REVIEW

ANTIBIOTICS IN ACUTE APPENDICITIS - WHEN AND HOW? A NARATIVE REVIEW**L. Alecu¹, C. Nițipir², I. Slavu³, V. Braga³, D. Mihăilă¹, A. Tulin¹**¹General Surgery Clinic, Prof. Dr."Agrippa Ionescu" Emergency Clinical Hospital, Bucharest, Romania²Emergency Clinical Hospital, Elias, Bucharest, Romania³General Surgery Clinic, Emergency Clinical Hospital, Bucharest, Romania

Corresponding author: Slavu Iulian

Phone no.: +40752596675

E-mail: iulian.slavu@yahoo.com

Abstract

An increasing interest exists towards the use of antibiotics in the treatment of uncomplicated acute appendicitis. For a long period of time, surgery was the only treatment for acute appendicitis. Due to recent research in the etiology of acute appendicitis which seems to be driven by intraluminal bacterial proliferation, new data suggests that for non-perforated appendicitis confirmed with the help of CT, antibiotics may play a central role in the treatment. As relapse rates amount in some cases to only 5% after antibiotic treatment, a discussion is required regarding the risks of interval appendectomy and its use. The debate regarding the optimal antibiotic course is on-going as some surgeons advocate for amoxicillin/clavulanic while others, due to acquired resistance recommend ertapenem. Selective antibiotic treatment for selected forms of acute appendicitis, uncomplicated without perforation is safe and has a relatively low complication rate. However, certain mentions must be made: surgery must not be delayed if failure of antibiotics exists as it can lead to higher rates of peritonitis. Close clinical surveillance is of utmost importance.

Keywords: antibiotic treatment, acute appendicitis**Introduction**

Appendectomy for acute appendicitis is one of the most common surgical interventions worldwide [1]. Any change regarding the operative indication is significant due to the fact it bears important implications for perioperative morbidity and cost [1].

The risk of developing acute appendicitis during one's lifetime is 8% and is higher in the second decade of age [2].

Historically, the conservative treatment of acute appendicitis was not an objective for the surgeon, quite the opposite. In 1886 Fitz published an article in which he studied the

impact of early appendectomy [3]. Over 130 years ago, the first elective appendectomy was performed by Grooves [4]. One of the first studies in which the conservative treatment (antibiotic) in acute appendicitis was investigated was published by Coldrey et al in 1959 and included a group of 471 patients [5].

McBurney performed the first appendectomy for acute appendicitis in 1889, making this intervention a "gold standard" in treatment of acute appendicitis [6]. Since then appendectomy has been rapidly adopted as an elective treatment as it significantly reduces the mortality and morbidity of this pathology. The complications of surgery are inherent and

impossible to avoid altogether. The most common complication considering the fact that it is a septic surgery is wound infection and postoperative abdominal abscess. Also frequently encountered are postoperative ileus, postoperative hemorrhage and appendicular fistula [7, 8]. These complications vary in incidence, with a global average of 11% and a mortality of 0.5% [9].

Treatment guidelines recommended that after the confirmation of acute appendicitis, the subsequent treatment should be dictated by its form, so uncomplicated acute appendicitis which manifests by inflammation and the absence of perforation allows for delayed surgery, so first antibiotic treatment required.

This conservative strategy was further developed by Salminen et al; Hansson et al; Vons et al; and Styrd et al. [10-13]. Recent prospective randomized studies have shown that surgical intervention and implicitly appendectomy can be completely eliminated from the treatment protocol. This solution has been shown to be safe for the patient with a success rate of up to 85% depending on the form of the inflamed appendix [10-13].

Discussion

For an important period of time, the elective treatment in acute appendicitis was surgical intervention and appendectomy. Even today conservative treatment with antibiotic therapy for a positive diagnosis of acute appendicitis is a controversial topic. This practice of performing appendectomy in all cases of acute appendicitis stems from the theory that any acute appendicitis will evolve to perforation since its etiology is intraluminal obstruction by coprolites [14].

This theory has been taken up and perpetuated until 1984 when Benmark et al; demonstrated in its complex study of measuring intraluminal pressure in acute appendicitis that this is normal in the vast majority of cases. Thus obstructive etiology caused by coprolites was eliminated as the main cause of appendicitis. The attention shifted on bacterial proliferation in the lumen of the appendix, thus giving an increasingly important role to antibiotics in the treatment protocol [15].

To date, multiple meta-analyses, systematic reviews, and randomized prospective studies have been published, which have studied comparatively the surgical treatment VS antibiotic treatment in acute appendicitis [16-24].

