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Original Article

Complicated acute appendicitis in children: the importance of stewarding antibiotic prescriptions

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ABSTRACT

Background. The aim was to assess the success of a three-drug regimen, consisting of cefazoline, metronidazole and gentamicine, for the antimicrobial treatment of complicated appendicitis and to investigate predictors of failure.

Methods. This retrospective study included patients who had undergone appendectomy for complicated appendicitis from 2013 to 2018. The shift to second-line antibiotics was considered a failure. The choice was based upon clinical deterioration. Patients were grouped into 2 groups: localized complicated appendicitis (LCA) and extensively complicated appendicitis (ECA) for the study purpose. Univariate and multivariate analysis were performed to identify predictors of failure.

Results. Ninety patients (65.2%) with LCA and 48 patients (35%) with ECA were included. Three-drug regimen failed in 50 patients (36%) with a higher rate in the ECA group (50%, p=0.017). In a multivariate analysis, this failure was found to be associated with ECA (adjusted OR 3.00 [1.2-7.4], p=0.041). Children with ECA experienced a longer hospital stay (median length 8 days, p<0.001) and antimicrobial therapy (median length 8 days, p<0.001). However, no difference in the rate of surgical site infections was found (p=0.514).

Conclusions. The institutional antibiotic stewardship program highlighted a high failure rate for the old three-drug regimen. A new protocol should be recommended, especially for the patients affected by ECA.

Key words: complicated acute appendicitis, three-drug regimen, antibiotics, antibiotic stewardship, surgical site infections.

Acute appendicitis is one of the most common urgencies in pediatric surgery.[1] The disease might be complicated in 25-39% of pediatric cases.[2] The definition of complicated acute appendicitis (CAA) might be controversial because it is currently based on intra-operative findings. Nevertheless, a recent multicenter study by Cameron et al.[3] identified four intraoperative features pathognomonic for CAA: visible perforation, purulent exudate, free fecalith and intra-abdominal abscess. It is crucial to formulate the correct diagnosis and to describe the extension of peritoneal contamination because CAAs are associated with worse clinical outcomes, higher rates of complications and higher costs.[4,5] Recently, the number of abdominal quadrants involved in the infectious process has been described as a predictor of the outcome.[6]

Furthermore, CAAs required a more demanding antibiotic therapy to control the source of infection. This aspect was remarked to the international guidelines for the treatment of complicated intra-abdominal infections.[7]

For many years, a three-drug regimen, consisting of aminoglycoside together with a first-generation cephalosporine and metronidazole, has been the first choice in the treatment of

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complicated intra-abdominal infections. This empirical triple association provided broad coverage for the commonest pathogens.[8]

Antimicrobial - resistant strains increased from 25.2% to 42.1% over the last decade, mainly due to the growth of extended spectrum beta-lactamase (ESBL) producing *E. coli* and the emergence of *Pseudomonas aeuroginosa*.[9] For this reason, broad-spectrum beta-lactamase and carbapenemes were successfully introduced for the treatment of CAAs. Moreover, these latter drugs might be used as monotherapy providing further benefits in terms of compliance and costs.[10,11]

The significant variability in the choice of antibiotics together with the increase of antimicrobial resistance and the potential side effects related to antimicrobial misuse required the establishment of antimicrobial stewardship. These programs are extremely important to optimize patients' clinical outcomes and minimize exposure to unnecessarily broad-spectrum drugs.[12]

The primary aim of this study was to describe our experience with the use of a three-drug regimen in the treatment of CAAs and to assess its rate of success. The secondary aim was to investigate potential predictors of treatment failure, especially the extension of peritoneal contamination. This process should help clinicians in the choice of the proper antibiotic regimen and in the identification of patients who required an escalation of antibiotics.

Material and Methods

Study Design

Our Institutional Review Board was notified. This was a retrospective and observational study and exempted from approval.

The 6-year period of the study ranged from January 2013 to December 2018. All children aged <18 years, who had undergone an appendectomy for CAA within 48 hours of admission to Padua University Hospital (Italy), were included. The diagnosis of CAA was based on the intra-operative findings of a necrotizing or visible perforated appendix, the presence of purulent exudate, extraluminal fecalith or intra-abdominal abscess.[3] Abdominal ultrasound was performed only in the case of doubtful clinical diagnosis of acute appendicitis.

As of November 2017, conservative therapy, and delayed appendectomy for CAAs with abscess were proposed, but these patients were excluded from the study. Among the cohort of patients affected by CAA, we excluded the patients who did not receive the standard three-drug regimen at the time of diagnosis.

