

Safety and efficacy of antimicrobial versus surgical treatment in uncomplicated acute appendicitis in adults

Seguridad y eficacia del tratamiento antimicrobiano versus quirúrgico en apendicitis aguda no complicada en adultos

Jorge Luis López-Rodríguez,* Jesús Tapia-Jurado,‡
Carlos Martín Gaitán-Mercado,§ José Luis Medina-Chávez,¶
Valery Melnikov,|| Emilio Prieto-Díaz-Chávez**

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* Private practice,
Humanitas Medical
Group. Aguascalientes,
Ags., Mexico.

‡ Head of the
Postgraduate Simulation
Unit (USIP). Division
of Postgraduate Studies,
Faculty of Medicine,
National Autonomous
University of Mexico
(UNAM). President of
the Mexican Academy
of Surgery (2017/2018).
Mexico City, Mexico.

§ Director of Operations.
Centenario Hospital
Miguel Hidalgo.

ABSTRACT

Introduction: antibiotic therapy for acute uncomplicated appendicitis in adult patients has been proposed as a safe and effective alternative. **Objective:** to review the available evidence to assess the safety and efficacy of antibiotic treatment. **Material and methods:** a literature search in databases comparing antibiotic therapy and appendectomy was made to identify the most recent systematic reviews and meta-analyses with the results on the safety and efficacy of the intervention. **Results:** four systematic reviews with meta-analyses met the inclusion criteria. The antibiotic treatment group had a lower success rate, overall effectiveness, and complication rate. The rates of complicated appendicitis with peritonitis identified at the time of operation and surgical complications were equivalent in both groups. The appendectomy group had a higher success rate and treatment efficacy at 1-year follow-up. **Conclusions:** appendectomy is still the most effective treatment than antibiotic therapy for a definitive cure of acute uncomplicated appendicitis. Antibiotic therapy can be an alternative for those patients who wish to avoid surgery and do not have predictors of treatment failure.

RESUMEN

Introducción: el tratamiento conservador para la apendicitis aguda no complicada en el adulto se ha propuesto como una alternativa segura y eficaz. **Objetivo:** revisar la evidencia disponible para evaluar la seguridad y eficacia del tratamiento antibiótico. **Material y métodos:** mediante una investigación bibliográfica en bases de datos se identificaron las revisiones sistemáticas y metaanálisis más recientes que incluyen los resultados de la seguridad y eficacia de la intervención. **Resultados:** cuatro revisiones sistemáticas con metaanálisis cumplen con los criterios de inclusión. La evidencia muestra que el éxito del tratamiento conservador es significativamente menor, la eficacia del tratamiento en seguimiento a un año es mayor en el grupo control con menor cifra de recurrencia. La apendicitis complicada es similar entre grupos y las complicaciones postintervención son significativamente mayores en el grupo control. Las complicaciones quirúrgicas son similares entre grupos, al igual que el absceso postoperatorio, infección del sitio quirúrgico, obstrucción intestinal y hernia ventral. **Conclusiones:** la apendicectomía es un tratamiento invasivo sujeto a eventos adversos con un perfil de riesgo conocido, por lo que continúa como tratamiento estándar. La terapia con antibióticos puede considerarse como alternativa para los pacientes que desean evitar la cirugía y no tienen predictores de falla al tratamiento.



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Aguascalientes,
Ags., Mexico.

† Professor. Education
and Surgical Technique.
Faculty of Medicine of
the University of Colima.
Colima, Colima, Mexico.

‡ Full-time professor
and researcher. Faculty
of Medicine of the
University of Colima.
Colima, Colima, Mexico.

