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Optimization of the Medical Management of Appendicular Abscess and Plastron in Children: A 2009 to 2019 Cohort Study

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Abstract

Background: In our hospital, children with appendicular plastron or abscess receive a medical treatment with cefotaxime, metronidazole and gentamicin followed by amoxicillin/clavulanic acid as an oral switch. Appendectomy is performed 10 to 12 weeks after the beginning of the discharge. A high failure rate was noticed with a switch to a second line treatments, rehospitalization or an emergency surgery. The objective of our study was to highlight predictive factors for the treatment response.

Methods: We conducted a retrospective monocentric study between 2009 and 2019. Inclusion criteria were children under 16 years old diagnosed with appendicular plastron or abscess, treated with a medical treatment. We divided the cohort into a success and a failure group and compared their demographic data, clinical symptoms, inflammatory markers, abdominal imaging and antibiotic regimen.

Results: Seventy-four patients were enrolled in the study and the failure rate was 36% (n=27). The median age in the success group was 8.7 years old (2-14) and 9.4 years old (2-15) in the failure group. Multiple abscesses (6.5% *vs.* 32%, p=0.02) and diarrhea at admission (19% *vs.* 44%, p=0.02) were significantly associated with a failure. Palpable mass (47% *vs.* 67%, p=0.09) and stercoliths (34% *vs.* 52%, p=0.13) appeared to be more important in the failure group.

Discussion and Conclusion: Several factors were analyzed to predict the response to the medical treatment for children with appendicular abscess or plastron. Patients with multiple abscesses will no longer be treated with antibiotics. We also recommended greater vigilance after detecting stercoliths in the medical imaging based on other studies results. Time to hospitalization, time to apyrexia, CRP and white blood cells level at admission were not different between the success and the failure group. Finally, a wider bacterial epidemiology study is needed in order to adjust our local guidelines and the antibiotic therapy.

Keywords: Perforated appendicitis; Abscess; Antibiotic; Children

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Introduction

Appendicitis is an acute inflammation of the appendix and is a common surgical disease of children. It is classified as complicated or uncomplicated depending on the extent of the infection. The incidence of the perforation of the appendix has been reported from 19% to 57% [1,2]. In case of isolated appendicitis without any perforation of the appendix: The treatment is based on an emergency appendectomy or in some cases on a conservative treatment with antibiotics [3-8]. In case of a peritonitis due to a perforated appendicitis, the treatment is also based on a surgery with a peritoneal lavage [9-13]. However, the perforation of the appendix can be circumscribed and evolve to an abscess or a plastron.

Currently, there has been no unique guidelines for the management of children with appendicular plastron or abscess especially for the surgical approach, the antibiotic therapy, time to the appendectomy, the diagnostic aspect, etc. Several studies showed that the medical treatment with antibiotics followed by an interval appendectomy was effective and could reduce post-operative complications. Indeed, remote surgical management is optimal to avoid intraoperative complications (small bowel wound, ileo-caecal resection, and stoma) and postoperative complications (flange occlusion, wall abscess) [14-23].

Failures of the medical treatment of appendicular abscess or plastron are poorly described in the literature and can lead to serious consequences for the patients [24,25]. The aim of this study was to attempt to identify predictive factors of success or failure of the initial antibiotic treatment.