Demographic data, blood test results (white blood cells (WBC) count, C-reactive protein (CRP) value, operative findings from standardized surgical reports and antibiotic therapy administered were collected. Patients included were further divided into two groups according to the severity of the abdominal infection. As previously reported in the literature, CAAs were categorized as localized complicated appendicitis (LCA) or extensively complicated appendicitis (ECA).[4-6] The ECA subgroup was characterized by the involvement of two or more abdominal quadrants in the infectious process.

Preschool age (<6 years), WBC > 18 x 10^9/L and CRP value > 100 mg/L were considered as potential predicting factors of severity according to literature and clinical experience.[13,14]

As to the primary outcome, the assessment of the treatment failure of the three-drug regimen was based on the rate of shift to a broader antimicrobial regimen. The escalation was indicated in the case of persistent fever together with worsening of clinical symptoms (i.e., abdominal tenderness, feeding intolerance, diarrhea and dysuria) after 72 hours from the beginning of the antibiotics. The length of antibiotic therapy and the length of hospital stay, the rate of surgical site infections (SSI) and organ/space surgical site infections

(OSSI), according to the CDC definition[15], were considered as a measure of success of the treatment.

Electronic medical charts were searched for long-term complications related to the CAA that occurred after the patient was discharged from the hospital.

Treatment protocol

Once the diagnosis of CAA was intra-operatively established by the surgeon, a three-drug regimen was administered. This protocol was established during previous meetings with infectious diseases specialists from our Department and consisted of intravenous cefazoline 30 mg/kg/dose every 8 hours (maximum dose 1 g), metronidazole 7.5 mg/kg/dose (maximum dose 500 mg) every 8 hours and gentamicin 5 mg/kg/dose. In most cases, gentamicin was added after the intraoperative confirmation of a CAA. The interval between the last shot of antibiotics and the surgical procedure should be no more than 60 minutes. The therapy continued for at least 5 days after the intervention. No intraoperative specimen of purulent fluid was routinely collected for microbiological culture.

The placement of an abdominal drain depended on the senior surgeon's decision.

If the patient was still febrile with clinical signs of abdominal involvement (i.e. abdominal tenderness, intestinal obstruction, diarrhea, vomits) after 72 hours from the intervention, that is to say half-course of the antibiotic therapy, blood tests were repeated. Urinary tract infection was excluded by performing a urine analysis. In case of respiratory symptoms, a chest X-ray was performed to exclude pneumonia or pleural effusion. After that, a shift to another regimen was taken into account. Our practice consisted in introducing a third-generation cephalosporin (ceftazidime 25 mg/kg/dose every 8 hours) to replace cefazolin, whilst maintaining the other two antibiotics unaltered. Ceftriaxone 75 mg/kg/day or broad spectrum beta-lactams (amoxicillin-clavulanate 30 mg/kg/dose every 8 hours, piperacillin-tazobactam 100 mg/kg/dose every 6 hours) were used in a few cases, after consultation with the infectious diseases specialist. In both cases, the second-line regimen continued for 5 days or longer, according to the clinical response.

Statistics

Categorical variables were reported as numbers (%) and they were compared by using Fisher's exact tests. Continuous variables were reported as median (M) and inter-quartile range (IQR). Odds-ratio of the risk factors for treatment failure were calculated by logistic regression analysis.

A p-value ≤ 0.05 was considered statistically significant.

Logistic regression and multivariate analysis were performed using the Windows version 9.4 of the program SAS (SAS Institute Inc., Cary, NC, USA).

Results

During the 6-years, 143 children underwent appendectomy for CAA in our tertiary-care hospital. Five patients (two ECAs and three LCAs) were excluded because they did not receive the standard three-drug regimen. Most of the patients were referred from other hospitals.

One hundred and thirty-eight children were eligible for the study. At the time of the diagnosis, the median age was 9.1 years (IQR 6.0-11.6 years), the median value of the WBC count was 17 x 10^9/L (IQR 14-21 x 10^9/L), and the median value of CRP was 61 mg/L (IQR 28-134 mg/L). The median hospital stay was 7 days (IQR 6-8 days) similar to the median duration of the antibiotic therapy (7 days, IQR 5-8 days).

We identified 90 LCAs (65%), including 38 appendicular abscesses (28%) that were treated by surgery in first instance. The rest of the population (48 children, 35%) was affected by

ECA (Table I). None of them presented with signs of septic disease at diagnosis.

