAS greater than or equal to 7
Perez Otereo [22]	RCT, single center, 39 patients	Patients between the ages of 6–17 years presenting with their first episode of uncomplicated acute appendicitis. Inclusion criteria for uncomplicated appendicitis consisted of < 48 h of symptoms, WBC < l8,000 μL, temperature < 103• Fahrenheit, appendix diameter < 11 mm, and radiographic absence of perforation or abscess on ultrasound and/or computed tomography (CT). Presence of an appendicolith did not exclude patients from eligibility	Primary outcomes: one–year success rate of antibiotics-alone and QOL measures assessed 1 month post discharge. Secondary outcome: length of stay and readmission rate	Abdominal US in 31 patients, while 5 patients were diagnosed solely by CT scan, and 3 were evaluated by both Imaging modalities when ultrasound was inconclusive
Svensson [21]	RCT, single center, 50 patients	All children between 5 and15 years of age of both genders admitted in the pediatric surgery emergency	Primary outcome: proportion of children in each group achieving •resolution of symptoms without significant complications"; Secondary outcomes: time from randomization to discharge, complications (wound infection, wound dehiscence, diarrhea, etc.), and recurrent appendicitis within 1 year of randomization	The diagnosis was made with the combination of clinical findings and imaging. All children underwent abdominal ultrasound scan, and a computed tomographic (CT) scan was performed when there was diagnostic: uncertainty

Study	Intervention	Surgical approach	Age OM	Age NOM	CRP OM (mg/L)	CRP NOM (mg/L)	Follow-up
Sajjad [4]	Intravenous meropenem (10 mg/kg/dose intravenous infusion 8 hourly) and metronidazole (20 mg/kg/day intravenous divided doses 8 hourly) for at least 48 h. Once the child started tolerating oral intake and clinically improved, the treatment was changed to oral ciprofloxacin (10 mg/kg/dose twice daily) and metronidazole (20 mg/"q./day two divided doses) for another 8 days	Not specified	10.11 ± 1.83	9.56 ± 1.82	7.79 ± 1.76	7.77 ± 1.8	1 Year
Perez Otero [22]	Intravenous piperacillin/tazobactam for 24–48 h followed by 10 days of oral ciprofloxacin and metronidazole	Laparoscopic	9.7 (7.3–14.4)	10.2 (8.5–11.1)	12.5 (5.0–41)	9.6 (3.3–22)	1 Year
Svensson [21]	Days 1–2: IV meropenem (10 mg/kg × 3 per 24 h) plus metronidazole {20 mg/kg × 1 per 24 h) Days 3–10**:** PO ciprofloxacin (20 mg/kg **×** 2 per 24 h) and metronidazole (20 mg/kg **×** 1 per 24 h)	Laparoscopic	11.1 (6.2–14.8)	12.2 (5.9–15.0)	27.0 (1.0–175.0)	30.5 (1.0–185.0)	1 Year

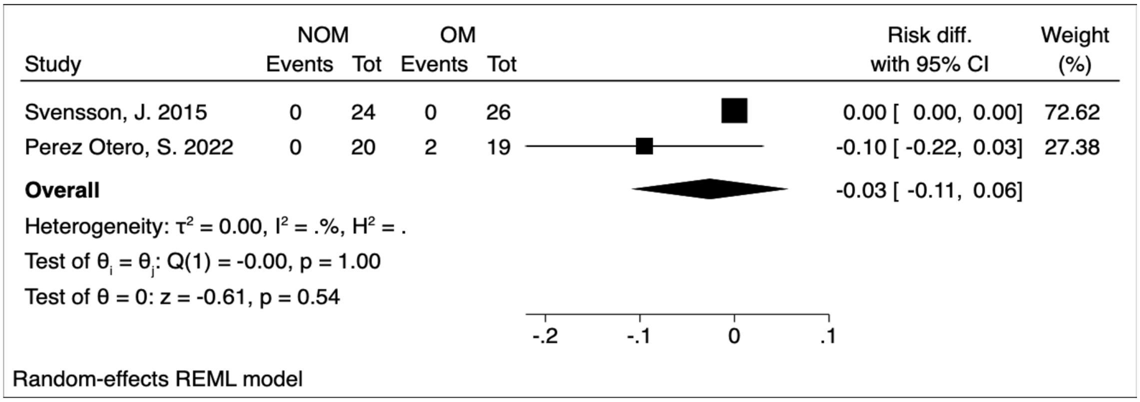

Fig. 2 Postoperative complications. Three studies reported complications

Complication-free treatment success rate (treatment efficacy) (Fig. 3)

