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CLINICAL STUDY PROTOCOL

A prospective non-randomized controlled, multicenter trial comparing Appendectomy and Conservative Treatment for Patients with Uncomplicated Acute Appendicitis (the ACTUAA study)

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Abstract
Purpose Acute appendicitis (AA) is among the most common causes of lower abdominal pain and admissions to the emergency department. Over the past 20 years, there has been a renewed interest in the conservative management of uncomplicated AA, and several studies demonstrated that an antibiotic-first strategy is a viable treatment option for uncomplicated AA. The aim of this prospective non-randomized controlled, multicenter trial is to compare antibiotic therapy and emergency appendectomy as treatment for patients with uncomplicated AA confirmed by US and/or CT or MRI scan.

Part of this study has been presented at the 36th National Congress of the Italian Society of Hospital Surgeons (ACOI), Montesilvano-Pescara, Italy, May 21–24, 2017.

Strengths and limitations of this study
1. Over the past 20 years, there has been a renewed interest in the conservative management of uncomplicated acute appendicitis. However, despite all the improvements in the diagnostic process, the crucial decision of whether to operate or not remains challenging.
2. The aims of the study are to investigate the efficacy, safety, and feasibility of the antibiotic-first approach and to perform a comparative analysis of the quality of life of the patients following either surgery or antibiotic therapy. Furthermore, the study aims to investigate which patient-specific variables are related to antibiotic therapy failure, if any.
3. In order to overcome the limitations reported by previous studies, we developed this prospective non-randomized controlled, multicenter trial comparing appendectomy and conservative treatment for patients with uncomplicated acute appendicitis.
4. In order to overcome possible selection bias due to the non-randomized design of the study and reduce both the rate of negative appendectomy and that of complicated appendicitis, this study protocol provides clear inclusion criteria and standardized CT and US scan templates for the diagnosis of uncomplicated acute appendicitis.

On behalf of the Italian Society of Hospital Surgeons-ACOI Study Group on Acute Appendicitis.

Sponsor: The publication of this study protocol was endorsed by the Italian Society of Hospital Surgeons ACOI—Via C. Morin 45–00195, Rome (Italy).
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Methods All adult patients in the age range 18 to 65 years with suspected AA, consecutively admitted to the Surgical Department of the 13 participating Italian Hospitals, will be invited to take part in the study. A multicenter prospective collected registry developed by surgeons, radiologists, and pathologists with expertise in the diagnosis and treatment of uncomplicated acute appendicitis represents the best research method to assess the long-term role of antibiotics in the management of the disease. Comparison will be made between surgical and antibiotic-first approaches to uncomplicated AA through the analysis of the primary outcome measure of complication-free treatment success rate based on 1-year follow-up. Quality of life, length of hospital stay, pain evaluation, and time to return to normal activity will be evaluated as secondary outcome measures.
Trial registration Clinicaltrials.gov ID: NCT03080103

Keywords Acute appendicitis · Uncomplicated appendicitis · Appendectomy · Antibiotic treatment · Conservative treatment · Study protocol

Abbreviations

AA	Acute Appendicitis
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
US	Ultrasound Scan
AIR	Appendicitis Inflammatory Response
VAS	Visual Analogue Scale
IBD	Inflammatory Bowel Disease
SF-12	Short Form-12
WBC	White Blood Cell
CRP	C-Reactive Protein
CDC	Center for Disease Control (Atlanta)
SSI	Surgical Site Infection

Introduction

Background

Acute appendicitis (AA) is among the most common causes of lower abdominal pain leading patients to attend the emergency department and the most common diagnosis made in young patients admitted to hospital for acute abdomen. In the general population, the lifetime risk of developing AA is 8.6% for males and 6.7% for females [1].

While most cases of AA are uncomplicated, around 20% present with complications including gangrene, abscesses, perforation, or diffuse peritonitis [2].

Since Lawson Tait performed the first successful appendectomy in 1880, surgery has been the most widely accepted treatment of choice, with more than 300,000 appendectomies performed annually in the USA [3]. Current evidence shows laparoscopic appendectomy to be the most effective surgical treatment, being associated with lower incidences of wound infections and post-intervention morbidity, a shorter hospital stay, and better quality of life scores when compared to open surgery [4, 5].

