

Antibiotics Post-Appendectomy in Pediatric Patients

A Literature Review Leading to Proposition of a New Treatment Protocol

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Abstract

Although acute appendicitis is a common occurrence in the pediatric population, there is still considerable debate surrounding the optimal postoperative antibiotic treatment. Currently, there is a lack of a clear, evidence-based protocol for postoperative treatment.

The objective of this review is to develop a protocol for postoperative antibiotic treatment in children with acute appendicitis. By introducing this protocol, we aim to establish a more straightforward policy and avoid overtreatment with antibiotics.

Introduction

Acute appendicitis (AA) is a common surgical presentation with a lifetime incidence of 9% (1). Despite being one of the most common reasons for abdominal surgery in pediatric patients, there is a wide variation management. In general, AA is treated with appendectomy, followed by antibiotics in the case of complicated appendicitis.

The indication and the optimal duration of postoperative antibiotics for AA still pose significant ambiguity, as described in the 2015 European Association of Endoscopic Surgery (EAES) consensus document, where

the duration of antibiotic treatment varied between 3, 5, 7, and 10 days. They also stated that the evidence regarding the duration of postoperative antibiotic treatment is limited (2).

The World Society of Emergency Surgery (WSES) recommends transitioning to oral administration of postoperative antibiotics after 48 hours, advocating for a total treatment duration of less than 7 days (3). However, they do not provide specific guidance on duration based on classification or define parameters for discontinuation.

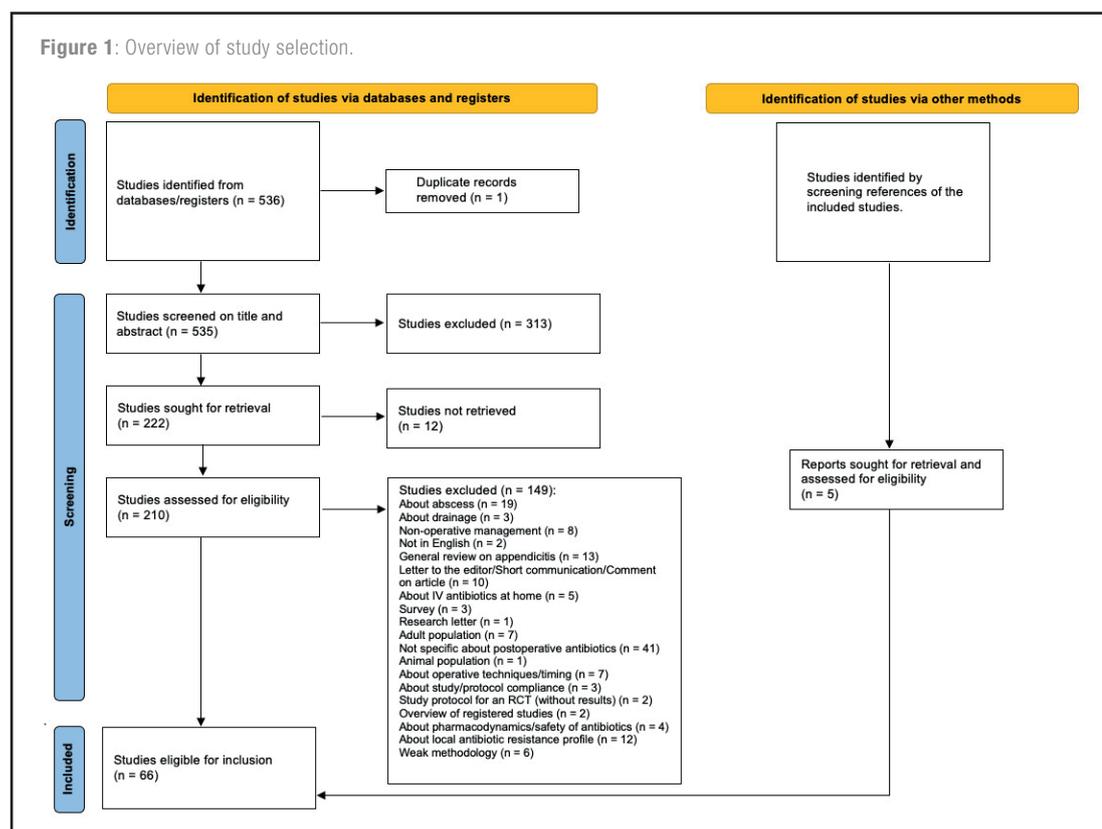
Experience has shown that treatment is often based on the preference of the treating physician. Therefore, we aimed to create a protocol for antibiotic use after appendectomy in the pediatric population based on the most recent literature.

Methods

Exclusion and inclusion criteria

Only studies reporting on postoperative antibiotic treatment of acute appendicitis in children (< 18 years) written in Dutch or English were included. Randomized controlled trials, pro- and retrospective studies, (systematic) reviews and international guidelines were included. Articles describing planned postoperative treatment were included whereas studies describing

Figure 1: Overview of study selection.



prolonged treatment due to postoperative complications (such as surgical site infections) were excluded.

We excluded letters to the editor, comments on articles, surveys or research letters.

Studies describing a conservative antibiotic treatment approach without appendectomy were not included. Patients with an appendicular mass at first presentation were also excluded, since in these cases different approaches are possible depending on disease duration and clinical signs (appendectomy, conservative treatment with antibiotics, percutaneous drainage) and this was beyond the scope of this review.

Literature search

To identify potential studies and guidelines, a literature search was performed according to the PRISMA guidelines in Pubmed (Figure 1) using the Medical Subject Heading (MeSH) terms ‘acute appendicitis AND (pediatric OR children OR child) AND (antibiotics OR antibiotic) AND (postoperative OR appendectomy OR surgery).

To include the most recent literature, we decided to review publications from the last 11 years from 01/08/2012 to 01/03/2024. Duplicates were removed using Covidence.

An overview of the study selection is shown in Figure 1.

Our literature search identified 61 studies eligible for inclusion. By screening references of the included studies, 5 additional articles were added. Details of these studies are provided in the supplementary table.

Results

Classification

By reviewing the literature, we noted a great variability in the classification of AA. In general, everyone agrees that AA is a continuum from an inflamed appendix to perforated appendicitis with generalized peritonitis.

An inflamed appendix is classified as simple or uncomplicated/noncomplicated appendicitis and perforated appendicitis as complex or complicated appendicitis. However, the so-called intermediate forms, such as gangrenous appendicitis (GA), are perceived differently by different studies.