All studies 4, 21, 22 included in the analysis provided data enabling us to evaluate the efficacy of the treatments. The risk difference is below zero for all the studies; the combined result is −0.05 (95% CI −0.13; 0.04). The risk of the favorable event (complication-free) in the antibiotic group is lower than in the surgery group. The effect is not statistically significant (*p*-value 0.29).

Heterogeneity between studies was not statistically significant (*p*-value = 0.91, I2 = 0.01%).

Furthermore, it was possible to conduct a subgroup analysis considering two studies 21, 22. The difference in risk of treatment success was calculated as risk in the appendicolith group alone and risk in the non-appendicolith group alone. In the non-appendicolith alone group the combined risk difference between NOM and OM was not statistically significant −0.01 (IC −0.17;0.16; *p*-value: 0.93). In the appendicolith alone group, the combined risk difference was negative but not statistically significant −0.10 (IC −0.45;0.24; *p*-value: 0.57).

Treatment efficacy based on 1-year follow-up (Fig. 4)

Two studies 21, 22 included in the analysis provided data to evaluate the efficacy of the treatments at 1-year follow-up. The results of the studies showed that there was no statistically significant difference in the risk of a favorable event (in terms of treatment efficacy based on 1-year follow-up) between NOM and OM group. The combined result was −0.06 (95% CI −0.21; 0.09), *p*-value: 0.44). Heterogeneity between studies was not statistically significant (*p* = 0.7; I2 = 0%).

Length of primary hospital stay (Fig. 5)

Two studies 21, 22 reported LOS at index hospital admission. The median difference of both studies shows that the median time for the antibiotic group is greater than for the surgery group. The combined difference of the

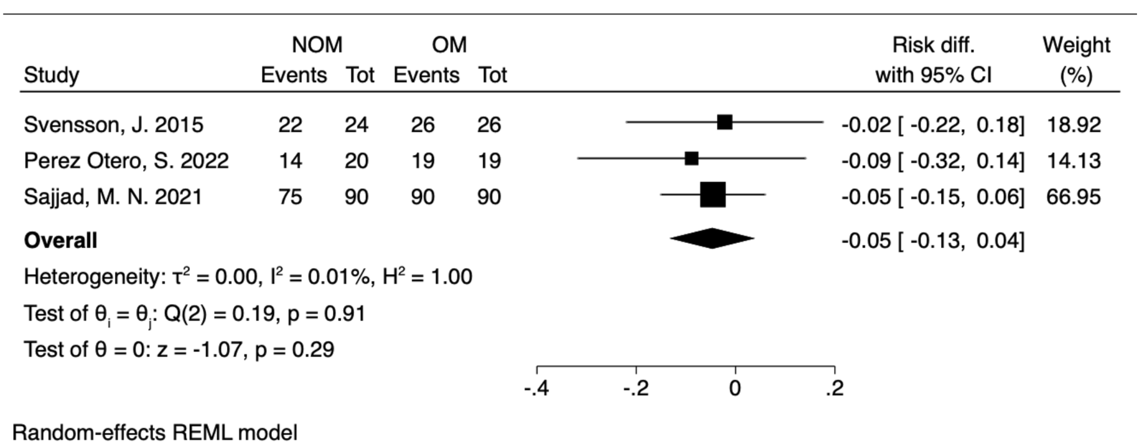

Fig. 3 Complication-free treatment success. Three studies were included in the analysis, defined as discharge without further complications

median was −19.90 h (95% CI −29.27; −10.53, *p*-value <0.0001). Heterogeneity between studies was not statistically significant (Q = 0.52, *p* value = 0.47, I2 = 0%).

