

Article

The Care of Appendicular Peritonitis in the Era of Antibiotic Resistance: The Role of Surgery and the Appropriate Antibiotic Choice

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Abstract: **Purpose:** Acute appendicitis (AA), classified as non-complicated acute appendicitis (NCAA) and complicated acute appendicitis (CAA), is the most common cause of abdominal pain in children requiring surgical treatment. If the first-line treatment for NCAA is to be debated between conservative management and surgery, authors find a consensus in choosing surgery as the first step for CAA in children. In the case of patients with CAA undergoing surgery, a broad-spectrum antibiotic therapy should be administered to reduce the risk of post-operative complications (POC). The rise in antibiotic resistance requires a review of recent data regarding bacterial species involved in AA. The primary aim of our study was to investigate the clinical effectiveness of different antibiotic protocols in patients undergoing surgery for CAA. The secondary aim was to verify the antibiotic's in vitro effectiveness based on cultural examinations. **Methods:** A retrospective and prospective study was conducted on all patients operated on at our pediatric surgery department for CAA from January 2017 to January 2023. The following data were collected: age at surgery, sex, surgical technique, duration of the procedure, antibiotic therapy, duration of the hospital stay, cultural examination of peritoneal effusion, and POC. **Results:** We divided the patients enrolled (n = 182) into three groups of antibiotic protocols; only one group resulted in a statistically significant lower rate of POC. Different pathogens were isolated (Enterobacteriaceae, non-fermentative Gram-negative bacilli, anaerobes, Gram-positive cocci), and the in vitro rate of antimicrobial sensitivity varied from 40% to 94% in the three groups of patients. **Conclusions:** Based on cultural examinations, our study showed a high rate of inadequacy regarding the therapy with amoxicillin + clavulanic acid despite a low rate of complications. Radical surgery seems to be the best way to reduce complications in children with CAA.

Keywords: complicated acute appendicitis; acute appendicitis; peritonitis; appendicitis; antibiotic; antibiotic resistance; appendectomy; children; minimally invasive surgery

1. Introduction

Acute appendicitis (AA) is the most common cause of abdominal pain in children requiring surgical treatment [1].

Symptoms of AA in children can be nonspecific. AA can present with abdominal pain, loss of appetite, emesis, and fever. An early diagnosis to prevent the evolution of complicated acute appendicitis (CAA) and its consequences poses a challenge for pediatric surgeons. However, young children may not present the typical history, progression, and migration of pain, arriving at the emergency department with symptoms of early perforation or sepsis in the worst cases [2]. Based on the timing of the inflammatory process, AA can be divided into non-complicated acute appendicitis (NCAA) and CAA.

NCAA includes catarrhal and phlegmonous appendicitis, while CAA includes gangrenous appendicitis, appendicular abscess, and peritonitis [3–5].

While the first-line treatment for NCAA is still debated between conservative management and surgery, a universal consensus has been reached in defining surgery as the first step for CAA in children [6–8].

Minimally invasive surgery (trans-umbilical laparo-assisted appendectomy—TULAA—and laparoscopic appendectomy—LA) is widely accepted as the gold standard for CAA. However, the use of suction, irrigation, and drain placement is still debated, and the most appropriate post-operative antibiotic treatment has not been detected yet [1,7,9].

In patients with CAA undergoing surgery, broad-spectrum antibiotic therapy is warranted in order to reduce the risk of post-operative complications (POC) [4], such as umbilical granuloma, wound infections, abdominal abscesses, or bowel obstruction [10].

Even though many antibiotic treatment protocols are described and recent guidelines are clear on which regimen should be chosen, the increase in antimicrobial resistances demands a periodical review of the pattern of bacterial species involved in AA in order to adapt the wide-spectrum antibiotic therapy to local resistances.

The main issue in treating peritonitis in children remains the high incidence of postoperative complications [11].

The primary aim of this study was to investigate the clinical effectiveness of our antibiotic treatment protocols, while the secondary aim was to verify their effectiveness in vitro based on cultural examinations. From our results, we hope to assess the current ideal post-operative antibiotic therapy protocol in pediatric patients undergoing appendectomy for CAA in our specific geographic area.