** Assistant Director.
Faculty of Medicine,
University of Colima,
Colima, Colima, Mexico.

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INTRODUCTION

Acute appendicitis (AA) is among the most common causes of acute abdomen. Worldwide, it affects 151 people per 100,000 inhabitants per year, mainly during adolescence, after which the incidence decreases as age increases. In older adults, it affects between 5 and 10%. The lifetime risk of the disease in men is estimated at 8.6 and 6.7% in women.¹

Disease severity is based on clinical presentation, imaging, and transoperative findings and is helpful for perioperative management. The World Association for Emergency Surgery (WSES) classifies it as uncomplicated and complicated, characterized by necrosis, phlegmon, perforation, and abscess formation.^{2,3} Distinctive histopathologic findings of simple AA include edema in the early stage and suppuration in the late stage. Appendiceal phlegmon, which is the formation of an inflammatory mass with peri appendicular pus, is considered by some authors to be complicated appendicitis.^{4,5} In complex or perforated AA, evidence of gangrene, perforation, localized or disseminated abscess, and extraluminal fecalith are recognized.^{6,7}

Appendectomy has been considered the mainstay of treatment for more than a century since Charles McBurney assumed that in the absence of surgery, the uncomplicated disease progresses to a complicated disease. Currently, it is a routine procedure; each year, more than 60,000 appendectomies are performed in our country, 50,000 in the United Kingdom and 300,000 in the United States, of which between 15 and 36% are negative or also called white,⁸ with a known risk profile: low mortality in uncomplicated AA that increases three to four times in the presence of complication.⁹ In the elderly patient, it can reach up to 8%.¹⁰ Postoperative morbidity varies between 2 and 23%.¹¹

It has been questioned whether the traditional treatment approach is appropriate given the number of negative appendectomies, surgical morbidity, and costs.¹² With this argument and others, antibiotic treatment (ABTx) has been proposed for patients with early and uncomplicated AA, similar to the management of other intra-abdominal

inflammatory processes such as colonic diverticulitis, acute cholecystitis, salpingitis, and, in children, enterocolitis.¹³ Recently, many clinical trials (RCT) have been published, with diverse methodologies and variable quality, comparing ABTx with appendectomy or surgical treatment (STx) and suggesting conservative management as a safe and effective alternative.¹⁴ This treatment modality is a matter of controversy in general surgery since it is a treatment modality that is not widely accepted. The objective is to review the best quality evidence available to answer the following question: what is the safety and efficacy of antibiotic treatment and appendectomy for uncomplicated AA in adults?

MATERIAL AND METHODS

Systematic reviews (SR), meta-analyses (MA), and systematic reviews with meta-analyses (SR/MA) comparing ABTx with STx in uncomplicated AA published in the period from 1999 to 2020 are identified through a bibliographic search in the Medline, ScienceDirect, Scopus, Google Scholar, and Cochrane Library databases, restricted to publications in Spanish and English. In both languages, the keywords in the search strategy are appendicitis / acute/ uncomplicated / treatment/antibiotic/adults. The selection criteria of publications for this work are the most recent ones that include the analysis of the primary and secondary results of the randomized clinical trials (RCTs) submitted for review in a complete way to extract the data of interest and document the evidence, which is helpful in the evaluation of the safety and efficacy of the intervention; i.e., success, failure and efficacy of treatment at one-year follow-up, recurrent appendicitis, complicated appendicitis, postoperative complications, mortality, postoperative complications, surgical site infection and postoperative abscess, bowel obstruction, and incisional hernia.

RESULTS

Bibliographic research

The database screening process for publication selection is shown in *Figure 1* and identifies

1,644 articles and 87 additional articles. The full texts of 48 SRs, MAs, and SR/MAs are reviewed after assessing the titles and abstract of the publications, and four SRs and SR/MAs published in 2019 met the inclusion criteria and are the evidence review material.¹⁵⁻¹⁸ They include 45 investigations, 31 practiced in adults, 12 in children, and two in a mixed population with majority adults; 27 are RCTs, 24 in adults; one quasi-RCT study in adults; seven retrospective studies, four in adults; and ten prospective cohort studies, four in adults. Each SR/MA assesses the risk of bias in each trial and is variable by variable criteria used for its qualification and different category. Five different intravenous (IV) and six oral (OV) ABTx schedules were used in the intervention, both for varying periods.