Despite all the improvements in the diagnostic process, the crucial decision as to whether to operate or not remains challenging. In fact, although conservative management with antibiotics has been well established for intra-abdominal infections from different sources, namely uncomplicated acute diverticulitis, the non-operative management of uncomplicated AA is still debated [6].

Over the past 20 years, there has been renewed interest in the conservative management of uncomplicated AA, probably due to a more reliable analysis of postoperative complications and costs of surgical interventions, which are mostly related to the continuously increasing use of minimally invasive techniques [7–9].

The most common postoperative complications, such as wound infections, intra-abdominal abscess, and ileus caused by adhesions, vary in frequency between open (overall complication rates 11.1%) and laparoscopic appendectomy (8.7%) [10, 11].

Nowadays, several studies, especially from Europe, demonstrated that an antibiotic-first strategy is a viable option, in particular for patients who prefer to avoid appendectomy [12–14].

The Italian Society of Hospital Surgeons (ACOI) study group on acute appendicitis recently published a systematic review and meta-analysis of randomized controlled trials comparing appendectomy and conservative management with antibiotics for patients with uncomplicated AA [15]. The results showed that antibiotic treatment was associated with a significantly lower treatment efficacy based on 1-year follow-up when compared to appendectomy (75.9 vs 98.3%, $P < 0.0001$). In particular, recurrence rate was 22.5%, with a mean length of time for recurrence of 4.65 months. The pooled analysis reported no statistically significant difference between the two groups regarding the length of hospital stay and period of sick leave. A higher rate of complicated appendicitis with peritonitis was identified at the time of surgical operation in the antibiotic therapy group, with a statistically significant difference (19.9 vs 8.5%, $P < 0.02$), and the majority of cases were reported for patients with persistent

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appendicitis (62%). Following such a finding, the question arises as to whether this could be related to a lack of accuracy in the diagnostic process for those patients for whom peritonitis was detected during surgery after the failure of antibiotic treatment. In fact, complicated appendicitis might already have been present in a percentage of patients at the time of randomization, as suggested by Vons et al. [14]. No statistically significant differences were found when comparing antibiotic therapy and appendectomy for overall post-intervention complications (Fig. 1).

Therefore, two main questions are raised: is it possible to safely and effectively treat patients with uncomplicated AA with antibiotics and how do we distinguish during the observation period those patients whose AA might resolve after antibiotic treatment alone from those who would require surgery?

Rationale

To date, several meta-analyses and randomized controlled trials comparing antibiotic therapy and appendectomy have been published in the literature [16–18].

The main problems found in the clinical studies on the issue, that should be overcome by a novel well-designed study, are as follows:

- Each trial published in the literature shows limitations in terms of patient selection bias, definition of primary endpoints, lack of a standardized computed tomography (CT), or ultrasound scan (US) diagnosis. Moreover, a lack of a standardized pathological criterion for the diagnosis of potentially clinically significant appendicitis has been reported in each of the studies published, making it difficult to achieve meaningful conclusions about the real effectiveness of the antibiotic therapy when compared to appendectomy.
- The majority of the appendectomies performed for patients enrolled in trials published so far were performed by open approach, whereas laparoscopic appendectomy is being increasingly performed worldwide and will likely be elected as the gold standard surgical approach in the near future.
- To date, the great majority of trials published in the literature show limitations in terms of investigating the quality of life of patients who underwent a surgical operation versus those managed with antibiotics, especially on a long-term follow-up basis.
- There is a lack of research into factors related to antibiotic therapy failure for patients with uncomplicated acute appendicitis.

At present, a multicenter prospective collected registry developed by surgeons, radiologists, and pathologists with expertise in the diagnosis and treatment of uncomplicated AA may represent the best research method to assess the role of antibiotics in the management of the disease.

For this project, a large registry will be created by collecting data from the different participating centers.