2. Methods

A retrospective and prospective study was conducted in our Department of Pediatric Surgery, IRCCS Sant'Orsola-Malpighi, Alma Mater Studiorum, University Hospital of Bologna (IT), following ethical committee approval with Ethic Code CHPED-22-03-AAC (25 May 2022).

Sample of this study

We enrolled all patients undergoing appendectomy for CAA between January 2017 and January 2023.

The following inclusion criteria were used to define the population of this study:

- Age < 16 years old.
- Appendectomy for CAA (gangrenous, appendicular abscess, and peritonitis).
- Peritoneal fluid culture.
- A minimum follow-up of 12 months

Data collection

The following data were extracted from clinical and surgical registers:

Demographic data: age at surgery, sex.

Pre-operative data: symptoms, white blood cells, neutrophils, and C-reactive protein.

Intra-operative data: surgical technique, duration of the procedure.

Post-operative data: antibiotic therapy, duration of the hospital stay, cultural examination of the abdominal effusion, complications (Figure 1).

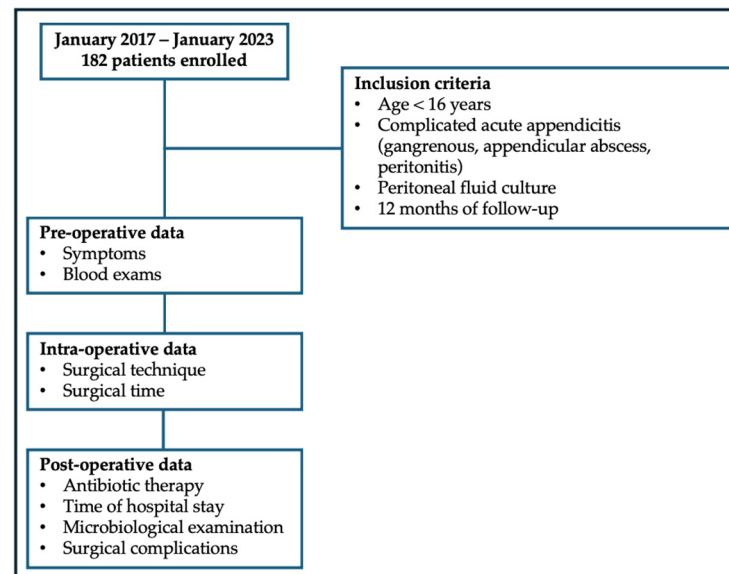


Figure 1. Materials and methods. Patients' data analyzed and inclusion criteria.

Surgery

Surgery was performed by different members of our surgical team, who have all received proper training on urgent appendectomy starting from the first years of residency.

As usual, the surgical approach was determined by the personal choice of the surgeon once the degree and extension of the infectious process were ascertained. In our center, we approach all patients with AA with a trans-umbilical laparo-assisted technique, which consisted of positioning a 10 mm trocar trans-umbilically and using a 0° 10 mm lens with a working channel; the cecum and appendix were identified and mobilized, the tip of the appendix was grasped, and the appendix was exteriorized through the umbilical incision. Therefore, the mesoappendix was ligated, and the base of the appendix was ligated and amputated extracorporeally.

Based on anatomy and the appendix's condition, the procedure was usually converted to a classic laparoscopic approach with two additional 5 mm operative trocars, placed in a suprapubic position and in the left lower quadrant, and the appendectomy was completed intraperitoneally. Conversion to an open technique, performing a McBurney incision, was needed in rare cases in which the extension of the infection and inflammation required complete control of the tissues to prevent intra-operative and further post-operative complications.

Suction and Irrigation: Following the removal of the appendix, all patients underwent irrigation of the abdominal cavity with a saline solution (NaCl 0.9%). Suction was routinely used during the procedure as needed, depending on the intra-operative findings. The volume of irrigation also depended on the clinical findings and on the amount of purulent peritoneal fluid found in the abdomen; we usually used approximately 2 L of saline solution.

Drain Placement: In all patients, two abdominal drains were placed to facilitate postoperative drainage of any remaining fluids or infection.

Post-operative complications were categorized as either major or minor. Major complications included abdominal abscesses and intestinal obstruction, both of which required a second surgical procedure. Minor complications, such as wound infections and umbilical granuloma, were managed with outpatient care.

