

Nonsurgical Management of Acute Uncomplicated Appendicitis in Children: the Analysis of Treatment Outcome in Relationship with Antimicrobial Regimens and Adverse Prognostic Factors

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Summary

Introduction. For acute appendicitis - the most frequent condition to perform an urgent abdominal operation in pediatric surgery - surgical appendectomy still remains the gold standard regarding treatment, nevertheless nonsurgical management has become more and more recognized as a treatment method for uncomplicated acute appendicitis (UAA). However there are still many unanswered questions regarding possible factors that could predict the treatment outcome as well as appropriate antimicrobial drug regimens.

Aim of the Study. The aim was to investigate if there is a possible association between factors such as C-reactive protein (CRP) level, presence of appendicolith, the diameter of the appendix and treatment outcome; as well as to identify most successfully used antimicrobial drug combinations.

Material and methods. A retrospective analysis of hospital cases, admitted to a single reference center during the time period from 2013 to 2015. Patients with clinical signs of acute appendicitis, elevated inflammatory markers and radiological findings suggestive for acute appendicitis were included in the study. Nonsurgical treated patients were divided in two groups based on the treatment outcome - successful or unsuccessful. Analysis of the three factors (CRP level, presence of appendicolith and the diameter of the appendix) and most commonly used antimicrobial drug regimen association with treatment outcome was performed.

Results. Overall 384 children medical records with acute appendicitis were registered and non-surgical treatment was initiated in 147/384 (38 %) cases. Successful treatment outcome of nonsurgical management was identified in 114/147 (78 %) cases.

Analyzing prognostic adverse factors results presents no statistically significant difference in association with CRP level >25 mg/l ($p=0,479$), presence of appendicolith ($p=0,183$) and the diameter of appendix >1 cm ($p=0,183$) with successful or unsuccessful treatment outcome. The two most commonly used antimicrobial drug combinations were - Ampicillin/Metronidazole for 49 patients and Ampicillin/Gentamicin for 44 patients. No relevance with treatment outcome and used antimicrobial agents was detected ($p=0,597$).

The overall recurrence rate after initial presentation is 15 % (17/114). In 3 cases (3 %) recurrent appendicitis developed one month after discharge and in 14 cases (12 %) up to one year after discharge.

Conclusions. Prognostic adverse factors - CRP, presence of appendicolith and diameter of appendix - were not statistically reliable in association with initial non-surgical treatment outcome.

The success rate of conservative treatment with narrow spectrum antibiotics was 78 %, which is just as high as in cases treated conservatively with broad-spectrum antibiotics from previous studies.

Therefore the question of which factors and antimicrobial drug combinations influence the course of treatment still remains unanswered and further studies are required.

Key words: uncomplicated acute appendicitis, nonsurgical management, antimicrobial regimens, adverse prognostic factors

INTRODUCTION

Acute appendicitis (AA) is a common condition in pediatric population and the appendectomy is the most frequent urgent abdominal operation performed by pediatric surgeons (1.) Despite that appendectomy still remains the gold standard for treatment of AA, in the last decade the nonsurgical management has become a well established treatment method. The need for an urgent surgical removal of appendix has been challenged, especially in uncomplicated cases. There are reports of high safety, efficiency and feasibility of nonsurgical treatment of AA (2,3). However, there are cases when clinical improvement is impossible without

performing the appendectomy. Some predictive factors for negative outcome of nonsurgical management or recurrence of AA have been established such as advanced inflammation, presence of appendicolith or intraluminal fluid and the diameter of appendix greater than 1,1 cm (4,5). It is clear that appliance of nonsurgical management requires careful selection of patients to avoid negative outcome and recurrence of AA. Once nonsurgical management is started, close monitoring of patient's clinical condition is mandatory. The major benefits of nonsurgical management of AA are avoidance of general anesthesia and potential postoperative complications. There are reports stating

that nonsurgical management ensures faster recovery and return to daily activities in shorter period of time (2). To date, there is relatively little experience in analysis of long term results and cost effectiveness. Therefore long term follow-up after nonsurgical management is of particular interest.

Despite growing experience of managing AA nonoperatively, still there is no consensus of most appropriate antimicrobial regimens. The antimicrobial treatment algorithms differ in published papers. It is clear that for most part of uncomplicated patients it is possible to achieve clinical improvement with highly effective broad-spectrum antibiotics, such as, Piperacillin/Tazobactam or Ciprofloxacin/Metronidazole, as suggests *P.Mineci et al* and *J.Armstrong et al* in their publications (2,3). However, these antimicrobial combinations usually are used to treat moderate or severe infections. The authors of this study presume that it is possible to achieve positive effects of nonsurgical management using narrow-spectrum antimicrobial combinations.