On September 15, 2015, Italian surgeons, radiologists, and pathologists with a special interest and expertise in the

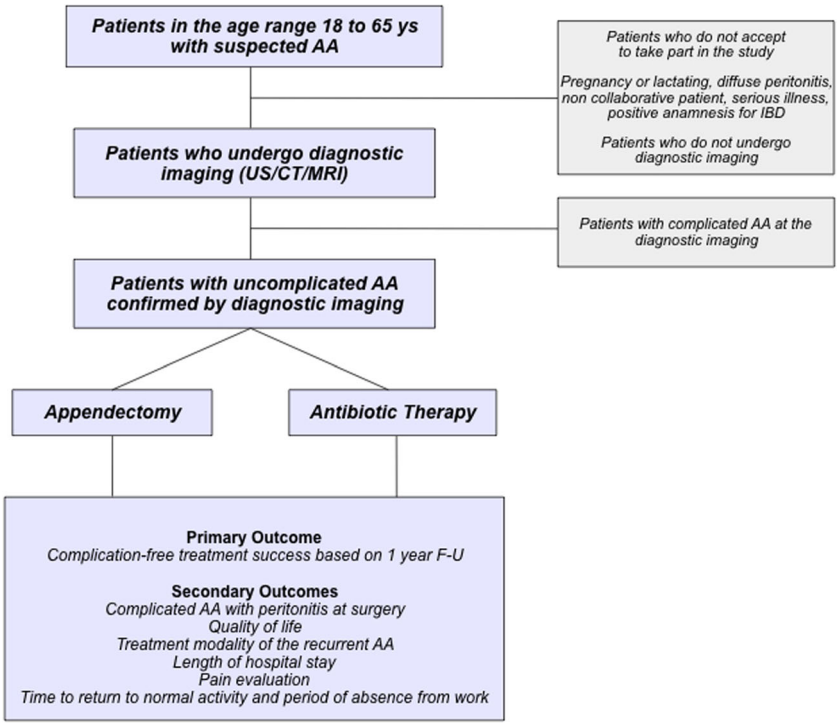

Fig. 1 ACTUAA study design and flow chart

diagnosis and management of AA met up under the auspices of the Italian Society of Hospital Surgeons (ACOI) in Oristano (Italy) to constitute the ACTUAA Collaborative Working Group. The main objectives of the working group are

1. To create a working basis for analyzing the diagnostic features, treatment modalities, and outcomes of interest of both the antibiotic-first approach and appendectomy for patients with uncomplicated AA.
2. To investigate the clinical, laboratory, and radiologic modalities adopted for the diagnosis.
3. To determine the outcomes of patients treated with antibiotics or appendectomy in the short-term and long-term periods.
4. To compare results according to the type of intervention.
5. To stratify the risk of recurrence for patients treated with antibiotics according to clinical, laboratory, and radiological findings.
6. To evaluate the sensitivity and specificity of clinical and laboratory measures for the diagnosis of uncomplicated AA.
7. To identify a subgroup of patients with uncomplicated AA for whom antibiotic treatment can be highly effective.

Methods and analysis

Objective of the ACTUAA study and general study design

The study protocol is designed according to the "SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials" [19].

The ACTUAA study has been designed as a prospective, non-randomized, controlled, open label, superiority multiinstitutional trial to compare conservative treatment with antibiotics and appendectomy for patients with uncomplicated acute appendicitis confirmed by US and/or CT or MRI scan.

We will test the hypothesis that surgical treatment with appendectomy is superior to the conservative approach with antibiotics (experimental group) for patients with uncomplicated acute appendicitis. Based on previous studies, we assumed that there would be a 20% difference in overall complication-free treatment success rates between the surgical and antibiotic groups favoring appendectomy [20].

The study period is estimated to be 12 months + 12 months of follow-up (with a second session of follow-up over 5 years), beginning on January 06, 2017.

Target population

All adult patients in the age range 18 to 65 years with suspected AA, consecutively admitted to the Surgical Department of the 13 participating Italian hospitals, will be assessed carefully by the on call (consultant) surgeon.

Patients will be then informed of the study protocol and invited to give written informed consent for participation and for sensible data collection for scientific purposes.

General characteristics, medical history, clinical findings, physical investigation, and blood tests will be reported in the medical record. Pain will be measured by visual analog scale (VAS) scoring system before administering any pain medications and after the treatment.

In order to enter the study, patients will have to undergo diagnostic imaging (US and/or CT scan or MRI scan), and only the diagnosis of uncomplicated AA confirmed by diagnostic imaging will allow patient enrollment in the study (Fig. 1).