Post-operative antibiotic therapy was based on the surgeon's preference and the choice, referring to our antibiotic therapeutic protocols, was guided by intra-operative findings. Antibiotic therapy was usually started during surgery.

The patients were divided into three groups based on the antibiotics administered:

- **Group 1:** Amoxicillin and Clavulanic Acid + Aminoglycoside + Metronidazole.
- **Group 2:** Ceftriaxone + Metronidazole.
- **Group 3:** Piperacillin/Tazobactam.

2.1. Microbiological Analysis

Peritoneal fluid was collected for all patients undergoing appendectomy for CAA as a specimen for cultural analysis and evaluation of in vitro antimicrobial susceptibility of microbial appendiceal pathogens. Samples were plated onto the following solid culture media: sheep-blood agar, Herellea agar, salt-mannitol agar, azide horse agar, and Brucella agar (Kima Meus, Arzergrande, Italy). The aerobic and anaerobic media were incubated at 35–37 °C for 2 days and 3 days, respectively (using anaerobic gas generators to produce an anaerobic atmosphere). Bacterial and fungal pathogens were identified using MALDI-TOF mass spectrometry (Maldi Biotyper, Bruker, Billerica, MA, USA). Antimicrobial susceptibility testing (AST) was performed on aerobic organisms using Microscan WalkAway panels (Beckman Coulter, Milano, Italy), while for anaerobic organisms, disk diffusion or gradient methods were performed. All AST results were interpreted following EUCAST criteria.

2.2. Statistical Analysis

Continuous variables were reported as mean values and standard deviations. Categorical variables were expressed with absolute frequencies and percentages. Statistical analysis between groups of categorical variables was conducted with the chi-squared test, Fischer's exact test, Mann–Whitney test, and Kruskal–Wallis test. The practical importance of our results was profiled using Cramer's V coefficient to estimate the effect size. A *p*-value below 0.05 was considered statistically significant.

3. Results

3.1. Demographic Data

Between January 2017 and January 2023, a total of 182 patients underwent appendectomy for CAA at our department. All the patients were considered eligible as they met the inclusion criteria for our study. The final population consisted of 182 patients, of whom 112 were males and 70 were females, with a mean age at surgery of 10 ± 3 years for the entire population (Table 1).

Table 1. Results—Complete data on the enrolled patients and statistical association with the onset of POC in different antibiotic therapeutic protocol groups.

Results				
DEMOGRAPHIC DATA				
Patients Enrolled (n)		182		
Sex	Male: 112 (61.5%), Female: 70 (38.5%)			
Age	10.0 ± 3.0 years			
PRE-OPERATIVE DATA				
Symptoms	Group 1 (n)	Group 2 (n)	Group 3 (n)	p-value
Fever	46	45	47	p = 0.973
Vomit	42	37	39	p = 0.851
Fever and vomit	31	32	30	p = 0.968
White blood cells (×10 ⁹ /L)	15.8 ± 4.8	16.5 ± 5.2	16.6 ± 3.8	p < 0.01
Neutrophils (%)	80.8 ± 4.2	81 ± 5.2	83.8 ± 7.2	p < 0.01
C-Protein reactive (mg/dL)	10.6 ± 8.6	13.5 ± 8.6	11.2 ± 8.6	p < 0.01

Table 1. Cont.

Results			
INTRA-OPERATIVE DATA			
	n (%)	Mean time (h)	
TULAA	36 (22%)	2.1 ± 0.4	
LA	123 (72%)	1.3 ± 0.3	
Open	11 (6%)	2.6 ± 1.1	
Abdominal washing	182 (100%)		
Drain tube placement	182 (100%)		
POST-OPERATIVE DATA			
	n (%)	Antibiotic regimen	p-value
Group 1	32 (17%)	Amoxicillin/Clavulanate	p = 0.543
		Aminoglycoside Metronidazole	
Group 2	97 (53%)	Ceftriaxone	p = 0.065
		Metronidazole	
Group 3	53 (30%)	Piperacillin/Tazobactam	p = 0.043
Overall POST-OPERATIVE COMPLICATIONS: 22 (12%)			
Minor complications: 16 (8.8%)		Major complications: 6 (3.3%)	
● Umbilical abscess: 14 (7.6%)		● Abdominal abscess: 5 (2.7%)	
● Umbilical granuloma: 2 (1%)		● Abdominal occlusion: 1 (0.5%)	

3.2. Pre-Operative Data

The 76% (n = 138) and 65% (n = 118) of patients presented with fever or vomit, respectively, at admission to our emergency department. In 51% of cases, both fever and vomiting were found in the same patient.