Presence of appendicolith (Figs. 6, 7, 8)

All the studies 4, 21, 22 reported data regarding appendicolith. The difference in risk of NOM success was

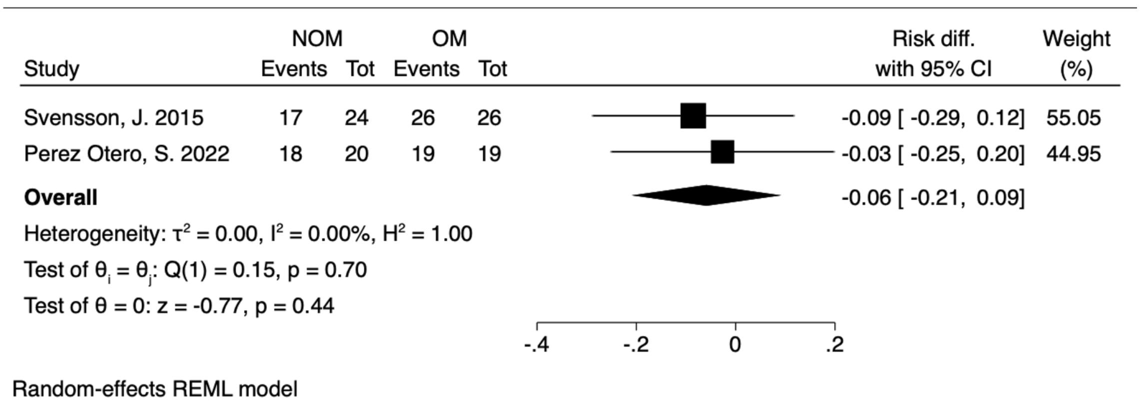

Fig. 4 Treatment efficacy based on 1-year follow-up. Two studies were included

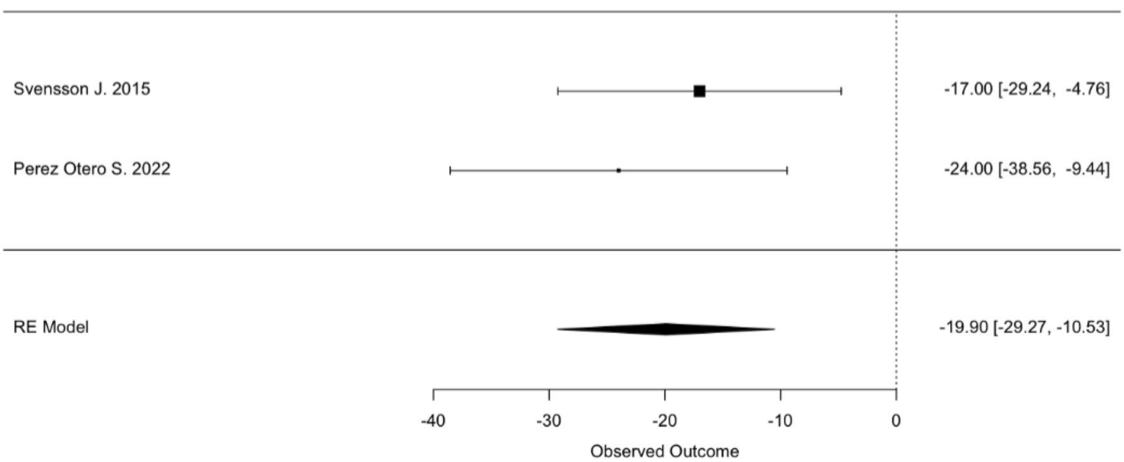

Fig. 5 Length of primary hospital stay was compared based on data from two studies

