Are antibiotics a safe and effective treatment for acute uncomplicated appendicitis?- First update

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Abstract

Update

This Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in January 2016.

Introduction

Appendicitis is a typical cause of acute abdominal pain and the most frequent cause of emergency abdominal surgery. In the last two decades, increasing evidence has been published about the use of antibiotics as an exclusive treatment for acute appendicitis.

Methods

To answer this question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained through searches from multiple sources of information, including MEDLINE, EMBASE, Cochrane, among others. We extracted the data from the identified reviews, reanalyzed the data from the primary studies, performed a meta-analysis and prepared a summary of findings table using the GRADE approach.

Results and conclusions

We identified 23 systematic reviews including 28 primary studies, of which eight were randomized trials. We concluded the exclusive use of antibiotics for the treatment of uncomplicated acute appendicitis could be less effective than appendectomy, but it might be associated with a lower rate of complications.

About this update

This Living FRISBEE (Living Friendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in January 2016 (doi: 10.5867/medwave.2016.6375), based on 14 new systematic reviews including two new randomized trials not included in previous reviews. In addition, we added a trial that had not been previously incorporated into the analysis, and a trial previously incorporated was removed because it was retracted due to plagiarism. Finally, the outcome 'major complications'

was replaced by 'complications', since most identified systematic reviews analyzed this variable as the outcome of choice. The incorporation of this new evidence leads to a change in the direction of the effect on complications, and therefore to changes in the key messages and considerations for decision-making.

Problem

Acute appendicitis is a common cause of acute abdominal pain and the most frequent cause of emergency abdominal surgery, with an estimated life incidence between 7 and 14%[1,2]. Since the 1890s, when McBurney described early appendectomy as the therapy of choice for acute appendicitis[3,4], surgery has become the mainstay for the treatment of this condition, drastically decreasing its mortality rate[5].

The treatment of acute appendicitis with antibiotics as an initial strategy was historically reserved for patients with several days of evolution of the inflammatory process, who presented a plastron or appendicular abscess, to avoid major surgery[2]. In 1953, Harrison reported 42 out of 47 cases of acute appendicitis successfully treated with antibiotics only. Coldrey published in 1959 an article with 471 cases of acute appendicitis treated conservatively, with only one death, nine patients requiring abscess drainage and only 48 patients requiring appendectomy[6]. In the last two decades, the production of research on the use of antibiotics as an exclusive treatment for acute appendicitis has steadily increased, so it is important to synthesize the existing evidence.

Key messages

- The use of antibiotics for the treatment of uncomplicated acute appendicitis may be less effective than appendectomy and it might be associated with a longer hospital stay.
- The use of antibiotics for the treatment of uncomplicated acute appendicitis might be associated with fewer complications.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 23 systematic reviews[5-27] including 28 primary studies[28-55], of which eight are randomized trials[28-33,38,47]. We decided to exclude a trial[47] from the analysis as it was retracted from the journal that published it for plagiarism. This table and the summary in general are based on seven randomized trials[28-33,38], since the observational studies did not increase the certainty of the existing evidence, nor did they provide relevant additional information.
What types of patients were included*	All trials included patients with suspected acute appendicitis. Six trials[28-33] excluded children and one trial also excluded women[32]. One trial only included pediatric patients between 5 and 15 years old[38]. All trials based the suspicion of acute uncomplicated appendicitis on clinical criteria. Five trials ruled out complications by imaging, of which two[30,33] used computed tomography, two ultrasound[28,38] and one both ultrasound and computed tomography[31]. One trial resorted to ultrasound or computed tomography in some cases[29], and one trial did not use diagnostic imaging[32].

