

Not complicated acute appendicitis in adults: clinical or surgical treatment?

Apêndicite aguda não complicada em adultos: tratamento cirúrgico ou clínico?

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INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdomen and can be classified into uncomplicated and complicated (phlegmon and / or peritonitis). Although it was originally described more than 125 years ago, the etiology of acute appendicitis continues to be debated. Classically, the obstruction of the appendix by a fecalith, foreign bodies, parasites, tumors and lymph node hyperplasia, have been implicated in the development of acute appendicitis. According to this theory, acute appendicitis is considered as a progressive condition, which begins with the increase in mucus secretion and intraluminal pressure, resulting in venous stasis and arterial ischemic compression of the walls of the viscus. With ischemia, mucosal protective mechanism of the barrier is lost, leading to bacterial invasion of the appendix wall, which in turn facilitates perforation and infarction of the appendix. Based on the concept of unavoidable complication, surgical removal of the appendix has been the treatment of choice for over a century¹. However, the observation of spontaneous resolution of acute appendicitis cases and reports of some authors of a good outcome in patients treated with antibiotics suggest that not all cases of acute appendicitis fall in the theory of mechanical obstruction and progression to complicated disease^{2,3}. Some researchers suggest that the forms uncomplicated and complicated of appendicitis are two distinct diseases, with different etiologies. As in other intra-abdominal infections, such as salpingitis, diverticulitis and enterocolitis, which are often treated only with antibiotics, the infectious etiology of acute appendicitis is advocated by some scholars⁴.

Although appendectomy is the approach adopted in most institutions, there have been, since 1959, reports

of non-operative treatment with use of antibiotics of both clinical presentations². In cases of appendiceal phlegmon, medical treatment with antibiotics in the initial phase is commonly used by many surgeons^{5,6}.

In recent years a number of retrospective and prospective scientific studies have been conducted with the purpose of comparing surgical treatment with conservative (nonoperative) one⁶⁻¹⁰. Nevertheless, the conduction of comparative studies in this area is challenging due to the following factors: 1) Acute appendicitis is a disease that has a broad spectrum of clinical presentations and various diagnostic methods (clinical, laboratory, ultrasound, CT and surgical) can be used and vary between the various surgical services, which challenges the diagnostic classification of patients for inclusion in studies; 2) The population affected by appendicitis is heterogeneous, including different age groups, making the comparison between patients burdensome; 3) The overall mortality rate associated with acute appendicitis is relatively low, which makes it extremely difficult to assess and demonstrate differences in mortality in scientific papers; 4) There is difficulty in defining "success" or "superiority" of surgical treatment when compared to the conservative one, and "equivalence" or "no inferiority" of antibiotic therapy to appendectomy, in order to allow comparison. The variability of the profile of the population studied, the surgical technique used, the diagnostic methods, the choice and duration of antibiotic therapy, the frequency and criteria for review, the inclusion and exclusion criteria, and methods of study, are responsible for inconsistency of results, hampering inter-trial interpretation⁶⁻⁸.

Institutions that participated in the TBE-CiTE conducted a critical analysis of two original articles and two recent systematic reviews on the subject and generated

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recommendations “based on that evidence” about the validity of nonoperative treatment of uncomplicated acute appendicitis in adults.

STUDY 1

Randomized clinical trial of antibiotic therapy versus appendectomy as initial treatment of acute appendicitis in unselected patients⁹.

Rationale

The result of the non-operative treatment (antibiotics) of acute appendicitis is uncertain. This study was designed to evaluate the use of antibiotics in the treatment of acute appendicitis in unselected adult patients.

Question

Is antibiotic therapy effective as the first choice for treating acute appendicitis in adults?

Major findings of the study

It was a prospective, not fully randomized study in three hospitals in Sweden that included all adult patients (> 18 years) with probable diagnosis of appendicitis (clinical diagnosis with or without laboratory confirmation, ultrasound or CT). The patients were divided into three groups: reference (patients operated in Ostra Hospital), antibiotic therapy or surgery. Surgery could be open or laparoscopic surgery, while antibiotic therapy began with intravenous cefotaxime and metronidazole for the first 24 hours, followed by oral ciprofloxacin and metronidazole for a total of 10 days. Patients received a questionnaire one and 12 months later and, if they did not answer it, they were contacted by telephone. The study had two main outcomes: efficacy and serious complications. The definition of efficacy changed according to the group: for antibiotic therapy it was defined as “no need of operation”; and for the surgical group, the confirmation that “the diagnosis of appendicitis was correct or there was an illness that required operation.” The authors evaluated several secondary outcomes, including cost.