All patients underwent analysis of the blood cells and the C-reactive protein (CRP).

The mean white blood cell (WBC) count was $16.3 \pm 5.8 \times 10^9/L$ with a mean percentage of neutrophils cells of $81.8 \pm 8.2\%$. The main CRP level was $11.7 \pm 8.6 \text{ mg/dL}$.

3.3. Intra-Operative Data

The 22% (n = 36) of patients were approached by TULAA, while 72% (n = 123) and 6% (n = 11) of patients underwent LA and open appendectomy, respectively. The mean surgery times were $2.1 \pm 0.44 \text{ h}$, $1.3 \pm 0.3 \text{ h}$, and $2.55 \pm 1.1 \text{ h}$, respectively, for TULAA, LA, and open techniques. After the appendix removal, an abdominal lavage with saline solution (NaCl 0.9%) was performed in all patients, followed by the placement of two abdominal drains (Table 1).

3.4. Post-Operative Data

Patients were divided into three groups, based on the antibiotic regimen (Table 1):

- Group 1 (n = 33–17%): Amoxicillin and Clavulanic Acid + Aminoglycoside + Metronidazole.
- Group 2 (n = 98–53%): Ceftriaxone + Metronidazole.
- Group 3 (n = 54–30%): Piperacillin/Tazobactam.

All patients received intravenous antibiotics during the entire hospitalization. Treatment was passed orally at discharge and continued for a total of 5 days based on the antibiogram results.

The length of hospital stay was 7 ± 2 days, 8 ± 2 days, and 10 ± 2 days, respectively, for TULAA, LA, and open techniques. Extracting data from the follow-up of the patients, we observed 16 (8.8%) minor complications (skin infection, umbilical granuloma) and 6 (3.3%) major complications (abdominal abscess and intestinal occlusion) (Table 1). Comparing the rate of complications observed in each of the groups, no statistically significant differences between groups 1 and 2 were found, while group 3 resulted to be associated with a lower incidence of minor complications ($p < 0.05$). Unfortunately, Cramer's V coefficient

cient, calculated on a contingency table with 4 degrees of freedom, was 1.19, meaning a low effect size.

We also performed a logistic regression analysis to assess the relationship between antibiotic regimens and the occurrence of postoperative complications (both minor and major). The models did not show a statistically significant association between the groups and the occurrence of minor complications ($p = 0.140$) or major complications ($p = 0.424$).

The power of this study to detect a significant effect was calculated based on the logistic regression models. For minor complications, the power was 5.9%, and for major complications, it was 5.3%. These values indicated that this study's power is below the conventional threshold of 80%, suggesting that a larger sample size or a more pronounced effect would be needed to achieve adequate power.

While the simpler contingency table analysis found a significant difference between groups, more complex analyses (logistic regression) suggested that the effect may be smaller or less solid than initially observed. This could be supported by further validation with larger datasets or additional covariate adjustments.

On the other hand, no significant difference was found when comparing mean operative times between the group of patients with and without complications (the group with complications: 129 ± 47 min; the group with no complications: 117 ± 47 min; p -value: 0.155).

Hypothesizing that a long interval between the onset of symptoms and admission for surgery may influence the onset of postoperative complications, we divided the patients into two groups: group A (post-operative complications) and group B (no complications). For both groups, the mean duration of symptoms before surgery was 3 ± 1 days. Comparing the duration of symptoms and the onset of post-operative complications between the two groups, no statistically significant differences emerged.

Finally, we investigated the duration of symptoms before surgery could be linked to the choice of surgical technique. Our findings showed that patients treated with TULAA or LA had a mean symptom duration of 2 ± 1 days, while those treated with open surgery had a mean duration of 5 ± 1 days. The statistical analysis indicated a significant difference between patients treated with TULAA vs. open surgery and LA vs. open surgery ($p < 0.001$). This suggests that patients with a longer duration of symptoms were more likely to undergo open surgery, which may reflect the severity of their condition, as more severe or advanced cases (e.g., peritonitis) often require an open approach for better control and treatment.

