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**Protocol**

# A randomized clinical single-center trial comparing antibiotics to surgery for the treatment of computed tomography-uncomplicated acute appendicitis in adults: the Kouba non operative management of acute appendicitis trial protocol

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## ABSTRACT

**Background:** Several Western studies support the idea that some acute appendicitis (AA) can be successfully treated by antibiotics. The rationale for the non-operative treatment is essentially based on the non-futility of the vermicular appendix which seems to play a major role in the pathophysiology of the digestive tract. However, this approach still suffers from a failure rate of around 20-30% in the first year, rising to nearly half of patients within 5 years. In Algeria, appendectomy is still the standard of care. Through rigorous selection, the Kouba non operative management of acute appendicitis (KNOMA) trial aims to determine whether non-operative treatment (NOT) is non-inferior to surgery.
**Methods:** KNOMA is a randomized, controlled, non-inferiority trial designed to enroll 180 adults with CT-confirmed uncomplicated AA. Participants are randomized to appendectomy or 9 days of antibiotics (Abx). The primary endpoint is the failure rate at 12 months. This trial was designed to take into account the specifics of the Algerian population and practices in Algeria.
**Conclusions:** This is the first trial in Africa and middle-income countries to evaluate the comparative efficacy of antibiotics and appendectomy for the treatment of CT-confirmed uncomplicated acute appendicitis based on failure rate assessment.
**Trial registration:** This trial was registered on pactr.org on 28 March 2022 (PACTR202203751640059).

**Keywords:** Acute appendicitis, Appendectomy, Antibiotic therapy, Non operative management

## INTRODUCTION

Acute appendicitis is the most common cause of acute abdominal pain but also the most frequent surgical emergency with an estimated incidence of about 1/1000 person-years.[1] The lifetime risk of acute appendicitis in males is 8.6 and 6.7% in females.[2] Appendectomy, by laparotomy or laparoscopy, is still the standard treatment for AA; with over 300,000 procedures performed each year in the United States.[3,4] However, the best treatment is still debated, at least for uncomplicated AA.[5] For a long time, perforation was considered as the ultimate outcome of AA; motivating appendectomy. Data have come to clarify the role of the appendix, providing the rationale for conservative treatment. NOT has been evaluated through several recent trials and meta-analyses.[6-14] Despite its significant recurrence and failure rate, NOT does not seem to increase the risk of

appendicular perforation.[10,15] In addition, NOT, compared to appendectomy, appears to be associated with less morbidity, lower cost of care and quality of life preservation.[11,16-18] Although the non-inferiority of the NOT has still not been established, it seems to be as interesting as reasonable alternative for the management of CT scan-confirmed uncomplicated AA.[11,14,19] Strict patient selection would certainly improve the success rate.

### *Rational*

A number of arguments have been advanced to support the non-operative approach. For a long time, it was believed that the vermicular appendix in the human being had no significant function. But recent studies suggest otherwise. In fact, the appendix would be able to produce stem cells with properties of differentiation in highly specialized cells.[20,21] On the other hand, the incidence of uncomplicated appendicitis appears to correlate with the rate of negative appendectomies, suggesting a spontaneous resolution for many AA; and thus supporting the concept that perforated appendicitis and non-perforated one might be two completely distinct entities.[22] Moreover, despite the fact that appendectomy is a well-standardized procedure and the considerable progress in anesthesia-intensive care, this surgery is still associated with a non-negligible morbi-mortality.[22] Indeed, appendectomy is burdened with short-term complications, delayed return to work, and long-term morbidity such as bowel obstruction up to 10.7%.[23-25] The rate of negative appendectomy remains high, with a significant proportion of patients having no inflammation on histology.[26] The overall cost of managing these negative appendicitis was estimated at $741.5 million.[27] Therefore, the NOT could be part of a resource preservation policy, especially during the covid-19 pandemic, which has put a heavy strain on health care facilities worldwide.[28] So far, no western trial has been able to demonstrate the non-inferiority of antibiotics compared to surgery in terms of failure rate. The research question discussed is briefly summarized in Figure 1. The purpose here is to describe the design of the Kouba Non Operative Management of Acute Appendicitis (KNOMA) trial and justify the design elements included in the study.

**Research question:** Are antibiotics not inferior to surgery in the treatment of uncomplicated acute appendicitis in adults?