This study included 369 patients, 202 in the antibiotic group and 167 in the surgery one. Only 52% of patients assigned to antibiotic treatment were non-operatively treated, while 96% of allocated to surgery group were operated. The groups were similar regarding gender, age, levels of C-reactive protein, white blood cell count, body temperature and the presence of local peritonitis. Only 11 of 119 patients treated with antibiotics had to be operated, resulting in an efficiency of 90.8% for antibiotic therapy. For appendectomy, efficacy was 89.2% (correct diagnosis of appendicitis or other surgical pathology). Of the 108 non-operated patients, 15 had recurrent appendicitis (13.9%) within one year. One third of the recurrences occurred within the first 10 days and 2/3 between 3 and 16

months after hospital discharge. Minor complications were similar between groups. Major complications were three times more frequent in patients undergoing surgical treatment ($p < 0.05$). Mild complications were similar in both groups, but total costs were higher in operated patients.

Strengths

- The study can be considered as generalizable, as it included all adult patients with probable diagnosis of acute appendicitis; a prospective study design allows better evaluation of outcomes and data collection; major complications were analyzed: reoperation, abscess, intestinal obstruction, suture dehiscence, hernias and serious problems of anesthesia; it reports diagnostic findings associated with complicated forms of appendicitis. Phlegmon and gangrenous appendicitis are associated with leukocytosis, while perforated appendicitis is associated with elevated C-reactive protein, leukocytosis and elevated body temperature ($p < 0.001$). This information can be used to assist doctors in the early identification of patients who develop complications; it evaluated complications according to the technique applied. Surgical complications were similar in open and laparoscopic surgery; it assesses outcomes related to the well being of the patient. Patients treated with antibiotics had abdominal pain for a longer time than the control group.

Limitations

- The study was not completely randomized, as the inclusion of patients in a given study group was made according to their date of birth, and once determined, the doctors in charge could follow or not the randomization rules. Due to the inability to mask the interventions of the study, this may introduce a bias in the randomization of certain patients;
 - A high rate of exchange at randomization. Of the 202 patients assigned to antibiotic therapy, almost half (96 patients or 48%) underwent surgery, which reduces the ability of the study to demonstrate a positive effect of this intervention if this effect actually exists. Moreover, this exchange of randomization may indicate a failure in the study inclusion criteria, or even a real problem with the study design itself;
 - There was a high rate of loss of follow-up of patients to evaluate the outcomes of the study. Half the patients were followed for 12 months. This always leaves a question about the outcome of interventions in patients who did not complete follow-up;
 - It includes both uncomplicated and complicated appendicitis and did not exclude phlegmon, which is non-operatively treated by many surgeons;
 - One cannot know for sure if the groups are really similar. The two groups have different sizes (250 vs. 119) and the operated patients had more diffuse and localized peritonitis; it is not possible to know with certainty

the severity of patients in each group or how many actually had appendicitis;

- Failure to consider the two patients who had a cancer that was discovered only because of the operation;
- The population studied may not reflect the reality of poor countries or those where the commitment to long-term treatment (10 days) is small;
- It does not evaluate the pediatric population (less than 18 years).

STUDY 2

Amoxicillin + clavulanic acid *versus* appendectomy for the treatment of non-complicated acute appendicitis: a randomized, controlled, open and non-inferior study¹⁰.

Rationale

Several studies have indicated antibiotic (ATB) as treatment of acute appendicitis. However, due to limitations of the methodological point of view, the studies do not allow a definitive conclusion. Its objective was to evaluate the use of amoxicillin + clavulanate *versus* appendectomy in adult patients with uncomplicated acute appendicitis.

Question

Is the use of antibiotics for the treatment of acute appendicitis as safe and effective as the surgical procedure?

Major findings of the study

The rate of peritonitis within 30 days was significantly higher in the group treated with antibiotics. The ATB group patients who underwent surgery had a higher incidence of postoperative complications following a year.