The WSES updated the Jerusalem Guidelines on diagnosis and treatment of AA in 2020. They recommend using an intra-operative grading system for AA. A grading system can help to identify homogeneous groups of patients and assist in determining the optimal postoperative management according to the grade of the disease (3).

Two validated classifications systems are available: the grading system proposed by Gomes and the Anatomic Severity of Disease Grading System for Acute Appendicitis by the American Association for the Surgery of

Trauma (AAST) (4,5). Both grading systems are based on clinical, imaging and operative findings and have been validated in prospective, observational studies. An overview of these classifications is shown in Table 1.

Gomes further divides AA in non-complicated AA, grade 0 and grade 1, and complicated AA, grades 2 to 4 (4). The AAST does not make this distinction but remarks an increasing complication rate associated with the severity grade (5).

The classification systems proposed by Gomes and the AAST do not specifically take into account the purulent/suppurative appendix lacking signs of perforation, which we believe warrants inclusion. A multicenter analysis by Cramm showed that presence of gangrenous, suppurative or exudative changes of a nonperforated appendix was associated with an increased risk of organ space infections and prolonged postoperative length of stay (6). Do-Wyeld also describes advanced appendicitis as gangrenous or suppurative appendicitis without perforation (7).

To address this gap, we suggest the classification outlined in Table 2.

We decided not to divide AA into uncomplicated and complicated appendicitis because of the heterogeneous definitions of (un)complicated appendicitis. We will use the grading classification described in Table 2 since it clearly describes the surgical findings and the continuum of severity of AA.

As mentioned before, in this paper we will not discuss appendicitis presenting with a phlegmon or abscess (grade 4) since this was beyond the scope of this review. We do acknowledge that for a complete treatment protocol, a specific literature search on these subtypes should be done.

Duration and administration of antibiotics

Based on the aforementioned literature review, we made a proposition for duration for antibiotic therapy for the different subtypes of AA. An overview of the protocol is shown in Figure 2.

Grade 1: Simple, acutely inflamed appendix

While there was one article suggesting that 2 postoperative doses of antibiotics can reduce postoperative wound infections, there exists a widespread consensus supporting a single preoperative dose of prophylactic antibiotics, with no indication for postoperative antibiotic administration (8). Antibiotics should be administered within 60 minutes prior to skin incision (2,3,9,10). Hospital discharge should be scheduled within 24 hours after surgery.

Grade 2: Purulent appendicitis

Our comprehensive literature review unveiled a paucity of articles addressing this particular type of AA, with treatment protocols varying from no intervention to a total duration of 7 days (7,11,12). Although suppurative changes in a nonperforated appendix were associated with

Table 1: Overview of the grading systems by Gomes (4) and the AAST (5).

	Grading by Gomes (4)	AAST Grading System (5)
Grade 0	Normal looking appendix (Endoappendicitis/Periappendicitis)	
Grade 1	Inflamed appendix (hyperemia, edema, ± fibrin without or little pericolic fluid)	Intact but acutely inflamed appendix
Grade 2	Necrosis A – Segmental necrosis (without or small amount of pericolic fluid) B – Base necrosis (without or small amount of pericolic fluid)	Intact but gangrenous appendix
Grade 3	Inflammatory tumor A – Phlegmon B – Abscess less than 5 cm without peritoneal free air C – Abscess over 5 cm without peritoneal free air	Perforated appendix with local contamination
Grade 4	Perforated – Diffuse peritonitis with or without peritoneal free air	Perforated appendix with peri-appendiceal phlegmon or abscess
Grade 5		Perforated appendix with generalized peritonitis

Table 2: Classification of subtypes of appendicitis.

Our classification on which we further base our treatment protocol. It is based both on the grading system of Gomes (4) and the AAST (5) with inclusion of suppurative appendicitis.

Grade 1	Simple – inflamed appendicitis: intact, hyperemic, edemic appendix
Grade 2	Purulent appendicitis with or without purulent fluid: thickened, yellowish discoloration of the appendix, no signs of perforation, with or without purulent liquid adjacent to the appendix, not extending to other intra-abdominal quadrants
Grade 3	Gangrenous appendicitis: appendiceal wall necrosis, no signs of macroscopic perforation
Grade 4	Inflammatory tumor <ul style="list-style-type: none"> • A – Phlegmon • B – Abscess
Grade 5	Perforated appendicitis: visible hole in the appendix, intraperitoneal faecolith <ul style="list-style-type: none"> • A - With localized peritonitis: peritonitis/contamination in the right lower quadrant and/or pelvis • B – With generalized peritonitis: peritonitis/contamination outside the right lower quadrant and pelvis

an increased risk of organ space infection and prolonged hospital stay in a large retrospective study, the complication rate after withdrawal or limiting of postoperative antibiotics to 24 hours from the clinical pathway remained the same even in two prospective studies with gangrenous appendicitis (6,13,14).

Most studies try to facilitate discharge and minimize resource usage, yet some set ambitious treatment goals, as seen in the approach of Do-Wyeld et al., who treated all the advanced forms of AA, including suppurative AA, for a duration of 7 days (7). This seems however largely overshooting since this is a longer treatment duration compared to the treatment of some patients with a perforated appendicitis, which we will discuss below. Contrary to this, a retrospective study showed that adhering to 48 hours of postoperative antibiotics for purulent appendicitis, did not increase the risk of infectious complications in comparison to longer treatment durations (11) . Also, Cunningham subdivides suppurative

appendicitis as uncomplicated appendicitis and thereby implies to not treat it with antibiotics (12). This is in line with recent literature where a propensity-matched study showed that postoperative antibiotics could be omitted. The study could not show a significant difference rate of surgical site infections (both incisional surgical site infections as organ space infections) between patients who did or did not receive postoperative antibiotics (15).

Since postoperative antibiotics were not associated with a clinically meaningful reduction in rates of surgical site infections, nor omitting of postoperative antibiotics results in an increase of surgical site infections, we decided to not treat this subgroup of appendicitis with postoperative antibiotics. We aim for discharge within 24hours after surgery as for the simple, acutely inflamed appendix.

Grade 3: Gangrenous appendicitis (GA)

Considerable heterogeneity exists regarding the classification of GA, with debates whether it should be categorized as uncomplicated or complicated appendicitis or even a separate identity, leading to varying treatment protocols (9,12,13,14,16,17,18–28,29). Some studies even omit a distinct description of this subtype, inadvertently suggesting the treatment of GA as if it were uncomplicated (30–35).