**Population:** Adults between 15 and 65 years old, with a CT confirmed uncomplicated acute appendicitis.

**Intervention:** Patients are randomized to receive either antibiotics or appendectomy.

**Comparison:** Percentage of patients who underwent surgery in the antibiotics group compared to the percentage of patients who were re-operated for complications in the surgery group.

**Outcome:** Failure rate in randomized treatments.

**Time:** Outcome is measured during the entire 12-month follow-up period.

**Figure 1: KNOMA research question.**

### *Objectives*

*Primary objective*

Through rigorous patient selection, the main objective of the KNOMA trial, which is clearly the first African clinical trial in the field, is to demonstrate the non-inferiority in terms of overall failure of the antibiotic therapy compared to appendectomy in the treatment of acute uncomplicated appendicitis in adults.

*Secondary objectives*

The secondary objectives are to estimate the rate of recurrence in the Abx group, to estimate the readmissions rate, to evaluate pain intensity on day 1, to assess the amount of analgesics required during hospitalization, to assess postoperative morbidity, to assess length of hospital stay, to assess duration of physical disability, to estimate overall cost of care, to assess the satisfaction level at 12 months and to evaluate the quality of life at 12 months

## METHODS

### *Trial design*

The study known as KNOMA is an open label, non-inferiority randomized single-centre controlled trial, comparing antibiotic therapy to surgery for the treatment of uncomplicated AA. The study will be conducted in a university hospital in Algiers (Algeria). The feasibility of the trial should be ensured, in terms of recruitment and good clinical practices. The study was approved by the local ethical committee. Patient enrolment started in April 2022 and is expected to end in April 2024; Kouba university hospital is the study sponsor. The trial design is summarized in Figure 2.