The assignment of each patient to either the "antibiotic-first management" arm or the "immediate surgery" arm will be non-randomized and decided independently by the staff specialist surgeon on call, upon careful assessment of appendicitis inflammatory response (AIR) score, laboratory findings, and imaging. The decision of the management pathway will not be influenced in any case by the participation of the patient in the study, and the assignment of the treatment will be decided by the consultant surgeon according to current good surgical practice and standard practice patterns in Italy.

Inclusion criteria

- Signed informed consent.
- Age range 18 to 65 years.
- Uncomplicated AA confirmed by US and/or CT or MRI scan.

Exclusion criteria

- Pregnant or lactating.
- Non-consenting patients.
- Positive diagnosis for inflammatory bowel disease (IBD).

Study endpoints

Primary outcome

The analysis of the primary outcome measure aims to test and validate the safety and feasibility of both the antibiotic-first and the surgical approach to uncomplicated AA, through the analysis of

1. Treatment success (complication-free) based on 1-year follow-up. For antibiotic therapy, the outcome is defined as achieving a definitive improvement without requiring

surgery within a median follow-up of 1 year. Complications (post-treatment abdominal abscess, bowel obstruction, incisional hernia, pulmonary embolism, cardiovascular complications, surgical site infection, complications due to anesthesia, adverse drug reactions due to antibiotic administration) will be analyzed both for patients submitted to appendectomy and for those treated with surgery as a second-line approach, after primary antibiotic treatment. Possible treatment failure for patients treated with antibiotics will be evaluated as part of the overall post-intervention complication rate. Further subanalyses of the type and grade of complications will be carried out according to the arm of treatment [time frame 1 year].

Secondary outcomes

The analysis of secondary outcomes aims to evaluate the impact of antibiotic and surgical treatments on health-care costs and social impact.

1. Complicated appendicitis with peritonitis identified at the time of surgical operation. In the surgery group, perforated AA will be assessed at primary appendectomy. In the antibiotic group, the analysis will be carried out within the cohort of patients who will undergo appendectomy after the failure of the antibiotic therapy in order to assess whether or not a major risk of perforated appendicitis exists for patients who will be treated firstly with antibiotics [time frame 1 year].
2. Quality of life estimated by Short Form 12-scale (SF-12) [time frame 1 year] [21].
3. Length of postoperative hospital stay [time frame 1 week].
4. Type of treatment of the persistent or recurrent AA after antibiotic-first management (further cycles of antibiotics, open appendectomy, laparoscopic appendectomy, converted to open laparoscopic appendectomy) [time frame 1 month].
5. VAS score after appendectomy or antibiotic treatment [time frame 1 month].
6. Time to return to normal activity after surgery or antibiotic approach [time frame 1 month].
7. Period of sick leave, identified as “absence from work” [time frame 1 month].

Sample size calculation

Previous similar studies found a complication-free treatment success rate of approximately 68% in the antibiotic-first therapy group and of 89% in the surgical group [20]. We estimated that a minimum of 76 patients per group would yield a power of 0.90 (1-ß) to establish whether appendectomy is superior to antibiotic-first treatment using a one-sided significance *a* level of 0.05 (5%) with power sample size calculator (sealedenvelope.com). We anticipated a 15% loss to follow-up, resulting in our plan to enroll at least 175 patients.

The registry

The registry will allow the investigators to prospectively enter data of patients with uncomplicated AA treated with antibiotics or appendectomy at each participating center. The study lead surgeon of each center will collect and record patient’s data through a specific online shared system. Information gathered will be obtained from patient’s personal records, diagnostic tests, and surgical intervention descriptions.

Surgeons will be asked to complete the online questionnaire which is composed of 99 items and structured in six sections as follows:

1. General characteristics of the patient and clinical data at the admission.
2. US and/or CT Scan or MRI scan findings.
3. Data on surgical treatment.
4. Data on antibiotic-first treatment.
5. Pathology findings.
6. Follow-up data.