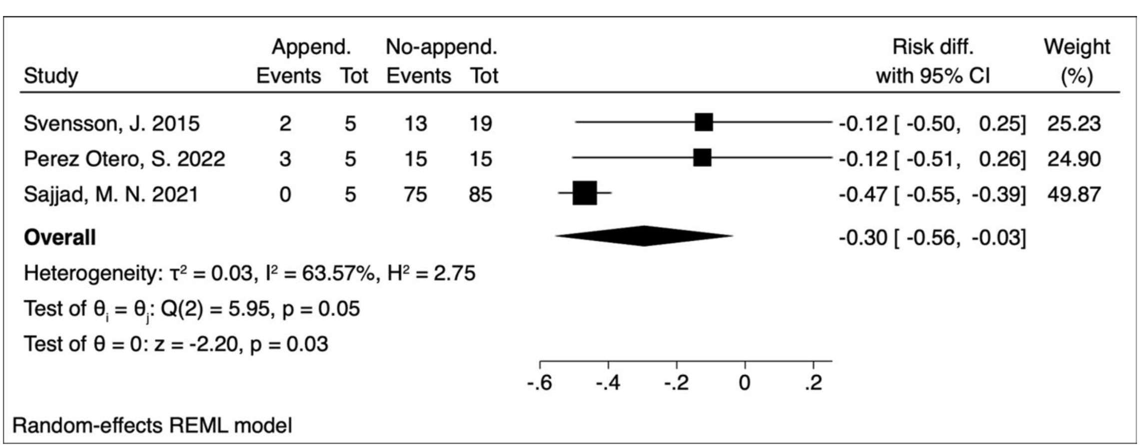

Fig. 6 NOM success rate comparing the appendicolith group and the non-appendicolith group