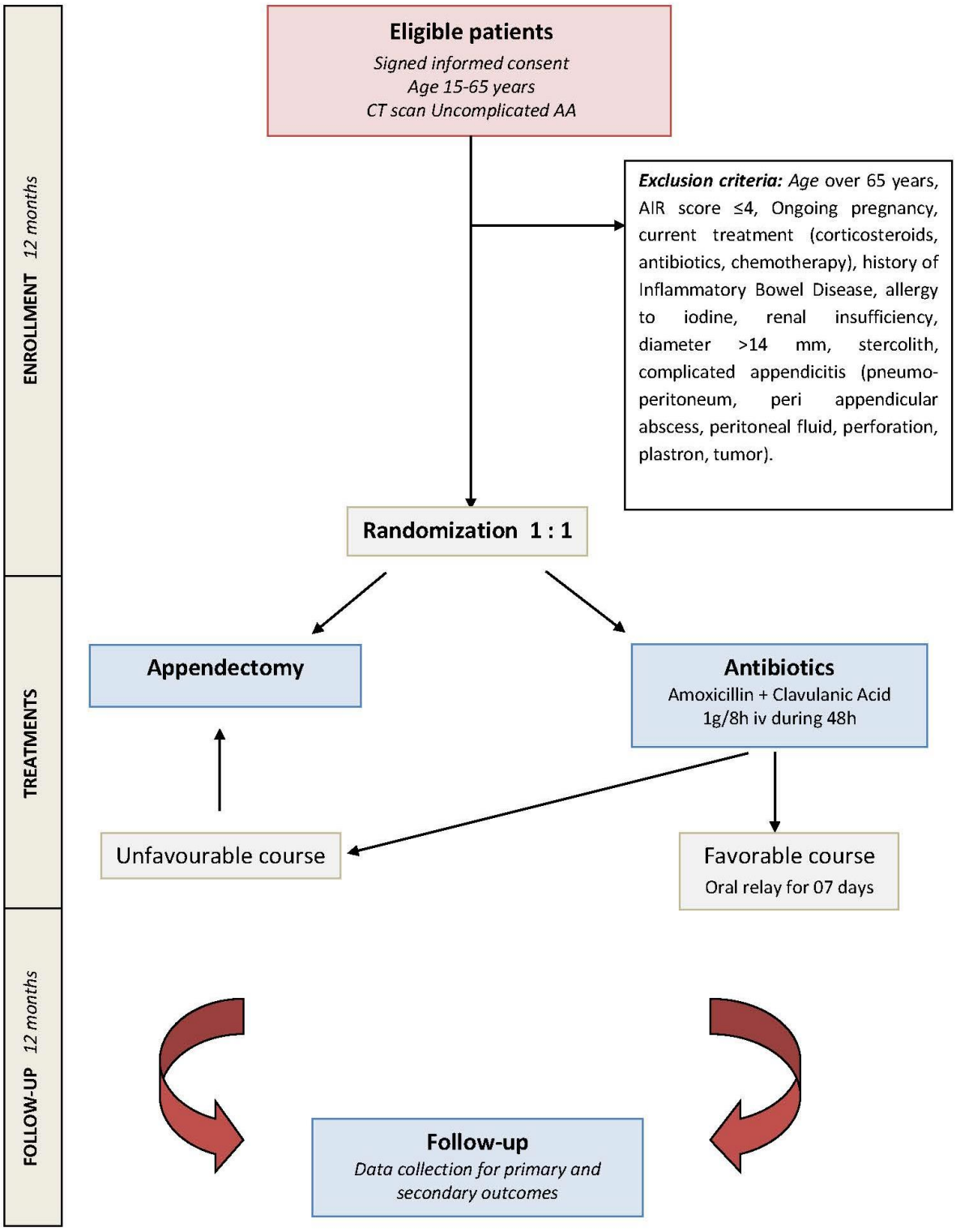


**Figure 2: KNOMA trial design.**

***Eligibility criteria***

All adults who consult the emergency department with acute appendicitis will be assessed for eligibility according to predefined criteria for eventual inclusion in the trial. At the end of the clinical and biological exams, the AIR (Appendicitis inflammatory response) score is calculated in order to decide on a radiological exploration.[29,30] An injected abdominal CT scan will be performed in all patients with a score ≥ 5 in order to rule out any AA in its complicated form. Eligible patients will be informed of the protocol and invited to participate in the study. Once the informed consent form has been read, approved and signed, patients will be randomized

between antibiotic treatment and surgery. The key inclusion criteria are male or female, aged 15-65 years, diagnosed with acute uncomplicated appendicitis whose diameter varies from 6 to 14 mm, confirmed by an injected CT scan. Also, the AIR score must be greater than or equal to 5. Will be excluded from the study, all patients over 65 years old, having a complicated acute appendicitis (stercolith, peri-appendicular abscess or intraperitoneal fluid, perforation, pneumoperitoneum, tumor suspicion), with a diameter larger than 14mm and an AIR score ≤4. Furthermore, history of inflammatory bowel disease (e.g., Crohn's, ulcerative colitis), ongoing treatment (e.g., Corticosteroid, antibiotics or chemotherapy), pregnancy in progress, Immunodeficiency, renal insufficiency (creatinine clearance <30 ml/min), severe allergy to iodine or to all proposed antibiotics, and refusal to participate are considered as exclusion criteria.

***Randomization***

The KNOMA trial is an unblinded study as participants will know their treatment. Patients who meet the eligibility criteria are randomized to receive either Abx or appendectomy. The randomization is performed in 1:1 equal allocation ratio to ensure an adequate comparison of the two groups, an identical number of participants in each group and to reduce variability. Permuted blocks of variable size (random block sizes of 4 and 6 participants) will be used. Allocation is determined by the holder of the sequence who is situated off site.

***Intervention***

*Antibiotic therapy*

NOT consists of intravenous antibiotic therapy with amoxicillin and clavulanic acid 3 gm per 24 hours or céfotaxime 1 g/8 h and metronidazole 500 mg/8h (depending on availability).[31] In case of allergy to Betalactam, ciprofloxacin 200 mg/8 h will be administered. At the term of the 48 hours of hospitalization, and in case of improvement of the clinical and biological signs; in other words, apyrexia, pain and abdominal defense attenuation as well as a decreasing WBC and CRP cinetics, the patient will be discharged with a per oral antibiotic relay during 7 days.

*Surgical treatment*

It consists in appendectomy by laparotomy or laparoscopy. An antibiotic prophylaxis (Cefotaxime 2 gm IV) will be given 30 minutes prior to the incision. Patients in the surgery group will receive no further antibiotics in the absence of postoperative septic complications; and will be discharged after 24 hours. All appendectomy specimens will be examined histo-pathologically, and appendicitis will be confirmed by neutrophil infiltration of the muscularis.

During their hospital stay, all patients will be examined twice daily. For patients treated with antibiotics, if there is no clinical improvement (fever, pain and/or RIF defense) during the first 48 hours, then appendectomy will be indicated. Beyond 48 hours, patients are invited to come to the emergency department for any symptoms recurrence (fever, RIF pain), which will be subject to a clinical, biological (WBC, CRP) and radiological (CT scan) re-evaluation in order to decide either to renew the antibiotic therapy for 7 additional days in the absence of complications on the CT scan (perforation, abscess, intra peritoneal fluid effusion, pneumoperitoneum); or to undergo an appendectomy, if necessary. After renewal of the antibiotic treatment, any new recurrence of the symptomatology will lead to an appendectomy without radiological re-evaluation (CT scan).