Data will not be sent via email or spreadsheets but entered by each investigator directly through a web link that will been sent to each local lead surgeon. Once logged into the web link, the investigator will be able to open the questionnaire and start inserting the data of the patient by filling out a form and selecting the various features from dropdown lists made available for each parameter. To facilitate the submission of data and subsequent analysis, the great majority of the features inserted will have been previously standardized and made close-ended, so data will be selectable from the choices already made available. Only eight questions need an open answer to be entered.

Investigators will have to provide the required answers as completely as possible, although the absence of certain data will not preclude submission of the questionnaire.

Data collection

Data will be recorded contemporaneously on a dedicated, secure server that allows collaborators to enter and store data in a secure system. No patient identifiable data (name, date of birth, address, telephone number, etc.) will be recorded.

Registered local investigators will have individual password-protected access to their center’s data entered on

to the server. During the running of the study, only local data will be visible to the investigators.

In order to facilitate entry of 1-month and 1-year follow-up data, investigators are asked to enter a unique patient's code on a separate Microsoft Excel® spreadsheet (Microsoft Excel, 2016), together with the patient's date of discharge and telephone number.

The potential risks of a breach of confidentiality of the medical record information and associated privacy of participants will be minimized by the use of an appropriate tailored system. Confidentiality and data security will be ensured removing direct participant personal details from the information stored in the research registry. The safety monitoring plan for the research registry will involve routine monitoring by the organizing committee which will remove direct identifiers from the information contained within the research registry and any conditions that may negatively impact the confidentiality of the information. The organizing committee will ensure that the confidential data will be secured and that the confidential health information will not be revealed. The pilot center (Department of General Surgery, Santissima Trinità Hospital) will host and support the online tool. Data will be stored on encrypted and certified servers for a minimum of 7 years under the governorship of the Italian Society of Hospital Surgeons (ACOI), and they may be used for further research.

Pre-interventional data

1. Date of birth.
2. Sex.
3. Previous episodes of acute appendicitis.
4. Pain score (VAS) on admission.
5. Time from symptom onset to treatment.
6. AIR score on admission [22].
7. White blood cell (WBC) count on admission.
8. % Neutrophils on admission.
9. C-reactive protein (CRP) levels on admission.
10. US or CT/MRI reports.
11. Written consent for the study and data collection.

Antibiotic treatment data

1. Type and dose of the administered intravenous antibiotic.
2. Clinical status within 24 h after admission and the start of the antibiotic therapy.
3. Daily assessment of WBC count and CRP.
4. Allergic reactions to antibiotic therapy.
5. Possible crossover to operative treatment.
6. Signs and symptoms that eventually led to surgical crossover.
7. Type of surgical approach for appendectomy (open/laparoscopic) in case of crossover.
8. Possible conversion from laparoscopic to open appendectomy.
9. Operative findings.
10. Post-interventional complications during hospital stay (reoperation, intra-abdominal abscess, bowel obstruction, pulmonary embolism, cardiovascular complications, complications due to anesthesia).
11. Daily pain assessment (VAS) during hospital stay.
12. Length of hospital stay.

Surgical treatment data

1. Antibiotic prophylaxis.
2. Timing of appendectomy and eventual reasons for possible operative delay.
3. Surgical approach (open/laparoscopic).
4. Operative findings.
5. Possible conversion to open surgery.
6. Reasons for conversion.
7. Drainage placement.
8. Intraoperative irrigation.
9. Operative time (the time between laparotomy and skin suture for open appendectomy and pneumoperitoneum induction and trocar site closure for laparoscopic appendectomy).
10. Postoperative complications during hospital stay (reoperation, intra-abdominal abscess, bowel obstruction, pulmonary embolism, cardiovascular complications, complications due to anesthesia).
11. Daily pain assessment (VAS) during hospital stay.
12. Surgical site infection (SSI) [23].
13. Pathology report.
14. Postoperative hospital stay.

Follow-up

Patient outcomes will be obtained in the outpatient clinic at 1 week and 1 month after discharge and afterwards by a phone interview at 1, 3, and 5 years after the intervention.