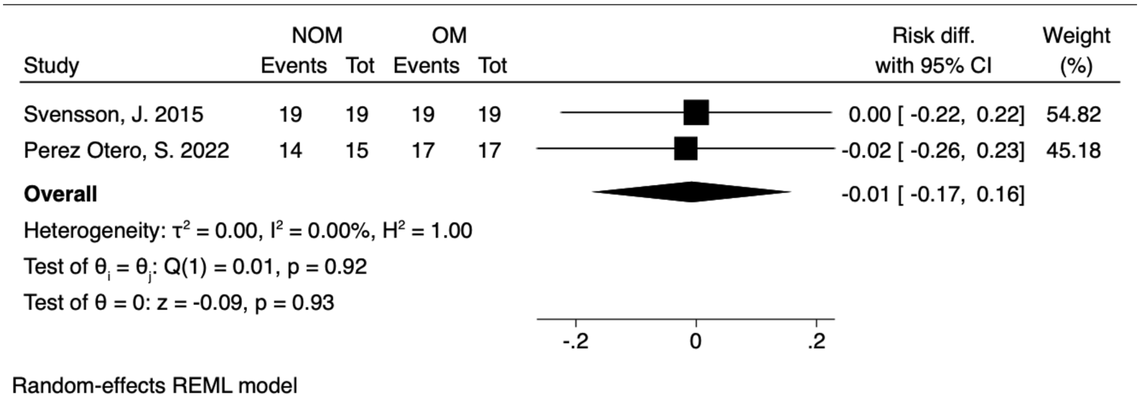

Fig. 7 NOM success rate in the non-appendicolith group alone

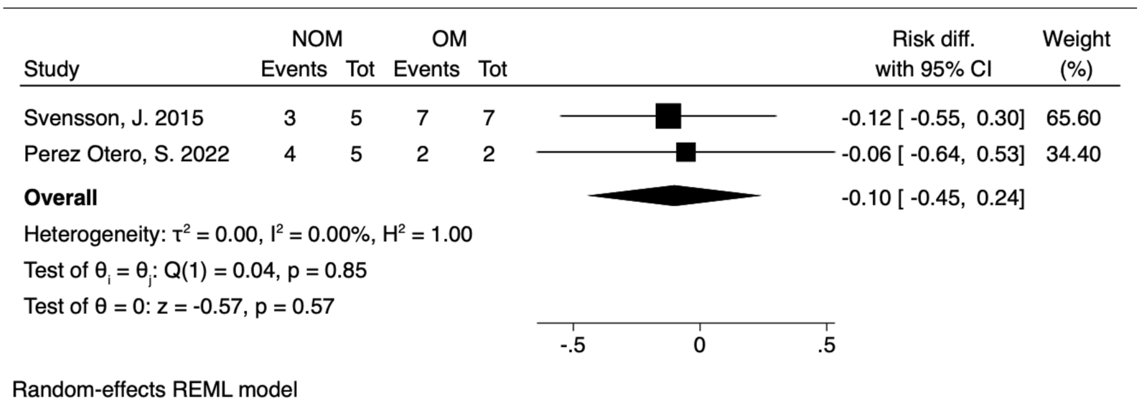

Fig. 8 NOM success rate in the appendicolith group alone

calculated as risk in the appendicolith group and risk in the non-appendicolith group. In all the studies the difference was negative: the risk of success was higher in the non-appendicolith group. The combined risk difference was −0.3 (IC −0.56; −0.03; *p*-value: 0.03). It is statistically significant. Heterogeneity between studies was not statistically significant (Q = 5.95, *p*-value = 0.05, I2 = 63.57%).

Quality of life

Only one study provided data regarding quality of life. Perez Otero et al. reported QoL using the PedsQLTM Generic Core Scale reported by parents, in addition to time to resume regular activities, missing school days, and lost parental work days at 30 days after randomization 22. In the antibiotic's cohort compared to the surgery cohort, they showed superior QOL indicators, with significant differences showing fewer lost work days (0.0 days vs. 2.5 days, $P = 0.03$) and a quicker return to normal activities (2.0 days vs. 12 days, $P = 0.001$).

Negative appendectomy rate

A meta-analysis of this secondary outcome was not possible due to a lack of data. Only the study by Svensson et al. 21 reports that there were no cases of negative appendectomy in the OM group, while one patient in the NOM group who underwent surgery for suspected recurrence had a non-inflamed appendix on histological examination. The studies by Sajjad et al. and Perez-Otero et al. 4, 22, on the other hand, do not specify the exact number of negative appendectomies.

Discussion

Appendectomy stands as the primary treatment choice for children with acute appendicitis, however the 2020 update of the WSES guidelines report that NOM is safe and feasible as initial treatment, particularly in a population without appendicoliths 23. However, surgery and the use of general anesthesia unavoidably entail complications, encompassing issues like bleeding, ileus, surgical site infection, and pneumonia. In addition to these short-term complications, there are also potential long-term complications, the extent of which is not yet fully understood, such as bowel obstructions and infertility caused by adhesions. Consequently, NOM has gained preference in some acute appendicitis cases due to these concerns [24–26. The hypothesis is that conditions resembling acute appendicitis, such as uncomplicated diverticulitis, salpingitis, and necrotizing enterocolitis, often respond well to early antibiotic treatment 27. While NOM and shared decision-making applications are established in the adult population, their use in pediatric patients remains less explored, with limited studies addressing their efficacy in this specific demographic setting 28.

To our knowledge, this study, including 269 patients from 3 RCTs 4, 21, 22 is the first meta-analysis of RCTs enrolling only children.

Our meta-analysis reveals comparable rates of intra-operative and postoperative complications between the OM and NOM group, even including the complications related to NOM failure. Two recent systematic reviews and meta-analyses 3, 30 reported similar results, concerning the rate of complications in the OM and NOM managed groups.

Then, our data add further evidence on the safety of conservative management, although we should account for the heterogeneity in the diagnostic assessment, antibiotic regimens, and treatment duration among the various studies, which could affect the results.

There is evidence that the risk of success in the antibiotic group is lower than the one in the group undergoing surgery. Undoubtedly, a clear advantage of appendectomy is the chance to remove the pathogenic entity with a negligible risk of stump appendicitis 29. Conversely, this is not possible with conservative treatment, which carries a significant risk of lifetime recurrence, estimated between 6.7 and 8.6% 30. However, considering the group of patients without appendicolith, there is no statistical difference in terms of treatment success between OM and NOM (100% vs 97%).