AIM OF THE STUDY

The aim of the study was to investigate if factors, such as, diameter of appendix, presence or absence of appendicolith and CRP (C-reactive protein) level, can be associated with the treatment outcome of uncomplicated acute appendicitis (UAA) and therefore could be used as prognostic factors. Another point of interest was to find out whether there is a specific antibacterial regimen associated with markedly higher percentage of successfully treated patients.

MATERIAL AND METHODS

A retrospective analysis of hospital cases, admitted to a single reference center during the time period from 2013 to 2015. Patients aged 0-17 years with clinical signs of AA such as right lower quadrant abdominal pain, fever, anorexia and increased inflammatory markers and radiological evidence of AA were included in the study. Patients with signs of complicated AA (peritonitis, periappendicular mass or abscess) were excluded from the study. Patients with chronic and/or concomitant diseases did not meet the inclusion criteria as well.

All included children were classified depending on the treatment method - surgical or nonsurgical. Those who underwent nonsurgical management were selected for further analysis. In order to carry out more accurate analysis selected patients were subdivided into two groups:

Group I- Successful nonsurgical treatment - improvement of clinical signs in 24 hours, allowing discharging the patient with further oral antimicrobial treatment.

Group II- Unsuccessful treatment - no signs of clinical improvement during 24 hours after hospitalization, thus surgical treatment was indicated with a following appendectomy.

Prognostic adverse factors: C-reactive protein (CRP) level >25 mg/l, presence of appendicolith and the diameter of appendix in radiological examinations -

in association with treatment outcome (successful or unsuccessful) were also analysed.

In both patient groups the most commonly used antimicrobial combinations were identified and their correlation with successful or unsuccessful treatment was analysed.

In patient group I the cases with recurrent AA were identified. The time period in which recurrent AA occurred - one month or one year - were registered.

Statistical analysis was performed by IBM SPSS Statistics 22 program.

RESULTS

Overall 384 children medical records with acute appendicitis (AA) were analysed. Surgical treatment was initiated in 237/384 (62%) and non-surgical treatment in 147/384 (38%) cases. Successful treatment outcome of nonsurgical management was identified in 114/147 (78%) cases.

C-reactive protein

Non-surgical successful treatment with CRP level higher than 25 mg/l was identified in 75 % (44/59), but with CRP level lower than 25 mg/L - in 80 % (70/88) cases. From all unsuccessfully treated patients CRP level higher than 25 mg/l was in 25 % (15/59), but below given CRP value in 21 % (18/88) cases respectively. For those data presented no statistical difference based on CRP level and association with successful or unsuccessful treatment outcome ($p=0,479$), shown in Fig. 1. In order to be p-value relevant it should be $p<0.05$.

Appendicolith

In cases where ultrasound for abdominal cavity was performed, appendicolith deposits were looked for. Successful treatment with identified appendicolith was in 67 % (16/24), but without presence of any deposits treatment was successful in 79 % (88/111) of cases. Nevertheless, unsuccessful treatment with visualized appendicolith was identified in 33 % (8/24), but with absence of any deposits - in 21 % (23/111). Defined information shows no statistically significant difference ($p=0,183$) between presence or absence of appendicolith with treatment result, Fig. 2.

Diameter of appendix

Successful nonsurgical treatment and appendix diameter greater than 1 cm was identified in 76 % (31/40) of cases, but with diameter less than 1 cm - in 82 % (55/67). Unsuccessful therapy with diameter larger than 1 cm was in 23 % (9/40), however with less than 1 cm diameter - in 18 % (12/67) of cases and appendectomy was performed. Also demonstrating no statistically significant connection ($p=0,563$) with diameter of appendix and treatment outcome, Fig. 3.

Antimicrobial combinations

In total 17 different antimicrobial drugs or drug combinations were used for nonsurgical treatment of UAA. The two most commonly used antimicrobial drug combinations were - Ampicillin/Metronidazole for 49 patients and Ampicillin/Gentamicin for 44 patients, followed by Ceftriaxone/Metronidazole - in 17 patients; Cefuroxime, Amoxicillin/Metronidazole and Ampicillin -

each for 5 patients; other antimicrobial drugs or combinations were used for 3 or less patients.