Outpatient assessment will include pain assessment (VAS), time to return to normal activity and possible additional need for sick leave, possible surgical site infections, quality of life estimation as assessed by the SF-12 scale, possible recurrence of AA, type of treatment of the possible recurrence (antibiotics, open/laparoscopic appendectomy), grading of the possible recurrent appendicitis (catarrhal, phlegmonous, gangrenous, perforated with local or diffused peritonitis), postoperative long-term complications (re-operation, abdominal abscess, bowel obstruction, pulmonary embolism,

cardiovascular complications, ileocecal resection, complications due to anesthesia), possible occurrence of incisional hernia, symptomatic adhesions, and possible occurrence of appendiceal or cecal tumors.

As specified above, the diagnosis of AA during the follow-up period must be confirmed by US or CT scan.

Statistical analysis

SPSS V.22 will be used to carry out this statistical analysis. The dichotomous variables will be expressed as numbers and percentages, while continuous variables will be expressed as mean and SD, or median and IQR (minimum and maximum values). Student's *t* test or ANOVA will be used for comparisons of continuous variables between groups. Chi-squared test or Fisher's exact test, as appropriate, will be used for analysis of categorical data. Multilogistic regression models will be used to investigate clinical, laboratory, and radiologic variables predictive of conservative treatment failure. A propensity score (PS) model will be calculated considering the following variables as covariates: age, sex, AIR score on admission, WBC count, % of neutrophils on admission, previous episodes of acute appendicitis, time from symptoms onset to treatment, and antibiotic therapy prescription. Treated patients and controls will be matched using "nearest neighbor matching" based on the individual PS with a caliper set at 0.2 and with a 1:1 matching model with replacement. A multiple logistic regression model will be used to investigate clinical, laboratory, and radiologic variables (independent variables) predictive of conservative treatment failure and success (dependent variable) by using the STATA/SE, version 14 (StataCorp LP, College Station, TX, USA).

The main analyses will be based on the intention-to-treat principle. However, both intention-to-treat and per-protocol analyses will be performed.

A value of $P < 0.05$ will be considered statistically significant**.**

Ethics and dissemination

Ethics, local approvals, and informed consent

All the investigators agreed to conduct the study in accordance with the principles of the Declaration of Helsinki and "good clinical practice" guidelines. The Medical Ethical Committee of the University of Cagliari has approved the protocol, and the Ethical Committees of the participating centers are applied for local feasibility (Acceptance Code PG/2017/8426, 29/05/2017). The investigators shall undertake to act according to the rules of the Ethics Committee regarding the prospective collection of data. A written informed consent will be obtained from all patients prior to the data collection and evaluation.

Publication of data

Data will be published as a pool from all participating surgical units. Subgroup analysis by grade of the disease based on the AIR score, surgical technique, histological grade of the appendicitis, type of antibiotic used, or outcome variables may be presented. In order to avoid the identification of an individual unit or surgeon, no hospital level or surgeon level data will be published. Each participating center, with equal rights, will be able to access the data of the registry, perform statistical analysis, discuss the results, and freely write scientific manuscripts, once the study period is terminated. Each manuscript that is generated based on the registry must be disseminated to all participating centers before final publication.

Discussion

The aims of the study are to investigate the efficacy, safety, and feasibility of the antibiotic-first approach, as well as to identify a subgroup of patients with uncomplicated AA who could benefit the most from conservative management with antibiotics and thus provide evidence-based data in order to decide which treatment plan is best suited to each patient.

Even though trials and reviews previously published have concluded that the majority of patients with uncomplicated AA can be treated with an antibiotic-first approach, conflicting data about rates of efficacy, especially at long-term follow-up, have been obtained.

In fact, the efficacy rate of the antibiotic-first strategy ranges in the literature from 60 to 91% [24, 25].

The most recent meta-analysis by Harnoss et al. reported a recurrence rate of symptoms within 1 year of 27.4%. Taking into consideration any kind of post-interventional complication (including treatment failure), the complication-free treatment success rate of the antibiotic therapy was significantly inferior to the same rate after surgery (68.4 vs 89.8%) [20].

The success of the conservative approach requires careful patient selection and exclusion of patients with gangrenous appendicitis, abscesses, and diffuse peritonitis. So, a further matter of debate is how to distinguish during initial assessment those who might respond well to antibiotic therapy alone from those who would require surgery.

Hansson et al. in their study on 581 patients with acute appendicitis published in 2014 found that patients with assumed appendicitis who fulfilled all criteria with CRP < 60 g/l, WBC < 12×10^9/l, and age < 60 years had an 89% of chance of recovery with antibiotics without surgery [26].