Material and Method

Study population

We conducted a retrospective single-center study between January 2009 until December 2019 in a primary care center regional hospital. We included all patients under 16 years old, hospitalized in the pediatric surgery unit and diagnosed with appendicular abscess or plastron. The protocol of the pediatric surgery unit of our hospital was based on a conservative treatment for children presenting symptoms for 3 days or more. This conservative treatment included an intravenous broad-spectrum antibiotic therapy with: Cefotaxime, metronidazole and gentamicin followed by an oral antibiotic therapy (amoxicillin/clavulanic acid) for a total duration of 2 weeks. Finally, an interval appendectomy was scheduled 10 to 12 weeks after the discharge. We defined a failure to the medical treatment as a patient who had at least one of the three criteria. The first one was a failure to the first line of antibiotics (cefotaxime, metronidazole and gentamicin) requiring a switch to a second line (piperacillin/tazobactam and amikacin). Sometimes a third line of antibiotics was considered. This is assessed on a case-by-case basis with the prescription of carbapenem, cefepime or vancomycin, etc. The second criterion was a sudden recurrence of the symptoms occurring between the discharge and the date of the scheduled appendectomy. In the event of a relapse, the patient received a new course of intravenous antibiotics during the hospitalization. The final criterion of failure was an unscheduled emergency appendectomy. All patients performed an ultrasound scan as a first-line protocol and a CT scan if needed. Children with symptoms for less than 3 days had an appendectomy and were excluded from the cohort. We also excluded all the children with generalized peritonitis as well as the children who started the intravenous antibiotic therapy in another hospital center. Ethical approval for this study was obtained from the ethic committee of the Robert Debre hospital, Paris, France (number 2021/590bis).

Study design

We divided the cohort into a success and a failure group in order to compare different type of data.

Study variables

We collected demographic, drug, clinical, biological, medical imaging and surgical data. Information for patients hospitalized between 2012 and 2019 were collected from electronic medical records while patients hospitalized between 2009 and 2011 had their information in both paper and electronic medical records.

We extracted clinical symptoms at the admission of the patient at the emergency department. Those clinical symptoms were the presence of fever, digestive disorders, vomiting and the presence of a palpable plastron.

Biological markers related to inflammation were collected such as the C-Reactive Protein (CRP) and white blood cells count. Then, we extracted the bacterial identification in the blood culture and the biological samples.

For the medical imaging we analyzed the ultrasound and pelvic abdominal scan records. The following information were collected: Whether an ultrasound or a scan were performed, the presence of an abscess or a plastron, the size of the abscess, the presence of a single or multiple abscesses, the presence of a stercolith, the size of the appendix, the presence of an effusion in the right iliac fossa or in the pouch of Douglas.

Drug data analyzed were drug taken before the hospitalization, the antibiotic therapy prescribed, the dose, the frequency of administration, the route of administration, the duration of the antibiotic therapy, the delay from the beginning of the hospitalization and the prescription as a first, second- or third-line treatment.

Statistical analysis

Statistical tests were carried out using SAS® software (version 9.4). Categorical variables are expressed as N (%) and quantitative variables are expressed as median (min-max). The data for the success versus failure group were compared using the Chi² test for categorical variables with numbers greater than 5 and a Fisher test for the opposite case. For the comparison of quantitative variables within the two groups, a Mann-Whitney test was performed. Values were considered significant when the p-value was less than 0.05.

Results

Demographic data

Between 2009 and 2019, 74 patients were diagnosed with an appendicular abscess or plastron and were treated with intravenous antibiotics (Figure 1).

The number of patients diagnosed with appendicular abscess treated with intravenous antibiotics varied each year with a minimum of 1 and up to 11 (Table 1).

Patients included in the success group (n=47, 64%) and the failure group (n=27, 36%) were respectively aged 8.7 years old (2-14) and 9.4 years old (2-15) (p=0.43) (Table 2). Length of hospitalization stay was significantly different between the two groups: 8 (5-12) in the success group compared to 15 days (6-29) in the failure group (p<0.0001).

Other medications received before admission

In our cohort, 6 (13%) patients of the success group were treated with antibiotics before the admission with amoxicillin (n=2), amoxicillin/clavulanic acid (n=1), cefixime (n=1) or cefpodoxime

Table 1: Evolution of the number of successes and failures to the medical treatment from 2009 to 2019.

2009	1 (100%)	0 (0%)	1
2010	4 (80%)	1 (20%)	5
2011	7 (64%)	4 (36%)	11
2012	2 (67%)	1 (33%)	3
2013	6 (67%)	3 (33%)	9
2014	0 (0%)	3 (100%)	3
2015	5 (100%)	0 (0%)	5
2016	4 (50%)	4 (50%)	8
2017	6 (55%)	5 (45%)	11
2018	6 (60%)	4 (40%)	10
2019	6 (75%)	2 (25%)	8

Table 2: Demographic, clinical and imaging description of the patients included in the study.