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

What types of interventions were included*	Six trials used intravenous antibiotics as the initial treatment, of which one did so for 24 hours[29], three for 48 hours[28,32,38] and two for 72 hours[31,33]. Of these, two trials used cefotaxime associated with tinidazole[28,32], one used cefotaxime associated with metronidazole[29], one used ampicillin associated with gentamicin and metronidazole[31], one used meropenem associated with metronidazole[38] and one used ertapenem[33]. The remaining trial[30] used intravenous amoxicillin with clavulanic acid only if the patient presented nausea or vomiting and for a time that was not specified. All trials continued the treatment using oral antibiotics. One trial completed eight days[30] and six completed ten days[28-33,38]. During the oral phase, two trials used the combination of ofloxacin with tinidazole[28,32], two used ciprofloxacin with metronidazole[29,38], one used levofloxacin with metronidazole[33], one used amoxicillin with clavulanic acid[30] and one trial did not specify the antibiotic used orally[31]. All trials compared antibiotic treatment against surgery. Two trials performed open appendectomy[28,33], one performed only laparoscopic appendectomy[38] and the remaining four trials performed the procedure open or laparoscopic according to surgeon's preference[29-32].
What types of outcomes were measured	The trials measured multiple outcomes, which were pooled by the systematic reviews as follows: • Effects of the treatment, defined as absence of symptoms within two weeks, without major complications or recurrences within a year. • Complications, such as perforations, superficial and deep surgical wound infections, incisional hernias, intestinal obstruction, diarrhea, abdominal discomfort or death. • Recurrences. • Duration of hospital stay.Time needed to return to work. All trials followed their patients up to 12 months.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

Summary of findings

The information on the effects of antibiotics or surgical treatment for uncomplicated acute appendicitis is based on seven randomized trials[28-33,38] that included 1770 participants, of whom 858 were initially treated with antibiotics and 912 with appendectomy. All trials reported treatment efficacy, complications and hospital stay.

The summary of findings is the following:

- The use of antibiotics for the treatment of uncomplicated acute appendicitis might be less effective than appendectomy, but the certainty of the evidence is low.
- The use of antibiotics for the treatment of uncomplicated acute appendicitis might be associated with fewer complications than appendectomy, but the certainty of the evidence is low.
- The use of antibiotics for the treatment of uncomplicated acute appendicitis might be associated with a longer hospital stay than appendectomy, but the certainty of the evidence is low.

Antibiotics versus appendectomy for uncomplicated acute appendicitis

Patients Adults with acute uncomplicated appendicitis
Intervention Antibiotic treatment
Comparison Appendectomy

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITH appendectomy	WITH antibiotics		
	Difference: patients per 1000			
Treatment efficacy	961 per 1000	682 per 1000	RR 0.71 (0.62 to 0.81)	⨁⨁◯◯[1,2] Low
	Difference: 279 patients less (Margin of error: 182 to 365 less)			
Complications	146 per 1000	79 per 1000	RR 0.54 (0.34 to 0.86)	⨁⨁◯◯[1,2] Low
	Difference: 67 patients less (Margin of error: 20 to 96 less)			
Hospital stay	2.72 days	3.13 days	--	⨁⨁◯◯[1,2] Low
	MD: 0.41 days more (Margin of error: 0.05 days less to 0.86 days more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk WITH appendectomy is based on the risk in the control group of the trials. The risk WITH antibiotics (and its margin of error) is calculated from relative effect (and its margin of error).

[1] A level of certainty of evidence was downgraded because of risk of bias in the trials.
[2] A level of certainty of evidence was downgraded due to inconsistency of results between trials.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The conclusions of this summary are applicable to adult patients with uncomplicated acute appendicitis.

These conclusions do not apply to patients presenting complicated acute appendicitis (perforation, appendiceal abscess, peritonitis, gangrene or others), since these have a different clinical course and treatment indications compared to acute uncomplicated appendicitis.

The conclusions of this summary are not applicable to children since they were poorly represented in the trials.

About the outcomes included in this summary

The selected outcomes were those considered critical for decision-making according to the authors of this summary, which agrees with those selected by most systematic reviews identified.

Balance between benefits and risks, and certainty of the evidence

Antibiotic treatment in uncomplicated acute appendicitis is a plausible and safe option as an initial intervention, considering that it could be associated with a lower risk of complications and avoid a surgical intervention on the patient. On the other hand, this therapy could be less effective and be associated with a longer initial hospital stay. Considering there is still uncertainty regarding the advantages of antibiotic therapy, the risk/benefit balance continues to lean towards appendectomy as the standard treatment.

In well-selected patients, with absence of complications confirmed by computed tomography and with high surgical risk, the risk/benefit balance could be tilted in favor of antibiotic treatment[2,56].

Resource considerations

The use of antibiotics is less expensive than surgery and does not require trained personnel.

Most systematic reviews and published trials have not evaluated resource considerations.