The treatment efficacy assessed at one-year follow-up is not statistically different between NOM and OM. This latter has an efficacy of 79.5% at one year compared to 100% for appendectomy.

The combined median difference of LOS between the antibiotic and surgical groups shows that the median time for the antibiotic group is greater than for the surgery group, and this difference is statistically significant. It is important, therefore, to determine whether a conservative treatment with a lower efficacy and with comparable rates of complications, can be considered acceptable and feasible as a first-line treatment. It seems that approximately one-fourth of patients treated with NOM experience a recurrence within the first year. However, according to the 5-year follow-up results of the APPAC trial conducted on an adult population, patients can be successfully treated again with antibiotic therapy, and if and when surgery is required, it does not appear to be associated with increased complications or technical difficulty 27, 32. This fact also leads to the emergence of intriguing theories suggesting that perforated appendicitis could be a distinct etiopathological entity from uncomplicated appendicitis 28. Hence, it might be inaccurate to assert that emergency appendectomy is, as of now, the optimal treatment for preventing the perforation of an inflamed appendix 33, 34. Aligned with these results, there is Svensson et al.'s pioneering trial that demonstrates the viability of conservative treatment for acute uncomplicated appendicitis in children. Over a 1-year follow-up, only 5% experienced recurrence, and 62% avoided appendectomy. In the subsequent 5-year follow-up, 46% underwent appendectomy, with histological confirmation in only 17%. Notably, no conservatively treated children developed complicated appendicitis 21, 35.

The three studies included in the present meta-analyses used, as NOM, intravenous therapy with meropenem combined with metronidazole (n = 2) or piperacillin/tazobactam (n = 1) for at least 48 h. Subsequently, the intravenous therapies were switched to oral ciprofloxacin combined with oral metronidazole for an additional 5–8 days. One potential concern may relate to the risk of Clostridioides Difficile Infection (CDI), a serious antibiotic-related complication that has been reported among children undergoing treatment for appendicitis. A retrospective cohort study of the Pediatric Health Information System has recently reported that only 0.2% of the nearly 106,000 patients developed CDI, suggesting that this event is rare. Furthermore, the antibiotic treatment duration is a key issue. Indeed, evidence is now available showing that prolonged antibiotic treatment can lead to the emergence of resistant bacteria. Accordingly, local antibiotic protocols have been established in some centers for the optimization of treatments for pediatric acute appendicitis. For instance, Surlemont et al., have proposed that to limit antibiotic overuse, treatment should not exceed 48 h for uncomplicated appendicitis, eventually prolonged to 5 days for perforated appendicitis/peritonitis 36.

Another important matter of concern is represented by the selection of the antibiotic to be given intravenously. All the 3 studies used carbapenems with broad spectrum, namely meropenem and the combination piperacillin/tazobactam, whereas most of the antimicrobial stewardship programs now suggest the use of narrow-spectrum antibiotic combinations (i.e. ceftriaxone/metronidazole, amoxicillin/clavulanate) for the treatment of appendicitis to limit the increasing prevalence of multidrug resistance

37. It must be, indeed, considered that in most European countries (such as Italy, Greece, Portugal, and Spain) the presence of carbapenems-resistant Enterobacteriaceae has become a serious life-threatening condition, and carbapenem-sparing regimens have been advocated 38. Thus, meropenem should not be considered as the first treatment option in countries with a high rate of resistance to carbapenems. Worthy of mention, some recent studies have confirmed the optimal clinical efficacy and safety of amoxicillin associated with clavulanic acid for the treatment of acute appendicitis in children 39. Accordingly, short-term therapy with this combined regimen should be considered as first-line treatment for uncomplicated peritonitis in children 36.