Characteristics of the publications selected for review

1. The study by Prechal et al.¹⁵ is an SR/MA that includes five RCTs performed in adults, selected for having a higher level of evidence, arguing that in previously published studies, the results and the level of possible bias differ. The heterogeneity among the studies is considerable, and in general, the risk of selection bias is

considered low, the risk of performance bias is unclear in all the studies, the risk of attrition bias is low, and the risk of reporting bias is high.

2. The publication by Poprom et al.¹⁶ is a double SR/MA, the traditional and one in a network, that evaluated treatment outcomes and risks and benefits of intervention by direct and indirect, individual or combined comparison of antibiotics with STx that examined the effects of treatments in a complete way, allowing to assess for each treatment the probability of being the best or having a range that can be derived from the posterior distributions of all treatments (surface under the curve). It includes nine RCTs, six in adults, one in a mixed population, and two in children. Overall, the risk of selection, outcome, and reporting bias is assessed as low. The table results correspond to the direct MA described in the RCTs.

3. The MA of Yang et al.¹⁷ compared the intervention results in managing complicated and uncomplicated AA. It included 11 studies, five RCTs, three retrospective, and three prospective, all rated with good methodological quality according to the Cochrane bias assessment tool. The data shown in the

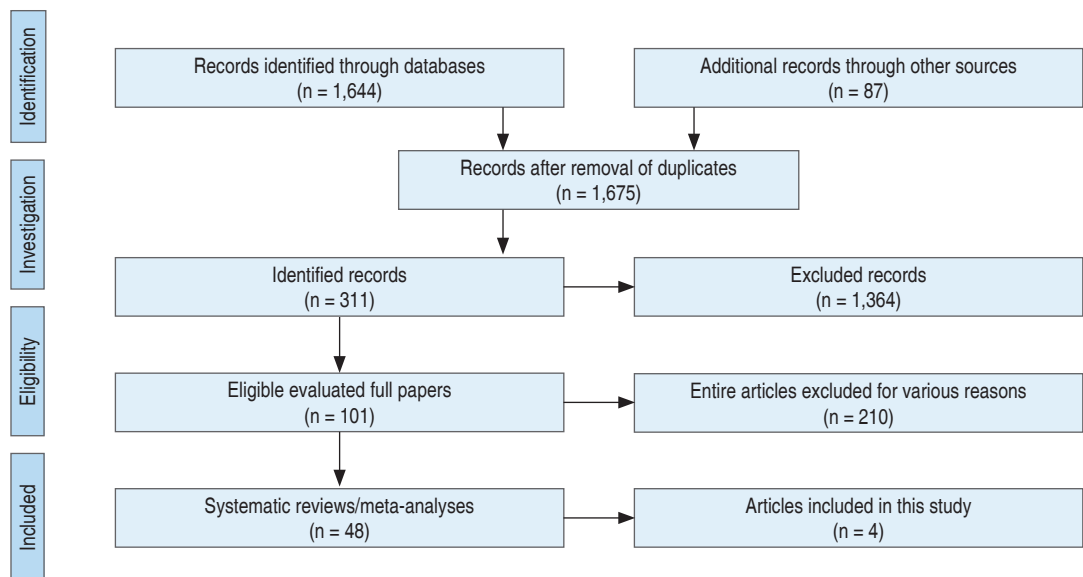


Figure 1: Flow chart of research and study selection.

Table 1: Efficacy of antimicrobial therapy versus appendectomy in uncomplicated acute appendicitis in adults.