Eleven (8.0%) patients developed SSI. There were five OSSIs (two patients with ECA) among them. A laparotomy was required in one case, and it was due to the presence of abdominal collection together with intestinal occlusion. The other four patients were admitted to the hospital for clinical observation and administration of parenteral antibiotic therapy.

The median follow-up was 2.4 years, ranging from 0.2 to 5.9 years. No episodes of intestinal occlusion or late re-admission were reported in this span of time.

The standard three-drugs antibiotic regimen was shifted to a second-line regimen in 50 cases (36%) (Table II). Moreover, four patients were not responsive to the second-line regimen either. These children presented with persistent fever, increased CRP-values and altered WBC count after 72 hours after the first shift of the antibiotic therapy. Three of them were in the ECA group. A further antimicrobial escalation was required, consisting of piperacilline-tazobactam in three of them. Meropenem (40 mg/kg/dose) was given only in one case.

Table II. Antibiotic agents used in second line.

Ceftazidime, n (%)	38 (76)
Piperacillin-tazobactam, n (%)	7.0 (14)
Amoxicillin-clavulanate, n (%)	3.0 (6.0)
Ceftriaxone, n (%)	2.0 (4.0)

Among the preoperative variables, the age at intervention was higher in the LCA group (p=0.016). Indeed, these children presented with a median age of 9.6 years, while the median age of those affected by ECA was 7.6 years. However, WBC count (p=0.617) and CRP value (p=0.197) were similar before the intervention. Furthermore, it is relevant to report that WBC-count and CRP-value were poor predictors of severity.

Six patients (6.7%) affected by LCA suffered from SSI, whilst 5 patients (10%) in the ECA group suffered from SSI. Nevertheless, there was no difference between the two groups (p=0.514).

The therapy in the ECA group needed to be changed more frequently (p=0.017) with an overall longer treatment duration (p<0.001). Consequently, the hospital stay was at least one day longer (p<0.001) (Table I).

Table I. Characteristic of children affected by CAAs.

	LCA n (%) 90 (65)	ECA n (%) 48 (35)	p-value
Age at intervention years (M, IQR)	9.6 (7.0-12)	7.6 (4.8-11)	*p=0.016
WBC count 10^9/L (M, IQR)	17 (14-20)	18 (14-22)	p=0.617
CRP mg/L (M, IQR)	57 (27-130)	62 (36-146)	p=0.197
Laparoscopic appendectomy, n (%)	32 (36)	21 (44)	p=0.364
Abdominal drain, n (%)	34 (38)	15 (31)	p=0.463
SSI, n (%)	6.0 (6.7)	5.0 (10)	p=0.514
Length of antibiotic therapy days (M, IQR)	6.0 (5.0-8.0)	8.0 (7.0-9.0)	*p<0.001
Length of hospital stay days (M, IQR)	7.0 (5.0-8.0)	8.0 (7.0-9.0)	*p<0.001
Shift to 2nd line therapy, n (%)	26 (29)	24 (50)	*p=0.017

CAA: complicated acute appendicitis
LCA: localized complicated appendicitis
ECA: extended complicated appendicitis
WBC: white blood cell
SSI: surgical site infection
*Statistically significant (p-value <0.05)

Furthermore, the outcomes of the patients with an abdominal drain were compared to those without it in the ECA group. As to the failure of the first-line regimen, seven patients (47%) with a drain required a shift to second-line drugs and 17 patients (52%) without a drain required a shift. This rate was similar (p=0.755). As to the occurrence of SSI, the rate was higher in the patients with a drain (p=0.013). Indeed, four patients with a drain (27%) presented with an SSI, whilst only one patient (3.0%) without a drain experienced this adverse event.

Twenty-four patients (48%) that failed the first-line therapy presented with ECA (Table III). Indeed, a univariate analysis, including several demographic and clinical factors (age at intervention, the technique of appendectomy, the presence of abdominal drain, the value of CRP, WBC count, and the severity of abdominal contamination), found that only the extension of the abdominal contamination was associated with an increased risk of failure for the first-line treatment. The estimated OR was 3.0 (95CI 1.3-7.0; p=0.036) (Table III).

The same results were replicated in a multivariate analysis adjusted for the values of CRP and for the age at intervention. The extension of the abdominal contamination was still associated to the failure of the first-line therapy. The adjusted OR was 3.0 (95CI 1.2-7.4; p=0.041) (Table IV).

Table IV. Results of the multivariate logistic regression on severity, age and CRP adjusted.