Similar to purulent appendicitis, the presence of GA correlates with an increased risk of surgical site infections (6). However, adopting the same treatment strategy for GA as for perforated appendicitis may lead to unnecessary overtreatment. Evidence supporting postoperative antibiotic use often relies on postoperative complication rates after altering the standard of care, highlighting persistent issues of broad-spectrum antibiotic overuse and prolonged therapy durations in surgical settings. Local guidelines for GA management vary, ranging from two single postoperative doses to 3-5 days in some centers (13,36) . Others advocate for administering intravenous (IV) antibiotics until clinical discharge with or without leukocyte count checks before discharge (29,37) .

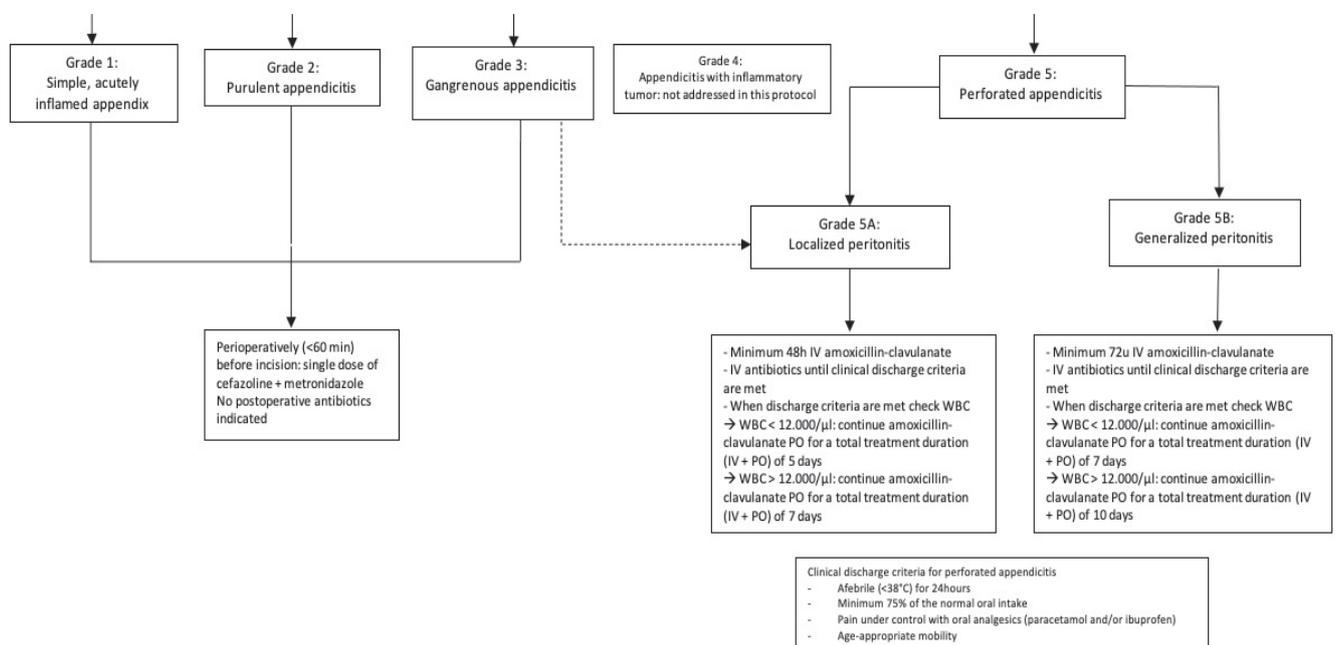
Cramm demonstrated that for both suppurative and GA there is no difference in rates of surgical site infections whether antibiotics are administered or not (15). We therefore advice to not administer postoperative antibiotics for GA and treat GA identical to suppurative and simple appendicitis.

Peroperatively a GA with in addition a local peritonitis (i.e. seropurulent or

Figure 2: Protocol for postoperative antibiotic treatment in acute appendicitis.

Abbreviations: AB = antibiotics, IV = intravenous treatment, PO = Per Os = oral treatment, WBC = white blood cell.

The dotted line is meant to show that gangrenous appendicitis is only treated with postoperative antibiotics if it is associated with local peritonitis.



fecal contamination of the peritoneum) can be seen. A microperforation is expected in this case. We could not deduce a clear advice on how to treat this subtype based on the literature review. We decided to treat a GA with local peritonitis similarly to macroscopic perforated appendicitis with local peritonitis, but we do acknowledge that this approach is expert-based. It is therefore debatable and should be prospectively analyzed.

Grade 5: Perforated appendicitis

In our literature review we found opposing recommendations on the duration of antibiotic treatment for perforated appendicitis and on the decision whether or not oral antibiotic treatment after discharge is necessary and, if so, whether a white blood cell (WBC) count at discharge is necessary to define if switch to oral antibiotics is possible.

The WSES guidelines from Jerusalem recommends transitioning from intravenous to oral antibiotics after 48 hours in perforated appendicitis, with a total treatment duration shorter than 7 days (3). However, they do not specify criteria for determining the timing of this switch. It's important to note that this recommendation is based largely on expert opinion and only supported by a limited number of studies. Whereas the consensus statement of the SPIGC in 2021 from Italy advises to treat complicated appendicitis (defined as a grade 4-5 AA according to table 2) for minimum of 3-5 days and to discontinue IV antibiotics depending on WBC count, fever and normalization of bowel function (10).

We decided to divide the management of perforated appendicitis in localized and generalized peritonitis because the more extensive the contamination, the higher the risk of postoperative complications and increased use of resource utilization (longer duration of antibiotics, narcotic analgesia, parenteral nutrition, postoperative imaging) is seen (38–40).

The subtypes of perforated appendicitis require different duration of antibiotic treatment, but the same clinical discharge criteria apply for both localized and diffuse peritonitis.

The four clinical discharge parameters, that each patient must meet before discharge, are (16,24,28,33,41–43):

1. Afebrile (<38°C) for 24hours
2. Minimum 75% of the normal oral intake
3. Pain under control with oral analgesics (paracetamol and/or ibuprofen)
4. Age-appropriate mobility

Grade 5A - Localized peritonitis

We found 4 studies advocating for intravenous (IV) antibiotic treatment until meeting clinical discharge criteria, without continuation of oral antibiotics at home or leukocyte count assessment before discharge (1,12,44,45). However, most other studies utilize leukocyte count as a discharge criterion (17,22,23,38,43,46–52). Depending on the study, an elevated leukocyte count may result in continuation of IV antibiotics, discontinuation of antibiotics or guide the duration of oral antibiotics after discharge.