Another important factor when dealing with NOM efficacy is the presence of appendicoliths. Multiple studies [40–43 have linked the presence of appendicolith to a high risk (up to 40%) of complicated appendicitis, and there is also evidence suggesting an elevated risk for recurrent appendicitis 31, 44. All included studies have analyzed these data. In the population without appendicoliths, NOM appears to have an efficacy rate of 86.55% vs. 33.33% in the population with appendicolith, and this evidence is confirmed by the statistical analysis, the risk of NOM success was significantly higher in the non-appendicolith group. In the subgroup analysis of the non-appendicolith group alone, at one-year follow-up, we observed comparable success rates between NOM and OM, 97% and 100%, respectively. Kessler et al., in their meta-analysis, successfully demonstrated that NOM is more prone to failure in the population with appendicoliths, and this particular type of appendicitis is more likely to frequently lead to complications, often involving perforation 11.

Furthermore, the study by Mahida et al., focusing on a population with appendicolith, had to be stopped early because the NOM's high failure rate was unacceptably high for pediatric patients and surgeons 45.

Certainly, there is a need for more RCTs focused on this subject to corroborate this outcome.

All the NOM failures have been ascribed to an early (within 48 h) failure of antibiotic therapy. However, not all of them are direct. Perez-Otero et al. 22 reported an early failure that, nonetheless, originated from an initially unnoticed perforated acute appendicitis on the diagnostic CT scan. Svennson et al. 21 documented an early failure in a patient who ultimately did not have acute appendicitis, but rather mesenteric lymphadenitis. In our analysis, we attempted to provide a pragmatic evaluation by excluding all indirect NOM failures from the various studies. However, these data are not entirely devoid of error.

In our study, there is a notable discrepancy in the overall hospital stay duration, the median time for the NOM group is greater than the one for the surgery group. Yet, Svensson et al.'s findings 21 demonstrated a prolonged stay in the conservative management group, potentially influenced by their stipulation of a minimum 48-h course of intravenous antibiotics 21. Certainly, individuals undergoing NOM will receive more frequent and closer monitoring. As a result, an extended hospital stay may be attributed not only to this heightened observation but also to the understandable concerns of the patient's parents.

Focusing on the quality of life, the only study reporting this outcome 22, showed that in the NOM cohort compared to OM cohort, they showed superior QOL indicators, with significant differences showing fewer lost work days and a quicker return to normal activities. However, Kessler et al. argued against the superiority of conservative treatment compared to appendectomy. Their study revealed a heightened readmission rate, which they attributed to parental concerns about relapse, prompting a preference for interval appendectomy 11.

Connected to the length of hospital stay is undoubtedly the issue of cost difference between the two therapeutic approaches. In their 2017 meta-analysis, Huang et al. underscore a diminished cost associated with NOM, particularly when assessing the patient's initial hospitalization 46. Unfortunately, due to a lack of data, our study was unable to incorporate costs as a secondary outcome. Certainly, we advocate for a comprehensive analysis of the cost issue, extending beyond the initial hospitalization. It is crucial to consider various factors, including the cost associated with hospitalizations when NOM proves unsuccessful, the expenses related to additional outpatient visits for NOM-managed patients compared to surgically treated ones, and other pertinent elements, like the time missed at work by the caregivers. This holistic approach aims to determine whether the cost savings from avoiding surgery for the majority of uncomplicated appendicitis cases adequately offset any complications arising from NOM, as stated by Huang et al. 46 Certainly, the key to gaining an advantage in this regard is to continue optimizing the selection of patients eligible for NOM.

Therefore, given these circumstances, an informed patient choice is crucial. In a study published by Hanson et al. 47 in 2018, 9.4% of the surveyed adult population responded that they would opt for NOM in the case of appendicitis. This number increased to 14.5% when asked about choosing for their children. The study focused on discussing the failure rates of NOM, and indeed, the authors themselves speculate that different numbers would have been obtained if the success rates were presented to patients.

Additional rigorous qualitative research will be necessary to investigate the factors behind the strikingly different outcomes observed in these two studies and to gain a deeper understanding of patient preferences in various situations.