The treatment with Ampicillin/Metronidazole was successful in 80 % (39/49), although with combination of Ampicillin/Gentamicin - in 75 % (33/44) of cases. Administering Ampicillin/Metronidazole led to unsuccessful antimicrobial treatment in 20 % (10/49), but prescribing Ampicillin/Gentamicin was also negative in 25 % of cases (11/40). Those patients after unsuccessful antimicrobial treatment and with no signs of clinical improvement, underwent appendectomy. No association was detected ($p=0.597$), Fig. 4.

All obtained parameters are shown in Table 1.

Recurrence

The overall recurrence rate after initial presentation is 15 % (17/114). In 3 cases (3 %) recurrent appendicitis developed one month after discharge and in 14 cases (12 %) up to one year after discharge.

DISCUSSION

The benefit of conservative treatment is the avoidance of surgery and general anaesthesia related complications, however very careful evaluation of number of factors needs to be done when selecting the best treatment strategy for specific patient. Studies have shown that there are some positive predictive factors to take into account. We analysed the correlation of CRP level higher or lower than 25 mg/l and conservative treatment effectiveness, but the outcome did not depend on the level of CRP. It is known that in uncomplicated appendicitis, the CRP level a priori is lower than in complicated cases (13). The majority of patients included in this study had CRP levels of less than 10 mg/l, which would explain why we were not able to obtain an association between CRP level and conservative treatment effectiveness.

The correlation between the presence or absence of appendicolith on ultrasonography (US) and conservative treatment effectiveness showed that treatment is successful in majority of cases, regardless of whether or not it was detected on US, although in a study carried out before appendicoliths were associated with conservative treatment failure (9). Some limitations that could affect the results were that not all patients were examined with US, in some patients the appendix was not visualised, so it is impossible to exclude effect of appendicolith presence in conservative treatment outcome, since for some of the patients it was not visualised on abdominal US, but was identified during the operation.

Results indicate that appendiceal diameter of less than 1 cm is associated with a better outcome of conservative treatment in comparison to a diameter larger than 1 cm, nevertheless in both cases conservative treatment was successful in majority of cases, indicating that the diameter is not a good prognostic marker in routine decision making of treatment of UAA. Possible confounding factors, such as the length of anamnesis, chronic and/or concomitant diseases, should be excluded and analysed in a following study. In previous trials the association between the diameter of appendix

and appendicitis was not found to be statistically significant (7), which would explain why the results in our study were inconclusive. The sample size of patients in whom US was performed, appendix was visualised and the diameter was measured too small for the results to be generalised on whole pediatric population, thus this issue could be addressed in a future studies.

The recurrence rate of AA is of great importance and interest for both, surgeons and parents. In previously carried out studies the recurrence rate ranges between 14 and 26 % (9-13), similar results were obtained in our study – 15 %.

The trends among pediatric surgeons in Latvia for nonsurgical treatment of UAA are directed towards narrow-spectrum antibiotics (also known as cost effective), such as Ampicillin and Metronidazole, in comparison to USA and Western Europe, where surgeons tend to use broad spectrum antibiotics, for example, Ciprofloxacin, third generation of Cephalosporins, Piperacillin-Tazobactam and others (3,6). Our study results demonstrate that the success rate of conservative treatment using narrow-spectrum antibiotics is 77,6% (similar rate of 88% was obtained in a previously carried out study (8)), comparing to success rate in patients treated with broad-spectrum antibiotics, establishing that there is no significant difference between the two groups. The broad-spectrum antibiotics are effectively used in treating complicated intraabdominal infections and (15) resistant Gram-negative bacteria, suggesting that these have a limited role in UAA. It means that administering narrow-spectrum antibiotics is not only less expensive than broad spectrum antibiotics, but it is also just as successful conservative treatment. The treatment of both most commonly used narrow-spectrum antibiotic combinations were equally successful regarding success rate and length of hospital stay. This data therefore could be useful in development of UAA treatment guidelines in children.

In cases when the initial treatment with antibiotics fails to improve the general status of patient, second and third-line antibiotics could be used, in order to improve the success rate of nonsurgical treatment, as results in a study (16) showed to have the initial success rate of 85,7% with treatment of first line antibiotics (Cefmetazole), which was improved to 98,7% after changing the primary antibiotic regimen to broad-spectrum antibiotics.

Many different factors need to be taken into account when analysing results. Because different protocols can affect the outcome of treatment, for example, receiving the antibiotics intravenously, orally or in both forms. Another point of interest is that in many cases the diagnosis was based on clinical presentation, so it is not possible to be completely sure that all of the patients, who received conservative treatment actually had UAA.