Strengths

- Design of a prospective, randomized and controlled study, what is important to reduce the possibility of bias in the formation of study groups and try to evenly distribute differences that may exist between patients in both study groups. In fact, the group of appendectomy and ATB are very similar in baseline characteristics evaluated; well-defined inclusion criteria, diagnosis made by computed tomography, including only cases of uncomplicated appendicitis based on CT criteria; it assessed, as the main outcome, a complication common to both treatments (peritonitis); it found that the presence a fecalith is an indicator of complicated appendicitis or failure of treatment with antibiotics; carried out in a defined population, in the case, in adults.

Limitations

- Non-inferiority margin of 10%, which can be considered high;

- Comparison of the surgical group with two different techniques (laparoscopic and open) where the postoperative evolution may be different;
- Did not directly compare the subgroup of patients assigned to ATB who were later operated with the surgical group. The rate of complications was calculated using the total number and not the number of patients operated on the ATB group, resulting in a lower level of morbidity;
- The cases operated on within 30 days due to peritonitis in the ATB group and the ones without perioperative confirmation of the diagnosis of acute appendicitis were not considered in the sample for comparison with the surgical group;
- The antibiotic mentioned in the introduction (ertapenem) was not the antibiotic used in the study;
- Two different tomography devices were used for the diagnosis of appendicitis;
- The socio-economic costs of each form of treatment for the patient were not assessed;
- No blood cultures were performed for better evaluation of the outcome of success or failure of antibiotic treatment.

STUDIES 3 AND 4

- The exclusive use of antibiotics for the treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis⁷.
- Appendectomy versus antibiotic treatment for acute appendicitis. (Cochrane Review)⁸.

Rationale

Although the nonoperative treatment is already a common practice in many centers in cases of appendicitis complicated by intraperitoneal abscess, controversies remain regarding the best approach for uncomplicated appendicitis. Studies show inconsistent, and difficult to interpret, results. Due to the high frequency of acute appendicitis and the certainly big impact with the widespread adoption of antibiotic therapy as first choice in the treatment of the uncomplicated form, the review and joint analysis of the best clinical trials on the topic is of utmost importance. Two systematic reviews of the literature of the last 30 years aimed at evaluating the evidence and to determine the usefulness of antibiotic treatment in relation to appendectomy for the treatment of acute appendicitis.

Question

Liu and Fogg⁷: Is the nonoperative treatment exclusively based on the use of antibiotics in uncomplicated appendicitis effective? Is the nonoperative treatment exclusively based on the use of antibiotics in uncomplicated appendicitis safe?

Wilms *et al.*⁸: Is the treatment with antibiotics as effective as appendectomy (open or laparoscopic) in healing within two weeks, without complications, for patients with acute appendicitis evaluated up to one year? This review considers an acceptable margin of 20% for defining non-inferiority of antibiotic therapy.

Major findings of these studies

Both reviews evaluated four randomized clinical trials in common. In these studies, Liu and Fogg⁷ included a retrospective scientific work of their own and the "quasi-randomized" controlled clinical study of Hasson *et al.*⁹, while Wilms *et al.*⁸ included the study of Vons *et al.*¹⁰, discussed earlier in this article, totaling 1444 patients in all studies combined. Although evaluating virtually the same studies, the two reviews reported distinct, and somewhat contradictory, findings.

Liu and Fogg⁷ observed that the early success rate of exclusive antibiotic therapy ranged from 88.1% and 100% in the six studies included, with a late recurrence rate of 5.3% to 14%, reaching 35% in one study. The complication rate of clinical treatment was 0% in five of the six included studies and ranged from 4.4% to 34% in patients undergoing appendectomy. The authors concluded that: 1 - Evidence suggests that nonoperative treatment is effective and safe in patients with uncomplicated appendicitis; 2 - Prospective, randomized, controlled trials are needed to define the role of nonoperative treatment of uncomplicated appendicitis.