In order to place a patient into the antibiotic treatment group, a central role is played by the correct diagnosis of the form of uncomplicated appendicitis. In this regard, the tool that can make a correct diagnosis is Computed Tomography (CT) due to its high sensitivity and specificity [25]. CT use significantly reduces negative appendectomy rates without producing a further increase in time in the number of acute perforated appendicitis [26, 27]. The routine use of CT reduces the number of unnecessary surgeries allowing better management of hospital resources. Livingston et al. demonstrated in 2007 that there was a relationship of inverse proportionality between the number of CT investigations performed and the incidence of acute non-perforated appendicitis diagnosed and operated [28].

Once the diagnosis of uncomplicated acute appendicitis has been confirmed and a non-obstructive etiology has been established, an antibiotic should be selected to allow good coverage of the bacteria in the colon. The combination of amoxicillin and clavulanic acid was tested with promising results by Vons et al; but this combination does not provide the best coverage against one of the most common germ cells in the colon, *Escherichia coli* [12]. The acquired resistance by this germ is increasing, so in the near future probably new therapeutic schemes will be needed [29].

Antibiotics with a broader sphere of coverage such as ertapenem have been tested by Paulina et al; with good results. After a three-day comparative administration of ertapenem and amoxicillin plus clavulanic acid, the efficacy rate was 97% for ertapenem and 86% for amoxicillin-clavulanic acid [30]. These newer antibiotics have a number of drawbacks, primarily the acquisition of resistance to one of the last-line antibiotics that are usually used for severe intra-abdominal infections is important. Also, the high cost of these antibiotics can represent a problem if they are widely adopted [31, 32].

The incidence of recurrence after antibiotic therapy in acute appendicitis is another factor which limits the widespread use of this treatment. In literature, it is placed between 4 and 15% [33, 34]. If one studies these recurrence rates, the question arises as to the usefulness of interval appendectomy if up to 96% of patients who were initially treated conservatively do not relapse? Statistics provide us with the data, but the decision to adopt a therapeutic decision belongs to every surgeon.

Neoplasm of the appendix has been reported as another limit of antibiotic treatment. The reported incidence is 0.09%. Adding to this low incidence, an effective CT allows the selection of these patients based on imaging criteria. The staging criteria for the appendicular neoplasm are the same as those of the colon tumors [35].

Regarding the duration of hospitalization and the return to social activities, some studies cite a shorter duration for patients with conservative treatment of about 5.8 days [36]. The results are conflicting, so Vons et al. reported a longer duration of hospitalization for patients with antibiotic treatment. Other meta-analyses did not identify a lasting difference between the subgroups.

Conclusions

Acute appendicitis treatment like other pathologies which once only knew surgery has recently seen a revolution. Selective antibiotic treatment for selected forms of acute appendicitis, uncomplicated and without perforation confirmed with the help of CT is safe and has a relatively low complication rate. However, certain mentions must be made: surgery must not be delayed if the failure of antibiotics exists as it can lead to higher rates of peritonitis. Close clinical surveillance is of utmost importance. The surgeon needs to clearly explain to the patient and family the evolution of such cases, so they can seek medical help ahead of time.

Conflicts of interest

The authors declare no conflict of interest.

References

- [1] Masoomi H, Nguyen NT, Dolich MO, Mills S, Carmichael JC, Stamos MJ. Laparoscopic appendectomy trends and outcomes in the United States: data from the Nationwide Inpatient Sample (NIS), 2004-2011.
- [2] Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *American Journal of Epidemiology* April 1990; 132(5):910–25.
- [3] Fitz RH. Perforating inflammation of the vermiform appendix. *Am J Med Sci* 1886;92:321–346.
- [4] Harris CW. The first elective appendectomy? *Can J Surg* 1961;4:405–410.
- [5] Coldrey E. Five years of conservative treatment of acute appendicitis. *J Int Coll Surg* 1959;32:255–261.
- [6] Lyall A. Treatment of acute appendicitis. *BMJ*. 1945;2(4429):719-721.
- [7] Hansson J, Korner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendectomy as primary treatment of acute appendicitis in unselected patients. *British Journal of Surgery* 2009;96(7):830.
- [8] Sauerland S, Lefering R, Neugebauer EAM. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database of Systematic Reviews* 2004, Issue Issue 4. [DOI: 10.1002/14651858.CD001546.pub2]
- [9] Guller U, Hervey S, Purves H, Muhlbaier LH, Peterson ED, Eubanks S, Pietrobon R. Laparoscopic versus open appendectomy: outcomes comparison based on a large administrative database. *Annals of Surgery* January 2004; 239(1):43–52.
- [10] Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA*. 2015;313(23): 2340-2348.
- [11] Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg*. 2009;96(5):473-481.
- [12] Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet*. 2011;377(9777):1573-1579.
- [13] Tyrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis: a prospective multicenter randomized controlled trial. *World J Surg*. 2006;30(6):1033-1037.