***Outcomes***

*Primary end-point*

*Failure rate of the randomized treatment:* defined as the number of patients operated on (Abx group) or reoperated on (Appendectomy group) for postoperative complications (peritonitis, intestinal obstruction, incisional hernia) during one-year follow-up.

*Secondary end-point*

*Recurrences rate:* defined as the number of patients with a recurrence of acute appendicitis in the Abx group during 1-year follow-up.

*Readmission rate:* number of re-hospitalizations for recurrence or complications.

*Pain intensity on day 1:* defined as the mean of the VAS values calculated on day 1.

*Quantity of analgesic received:* mean in grams of analgesic received during hospitalization.

*Morbidity rate:* number of postoperative complications according to the Clavien-Dindo classification.[32]

*Length of hospital stay:* number of days in hospital.

*Duration of physical disability:* number of days the patient is unable to carry out daily activities.

*Overall cost of care:* All related costs will be estimated in Algerian dinars (DA) on the basis of actual resource and person use during the 12-month follow-up period after randomization.

*Satisfaction level at 12 months:* by asking patients to rate their satisfaction on a five-point scale (very satisfied, satisfied, indifferent, unsatisfied, and very unsatisfied). Patients will also be asked if they would opt for the same

therapy again knowing the course and outcome of the treatment.

*Quality of life at 12 months:* using the validated EQ-5D-5L questionnaire (version 3.0 Updated September 2019; EuroQOL).[33]

***Sample size calculation***

This study will be based on the hypothesis that antibiotic therapy would not be inferior to appendectomy in terms

of failure rate. Taking into account a failure rate after appendectomy for uncomplicated appendicitis of 1% and a non-inferiority margin of 15%, meaning that the higher limit of the failure in antibiotic therapy would be 16%, we calculated that a sample size of 90 patients per group would give a power of 0.8 (1-β) to establish whether antibiotic treatment was not inferior to appendectomy (significance level of 0.05 α).[10] The lost to follow-up rate was estimated at 10 percent. For the secondary endpoints, the data will be compared as in a superiority trial, so a two-sided $p \leq 0.05$ will be considered statistically significant. Data will be analyzed on an intention-to-treat basis, but both intention-to-treat and per-protocol analyses will be performed.

***Follow-up***

The inclusion period will be for 12 months, and all patients will be followed up for at least 12 months, through outpatient visits under the responsibility of an attending surgeon other than the principal investigator, according to a predefined schedule (Table 1). Patients will be evaluated clinically and biologically (WBC, CRP). Phone calls from the investigating center are scheduled between visits to ensure their health status. These regular phone calls represent a retention program to minimize the number of the patients lost to the follow-up.

**Table 1: Schedule of visits.**

| Variables | V0, 48H | V1, day 7 | V2, day 30 | V3, day 90 | V4, day 180 | V5, day 360 |
|---|---|---|---|---|---|---|
| **Pain (VAS)** | x | x | x | x | x | x |
| **Physical exam** | x | x | x | x | x | x |
| **WBC** | x | x | x | x | x | x |
| **CRP** | x | x | x | x | x | x |
| **US or CT scan** | Unless there is a complication | | | | | |
| **Satisfaction** | | | | | | x |
| **Quality of life** | | | | | | x |

***Data management***

Data will be collected prospectively on observation forms specially designed for the trial (CRF). The principal investigator will have to collect and check the forms during the monitoring visits. Data entry will be done along the course of the study as visits are made. The investigator will be responsible for the validity of the data reported on the CRF in relation to the source documents. Corrections to the CRF may only be made by the investigator or by other authorized persons. The data will be entered after verification and validation in order to constitute a clean and quality database. SPSS software (IBM SPSS statistics 22) will be used to build the database, which must comply with the CRFs. The database will be frozen when all data have been entered. At that point, the statistical analysis can begin.

***Monitoring***

An independent specialist in epidemiology and public health will monitor the study. All original data, including all patient records, progress notes, and copies of medical and laboratory test results, will be available for monitoring. Approximately 20% of CRFs and written informed consents will be monitored. Documentation of each site visit will be submitted to the ethics committee. The data will be checked for accuracy by reviewing the above documentation.