Wilms *et al.*⁸ reported that 73.4% (95% CI 62.7 to 81.9%) and 97.4% (95% CI 94.4 to 98.8%) of patients treated with antibiotics and appendectomy, respectively, were cured within two weeks and without significant complications (including recurrence) up to a year. The bottom 95% of the confidence interval of 15.2% was less than the 20% acceptable to establish that the antibiotic is non-inferior. Hospital stay was shorter in the appendectomy group. No significant difference was observed for days off due to illness, which was evaluated in only two studies. Therefore, the authors concluded:

1 - Despite a lower rate of success in the antibiotic group, the study is inconclusive, due to the CI that did not reach the tolerated 20% level to declare that the treatment is non-inferior;

2 - Due to the low quality of the studies, the results should be interpreted cautiously and definitive conclusions cannot be drawn from them;

3 - The appendectomy remains the standard treatment for acute appendicitis; antibiotics can be used exclusively in the context of research or in situations where surgery is contraindicated.

Strengths

- Like any systematic review and meta-analysis, a larger number of patients combined usually allows the realization of a more definitive determination of the

effectiveness of treatment when compared to individual studies; the review by Wilms *et al.*⁸ follows the recommendations of the Cochrane group, using a well-established and rigorous scientific methodology, particularly in relation to quality assessment of selected studies and statistical analysis methods. This review has a primary outcome that allows a meaningful comparison between studies and treatments. The authors also evaluated factors related to the implications for the patient and the costs of the interventions; after a standardized and established assessment of the quality of the selected studies, the authors excluded the study by Hansson *et al.*⁹, rated as of poor quality; the two studies conducted a detailed review of the relevant literature, with inclusion criteria for studies clearly explained.

Limitations

- Regardless of being well managed and of high standard, any systematic review and meta-analysis represents the quality of the studies combined. In the review by Wilms *et al.*⁸ all selected studies were classified as of low or moderate quality;

- The review of Liu and Fogg⁷ considered all studies as being of high quality. Nevertheless, the authors used a rating scale (Newcastle-Ottawa Quality Assessment Scale for Cohort Studies) suitable for studies that are not randomized. Among the six studies included in this review, four were randomized trials, one "partially randomized" and only one retrospective, nonrandomized;

- The majority of studies included in the review does not report the use of prophylactic antibiotics in patients undergoing surgery, which is associated with a reduction of surgical site infection. This may introduce a bias in favor of surgical treatment;

- The studies do not provide information regarding the number of patients initially approached for inclusion in the scientific papers. This information is important to evaluate patients' opinion regarding the treatment studied. A high number of patients not agreeing to participate in a study of antibiotics for appendicitis suggests that this treatment is not well accepted;

- In the study by Liu and Fogg⁷, although the title suggests the conduction of a meta-analysis, it is really just a systematic review of comparative studies;

- While four of the included studies are defined as prospective and randomized, they lack information about the inclusion criteria, type of randomization and other data to better assess the level of evidence of all of them;

- The authors of the Cochrane systematic review accepted an inferiority margin of up to 20% for the antibiotic treatment in relation to appendectomy for the main outcome of the study to consider it non-inferior⁸. In practical terms, this would be the same as accepting that for every five patients treated with antibiotics, one would not be cured within two weeks or would had major complications within one year of follow-up. Some surgeons certainly consider

this a very high risk for their patients;

- Apparently, some of these studies included patients with localized or generalized peritonitis, which can hardly be classified as uncomplicated appendicitis, and may introduce an important selection bias;

- The methods of assessment and diagnosis of appendicitis vary widely from study to study, making it very difficult to assess the degree of evolution of appendicitis in different groups.

CONCLUSION OF TBE-CITE

The conclusions are based on the publications discussed above and the articles contained in these reviews.

There are some articles that suggest that the medical treatment with antibiotics for acute appendicitis display morbidity and mortality similar to, or higher than, surgical treatment.

The methodological quality of studies comparing antibiotic treatment with appendectomy is the most limiting factor for more definitive conclusions on the topic.

There is no evidence of advantages or greater efficacy in the treatment of acute appendicitis with antibiotics, either in clinical and surgical terms or regarding the socio-economic status of the patient.

The role of exclusive antibiotics in the treatment of uncomplicated acute appendicitis in adults needs to be better determined through better quality studies.

Treatment results in children were not assessed.

Recommendations of TBE-CiTE on "Uncomplicated Acute Appendicitis in Adults: Clinical or Surgical Treatment?"

1. The treatment of choice for uncomplicated acute appendicitis in adults continues to be surgical;

2. The exclusive treatment with antibiotics cannot be routinely recommended in current medical practice and should only be considered in selected patients or in the context of clinical studies.

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