Even though an analysis suggests that post-discharge organ space infections may not reliably predicted by routine WBC counts before discharge, we have opted to include leukocyte count assessment at discharge to determine antibiotic duration in children with perforated appendicitis given the prevalence of articles using leukocyte count as a discharge criterion and alignment with the SPIGC consensus statement (53). For localized peritonitis, we recommend initiating IV antibiotic treatment for a minimum of 48 hours, following the WSES guidance. Transitioning to oral antibiotics is done after 48 hours if clinical discharge criteria are met (3).

Although 2 other studies advice that not all patients with complicated appendicitis should be discharged with antibiotics after appendectomy we suggest a minimum total treatment duration of 5 days (IV plus oral treatment) which is largely in line with the SPIGC consensus statement (10,(54,55)). In particular, two studies noted a potential trend toward undertreatment in children receiving less than 5 days of treatment, leading to increased intra-abdominal abscess rates (48,56). Regarding

the total duration of postoperative antibiotic treatment, we differentiate between 5 and 7 days based on the leukocyte count at discharge. A normal leukocyte count (<12,000/μL) allows discharge with a total treatment duration of 5 days total (IV and oral antibiotics combined).

An elevated leukocyte count (>12,000/μL) allows discharge but requires a total treatment duration of 7 days, consistent with various study protocols (22,23,33,49,50).

Grade 5B - Generalized peritonitis

WSES guidelines recommends a switch to oral therapy after 48 hours, but multiple treatment protocols still treat at least 72hours IV for perforated appendicitis with localized or generalized contamination (3,17,23,49,57).

Wakeman et al. more specifically saw a reduction of surgical site infections when they created a clinical practice guideline in which they advise IV therapy for at least 72hours postoperatively and they continue IV therapy until the WBC count is normalized before transitioning to oral antibiotics (17). This latter practice is confirmed by Fallon et al, showing that an elevated WBC count is associated with intra-abdominal abscess formation. In particular, 50% of patients with an WBC count over 14,000/μL developed an intra-abdominal abscess. But even then there is ambiguity considering treatment duration as they do not continue antibiotics at home if normalization of WBC count occurred (43).

Although not based on clear evidence, WSES guidelines advice to use an overall length of therapy shorter than 7 days. However, there are still different studies and treatment protocols advising a longer treatment duration of 10 days.

Theodorou et al. apply a treatment duration of 10 days for patients with an elevated WBC count at discharge (42). Wakeman et al. treat all complicated appendicitis for a total of 10 days (17). Simó et al. treat an appendicular peritonitis for 7 to 10 days without further specification (36). Lastly Lam et al. successfully studied the effect of implementing a standardized care pathway in the Alberta Children's Hospital in Calgary. Their guideline makes a differentiation between perforated and diffuse peritonitis. Diffuse peritonitis is treated with IV antibiotics until clinical discharge criteria are met and a normalization of WBC is reached. Subsequently they switch to oral antibiotics to finish a course for a total of 7-10 days. The final duration of the antibiotic therapy, varying between 7 and 10 days, is based on clinical judgement, without further definition of what this implies (37,58).

Considering the higher risk of postoperative complications with more diffuse peritonitis, we decided to treat this category more strictly by advising at least 72hours of IV treatment. After 72hours a transition to oral antibiotics can be made when clinical discharge criteria are met. To avoid further treatment duration based on clinical judgment, we decided to use the WBC count as a decisive parameter. If the WBC count at discharge is <12.000/μl, we recommend a total treatment duration of 7 days. If the WBC count is elevated (>12.000/μl) a total treatment duration of 10 days is applied.

Type of antibiotics

The most common bacterial species isolated from peritoneal cultures are *Escherichia coli*, *Streptococcus milleri/anginosus*, *Bacteroides fragilis* and *Pseudomonas Aeruginosa* (26,59,60).

For prophylactic antibiotic administration in the case of uncomplicated appendicitis cefazoline with metronidazole is used.

For postoperative antibiotic treatment, we use amoxicillin-clavulanate as first choice of antibiotics, both for IV as oral treatment of perforated appendicitis, according to our local antibiotic guidance.

In case of penicillin allergy, we recommend the combination of ciprofloxacin and metronidazole (17,28). While amoxicillin-clavulanate adequately covers *E. coli* (except for *Extended-spectrum beta-lactamase*), *B. fragilis* and *S. anginosus/milleri*, it does not treat infections with *P. aeruginosa*. However, studies investigating the use of broad-spectrum antibiotics covering *P. aeruginosa*, such as piperacillin-tazobactam, could not demonstrate a beneficial effect of broad-spectrum treatment compared to narrower treatment. Narrower treatment mostly consisted of

ceftriaxone combined with metronidazole (31,35,61–66). We decided to follow our local antibiotic guidance and treat with amoxicillin-clavulanate.

Discussion

We created a treatment protocol for postoperative antibiotic treatment after appendectomy in the pediatric population since this was in our opinion still missing in literature. An overview of the treatment protocol can be seen in Figure 2. Our aim is primarily to implement a straightforward policy and to avoid further treatments based on a physician's preference. We opted for a transparent and evidence-based yet safe protocol taking into account the clinical evolution of the patient and implemented the use of WBC counts to guide antibiotic duration trying to avoid unnecessary overtreatment based on the physician's preference.

Certain limitations in this study warrant acknowledgment. The studies identified from the literature search varied in quality, encompassing both prospective and retrospective analyses, often centered around modifications in local treatment protocols without randomization. In addition, the criteria guiding the establishment of these protocols remained unclear in many instances. The inherent ambiguity surrounding the topic prompted the inclusion of articles expressing divergent opinions and advice regarding antibiotic treatment, complicating the delineation of a definitive protocol. For some aspects of our protocol, such as addressing purulent appendicitis, decisions had to be made with reliance on scarce evidence.

Conclusion

Based on an extensive literature search, we made a proposition of a treatment protocol for planned postoperative antibiotic treatment after appendectomy. We plan to prospectively evaluate our treatment protocol by evaluating surgical site infections in the first month postoperatively. In addition, a prospective analysis of peritoneal cultures will be performed to re-evaluate whether a change in type of antibiotic use is necessary.

Disclosure

The authors have no financial interest to declare in relation to the content of this article. We have no conflict of interest to disclose.

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Supplementary Table:

An overview with more detailed information of the included articles.