		OR (95%CI)	p-value
Age <6 years		1.1 (0.5-2.6)	p=0.817
CRP ≥100 mg/L		1.4 (0.6-3.0)	p=0.424
Severity	Localized	1	
	Abscess	1.3 (0.5-3.4)	*p=0.041
	Extended	3.0 (1.2-7.4)	

*Statistically significant (p-value <0.05)

Discussion

The three-drug antimicrobial regimen used for the treatment of pediatric CAAs presented a relevant rate of failure that occurred in one-third of the patients. When the patients affected by ECA were separately considered, the rate of failure reached 50%, regardless of the age at intervention and CRP values. Moreover, patients suffering from ECA were usually younger and required a longer hospital stay, even though an increased number of SSIs did not occur. These aspects proved once again that CAAs concerned a wide range of clinical situations.

Our antibiotic protocol required the administration of the three-drug regimen, which was well-consolidated for decades.[8,16] However, surveillance of the outcomes was required by the occurrence of several cases of failure, even though the data of our Service

Table III. Results of the univariate logistic regression analysis.

		First line therapy n (%) 88 (64)	Second line therapy n (%) 50 (36)	OR (95%CI)	p-value
Age <6 years, n (%)		21 (24)	16 (32)	1.5 (0.7-3.3)	p=0.284
Laparoscopic appendectomy, n (%)		30 (34)	23 (46)	1.7 (0.8-3.4)	p=0.154
Abdominal drain, n (%)		31 (35)	18 (36)	1.1 (0.5-2.2)	p=0.890
WBC count ≥18 x 10^9/L†, n (%)		37 (42)	24 (48)	1.5 (0.7-3.1)	p=0.265
CRP ≥100 mg/L‡, n (%)		30 (34)	21 (42)	1.4 (0.7-2.9)	p=0.334
Severity, n (%)	Localized	39 (44)	13 (26)	1	
	Abscess	25 (28)	13 (26)	1.6 (0.6-3.9)	*p=0.036
	Extended	24 (27)	24 (48)	3.0 (1.3-7.0)	

†Frequency missing=5.0
‡Frequency missing=3.0
*Statistically significant (p-value <0.05)

of Microbiology reported that the presence of ESBL bacteria was less than 10% (data not shown). Conversely, a recent survey by Kwok et al.[9] reported an increased rate of resistances, especially caused by ESBL strains. The authors found that gentamicin provided coverage only in 45.3% of the children affected by CAA. Similarly, in our series, the overall rate of failure was 35.6%. This rate was largely above 10%, namely the threshold established in literature in order to define the lack of efficacy of an antimicrobial therapy.[7]

It is relevant to underline that our measure of failure was the shift to a second-line regimen. This was based on the worsening of clinical conditions, rather than the results of intraoperative cultures which were not performed routinely. In the previous years, we found no relationship between the intraoperative cultures after appendectomy and those taken from abdominal collections secondary to CAA. Most of the strains that grew after the appendectomy were polymicrobic or sensible to the first-line regimen (data not shown). This might be a further reason to abandon the intraoperative cultures during an appendectomy.

Moreover, since no randomized trial has demonstrated the superiority of intraoperative cultures, an approach based on clinical conditions was preferred to avoid an escalation of antibiotics, that was not supported by clinical deterioration.[17] It is well known that there is not a cause-effect association between the intraoperative samples and the occurrence of postoperative abdominal abscesses. Indeed, an escalation of the antimicrobial therapy, tailored to the microbiological results, did not prevent abscess formation in both the adult and pediatric population.[18,19]

This consideration was further supported by our findings. In the ECA group, the presence of the abdominal drain did not reduce the rate of failure of the first-line therapy. However, the rate of SSIs was surprisingly higher in the patients with the abdominal drain. This might be due to the retrospective design of the study. Indeed, the abdominal drain might have been used for the worst ECAs that presented a higher risk of complications.[4,5]

As to the potential factors associated with the failure of the standard regimen, several aspects were investigated. Nevertheless, the only significant variable turned out to be the severity of the abdominal contamination. This result was independent from the CRP values and the age at intervention in a multivariate analysis. This was more evidence of how the extension of the infection could be determinant in the workload of the postoperative management of CAAs, confirming the findings reported by Feng et al.[5]

Pediatric CAAs might present a heterogeneous spectrum of severity, that might not be pre-operatively predicted by blood tests or clinical variables.[4,5] However, in our series, the age of the children affected by ECA was sensibly lower. This was consistent with the previous literature, as younger children with acute appendicitis were more prone to present with more extended abdominal infections.[14]