The examination of the biological samples of the purulent intraperitoneal fluid led to the isolation of different pathogens from 117 patients, divided into the following species (Figure 2):

- Enterobacterales: $n = 63$ (54%).
- Non-fermentative Gram-negative bacilli: $n = 22$ (19%).
- Anaerobes: $n = 19$ (16%).
- Gram-positive cocci: $n = 13$ (11%).

Regarding Enterobacterales, $n = 63$ (54%), we isolated the following genera:

Escherichia coli $n = 55$ (87%).
Klebsiella pneumoniae $n = 3$ (5%).
Klebsiella oxytoca $n = 2$ (3%).
Raoultella ornithinolytica $n = 2$ (3%).
Citrobacter braaki $n = 1$ (2%).

Evaluating the microbiological efficacy and the spectrum of antimicrobial susceptibility in vitro for each patient, only 40% of the cases recorded an appropriate therapeutic choice to the antibiotic therapy scheme of group 1, while for groups 2 and 3, the susceptibility rate reached 90% and 94%, respectively (Figure 3).

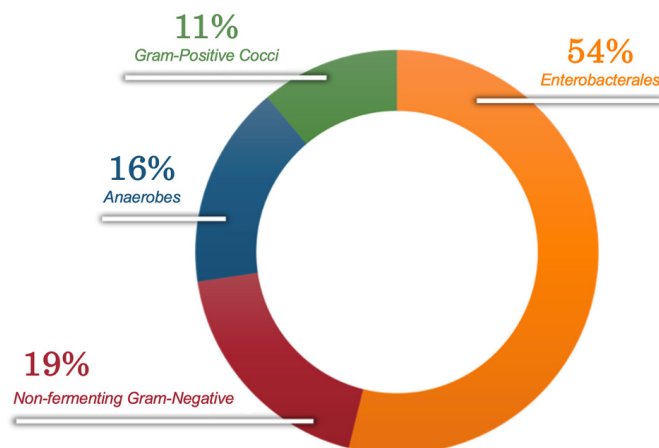


Figure 2. Species isolated from biological samples.

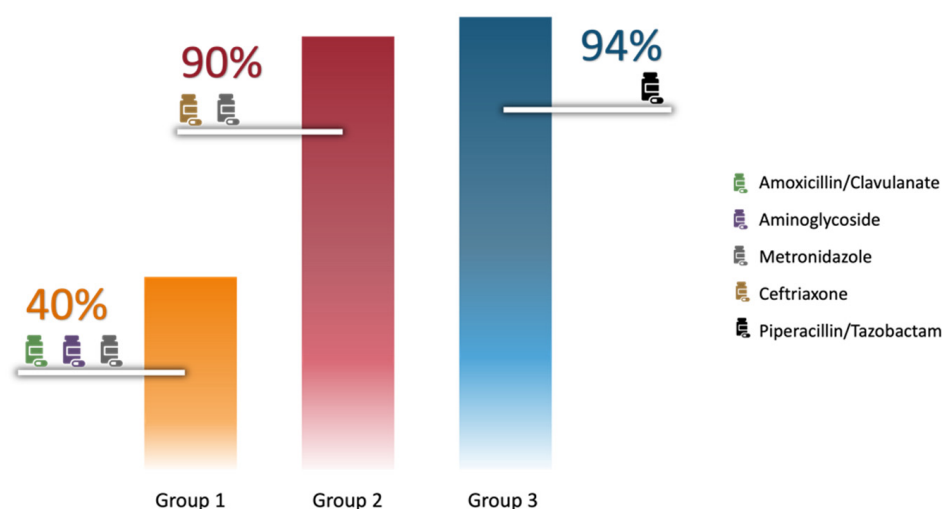


Figure 3. Appropriateness of therapeutic prescription compared for each group of patients.

4. Discussion

Although some authors prefer to adopt non-operative management for NCAA, an increasing amount of scientific evidence endorses operative management followed by post-operative antibiotic therapy as the gold standard treatment for children with CAA [12]. The latter approach is the standard protocol in our center, and all children admitted with the suspicion of AA undergo surgical treatment.

In general terms, the aim of antibiotic therapy in CAA is to reduce post-operative infective complications [13].

The distribution of bacterial species and their antimicrobial resistance in patients with CAA can differ year by year and depending on the geographical areas.