Data expressed in n (%) or median (min-max)	Successes	Failures	p-value
N	47 (64%)	27 (36%)	-
Gender			
Male	26 (55%)	13 (48%)	0.55
Female	21 (45%)	14 (52%)	0.55
Age (years old)	8.7 (2-14)	9.4 (2-15)	0.43
Weight (kg)	30.9 (12.5-69)	30.6 (11-68)	0.36
Duration of symptoms before admission (days)	5 (2-15)	4.85 (3-10)	0.97
Antibiotic(s) before admission	6 (13%)	7 (26%)	0.21
NSAI before admission	2 (4%)	2 (7%)	0.62
Length of hospitalization stay (days)	7.9 (5-12)	14.9 (6-29)	**<0.0001**
Total duration of anti-biotherapy (days)	13.2 (5-21)	18.8 (7-45)	**0.016**
Clinical signs at the admission			
Vomiting	27 (57%)	18 (67%)	0.43
Diarrhea/liquid stools	9 (19%)	12 (44%)	**0.02**
Palpable mass	22 (47%)	18 (67%)	0.09
Fever	36 (77%)	21 (78%)	0.91
Intestinal occlusion	3 (6.4%)	3 (11%)	0.66
Medical imaging			
Plastron	16 (34%)	5 (19%)	0.15
Abscess	31 (66%)	22 (81%)	0.15
- Simple abscess	29 (93.5%)	15 (68%)	**0.02**
- Multiple abscesses	2 (6.5%)	7 (32%)	**0.02**
Stercolith	16 (34%)	14 (52%)	0.13

(n=1). Two patients (4%) also received non-steroidal anti-inflammatory drug. In the failure group, 7 (26%) patients were also treated with antibiotics such as: Amoxicillin (n=4), cefpodoxime (n=1) or ceftriaxone (n=1, for a suspected acute gastroenteritis with *Salmonella* spp.)

Clinical symptoms

Among all the clinical signs, a significant difference was found in the number of children with diarrhea and loose stools in the failure group at admission (p=0.02). A trend towards a predominance of palpable mass was also observed in this group ($n_{success}$ = 22 (47%) and $n_{failure}$ = 18 (67%), p=0.09).

Medical imaging

Of the 53 patients with abscess, 44 (83%) had a single abscess and 9 (17%) were multiple. Multiple abscesses were more likely to escape the medical treatment (7/9, 78%) compared to single abscesses (15/44, 34%) (p=0.02). Finally, 30 (40.5%) of the patients had stercoliths: 14 (52%) in the failure group and 16 (34%) in the success group. However, this trend was not statistically significant between the two groups (p=0.13).

Biological values

At the admission, the CRP level was slightly higher in the failure group (157.4 mg/L [55-341]) than in the success group (131.7 mg/L [9-386]) (p=0.22) (Figure 2). On the second biological check-up (S2) - i.e., at day 3 [1-9] - it was not possible to dissociate one group from the other ($n_{success}$ = 99.4 mg/L, $n_{failure}$ = 94.8 mg/L, p=0.43). The 3rd biological check-up - i.e., at day 6 [3-10] – was the tipping point to distinguish whether the medical management was effective or not because the CRP rate fell by an average of 33% in the success group while it was stable or increasing in the failure group (p=0.0038).

The Figure 3 representing the white blood cell count showed that the values for the first and second biological check-up were not significantly different between the two groups. There was a clear difference between the two group at the third biological check-up (S3) - i.e., at day 6 [3-10] - with a decrease of the values in the success group (10.9 G/L [3.6-21.3]) and an increase in the failure group (15.1 G/L [5.3-28.5]) (p=0.0018).