Treatment efficacy	Prechal D, et al. ¹⁵		Poprom N, et al. ¹⁶		Yang Z, et al. ¹⁷		Podda M, et al. ¹⁸	
	ABTx (%)	STx (%)	ABTx (%)	STx (%)	ABTx (%)	STx (%)	ABTx (%)	STx (%)
Treatment success	NR	NR	0.68-0.88 NS, similar in groups*	NR	82.8	96.6	68.7	80.9
Treatment efficacy (1 year)	62.5	96.3	NR	NR	NR	NR	73.6	91.9
Treatment failure	NR	NR	NR	NR	NR	NR	8.5	NR
Recurrent appendicitis	NR	NR	18.2 Signif. higher in ABTx*	NR	5.6	NR	19.2	NR
Complicated appendicitis	NR	NR	2.7-35 No comment	NR	NR	NR	21.8	12.7
Post-intervention complications	17.9	10.2	NR	NR	10.3	NR	6.6	14.5
	Signif. lower in ABTx*				Signif. higher in STx*		Signif. higher in STx*	

* Commentary of the publication when comparing the results.

ABTx = intervention group, treatment with antibiotics. STx = control group, appendectomy. NR = No report. NS = Non significant.

tables reflect the results obtained in uncomplicated AA.

- Podda et al.¹⁸ published the most recent SR/MA, and its objective was to summarize the most current available evidence on non-operative management derived from 20 studies to have more sensitive results. It included ten studies practiced in adults, and ten in children, seven RCTs, one quasi-randomized study, eight prospective cohort studies, and four retrospective studies. The heterogeneity between studies was high, and the risk of bias was generally low; the risk is high in non-randomized trials. The results of this publication in the tables correspond to the adult group.

Treatment efficacy and safety results

Table 1 shows the results of treatment efficacy. Conservative treatment success was significantly lower in ABTx in one publication, not reported in another, and similar between research groups in the two. Treatment efficacy at 1-year follow-up was significantly higher in the control group in one publication, was like groups in another publication,

and was not described in two. Failure of conservative treatment, that is, during the initial hospitalization and within the first month of follow-up, is reported in only one publication and is 8.5%, an eventuality that does not occur in STx. Recurrent appendicitis was significantly higher in ABTx than in the control group. The finding of complicated appendicitis was similar between groups; one publication does not comment on this. The incidence of postoperative complications was significantly higher in STx in three publications.

Table 2 summarizes the results of treatment safety. None of the publications report mortality. Surgical complications were similar between groups and without significant difference in two publications, without comment in one, and not reported in another. A postoperative abscess was similar between groups, only described in one publication. Surgical site infection in the ABTx did not differ from the control group according to the report in one publication, no comment in another, and no description in two. Intestinal obstruction in the conservative group was similar to the surgical group, with no significant difference. The ventral hernia had a similar frequency between groups.

DISCUSSION

When evaluating the safety and efficacy of ABTx versus STx in uncomplicated AA, it is convenient to consider that two treatment strategies of different nature and not different surgical techniques are compared. Surgery is an invasive treatment subject to adverse events of various kinds that do not occur with conservative treatment.¹⁹ Furthermore, to determine the validity of the conclusions of RCTs, it is necessary to know their methodological quality since the benefits of treatment can be overestimated, and in SR/MA, the risk of bias increases when few RCTs are included.²⁰ Methodological inconsistencies include diagnostic and inclusion criteria variability, high crossover rates between research groups, small study populations that limit generalization to large populations, lack of standardized definitions of treatment success or failure, and recurrent disease. Heterogeneity between studies is noted in each SR/MA using various antimicrobial regimens, including drugs for varying periods, different routes, and a lack of comparative RCTs of antibiotics used as an intervention.^{4,13}

If the figure for treatment failure during the initial hospitalization and in the first month,

which is 8.5%, we add the recurrence during the first year of surveillance, estimated between 5.6 and 19.2%, the risk of experiencing a new episode of AA can be between 26.4 and 47.5%; of these patients, up to 42% will require surgery, which increases hospital readmission and the costs of care.^{13,21}

Most of the surgical procedures in the RCTs were performed with open surgery, more susceptible to infectious complications in whom postoperative antibiotics are not used in the presence of contamination. The studies do not report wound protection measures, peritoneal contamination control, drains use, and abdominal wall closure. Antimicrobial prophylaxis reduces the risk of surgical infection by 5 to 15%, not using it as a possible outcome bias in favor of conservative management.²²

The total cost of conservative management is approximately 5.5% higher than STx if one considers the extra expenses imposed on the conservative treatment group: follow-up consultations, repeated hospitalizations, additional surveillance procedures such as control computerized tomography (CT) scans, and colonoscopy in patients over 40 years of age, treatment of recurrence, and appendiceal neoplasia.²³ The rate of negative or non-

Table 2: Safety of antimicrobial therapy versus appendectomy in uncomplicated acute appendicitis in adults.