As a matter of fact, broad-spectrum antibiotic therapy in the management of AA could be considered always ideal as it guarantees adequate coverage against anaerobes, Gram-positive, and Gram-negative bacteria, despite intensive review of the postoperative management of CAA in recent years, due to the large variability in treatment protocols adopted between centers and among clinicians within the same center, leading to the drafting of guidelines. Moreover, the literature reports many studies investigating the efficacy of antibiotics for the prevention of post-operative intra-abdominal abscesses in pediatric acute appendicitis with conflicting results [14–16].

Triple antibiotic therapy was the mainstay in the past, but nowadays, authors are aiming to reduce the use of unnecessary antibiotics. Furthermore, the rise of antimicrobial resistance has made the traditional therapy scheme not as effective as before [17].

Goldin et al. [15] compared the aminoglycoside-based triple antibiotic therapy with piperacillin/tazobactam monotherapy, showing no differences in the rate of POC.

Shang et al. [16] analyzed the efficacy of combined therapy with metronidazole and broad-spectrum antibiotics (piperacillin/tazobactam, ceftriaxone, or cefoperazone sodium and sulbactam) compared with only broad-spectrum antibiotics for patients with perforated appendicitis who underwent surgical intervention. In this study, no differences were found between the use of combined therapy with metronidazole and the use of solely broad-spectrum antibiotic agents regarding the post-operative duration of intravenous antibiotic treatment, the trend of inflammatory markers, and the post-operative length of hospital stay. There were also no differences in the incidence of post-operative complications, including the intra-abdominal or pelvic abscess rate, wound infection, and the 30-day readmission rate. Kronman et al. [14] performed a retrospective cohort study of children affected by NCAA and CAA with the aim to compare the effectiveness of narrower-spectrum antibiotics (e.g., cefoxitin, ceftriaxone + metronidazole, ampicillin/sulbactam + metronidazole, cefotetan, clindamycin + gentamicin, cefazolin + cefoxitin, ampicillin/sulbactam, or cefoxitin + ceftriaxone + metronidazole) versus extended-spectrum antibiotics therapy (e.g., piperacillin/tazobactam, ertapenem, meropenem, piperacillin/tazobactam + ertapenem, or ceftazidime). In conclusion of this study, extended-spectrum antibiotics seemed to offer no advantage over narrower-spectrum agents for children with surgically managed NCAA or CAA. Obayashi et al. [13] compared the effects of broad-spectrum antibiotics with narrow-spectrum monotherapy in preventing post-operative intra-abdominal abscesses in pediatric acute appendicitis. Their results proved that broad-spectrum antibiotics do not prevent post-operative intra-abdominal abscesses neither in low nor high-risk groups.

These longstanding results impacted the medical practice in centers in which, historically, the triple antibiotic regimen was the first choice in CAA, prompting a remodulation of the post-operative antibiotic therapy based on less and more targeted antimicrobial active principles [18–20]. The WSES guidelines clearly state which antibiotic should be administered after surgery and the length of the therapy. However, it is well known that some surgeons still prefer the outdated triple antibiotic therapy, believing that these drugs are more reliable. For such reasons, we strongly believe that it is necessary to highlight the importance of the appropriate therapy [7].

Coakley et al. [21] analyzed the role of antibiotic therapy in non-perforated appendicitis in an adult sample, reporting that antibiotics did not reduce the incidence of abdominal abscess and abdominal obstruction. However, the results showed a statistically significant increase in post-operative morbidity due to *Clostridioides difficile* infection ($p = 0.02$), urinary tract infections ($p = 0.05$), post-operative diarrhea ($p < 0.001$), and longer length of hospital stay (LOS). In the review reported by Lee et al. [22], the American Pediatric Surgical Association identified no differences in terms of efficacy between broad-spectrum, single- or double-agent therapy in CAA, but only in terms of costs associated with the different treatment regimens.

Although our management slightly differs from what is stated in the WSES guidelines, our study confirmed previous evidence reported in the literature as it showed no statistical correlation between the antibiotic choice and the post-operative complications rate. Therefore, such assertions are valid not only at present but also in our local geographical area.