Finally, only 17 (23%) patients had a documented infection with bacteria growing in their biological samples. The main bacteria found were strict anaerobic bacteria, *Escherichia coli* and *Streptococcus* spp.

Discussion

The management of children with appendicular abscess remains controversial as there is no consensus regarding the guidelines. Several studies proved that conservative treatment with antibiotics could ease and optimize a delayed surgery. The meta-analysis by Similis et al. included 17 randomized and non-randomized studies comparing immediate surgery with conservative treatment [14]. The complications were significantly higher after an immediate appendectomy: Bowel obstruction, deep abdominal or pelvic abscesses and wound infections. This result was then confirmed by the recent meta-analysis by Vaos et al. and by other studies [15,16,18,21,26].

The medical management was interesting by reducing postoperative complications [14]. Still, the success of this medical protocol was not entirely guaranteed. Depending on the study, the success rate varied between 74 and 92% [24,27,28]. The success rate of our study was lower with 64% of our cohort. The definition of non-response to the medical treatment was quite different from one study to another. Indeed, in our study, the failure criteria were broader as we included all patients for whom the first line of treatment was not effective enough and who therefore required a change in the antibiotic therapy (which is not the cause of most of the similar studies), re-hospitalization or an unscheduled surgery.

The failure of the treatment could lead to serious consequences: Prolonged hospitalization, parental anxiety and sometimes treatment impasses. For example, one patient of our cohort received a total course of 21 days of intravenous antibiotics with cefotaxime, metronidazole and gentamicin until day 7, piperacillin/tazobactam and amikacin until day 14 and finally ceftazidime, metronidazole and vancomycin until day 21. At the end, the patient was still not responding to the antibiotics with growing abscesses and clinical deterioration. In our hospital, this patient was not eligible for a surgery as it is not recommended after one week of hospitalization because of the adherences and the strong risks of surgery complications. This highlights the importance of early identification of patients who may not respond to the medical treatment and who may benefit from a surgery during the first week of hospitalization.

Early identification of those patients is a real challenge. Some predictive factors were analyzed in previous studies as well as in our study [27,29,30]. First of all, the two groups of our cohort showed no major differences of the CRP and the white blood cell levels at admission. We paid particular attention to the dynamics of the CRP and the with blood cells, all along the hospitalization. We