Title	1st Author	Year	Type of study	Number of patients	Aim of the study
Acute appendicitis: Proposal of a new comprehensive grading system based on clinical, imaging and laparoscopic findings. (4)	C. Gomes	2015	Literature Review	Not applicable	The goal is review and update the laparoscopic grading system of acute appendicitis and to provide a new standardized classification system to allow more uniform patient stratification.
Amoxicillin/clavulanic acid monotherapy in complicated paediatric appendicitis: good enough? (21)	Rochelle van Coller	2022	Retrospective review	455 patients with acute appendicitis	We examined the transition to single antimicrobial agent (amoxiclav) with respect to clinical consequences
Analysis of a clinical guideline for treatment and early discharge in complicated acute appendicitis (47)	C. Pérez Costoya	2023	Retrospective analytic study	314 patients with complicated appendicitis	The objective of this study was to assess the results in terms of infectious complications and hospital stay of applying a clinical guideline introduced in June 2018 for the treatment of acute appendicitis in our department and aimed at standardizing its management.
An evidence-based care protocol improves outcomes and decreases cost in pediatric appendicitis (16)	Sidrah Khan	2020	Prospective and retrospective observational study	1289 patients with acute appendicitis	We aim to examine the outcomes of these patients with a specific focus on length of stay (LOS), healthcare cost, the type and course of antibiotic use, and postoperative complications. We hypothesized that the introduction of an evidence-based clinical care protocol would decrease LOS and health care cost in the post-intervention group without compromising clinical outcomes.
Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis (19)	Charles C. van Rossem	2016	Multicenter, prospective, observational cohort study	415 patients with acute complicated appendicitis	The objectives of this prospective study were to investigate the relation of antibiotic duration and infectious complications and to identify possible risk factors for a postoperative infectious complication after laparoscopic appendectomy for acute complicated appendicitis.
Antibiotic therapy in acute appendicitis: compliance with local protocol to reduce antibiotic overuse (11)	J. Surlemont	2020	Retrospective study	142 patients with acute appendicitis	The primary objective was to assess the concordance between the antibiotic therapy defined by the ATBP, and the antibiotic therapy actually received by the patients. The efficacy of the ATBP was also evaluated by assessing whether the intended antibiotic was adapted to the bacteria isolated from intraoperative samples. Infectious complication rates were compared between patients receiving antibiotics according to the ATBP and patients receiving non-recommended antibiotic therapy.
Are postoperative Intravenous antibiotics indicated after laparoscopic appendectomy for simple appendicitis? A prospective double-blind randomized controlled trial (8)	Nicole Mennie	2020	Prospective double blind RCT	243 patients with simple appendicitis	Our aim was to perform a prospective double-blinded randomized controlled trial (RCT) comparing 2 postoperative intra- venous doses of Abx to placebo to ascertain the incidence of postoperative WI after a laparoscopic pediatric appendicectomy.
A simple intervention to improve the use of postoperative antibiotics and intra-abdominal drains in appendicectomy patients (20)	P. Sorooshian	2022	Retrospective study	130 patients	Assess whether the simple intervention of an educational poster can improve the appropriate use of postoperative antibiotic and intra-abdominal drain use in appendicectomy patients
Association of Gangrenous, Suppurative, and Exudative Findings With Outcomes and Resource Utilization in Children With Nonperforated Appendicitis (6)	Shannon L. Cramm	2022	Retrospective, multicenter cohort study using NSQIP-P database	867 patients with appendicitis with GSE findings	The goal of this multi-center study was to evaluate whether the presence of GSE findings in patients with nonperforated appendicitis is associated with increased risk of surgical site infections (SSIs) and resource utilization
Association of Intraoperative Findings With Outcomes and Resource Use in Children With Complicated Appendicitis (39)	Seema P. Anandalwar	2018	Retrospective cohort study	1333 patients with complicated appendicitis	the goal of this study was to examine the association of different combinations of intraoperative findings with resource use and rates of adverse events in children with complicated appendicitis.
A standardized protocol for the management of appendicitis in children reduces resource utilization (49)	Christopher Pennell	2020	Prospective and retrospective cohort study	699 children with acute appendicitis	Determine whether delivering uniform and protocolized care to children with appendicitis would improve healthcare resource utilization and clinical outcomes
Bacterial peritonitis in paediatric appendicitis: microbial epidemiology and antimicrobial management (59)	Keir Bhaskar	2023	Retrospective observational analysis	530 patients with appendectomy	This retrospective study aims to determine the microbial epidemiology of paediatric appendicitis from intra-operative cultures in order to assess the appropriateness of empirical antimicrobial prophylaxis during surgery.
Benefits of an abridged antibiotic protocol for treatment of gangrenous appendicitis (13)	Layla Shbat	2014	Prospective cohort study	58 patients with gangrenous appendicitis (38 patients prolonged antibiotics, 20 patients abridged antibiotics)	Determine if shortening the duration of postoperative antibiotics for children with gangrenous appendicitis can decrease the length of stay without increasing complications