Long-term risks associated with NOM warrant careful consideration. Prolonged or broad-spectrum antibiotic use, often required in NOM protocols, raises concerns about the development of antibiotic-resistant bacteria, which could have significant public health implications. Furthermore, retaining the appendix may pose a theoretical risk of missed pathology, including rare malignancies, though these events remain uncommon. Balancing these potential risks with the benefits of avoiding surgery and its associated complications highlights the need for optimized antibiotic stewardship and continued long-term studies to assess the safety and feasibility of NOM in pediatric populations.

It is important to note a limitation in our study stemming from the complexity of establishing appropriate endpoints for comparing treatments across diverse forms of uncomplicated appendicitis. Additionally, it should be noted that the inclusion of only three RCTs resulted in a total population of 269 patients, which may not be considered a substantially large number.

Furthermore, there is a restricted set of outcome parameters hindering the evaluation of factors like hospital stay and costs. Small patient cohorts reduce statistical power, particularly in analyzing appendicoliths. Variable follow-up durations (1 to 4 years) may bias long-term complication assessment. Infants below 5 years are not addressed, and results lack age-specific reporting. Additionally, the structural similarity of those over 14 years to adults questions the findings' generalizability to a broader pediatric population. These limitations underscore the need for cautious interpretation across diverse age groups in pediatrics.

The two treatment options are equivalent in terms of safety. NOM may be less expensive, less effective, but non-invasive and associated with a higher reported quality of life; while appendectomy is more expensive, more effective, but invasive and associated with a lower quality of life in terms of more lost work days and a slower return to daily life activities. In particular, in the group of patients without appendicolith, there is no even difference between the two treatments in terms of treatment efficacy. Beyond the decision of which therapy should be considered the first choice, the outcome that matters the most could be the patient's quality of life. Regarding this topic, there is a need for more literature, particularly focused on the pediatric population. To establish more reliable analyses, it is crucial to use homogeneous scales across various trials. Possibly, addressing this final aspect could be achieved by ensuring precise and thorough communication with the patient's parents. In practice, for a more complete vision of both the outcomes and the quality of life, it would also be necessary to analyze the long-term outcomes, i.e. the risk of obstruction or infertility in adults (both in terms of hospital admissions, healthcare expenditure, and QoL) in patients who underwent NOM or OM as children.

Finally, the absence of a cost-effectiveness analysis is a limitation of our study. While our meta-analysis focused on clinical outcomes such as efficacy, complications, and quality of life, the economic impact of NOM versus OM is an important consideration, particularly in resource-limited settings. Future studies should incorporate cost analyses to provide a more comprehensive evaluation of these treatment strategies.

Conclusions

This systematic review and meta-analysis provide evidence that NOM in a children population is safe and feasible for all patients and, in the group of patients without appendicolith, it is associated with a similar success rate than OM. However, more high-quality studies with adequate power and construction are still needed and should be directed toward the attempt to provide surgeons with tools that allow the early identification of those patients who might respond adequately to NOM.

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Author contributions
FB and CF designed and wrote the manuscript, EL, DC and SF did the statistical analysis, GZ, SF, PD and GP did the substantial review.

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Declarations

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Author details
[1]University of Milan, Via Festa Del Perdono 7, 20122 Milan, Italy. [2]Pediatric Surgery Department, Buzzi Children's Hospital, 20154 Milan, Italy. [3]Department

Biomedical Sciences for Health, University of Milan, 20133 Milan, Italy. [4]IRCCS Fondazione Policlinico San Matteo, Pavia, Italy. [5]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Via Alessandro Brambilla, 74, 27100 Pavia, Italy. [6]Department of Pediatrics Buzzi Children 's Hospital, 20154 Milan, Italy. [7]Department of Infectious Diseases, ASST Fatebenefratelli University Hospital, Milan, Italy. [8]Department of Biomedical and Clinical Sciences, University of Milan, 20157 Milan, Italy. [9]Department of General Surgery, Luigi Sacco University Hospital, Milan, Italy.

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