Safety of treatment	Prechal D, et al. ¹⁵		Poprom N, et al. ¹⁶		Yang Z, et al. ¹⁷		Podda M, et al. ¹⁸	
	ABTx (%)	STx (%)	ABTx (%)	STx (%)	ABTx (%)	STx (%)	ABTx (%)	STx (%)
Mortality	NR	NR	NR	NR	NR	NR	NR	NR
Surgical complications	13.3	14.4	NR	NR	NR	18.4	14.0	14.5
Post-operative abscess	NS, similar in groups*		NR	NR	No comment*		NS, similar in groups*	
Surgical site infection	5.8	6.6	NR	NR	NR	NR	0.9	1.9
Intestinal obstruction	No comment*		NR	NR	NR	NR	NS, similar in groups*	
Incisional hernia	NR	NR	NR	NR	NR	NR	3.2	3.9
							NS, similar in groups*	
							0	0.6
							NS, similar in groups*	

* Commentary of the publication when comparing the results.

ABTx = intervention group, treatment with antibiotics. STx = control group, appendectomy. NR = No report. NS = Non significant.

curative appendectomies is currently between 3 and 6%, attributed to the implementation of clinical practice guidelines incorporating imaging studies (ultrasound and CT scans) as part of the standard evaluation process and the routine use of laparoscopy.²⁴

A missing component in the safety profile of non-operative management is the risk of not recognizing other diseases, such as Crohn's disease or neoplasms. Appendiceal cancer comprises less than 1% of neoplasms of the gastrointestinal tract and is found in less than 2% of surgical specimens. Between 2000 and 2009, the incidence increased by 54%; a retrospective review of cases in one institution found 28% of incidental neoplasms in patients undergoing interval appendectomy.²⁵ Conservative treatment has been proposed as a valid short-term option for elderly patients with high surgical risk due to comorbidity.¹⁰ Although AA is rare in the elderly, patients over 65 are more likely than any other age group to have complicated appendicitis ranging from 18 to 70%,⁹ higher rates of postoperative complications such as surgical site infection and prolonged ileus, and prolonged hospital stay.²⁶

The antibiotics used in the RCTs are the subject of observations, criticisms, and risk signals we try to avoid. Among the most important observations are the low susceptibility and resistance of *E. coli* to amoxicillin and clavulanic acid, which make the scheme ineffective for treating gastrointestinal bacteria.^{13,27} The same observation is made for ampicillin/sulbactam, piperacillin/tazobactam and fluoroquinolones. Among the criticisms is the inappropriate use of antibiotics, especially carbapenems, due to widespread use and overprescribing, qualified as overtreatment, which promotes bacterial resistance and more incredible difficulty in controlling severe infections when they occur in patients with intra-abdominal infections and neutropenia.¹² The main risk to be avoided is bacterial resistance to multiple antibiotics, which the World Health Organization (WHO) has warned about due to the worldwide increase in infections caused by multidrug-resistant bacteria.⁴

The promoters of ABTx in uncomplicated AA have identified the predictors of treatment failure: age older than 45 years, symptoms

of more than 48 hours of evolution, mainly fever, the elevation of biochemical markers of inflammation such as C-reactive protein (CRP) and in a CT scan, demonstration of appendicular diameter greater than 15 mm, presence of fecalith, fluid or extraluminal air.^{28,29}

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Correspondence:

Jorge Luis López-Rodríguez, MD

E-mail: drjorgelopezrdz@live.com.mx