Moreover, the role of intra-abdominal washing is debated in the literature. Zhou et al. [23], in a systematic review and meta-analysis on the role of intra-operative peritoneal lavage (IOPL) with saline in patients with intra-abdominal infections, showed that the IOPL with saline was not associated with a significantly decreased risk of mortality, intra-abdominal abscess, incisional surgical site infection, post-operative complication, reoperation, and readmission compared with non-IOPL. However, data available in the literature disagree. Burini et al. [24], in a meta-analysis of a sample of 5315 patients, compared the role of aspiration versus IOPL in appendicitis. They failed to demonstrate the statistical superiority of employing IOPL and suction over suction-only to reduce the rate of postoperative complications after appendectomy.

Puttock et al. [25], comparing 115 children divided into two groups (lavage = 52 vs. suction = 63), did not show a statistically significant increasing rate of postoperative morbidity for the lavage group. In our series, all patients underwent IOPL with a saline solution of 0.9%. Although we cannot make any comparison with a control group (suction), we can state that our POC rate is lower compared to the literature. So, we cannot prove a significant superiority of IOP, but we believe it has the potential to decrease POC. While many studies focused on the length of the hospital stay and the rate of complications, a few authors based their research on microbiological examinations and the development of new antibiotic resistance. Chan et al. [26] analyzed the results of peritoneal swabs collected from 158 children, isolating *Escherichia coli* (*E. coli*) (n = 75), *Bacteroides fragilis* (n = 53), *Streptococcus milleri* (n = 37), *Pseudomonas aeruginosa* (n = 20), non-hemolytic streptococcus (n = 15), *Pseudomonas* species (n = 8), and *E. coli* (ESBL) (n = 3). Gerber et al. [27] studied 95 patients who presented with a CAA and post-operative infectious complications. They found that the most frequent pathogens were *E. coli* (66%), *Streptococcus anginosus* (45%), *Bacteroides fragilis* (22%), and *Pseudomonas aeruginosa* (17%). Antibiotic susceptibility analysis showed that 10 (15%) of *E. coli* strains were resistant to amoxicillin-clavulanate but sensitive to ceftriaxone + metronidazole. Garcia-Marin et al. [28] performed a microbiologic analysis of free peritoneal fluid in patients with NCAA and CAA. In the latter category, comprising 157 patients, they detected 17.2% of bacteria resistant to amoxicillin/clavulanic acid, 9.7% of microorganisms resistant to aminoglycoside (gentamicin or tobramycin), 6.5% of bacteria resistant to ciprofloxacin, and 14% of microorganisms resistant to ertapenem. These studies testify to a huge effort by the scientific community to identify the most appropriate antibiotic protocol for CAA in children. Regardless of the antibiotics used, our study highlights the importance of surgery, suggesting that controlling the source of infection through surgical removal is the most effective way to reduce post-operative complications. This makes sense from a biological standpoint, as the infection in appendicitis originates in the appendix. Surgery directly addresses the root cause, preventing further spread or progression of the infection.

Ghidini et al. [29] investigated 138 children who underwent appendectomy for CAA to report their experience with the use of a three-drug regimen and to assess its rate of success. Data analysis showed a high failure rate for the previously established three-drug regimen. Therefore, they concluded that a new protocol with ceftriaxone and metronidazole should be recommended as first-line therapy in patients with CAA.

Therefore, the importance of post-operative antibiotic therapy is resized, regardless of what regimen is chosen. In our cohort, the non-superiority of a specific antibiotic treatment protocol compared to the other supports this hypothesis. In fact, despite a high rate of inappropriate antibiotic therapy in group 1, we did not find any statistically significant differences when comparing the incidence of complications for each group. The low complication rate, notwithstanding the scarce in vitro efficacy of the administered antibiotics, suggests that beyond antibiotic therapy, the radicality obtained by surgery is the key to reducing complications in children with CAA. While this study suggests that radical surgery plays a crucial role in reducing complications, this does not deny the importance of antibiotics. Antibiotic therapy remains essential to prevent infections that may arise during the post-operative time, especially in cases where there is a residual infection or a high bacterial load. The low complication rate, despite the limited in vitro efficacy, likely reflects the effectiveness of surgery in removing the primary source of infection. However, antibiotics are still necessary in addition to surgery to prevent post-operative infections and to manage any remaining bacterial contamination. Therefore, surgery and antibiotics work together to reduce the risk of complications, and eliminating antibiotic use would likely increase infection risks (Table 2).