Title	1 st Author	Year	Type of study	Number of patients	Aim of the study
Benefits of standardization in the management of acute appendicitis (46)	I. Planas Diaz	2023	Observational, retrospective cohort study	771 patients with acute appendicitis	The objective of this work was to present our results following the optimization of this protocol in our institution, while establishing professionals' adherence, efficacy in terms of number of postoperative intra-abdominal infectious complications, and use of financial resources (control tests and HS).
Beyond perforation: Influence of peritoneal contamination on clinical severity and resource utilization in children with perforated appendicitis (40)	Christina Feng	2016	Retrospective analysis of prospectively collected data	417 patients with appendicitis	The goal of this study was to investigate the relationship between degree of peritoneal contamination in complicated appendicitis and its influence on resource utilization in the postoperative period.
Ceftriaxone combined with metronidazole is superior to cefoxitin alone in the management of uncomplicated appendicitis in children (30)	Mark A. Kashtan	2021	Multicenter retrospective cohort analysis (using data from NSQIP-Pediatric Appendectomy Pilot database and PHIS database)	846 patients with uncomplicated appendicitis	Compare the clinical effectiveness of ceftriaxone + metronidazole versus cefoxitin alone in preventing SSI's after appendectomy for uncomplicated appendicitis
Ceftriaxone with metronidazole versus piperacillin/tazobactam in the management of complicated appendicitis in children: results from a multicenter pediatric NSQIP analysis (31)	Mark A. Kashtan	2021	Multicenter retrospective cohort analysis using data from the NSQIP-Pediatric Appendectomy Pilot Collaborative database merged with PHIS database	654 patients with complicated appendicitis	Leverage data from a collaborative of 14 hospitals participating in the NSQIP-Pediatric to compare outcomes associated with CM and PT in children with complicated appendicitis
Cessation of Antibiotics for Complicated Appendicitis at Discharge Does Not Increase Risk of Post-operative Infection (44)	Katie W. Russell	2024	Retrospective study (NSQIP-P database)	306 patients with complicated appendicitis	We sought to evaluate our outcomes following this protocol change. We hypothesized that the elimination of home antibiotic therapy did not increase our rate of post-operative deep organ space infection or other complications in our patient population.
Comparative effectiveness of ceftriaxone plus metronidazole versus anti-pseudomonal antibiotics for perforated appendicitis in children (62)	Rana F. Hamdy	2019	Retrospective cohort study	353 patients with perforated appendicitis	Compare the clinical outcomes of children with perforated appendicitis who were treated with ceftriaxone + metronidazole versus a broader-spectrum, anti-pseudomonal regimen (cefepime, ceftazidime, piperacillin, cipro, imipenem or meropenem)
Consensus statement of the Italian polispécialistic society of young surgeons (SPIGC): diagnosis and treatment of acute appendicitis (10)	Eleonora Guatioli	2020	Consensus statement based on literature search		Consensus statement was built in relation to the most recent evidence for AA with the aim of summarizing evidence from the last published guidelines and latest studies on this topic.
Diagnosis and management of acute appendicitis. EAES consensus development conference 2015 (2)	Ramon R. Gorter	2016	Guideline based on best available evidence and expert opinions		The aim of this consensus meeting was to develop practical guidelines based on the available evidence combined with the expertise of a selected panel of EAES surgeons. The findings are reported in this manuscript.
Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines (3)	Salomone Di Saverio	2020	WSES Guidelines – consensus conference		WSES decided to convene an update of the 2016 Jerusalem guidelines.
Early transition to oral antibiotics for treatment of perforated appendicitis in pediatric patients: Confirmation of the safety and efficacy of a growing national trend (32)	Tara J. Loux	2016	Prospective and retrospective study	259 patients with perforated appendicitis	Analysis of a new protocol. We instituted a new protocol, expecting that the regimen would prove equally safe, more efficient and more cost effective for perforated appendicitis than the PICC line/IV protocol employed previously.
Effectiveness of a clinical pathway for pediatric complex appendicitis based on antibiotic stewardship principles (12)	Megan E. Cunningham	2020	Interrupted time series	465 patients with complex appendicitis	To evaluate the safety and efficacy of a complex appendicitis discharge protocol based on clinical parameters alone, limiting antibiotic prescription at discharge. We hypothesized that this simplified, antibiotic-limiting protocol would not have inferior postoperative outcomes with regards to postoperative LOS, readmission rates, and rates of intra-abdominal abscess formation when compared to a more traditional resource-intensive regimen
Effects of a paediatric antimicrobial stewardship program on antimicrobial use and quality of prescriptions in patients with appendix-related intraabdominal infections (36)	Silvia Simo	2020	Pre-post intervention study	2021 admissions for appendix-related intraabdominal infections	We aimed to describe and evaluate the results on antibiotic use, LOS and quality of prescriptions of the first 3 years of an ASP intervention directed to children admitted for appendix-related intra-abdominal infections in a European referral paediatric university hospital
Eliminating the use of home oral antibiotics in pediatric complicated appendicitis (1)	Bavana Ketha	2021	Retrospective study (pre- and post-protocol change)	170 patients with perforated appendicitis	Our aim with this study was to evaluate a further protocol change to eliminate a WBC check and oral antibiotics if patients were discharged before post-operative day 7. We hypothesized that this protocol change would further decrease our overall antibiotic use without an increase in our readmission rate or abscess rate.

Evaluating the effectiveness of a discharge protocol for children with advanced appendicitis (43)	Sara C. Fallon	2013	Retrospective review	450 patients with advanced appendicitis	The purpose of this study is to assess the effectiveness of laboratory parameters as part of discharge criteria in a clinical pathway for the treatment of advanced appendicitis.
Evaluation of white blood cell count at time of discharge is associated with limited oral antibiotic therapy in children with complicated appendicitis (22)	Patrick C. Bonasso	2019	Retrospective review	179 patients with complicated appendicitis	The purpose of our study was to investigate the impact of WBC at discharge on oral antibiotic therapy, abscess rate, and readmission rate. We hypothesized that evaluation of WBC at the time discharge criteria were met would decrease use of home oral antibiotics and total length of antibiotic treatment.
Evidence-based optimisation of empirical antibiotic regimens in paediatric complicated appendicitis: a retrospective study of 94 patients (60)	Filippo Gerber	2022	Retrospective study	94 patients with complicated appendicitis	This study's primary objective was to describe and analyse microorganisms' microbiology and antibiotic susceptibility in complicated appendicitis since 2017. Secondary objectives included evaluating the change of EAR on the rate of postoperative infectious complications in complicated appendicitis and identifying possible determinants of postoperative infectious complications in our population
Extended versus narrow-spectrum antibiotics in the management of uncomplicated appendicitis in children (35)	Danielle B. Cameron	2018	A Propensity-matched Comparative Effectiveness Study	1389 patients with uncomplicated appendicitis	The purpose of this study was to compare the relative effectiveness of extended and narrow-spectrum antibiotics in preventing SSI and hospital revisits in children undergoing appendectomy for uncomplicated appendicitis.
Fast-track surgery for acute appendicitis in children: a systematic review of protocol based care (24)	Montgomery Do-Wyeld	2019	Systematic Review	33 studies included	The aim of this systematic review is to evaluate the current evidence for standardization of care in childhood appendicitis and to identify future directions in this field.
Gangrenous appendicitis in children: a prospective evaluation of definition, bacteriology, histopathology, and outcomes (29)	Sherif Emil	2012	Prospective observational study	38 patients with gangrenous appendicitis	Our primary goal was to determine if the clinical and economic outcomes of gangrenous appendicitis can be further improved by decreasing length of stay without increasing complications.
Gangrenous appendicitis: no longer complicated (14)	Andrew B Nordin	2019	Prognosis study	1007 patients who underwent laparoscopic appendectomies	We sought to reduce inpatient length of stay and antibiotic utilization for patients with gangrenous appendicitis, and hypothesized that treating these patients according to the simple pathway would accomplish these goals without adversely increasing postoperative abscess rates or readmissions.
Home Antibiotics at Discharge for Pediatric Complicated Appendicitis: Friend or Foe? (54)	K Tinsley Anderson	2017	Retrospective review	6412 patients with complicated appendicitis	The purpose of this study was to evaluate the postdischarge outcomes of pediatric complicated appendicitis patients discharged with or without antibiotics, stratified by presence of a pre-discharge surgical site infection (SSI) and LOS.
Impact of implementing a fast-track protocol and standardized guideline for the management of pediatric appendicitis (37) Guideline available online: (58)	Jennifer Y. Lam	2020	Retrospective review	276 patients with acute appendicitis included	Study to determine the impact of implementation of the guideline at our institution on length of stay (LOS), antibiotic stewardship efforts and costs.
Implementation of an evidence-based protocol after appendectomy reduces unnecessary antibiotics (45)	Avery C. Rossidis	2020	Retrospective review	1562 patients with acute appendicitis	We hypothesized that the implementation of this protocol would result in reduced antibiotic usage and shorter lengths of hospital stay without increasing the incidence of surgical site infection (SSI) or other complications.
IMPACT (Intravenous Monotherapy for Postoperative Perforated Appendicitis in Children Trial) (50)	Justin Lee	2021	Randomized Clinical Trial	162 patients with perforated appendicitis enrolled	We conducted a prospective randomized clinical trial comparing a broad-spectrum, single-drug regimen of PT versus a 2-drug regimen of CM.
Improvements in antimicrobial prescribing and outcomes in pediatric complicated appendicitis (28)	Zachary I. Willis	2018	Prospective + retrospective study	313 patients with complicated appendicitis	We evaluated the effects of 2 successive interventions, an antimicrobial stewardship program (ASP) and a condition-specific clinical practice guideline (CPG), on antimicrobial utilization and patient outcomes in these patients.
Improving quality and efficiency of care for advanced appendicitis in children (7)	Montgomery Do-Wyeld	2021	Case-control study (pro+retrospective)	44 patients with advanced appendicitis enrolled	Study aims to design, implement and evaluate a clinical protocol for a proposed intermediate pathology cohort termed 'advanced' appendicitis in children based on a number of intra-operative and patient characteristics. The goal of our enhanced recovery pathway (ERP) is to facilitate discharge and reduce resource utilization for this targeted patient group with 'advanced' appendicitis without increasing existing post-operative complication or readmission rates.
Is Pseudomonas Infection Associated with Worse Outcomes in Pediatric Perforated Appendicitis? (66)	Christina M. Theodorou	2021	Single-center retrospective review	255 patients with perforated appendicitis	Given that Pseudomonas is a common gastrointestinal microbe that is not covered by our empiric antibiotic regimen, we hypothesized that post-operative outcomes of children with Pseudomonas identified on intraoperative cultures would be worse than children without Pseudomonas.