- [14] Wangenstein OH, Dennis C. Experimental proof of the obstructive origin of appendicitis in man. *Ann Surg* 1939;110: 629-47.
- [15] Arnbjornsson E, Bengmark S. Role of obstruction in the pathogenesis of acute appendicitis. *Am J Surg* 1984;147: 390-2.
- [16] Ansaloni L, Catena F, Coccolini F, Ercolani G, Gazzotti F, Pasqualini E, et al. Surgery versus conservative antibiotic treatment in acute appendicitis: a systematic review and meta-analysis of randomized controlled trials. *Dig Surg* 2011;28:210e21.
- [17] Kirby A, Hobson RP, Burke D, Cleveland V, Ford G, West RM. Appendectomy for suspected uncomplicated appendicitis is associated with fewer complications than conservative antibiotic management: a meta-analysis of post-intervention complications. *J Infect* 2015;70:105e10.
- [18] Liu K, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery* 2011;150:673e83.
- [19] Sakorafas GH, Mastoraki A, Lappas C, Sampanis D, Danias N, Smyrniotis V. Conservative treatment of acute appendicitis: heresy or an effective and acceptable alternative to surgery? *Eur J Gastroenterol Hepatol* 2011;23:121e7.
- [20] Fitzmaurice GJ, McWilliams B, Hurreiz H, Epanomeritakis E. Antibiotics versus appendectomy in the management of acute appendicitis: a review of the current evidence. *Can J Surg* 2011;54:307e14.
- [21] Gorter RR, Heij HA, Eker HH, Kazamier G. Laparoscopic appendectomy: state of the art. Tailored approach to the application of laparoscopic appendectomy? *Best Pract Res Clin Gastroenterol* 2014;28:211e24.
- [22] Malik AA, Bari SU. Conservative management of acute appendicitis. *J Gastrointest Surg* 2009;13:966e70.
- [23] Styruud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, et al. Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicenter randomized controlled trial. *World J Surg* 2006;30:1033e7.
- [24] Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis. The APPAC randomized clinical trial. *JAMA* 2015;313:2340e8.
- [25] Kim K, Kim YH, Kim SY, et al. Low-dose abdominal CT for evaluating suspected appendicitis. *N Engl J Med*. 2012;366(17):1596-1605.
- [26] Rao PM, Rhea JT, Rattner DW, Venus LG, Novelline RA. Introduction of appendiceal CT: impact on negative appendectomy and appendiceal perforation rates. *Ann Surg*. 1999;229 (3):344-349.
- [27] Coursey CA, Nelson RC, Patel MB, et al. Making the diagnosis of acute appendicitis: do more preoperative CT scans mean fewer negative appendectomies? a 10-year study. *Radiology*. 2010; 254(2):460-468.
- [28] Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. *Ann Surg* 2007;245:886-92.
- [29] de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *J Antimicrob Chemother* 2011;66:398e407.
- [30] Catena F, Vallicelli C, Ansaloni L, Sartelli M, Di Saverio S, Schiavina R, et al. T.E.A. study: three-day ertapenem versus three-day ampicillin-sulbactam. *BMC Gastroenterol* 2013;13:76.
- [31] The APPAC Randomized Clinical Trial Paulina Salminen, Hannu Paajanen; Tero Rautio; Pia Nordström, Markku Aarnio, Tuomo Rantanen, Risto Tuominen, MPH, PhD; Saija Hurme, MSc; Johanna Virtanen, Jukka-Pekka Mecklin, Juhani Sand, Airi Jartti; Irina Rinta-Kiikka, Juha M. Grönroos.
- [32] Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)*. 2010;11(1):79-109.
- [33] Dixon MR, Haukoos JS, Park IU, et al. An assessment of the severity of recurrent appendicitis. *Am J Surg* 2003;186:718- 22.
- [34] Hoffmann J, Rolff M, Lomborg V, Franzmann M. Ultraconservative management of appendiceal abscess. *J R Coll Surg Edinb* 1991;36:18-20.
- [35] Poon RT, Chu KW. Inflammatory cecal masses in patients presenting with appendicitis. *World J Surg* 1999;23:713-6.
- [36] Sallinen V, Akl EA, You JJ, Agarwal A, Shoucair S, Vandvik PO, et al. Meta-analysis of antibiotics versus appendectomy for non-perforated acute appendicitis. *Br J Surg* Mar 17 2016.