There is at least one study that directly evaluated costeffectiveness of antibiotics versus appendectomy[57]. It took effects data from a meta-analysis[17], trials[29-32] and observational studies[35,37,42,44], and it correlated them to costs obtained from a US database[58]. They concluded that in patients effectively treated with antibiotics (so, did not present recurrent appendicitis requiring appendectomy), the costs were reduced by more than 10,000 US dollars. On the contrary, when the initial antibiotic treatment required a subsequent surgical intervention, the cost per patient increased by more than 4,000 USD. Based on these data, the authors suggested antibiotics would be the most costeffective intervention when the recurrence rate is below than 40%.

Since there is uncertainty about the effectiveness of antibiotics compared with appendectomy for uncomplicated acute appendicitis, it is not possible to make an adequate costeffectiveness balance.

What would patients and their doctors think about this intervention

Faced with the evidence presented in this summary, some patients and health providers may prefer antibiotic treatment over appendectomy. However, this approach still has not permeated routine clinical practice [59] for various reasons, including the preference for definitive therapy, the infeasibility of obtaining computed tomography scans in all patients and the fear of health providers of eventual litigations in case of complications when using antibiotic therapy. Appendectomy is still considered the therapy of choice for this condition, and antibiotic therapy is reserved for selected cases.

Some clinical centers are opting for a pragmatic management in which patients are treated with antibiotherapy for 24 to 48 hours, after which it is continued if the patient is improving or appendectomy is performed if the patient is deteriorating[14].

Differences between this summary and other sources

The conclusions of this summary in terms of effectiveness and hospital stay are concordant with the systematic reviews identified and with a recent overview of reviews[56].

Regarding complications, most reviews[10,14,16,-18] agree that antibiotic therapy could be associated with a lower rate of complications.

On the other hand, a systematic review[23] that only included three trials found the number of peritonitis and abscesses were greater in those treated with antibiotics. Another[26] considered that the evidence was of very low certainty, and there were no differences when conducting a sensitivity analysis. In addition, a Cochrane review[5] used the composite outcome 'major complications' and found they were higher in the antibiotic group. This outcome included, in addition to the complications reported by the trials, recurrences and the increase in hospital stay. At least one additional review[16] has analyzed the outcome 'major complications', and included perforation, deep infection, incisional hernia, intestinal obstruction and death and found no significant differences between the groups.

The reviews that evaluated this question in pediatric population also considered antibiotic therapy as an optional treatment according to patient's particular circumstances, but more trials are necessary before conclusions of greater weight are given.

The main clinical guideline on this topic[60] states appendectomy continues to be the treatment of choice for acute appendicitis, agreeing with the results presented in this summary. It states that the use of antibiotic therapy can be safe as an initial intervention in patients with uncomplicated acute appendicitis, as long as absence of complications are certified through computed tomography, but that it is less effective in the long term due to significant recurrence rates.

Could this evidence change in the future?

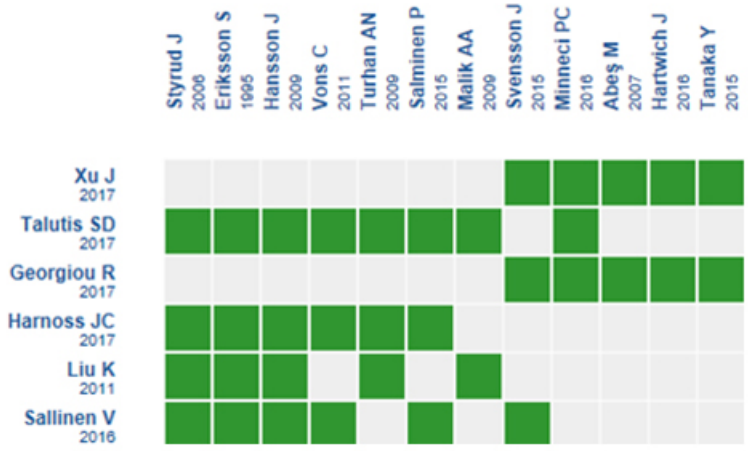
The Due to the existing uncertainty, the probability that future trials change the conclusions of this summary is high.

There are at least two published randomized trials not included in any systematic review identified[61,62].

At least nine randomized trials are ongoing, of which six evaluate this question in adults[63-68], two in children[69,70] and one in children and adults[71]. In addition, there is a registered trial whose status and results are unknown[72]. Finally, at least three systematic reviews are in progress[73-75].

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Antibiotics versus appendectomy for uncomplicated acute appendicitis.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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