Table 2. Studies included in the discussion sections.

Studies Included in the Discussion			
Manuscript	Authors	Journal	Years
Non-operative treatment for simple acute appendicitis (NOTA) in children during the COVID-19 era: new lessons from the pandemic	Alsaggaf A et al. [12]	<i>Scientific reports</i>	2023
The effect of the broad-spectrum antibiotics for prevention of post-operative intra-abdominal abscess in pediatric acute appendicitis	Obayashi J et al. [13]	<i>Pediatric surgery international</i>	2018
Aminoglycoside-based triple-antibiotic therapy versus monotherapy for children with ruptured appendicitis.	Goldin AB et al. [15]	<i>Pediatrics</i>	2007
The efficacy of combined therapy with metronidazole and broad-spectrum antibiotics on post-operative outcomes for pediatric patients with perforated appendicitis	Shang Q et al. [16]	<i>Baltimore</i>	2017
Extended- Versus Narrower-Spectrum Antibiotics for Appendicitis	Kronman MP et al. [14]	<i>Pediatrics</i>	2016
Bacterial Antibiotic Resistance: The Most Critical Pathogens	Mancuso G et al. [17]	<i>Pathogens</i>	2021
Role of Interval Appendectomy in the Management of Complicated Appendicitis in Children	Vane DW et al. [19]	<i>World journal of surgery</i>	2006
Fast track protocol for children undergoing appendectomy	Fanjul M et al. [20]	<i>Cirugia Pediatr</i>	2015
Dual versus Triple Antibiotics Regimen in Children with Perforated Acute Appendicitis	Feigin E et al. [18]	<i>European journal of pediatric surgery</i>	2018
Post-operative antibiotics correlate with worse outcomes after appendectomy for non-perforated appendicitis	Coakley BA et al. [21]	<i>Journal of American college of surgeon</i>	2011
Antibiotics and appendicitis in the pediatric population: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee Systematic Review	Lee SL et al. [22]	<i>Journal of pediatric surgery</i>	2010
Effectiveness of intra-operative peritoneal lavage with saline in patient with intra-abdominal infections: a systematic review and meta-analysis	Zhou Q et al. [23]	<i>World journal of emergency surgery</i>	2023
Aspiration versus peritoneal lavage in appendicitis: a meta-analysis	Burini G et al. [24]	<i>World journal of emergency surgery</i>	2021
Peritoneal Lavage during Laparoscopic Appendectomy for Complex Appendicitis is Associated with Increased Post-Operative Morbidity	Puttock D et al. [25]	<i>African journal of pediatric surgery</i>	2022
Evidence-based adjustment of antibiotic in pediatric complicated appendicitis in the era of antibiotic resistance	Chan KWE et al. [26]	<i>Pediatric surgery international</i>	2010
A. Microbiologic Analysis of Complicated and Uncomplicated Acute Appendicitis	García-Marín A et al. [28]	<i>Surgical infections</i>	2018
Complicated acute appendicitis in children: the importance of stewarding antibiotic prescriptions	Ghidini F et al. [29]	<i>The Turkish journal of pediatrics</i>	2022

Limitations of This Study and Future Perspectives

We are aware of the limits of this study. In the first place, the retrospective nature of this study. Secondly, the involvement of different surgical teams in this study results in an operator-dependent bias. Nevertheless, we believe our data could provide an interesting and encouraging preliminary result for further investigations, such as multicentric prospective studies. The future perspective of this study could be detecting pre-operative red flags as markers of possible bacterial resistance in order to administer a personalized antibiotic therapy based on clinical history.

5. Conclusions

The post-operative management of CAA in children remains challenging. Several studies analyzed the role of broad-spectrum therapy compared to monotherapy. Despite the limitations of this study, microbiological examinations showed a 60% rate of inappropriate antibiotic regimens in group 1 (amoxicillin/clavulanic acid + aminoglycoside + metronidazole), even though a low rate of POC.

Beyond antibiotic therapy, radical surgery associated with accurate abdominal washing stands out as the optimal choice to reduce complications in children with CAA. In the future, more extensive microbiological samplings could provide important information on the most appropriate broad-spectrum antibiotic therapy for children with AA.

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