CONCLUSIONS

Prognostic adverse factors - CRP, presence of appendicolith and diameter of appendix - were not statistically reliable in association with initial nonsurgical treatment outcome.

The success rate of conservative treatment with narrow spectrum antibiotics was 78 %, which is just as high as in cases treated conservatively with broad-spectrum antibiotics from previous studies.

Therefore the question of which factors and antimicrobial drug combinations influence the course of treatment still remains unanswered and further studies are required.

Conflict of interest: None

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Table 1. The analysis of treatment outcome in association with adverse prognostic factors and antimicrobial combinations

Factors	Value	Successful treatment, n	Successful treatment, %	Unsuccessful treatment, n	Unsuccessful treatment, %	P value
CRP	> 25 mg/l	44	75%	15	25%	0,479
	< 25 mg/l	70	80%	18	21%	
Appendicolith	Presence	16	67%	8	33%	0,183
	Absence	88	79%	23	21%	
Diameter of appendix	> 1 cm	31	78%	9	23%	0,563
	< 1 cm	55	82%	12	18%	
Combinations of antimicrobials	Ampicillin/ Metronidazole	39	80%	10	20%	0,597
	Ampicillin/ Gentamicin	33	75%	11	25%	

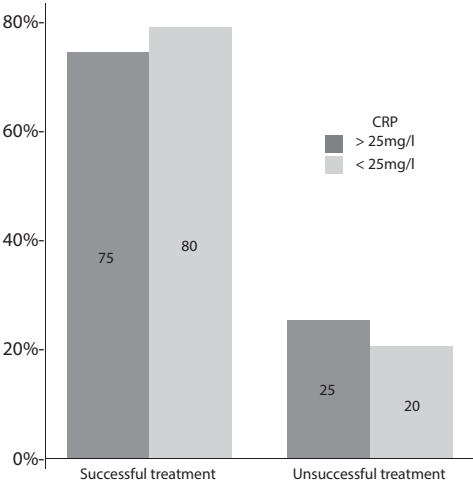


Fig. 1. CRP level in correlation with successful or unsuccessful treatment outcome

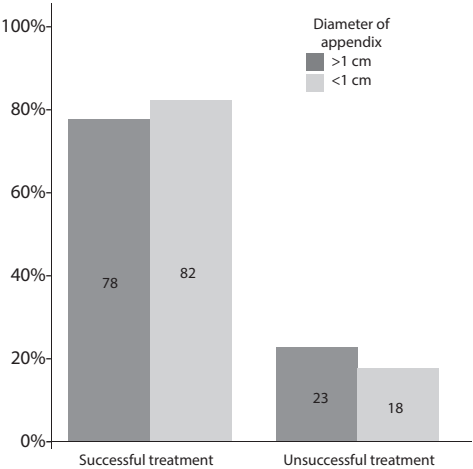


Fig. 3. Diameter of appendix in correlation with successful or unsuccessful treatment outcome

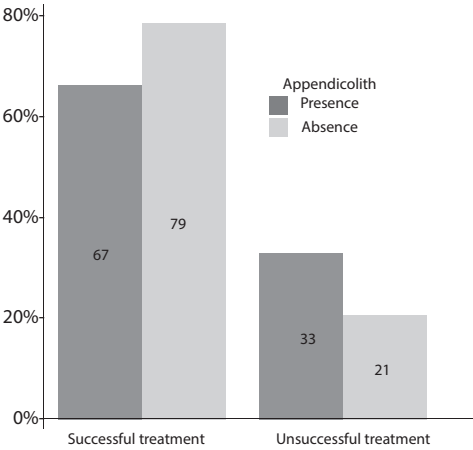


Fig. 2. Appendicolith presence or absence in correlation with successful or unsuccessful treatment outcome

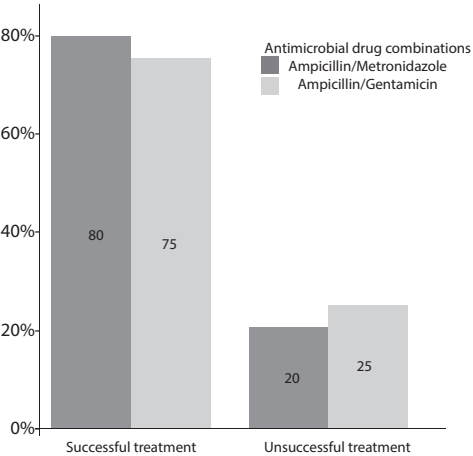


Fig. 4. Antimicrobial drug combinations in association with successful or unsuccessful treatment outcome