Finally, patients affected by ECA might develop SSIs more frequently, requiring more aggressive treatment.[20] In our population, even though quite a higher rate of SSI was found in the ECA group, there was no significant difference with the LCA group. However, the patients affected by more severe abdominal infections had longer hospital stays and required a shift of antibiotic therapy more frequently. Moreover, the duration of the antibiotic therapy was quite longer compared to the current trends reported in the literature. The introduction of broad-spectrum beta-lactamase allowed to reduce the scheduled course of post-operative antibiotic therapy to three days.[21]

The outcomes of the children affected by CAA were directly influenced by the antimicrobial therapy.[8,11] Only a periodic review might assess the real efficacy of the antibiotic protocols in use. For this reason, the establishment of an antibiotic stewardship program has

been highly recommended to improve antibiotic prescriptions and develop new treatment protocols. To reach this goal, the local epidemiology of bacterial infections, the periodic monitoring of the outcomes related to antibiotic therapy and the clinicians' compliance with the prescription protocols should be taken into account. A well-established antibiotic stewardship program might allow identifying potential antibiotic misuse and in-house protocol inefficacies. These considerations were recently reported by Wakeman et al.[11] The authors measured the success of an antibiotic stewardship program by finding a decrease from 35% to 15% in the rate of complications after appendectomy for CAA.

Given the high rate of failure for the three-drug regimen reported in our series, a revision of the antimicrobial protocol is necessary. First, the current epidemiology and the local microbiological reports should be considered for the choice of antibiotic spectrum. Abdominal infections in children presented a high frequency of polymicrobial specimens. Coliform Gram negative, anaerobes and *Streptococci spp* were the most common pathogens. Only about 5% of the cultures identified *Pseudomonas aeruginosa*, but without any evidence of its pathogenicity.[22] However, a recent update reported an increased occurrence of *Pseudomonas aeruginosa*, reaching 10% of the cultures.[9]

Secondly, treatment-related stress among children and caregivers should be reduced by the introduction of a simplified empirical antibiotic regimen.[23] Indeed, a decrease in intravenous infusions per day might avoid the necessity of central line insertion and multiple venous cannula replacements. For these reasons, new single-drug protocols consisting of a broad-spectrum beta-lactamase or a carbapenem have been successfully introduced.[10,17]

On the other hand, several studies recommended a two-drug regimen. A third-generation cephalosporin associated with metronidazole has been recommended and no antipseudomonal coverage has been indicated in the first instance.[24,25] Indeed, a narrow-spectrum regimen presented an equivalent rate of OSSI when compared to a regimen with anti-pseudomonas activity. This activity should be reserved for second-line therapy, sparing broad-spectrum drugs, such as piperacillin-tazobactam, for a potential escalation.[26] The efficacy of this regimen, including ceftriaxone as a third-generation cephalosporin, might be chosen, was proven when dealing with CAAs in children.[24]

As to the potential side effects, the utilization of this protocol might avoid the prescription of aminoglycosides, aiming to spare an antimicrobial agent with current low coverage and reduce potential toxicity.[9] Moreover, the majority of the patients treated by our second-line regimen had positive outcomes and the rate of complications seemed to be comparable to the series that used broad-spectrum beta-lactams without the administration of aminoglycosides.[21,25]

The monitoring provided by our antibiotic stewardship program reported a high rate of failure for the standard three-drug regimen. For this reason, the implementation of a new antimicrobial protocol for the treatment of CAAs in children should be recommended. According to the current evidence, a regimen with ceftriaxone and metronidazole should be considered, avoiding aminoglycosides and the drugs with anti-pseudomonas activity in the first instance. Currently, the outcomes of this new protocol are under assessment at our institution.

Nevertheless, this study presents some limitations. The single-center and retrospective design of the study limited the sample size. This might affect the statistical power and the generalization of the results. Another bias concerned the identification of the cut-offs for the statistical analysis. Finally, the classification of CAAs relied on the surgeon's discretion, as it is well known in the literature.[27]

The extension of abdominal contamination might influence the response to the medical treatment, leading to the identification of a subset of children poorly responding to standard antimicrobial treatment.

In addition, even though the evaluation of the length of antibiotic therapy and hospital stay were not the primary aims of this study, the program might also help in reducing the rate of OSSI and the overall length of hospital stay together with its related costs.

Ethical approval

Our institutional board was notified but as this was a retrospective observational study it was exempted from approval.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: FG, CV; data collection: FG; analysis and interpretation of results: ACF, FG, CV, DD, FFL; draft manuscript preparation: FG, CV, DD, FFL, PG. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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