Title	1 st Author	Year	Type of study	Number of patients	Aim of the study
Measuring the value of a clinical practice guideline for children with perforated appendicitis (41)	Jamie R. Robinson	2017	Analysis before and after implementation of CPG	122 patients with perforated appendicitis	Determine if a CPG is cost-effective for preventing adverse events (AEs) in children undergoing treatment for perforated appendicitis at a tertiary referral children's hospital.
Modification of an evidence based protocol for advanced appendicitis in children (27)	Sara C. Fallon	2013	Prospective + retrospective study	50 patients with advanced appendicitis	We prospectively studied peritoneal fluid microbial cultures at the time of appendectomy in children with perforated appendicitis in order to update our hospital's clinical pathway guidelines for advanced appendicitis.
Multi-center prospective study of restrictive post-operative antibiotic treatment of children with complicated appendicitis (55)	Qianyang Liu	2020	Randomized, controlled, parallel group, multi-center analysis	685 patients with complex appendicitis	The purpose of our study was to assess the effect of limiting a course of post-operative antibiotic treatment for complex appendicitis in term of abscess, incision infection rate, and re-admission rate. We hypothesized that restrictive post-operative antibiotic administration is equivalent to the standard regimen after surgery for complicated pediatric appendicitis.
Once-Daily Ceftriaxone Plus Metronidazole Versus Ertapenem and/or Cefoxitin for Pediatric Appendicitis (34)	Amanda L. Hurst	2017	Retrospective review	841 patients with acute appendicitis	Because we changed from a historical regimen of ERT (for perforated and abscessed at presentation cases) and cefoxitin (CFX) for nonperforated cases) to a current regimen of CTX plus MTZ for all appendicitis, we were presented with a unique opportunity to evaluate and compare these regimens for clinical efficacy and cost in a retrospective manner
Optimal first line antibiotic treatment of pediatric complicated appendicitis based on peritoneal fluid culture (26)	Tsubasa Aiyoshi	2021	Retrospective study	86 patients with complicated appendicitis	this study aimed to determine the appropriate first-line antibiotic treatment for pediatric CA.
Oral antibiotics and abscess formation after appendectomy for perforated appendicitis in children (51)	Alex J. Gordon	2020	Retrospective study	253 patients with perforated appendicitis	We sought to further assess the safety of discharging patients without oral antibiotics using a multicenter retrospective pre implementation/ postimplementation study design
Postoperative Antibiotics for Complicated Appendicitis in Children: Piperacillin/Tazobactam Versus Ceftriaxone with Metronidazole (63)	Suhail Zeineddin	2023	Retrospective comparative study	29,015 patients with complicated appendicitis	The aim of this retrospective, cross sectional analysis is to describe the relationship between antibiotic regimen and postoperative outcomes using a large administrative database.
Postoperative Antibiotics, Outcomes, and Resource Use in Children With Gangrenous Appendicitis (15)	Shannon L. Cramm	2024	Retrospective multicenter propensity-matched cohort study using NSQIP-P database	958 patients with appendicitis with GSE findings	The goal of this analysis was to evaluate whether use of postoperative antibiotics was associated with improved outcomes in children with nonperforated appendicitis with GSE findings
Predictive Value of Routine WBC Count Obtained Before Discharge for Organ Space Infection in Children with Complicated Appendicitis: Results from the Eastern Pediatric Surgery Network (53)	Shannon L. Cramm	2022	Retrospective multicenter cohort study (using data from NSQIP-P)	1264 children with complicated appendicitis (of which 348 had a WBC)	The goal of this multicenter analysis was to evaluate the predictive value of RPD-WBC data to identify children at risk of post discharge OSI after appendectomy for complicated appendicitis.
Prospective evaluation of a clinical response directed pathway for complicated appendicitis (23)	Nick Lansdale	2019	Prospective + retrospective cohort study	264 patients with acute appendicitis	The aim of this study was to assess whether a new response-based post-operative pathway was safe and effective and whether or not it offered benefit.
Protocolized management of pediatric complicated appendicitis leads to improved outcomes (33)	Armando Salim Munoz Abraham	2022	Retrospective review	246 patients with complicated appendicitis	For this study, our aim was to evaluate the effectiveness of our evidence-based complicated appendicitis management protocol at a stand-alone children's hospital. We set out to compare outcomes and resource utilization for complicated appendicitis treated with early versus interval appendectomy. We hypothesized that patients presenting with complicated appendicitis with or small abscess (≤ 3 cm) would most likely benefit from an early appendectomy.
Reducing Piperacillin and Tazobactam Use for Pediatric Perforated Appendicitis (61)	Talal B. Seddik	2021	Single center, retrospective cohort study	Forty children before and 109 after intervention were included	We aim to determine the efficacy of this intervention to decrease PT use for perforated appendicitis and whether this led to any differences in clinical outcomes.
Reducing resource utilization for patients with uncomplicated appendicitis through use of same-day discharge and elimination of postoperative antibiotics (9)	Courtney L. Devin	2020	Retrospective comparative study.	575 patients who underwent appendectomy for uncomplicated appendicitis	Our goal was to create a standardized perioperative pathway in the treatment of acute, uncomplicated appendicitis that would reduce variability among surgeons and increase compliance with evidence-based practices. We then compared our pre- versus post-pathway outcomes.