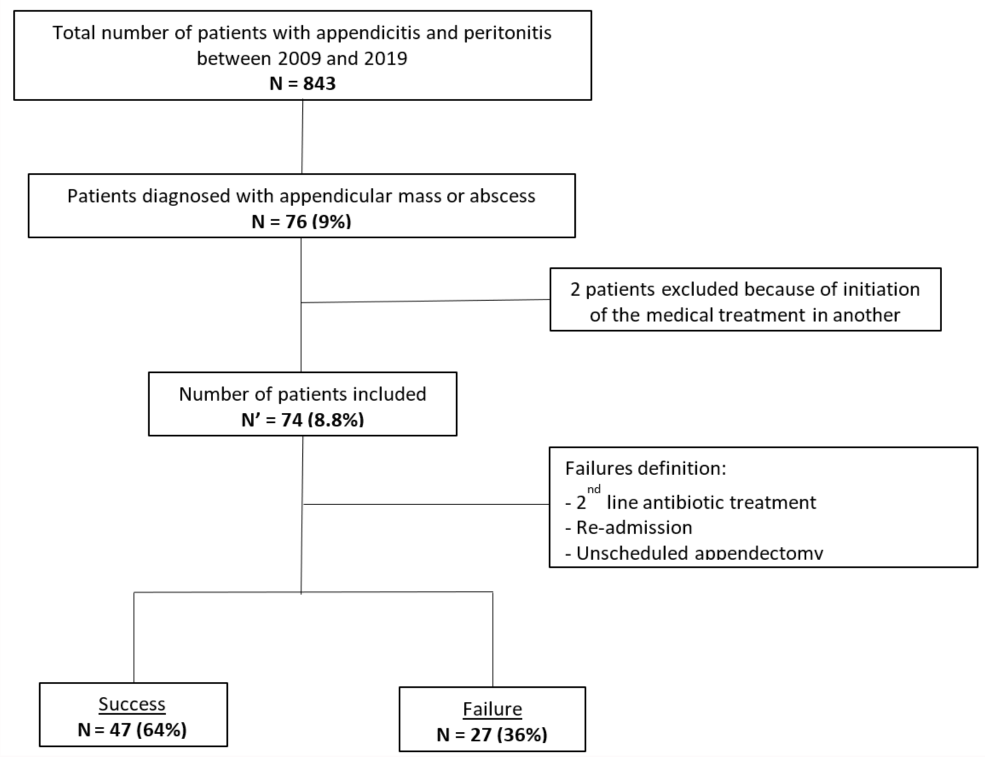

Figure 1: Flow chart of the study.

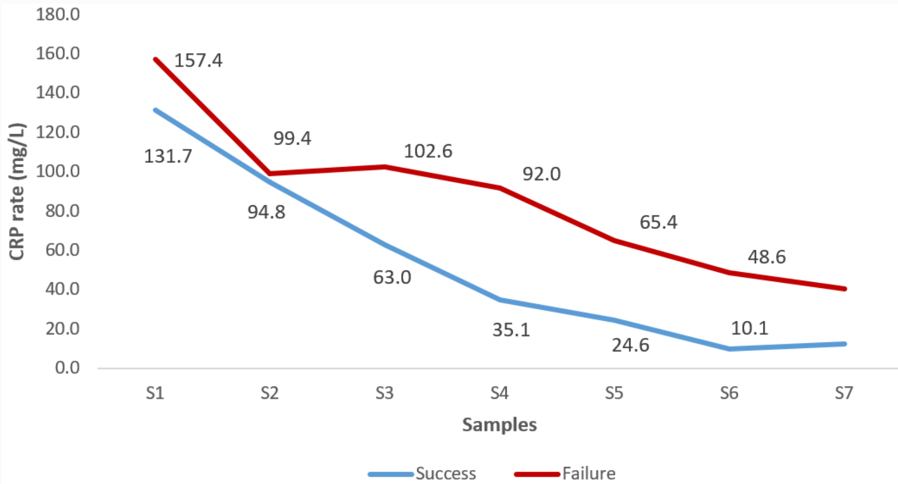

Figure 2: Comparison of the CRP rate between the success and the failure groups. Several biological samples were done during the hospitalization. To analyze the evolution of the CRP rate, we pooled all the CRP rate of the patients in the success group and in the failure group for each biological check-up (samples). Here are the median day corresponding to each sample: S1 (n=74), day 0 (0-4); S2 (n=74), day 3 (1-9); S3 (n=60), day 6 (3-10); S4 (n=37), day 8 (4-20); S5 (n=21), day 11 (7-24); S6 (n=9), day 15 (10-28).

observed that one week was needed to differentiate a patient who is not responding to the medical treatment with a stabilization or an increase of the inflammatory markers. This highlight the fact that it is crucial to find other early predictive factors in order to adjust the treatment sooner, during the first week of hospitalization. Children with multiple abscesses and diarrhea had statistically more failures than others. This is the first study to conclude with an exclusion of the children with multiple abscesses from the conservative treatment. Then, the presence of stercoliths was not significantly associated with failure, even though there was a trend. This contradicts the results of other studies, probably due to the number of patients included or the study design [29,31-33]. Indeed, in retrospective studies, it is not impossible that the presence or absence of stercoliths was not systematically specified by the radiologists when writing the report, making the analysis less reliable. However, we can recommend greater vigilance in the follow-up after detecting stercoliths in the medical imaging. We also observed more frequent palpable masses during the clinical examination of patients for whom the first line treatment was not effective – probably because of the size of the collection. Finally, time to apyrexia and time to hospitalization did not influence the