***Safety and reporting of adverse events***

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational intervention. All adverse events (AEs) reported spontaneously by the subject or the staff will be collected, fully investigated and reported in the CRF during the entire study period. Aes will be reported to the principal investigator within 24 hours of their detection. If an AE is considered unexpected and related to the study intervention, the principal investigator will submit a report to the ethics committee within three days. This includes the event dates, treatment, resolution, severity rating, and causal relationship to the intervention. In the case of significant differences in Aes between groups, a report will be submitted to the local ethics committee and the trial may be stopped by decision of the principal investigator for unsafety. An interim analysis to ensure safety of the antibiotic treatment will be performed after randomizing 90 patients. The KNOMA trial does not have a stopping rule if non-inferiority is shown before the required number of participants are fully enrolled or if it is determined that non-inferiority cannot be demonstrated in

the interim analysis. This is due to the importance of secondary outcomes requiring full recruitment.

### *Statistical analysis*

Baseline demographics, pre-, and postoperative, as well as follow-up data will be compared separately for each group. The analysis will be performed both on an intention-to-treat and per-protocol basis, by an independent statistician after completion of the study. The primary endpoint (Failure rate) will be compared between the two groups using the Pearson chi-square test. As for the secondary outcomes, continuous and categorical variables will be respectively analyzed using the Student t test (or Mann-Whitney U test) and the chi-square test (or Fisher exact test). A two-sided $p<0.05$ will be considered significant.

### *Ethics and dissemination*

This study will be conducted in accordance with the Helsinki declaration and the "good clinical practice" guidelines.[34] The study protocol has been approved by the medical ethics committee of the Kouba university hospital. Each patient or his or her legal guardian will be explained the nature of the study, its purpose, the clinical, biological and radiological procedures, the expected study duration, the potential benefits and the risks involved. Each participant will be informed that participation in the study is completely voluntary and that he or she may withdraw from the study at any time without affecting his or her therapeutic management. Prior to CT evaluation and randomization, written informed consent will be obtained from all patients. The trial protocol has been drafted in compliance with the CONSORT recommendations and SPIRIT guidelines.[35,36] The results of the study will be presented at national and international conferences in the areas of interest. Written publication of the results is planned in a peer-reviewed medical journal. Authorship for written publications must be confirmed by all principal investigators and will only be granted in the case of substantial contributions as stipulated by the international committee of medical journal editors.[37]

## DISCUSSION

The KNOMA study is a prospective single-center randomized non-inferiority trial comparing surgery to Abx in the treatment of uncomplicated AA. In the light of literature data, we wished to conduct this clinical trial in order to determine the real potential of this non-operative approach under local conditions and in a population different from that of previous published studies. This trial was designed to answer the question: is NOT non-inferior to surgery in terms of failure rate. We hypothesize that with careful patient selection, we could decrease both the failure and recurrence rates of NOT. In this trial, we were inspired by previous experiences, particularly in terms of eligibility criteria.[6-11] Therefore, the age limit will be set at 65 years old; given that elder age appears to be a risk factor for not only recurrence of appendicitis, but also for appendicular neoplasm.[38] Flum et al, found appendiceal neoplasm in seven patients in the appendectomy group and four in the Abx group who had surgery.[11] Consequently, all of our participants receiving Abx therapy will be informed of this potential risk. The AIR score developed by Andersson et al, is much more accurate at predicting AA than the Alvarado score, and will be broadly used to order imaging.[29,39] For enhanced recognition of uncomplicated cases, CT with its high sensitivity and specificity, is the preferred test.[19] As in the last three RCTs, all patients will be selected based on CT scan before any randomization.[9-11] Knowing the high correlation between stercolith and complicated appendicitis, we considered it as an exclusion criterion.[9] More recently, in the CODA trial, the authors showed that the risk of NOT failure was three times higher in the presence of a stercholith within the first 48 hours HR=2.9 (95% CI, 1.9-4.4).[11] Because of its availability and simplicity of use, we opted for Amoxicillin-clavulanic acid as did Vons et al.[9]

## CONCLUSION

Finally, here are the expected benefits of this study: 1. Identify the best profile of candidates who will benefit the most from antibiotic treatment. 2. Conserve an organ which plays a major role in the pathophysiology of the digestive tract. 3. Reduce operative morbidity and cost of care and 4. Preserve resources, both human and material; especially in particular situations that may put a strain on the health care system, as was the case during the COVID-19 pandemic.

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