

Is amoxicillin plus clavulanic acid non-inferior to appendicectomy for the treatment of uncomplicated acute appendicitis?

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Background

Urgent appendectomy is still considered the gold standard treatment for patients with acute appendicitis. Although it is well tolerated by most patients, it can be associated with postoperative complications in a significant number of individuals: small bowel obstruction requiring surgical intervention occurs in 3% of patients undergoing appendectomy over 10 years [1]. Furthermore, more than 15% of individuals with suspected acute appendicitis have a normal appendix at laparotomy, with a higher percentage in infants, young women and elderly patients [2]. It is still unclear if the use of diagnostic imaging reduces the frequency of unnecessary appendectomy. Therefore, in recent years there has been increased interest in antibiotic therapy as the primary treatment for acute appendicitis. Previous randomized trials comparing antibiotic therapy with emergent appendectomy conclude that acute appendicitis can be successfully treated with antibiotics [3, 4]. However, protocol design limitations of these studies weaken the relevance of their results. Consequently it is still unclear whether antibiotics are a valid alternative to surgery for patients with acute uncomplicated appendicitis.

Summary

The study by Vons et al. [5] is an open-label, non inferiority, randomized controlled clinical trial comparing antibiotic therapy and appendectomy for the treatment of uncomplicated acute appendicitis. 243 adult patients presenting to the emergency department (ED) with uncomplicated acute appendicitis as assessed by abdominal computed tomography (CT scan) were enrolled at 6 university hospitals in France. They were randomized to receive either amoxicillin/clavulanate for 8–15 days or emergency appendectomy. Follow-up at 8, 15, 30, 90, 180 and 360 days was carried out. The primary endpoint was the occurrence of peritonitis within 30 days of treatment. Study outcomes were assessed by both intention to treat and per protocol analysis. Antibiotic treatment was considered non-inferior to appendectomy if the upper limit of the two-sided 95% confidence interval (CI) for the difference in rates was lower than 10 percentage points.

Four patients refused to participate after randomization. Considering the 239 patients belonging to the intention to treat population, 119 were allocated to emergency appendectomy group and 120 to antibiotic treatment group. 30-day post-intervention peritonitis was significantly more frequent in the antibiotic group than in the surgery one. The treatment difference was 5.8% (95% CI: 0.3–12.1%) showing that antibiotics were not non-inferior to urgent appendectomy for the treatment of acute appendicitis. 204 patients constituted the per-protocol population, which included all patients who completed the study (1 year), and for whom the second reading of the CT scan confirmed the diagnosis of uncomplicated appendicitis. Even in this population a treatment difference of 6.0 percentage points (95% CI: 0.3–12.5%) showed that antibiotics were not non-inferior to urgent appendectomy for the treatment of acute

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appendicitis. No significant difference was identified between the two groups for secondary endpoints (duration of severe pain, duration of hospital stay and absence from work).

Considering the surgical group, 21 (18%) of 119 patients had a complicated appendicitis with peritonitis identified at surgery despite CT-scan findings. On a logistic regression model the presence of stercolith on a preoperative CT scan was the only factor associated with an increased risk of complicated appendicitis in this group of patients ($p < 0.0001$).

In the antibiotic group, 14 (12%) of 120 patients had no improvement with treatment and underwent appendectomy within the first month. Nine of them were identified to have a complicated appendicitis at surgery. The presence of a stercolith on CT scan was the only factor associated with failure of antibiotic treatment for appendicitis on a logistic regression analyses ($p = 0.0072$).

Strengths of the study

- This study addresses a clinical relevant issue.
- Good internal validity. In this study, the diagnosis of uncomplicated acute appendicitis was confirmed by a CT-scan assessment in all the patients. On the contrary, in previous investigations the diagnosis was based on clinical findings, and was not supported by diagnostic imaging.
- Protocol design was clear and well conducted: all the patients were monitored with close follow-up visits and clear criteria of clinical assessment.
- A sensitivity analysis was performed to establish the effect of missing cases.

Weakness of the study

- External validity: systematic performance of urgent CT scan to confirm the diagnosis of acute appendicitis is not a common procedure. Consequently, inclusion criteria of the present study may have selected a population that does not reflect the spectrum of individuals presenting for suspected acute appendicitis in most EDs.

Question marks

- It would be interesting to know the clinical probability of acute appendicitis in the present population. These data were not reported.
- It is not clear why an appendiceal diameter greater than 6 mm and no opacification of the appendix have been

considered as the only CT-scan diagnostic criteria for acute appendicitis in this study. It has been recently shown that the use of appendiceal diameter is often unreliable for the diagnosis of acute appendicitis, and should be interpreted in the context of other CT findings (appendiceal wall thickening, wall hyperenhancement, periappendiceal fat stranding) [6].

Sponsorship

- The study was funded by the French Ministry of Health. The sponsor had no role in the study design, data collection, data analysis or writing of the report.

Clinical bottom line

The results of this study do not provide evidence to support the use of antibiotics as a valid alternative to urgent appendectomy for the treatment of uncomplicated acute appendicitis. However, since the majority of patients allocated to antibiotics did not need an urgent appendectomy during the 1-year follow-up, future efforts should be directed at identifying a population at low risk of complicated appendicitis who may benefit from antibiotic treatment. Use of clinical and radiological predictors of complicated acute appendicitis may allow selection of such a subset of patients.

Conflict of interest None.

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