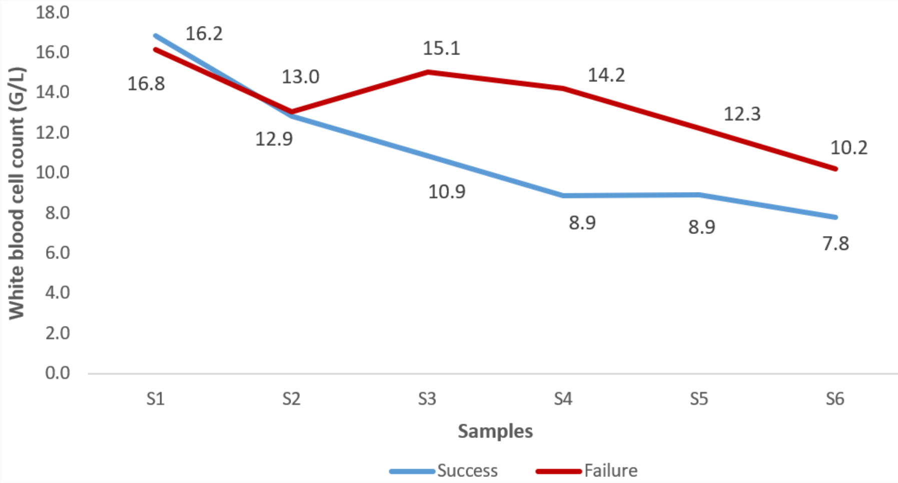

Figure 3: Comparison of the white blood cell count between the success and the failure groups. Several biological samples were done during the hospitalization. To analyze the evolution of the white blood cell count, we pooled all the CRP rate of the patients in the success group and in the failure group for each biological check-up (samples). Here are the median day corresponding to each sample: S1 (n=74), day 0 (0-4); S2 (n=74), day 3 (1-9); S3 (n=60), day 6 (3-10); S4 (n=37), day 8 (4-20); S5 (n=21), day 11 (7-24); S6 (n=9), day 15 (10-28).

complexity of the patient's management in our cohort. It seemed that these two criteria, although logical, did not allow us to identify groups at risk of failure.

Also, the small amount of patient who benefited from an ultrasound guided drainage of the abscesses in our cohort was also to consider as it was essential for a successful treatment. This is mainly due some logistical issues specific to our hospital but it is also due to the invasiveness of the act difficult to program in a pediatric population.

The main limitation of our study was the retrospective nature which may lead to bias, but also the small number of patients included. Thus, the lack of power due to the small number of data did not allow us to show any significant differences for some criteria between the two groups although some trends was observed.

Indeed, for example, the bacteria causing appendicular abscess were rarely documented but the main germs found in the few samples of our cohort were strict anaerobic bacteria, *Escherichia coli* or *Streptococcus* spp. These results were similar to other studies [34,35]. However, these results cannot be interpreted as the drainage was done after the initiation of the antibiotic therapy and because of the small number of documented infections. The choice of the antibiotic therapy should be assessed as it could be one of many reasons leading to the failure. The hypothesis raised here is that the first line of the antibiotic therapy may not cover the majority of the bacteria causing pediatric digestive infections in our sector. In the future, a wider bacterial epidemiology study is needed to complete our results and to fully adjust our local guidelines and the antibiotic therapy for children with appendicular abscess or plastron.

Conclusion

The management of children with appendicular abscess and plastron remains controversial and is different from one hospital to another. Many studies proved the benefits of the medical treatment although a significant rate of failures has been observed in our hospital from 2009 until 2019. Several factors were analyzed to predict the response to the medical treatment. Patients with multiple abscesses will no longer be treated with antibiotics. We also recommended greater vigilance after detecting stercoliths in the medical imaging based on other studies results. Time to hospitalization, time to apyrexia, CRP and white blood cells level at admission were not different between the success and the failure group. Finally, a wider bacterial epidemiology study is needed in order to adjust our local guidelines and the antibiotic therapy.

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