Reduction of surgical site infections in pediatric patients with complicated appendicitis: Utilization of antibiotic stewardship principles and quality improvement methodology (17)	Derek Wakeman	2022	Pre- and post-implementation cohort study	104 patients with complicated appendicitis	We hypothesized that implementing clinical practice guidelines to standardize post-operative care would improve clinical outcomes for CA and reduce healthcare utilization. Our aim was to reduce surgical site infection after appendectomy for CA by 25% in 1 year.
Response-based therapy for ruptured appendicitis reduces resource utilization (65)	David E. Skarda	2014	Prospective and retrospective query of a database	306 patients with ruptured appendicitis	We sought to evaluate the differences in patient outcomes and resource utilization between a previously implemented fixed-duration IV antibiotic therapy protocol that included Pseudomonas coverage vs. our newer patient response-based IV antibiotic therapy protocol that did not include Pseudomonas coverage and utilized home oral antibiotics in potentially high-risk patients.
Risk stratification in pediatric perforated appendicitis: prospective correlation with outcomes and resource utilization (38)	Yasmine Yousef	2018	Prospective cohort study	122 patients with perforated appendicitis	We prospectively validated the ability of a grading system for perforated appendicitis to predict outcomes and resource utilization associated with treatment of the disease. We believe such a grading system can finally standardize outcomes reporting, and accurately reflect the resource burden across the disease spectrum.
Safety of a new protocol decreasing antibiotic utilization after laparoscopic appendectomy for perforated appendicitis in children: A prospective observational study (56)	Amrita A. Desai	2015	Prospective + retrospective observational study	540 patients with perforated appendicitis	In order to progress the protocol further, we conducted a prospective observational study in the next 270 patients admitted in which patients could be discharged home early without PO antibiotics if a leukocytosis is not identified at time of discharge prior to completion of a 5 day IV antibiotic course.
Splitting hairs and challenging guidelines: defining the role of perioperative antibiotics in pediatric appendicitis patients (57)	Kimberly K Somers	2019	Prospective, observational, cohort study	988 patients with AA and 561 patients with CA	This study asked questions relevant to the impact of timing and duration of pre- and postoperative antibiotics on SSIs in AA and CA
Standardized discharge antibiotics may reduce readmissions in pediatric perforated appendicitis (48)	Dalya M. Ferguson	2020	Retrospective cohort study	617 patients with acute and perforated appendicitis	Given the paucity of high-quality evidence available on the ideal duration of postoperative antibiotics, we aimed to assess patient outcomes before and after our institutional CPG was modified. We hypothesized that receiving an additional 7 d of oral antibiotics after discharge would be associated with a reduced risk of IAA in children with perforated appendicitis.
Standardization and improvement of care for pediatric patients with perforated appendicitis (52)	Joyce Slusher	2014	Prospective and retrospective chart review	Retrospective 119 patients with perforated appendicitis, prospective 134 patients	By standardizing care, we hoped to reduce variation in practice and in turn reduce consumption of health care resources while maintaining excellent patient outcomes.
The Utility of Discharge Antibiotics in Pediatric Perforated Appendicitis Without Leukocytosis (42)	Christina M Theodorou	2022	Pre- and post-cohort study	210 patients with perforated appendicitis	As part of a quality improvement initiative, our institutional pediatric perforated appendicitis clinical practice guideline was modified to discontinue antibiotics on discharge in the presence of a normal white blood cell count (WBC) without neutrophilia. We aimed to assess the effect of this practice change on rates of discharge antibiotics. We hypothesized that patients would receive fewer antibiotics without increased adverse events.
Timing of antimicrobial prophylaxis and infectious complications in pediatric patients undergoing appendectomy (25)	Cristen N. Litz	2018	Retrospective cohort study	478 patients with acute appendicitis	The purpose of this study was to determine the impact of administering antibiotics within one hour prior to incision on infectious complications in pediatric patients with acute appendicitis who are started on parenteral antibiotics upon diagnosis.
Updates on bacterial resistance and empirical antibiotics treatment of complicated acute appendicitis in children (18)	Chun Pong Daniel Kwok	2021	Retrospective Historical Comparative Study	257 children with acute appendicitis	We aim to provide updates on bacterial resistance and evidence-based recommendation on choice of empirical antibiotics over the decade.
Use of Antipseudomonal Antibiotics is not Associated with Lower Rates of Postoperative Drainage Procedures or More Favorable Culture Profiles in Children with Complicated Appendicitis: Results from a Multicenter Regional Research Consortium (64)	Shannon L Cramm	2023	Multicenter cohort study (using NSQIP-P data)	1268 patients included with complicated appendicitis	The goal of this analysis was to compare rates of postoperative drainage procedures and microbiological culture profiles between children treated with PT or CM at 15 children's hospital
Validation of the American Association for the Surgery of Trauma grading system for acute appendicitis severity (5)	Charles A. Mouch	2020	Retrospective cross-sectional analysis of prospectively collected	734 patients with acute appendicitis	Our objective was to conduct a retrospective cross-sectional analysis of prospectively collected data to determine the relationship between AAST grade and clinical outcomes in acute appendicitis. We hypothesized that prospectively collected AAST grades for appendicitis would be associated with clinical outcomes such as complications and hospital length of stay. By conducting this study, we provide support for use of the AAST grading scale as a valid and optimal measure for risk-adjustment in clinical benchmarking and outcomes research.