The clinical diagnosis of AA is often challenging and involves a synthesis of clinical, laboratory, and radiology information. The diagnostic workup could be improved by using a clinical scoring system that involves physical examination

findings and inflammatory markers. In this context, the AIR score is a simple and user-friendly tool that can be used as a structured algorithm to correctly classify the great majority of patients with suspected appendicitis, leaving the need for radiological investigation to a smaller subgroup of patients with an indeterminate scoring result [22, 27].

Although the high sensitivity and specificity rates achieved with the use of clinical scoring systems, imaging techniques such as US and CT scan are currently used with the objective of a rapid and precise diagnosis [28, 29].

Contrast-enhanced CT is often used in most centers as it shows high accuracy in the diagnosis of appendicitis, allowing a precise differentiation between uncomplicated forms and appendicular abscesses or perforations. It plays an important role when the clinical presentation of the AA is atypical and a differential diagnosis needs to be explored [30–33].

Salminen et al. recently reported a 73% success rate with an antibiotic-first strategy for adults diagnosed with uncomplicated AA by CT scan, thus suggesting the utilization of the CT scan as the primary imaging method for identifying patients with uncomplicated forms [18]. However, AA has its peak incidence between 10 and 20 years of age, and concerns have been raised regarding the risks related to exposure to ionizing radiations conferred by CT in this young age group.

Furthermore, the routine use of CT in the emergency department for right iliac fossa pain from suspected appendicitis may result in increased costs and may lead to the detection of low-grade appendicitis that would otherwise have resolved spontaneously.

In Italy, with a few exceptions (age > 65 years, body mass index > 30 kg/m^2), sonography is the initial modality of choice for both for adult and pediatric patients with suspected AA [34].

In the EU, only around 13% of patients undergo preoperative imaging, which is typically reserved for elderly patients who might have cancer, atypical or delayed presentations, or those who have suspected appendicular masses or abscesses [35]. Young males with typical clinical histories and examination findings go straight to surgery first without any imaging. Conversely, in the USA, 86% of patients actually undergo pre-operative imaging, 91% of whom undergo CT [36].

Therefore, the mandatory use of CT scan within a trial comparing the efficacy of antibiotic therapy and appendectomy could affect the external validity of the study since there is no standard diagnostic approach worldwide. This would limit the transferability of the study results into everyday clinical practice.

Several evaluations of diagnostic strategies for patients with suspected AA favored a conditional CT scan strategy as the most judicious diagnostic pathway, with CT scan performed only after a negative or equivocal US [37, 38].

The imaging capabilities of US have improved substantially, and, according to recent studies, graded-compression US could be considered for primary diagnostic approach as it has sensitivity and specificity of up to 92.2 and 97.7% when a standardized and validated ultrasonography report template is adopted [39, 40].

Possible limitations of this study are related to its non-randomized design, which carries the risk of selection bias. In fact, we cannot exclude that antibiotic therapy was preferred for selected patients expected to have better chances of successful conservative treatment and better outcomes. However, in order to overcome this limitation, a propensity score analysis with a "nearest neighbor" matching will allow us to obtain two balanced groups in terms of age, sex, comorbidity, laboratory variables, and US and CT scan findings.

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Compliance with ethical standards All the investigators agree to conduct the study in accordance with the principles of the Declaration of Helsinki and its later amendments and "good clinical practice" guidelines. A written informed consent will be obtained from all patients included in the study prior to the data collection and evaluation.

Ethics and dissemination The study has been approved by the Medical Ethical Committee of the University of Cagliari (Acceptance Code PG/2017/8426, May 29, 2017).

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Appendix

A. Definitions and classifications adopted

Intraoperative complications

Any adverse event in the course of the surgical procedure will be recorded and described by each of the participating surgeons in the operation notes. Particularly, the rate of the following events will be detected and analyzed:

- Injury of visceral organs.
- Bleeding (intra-abdominal and/or from the trocar site).
- Vascular lesions.
- Anesthesia complications.
- Adverse drug reactions due to antibiotic administration will be recorded and described by each of the participating surgeons in the clinical notes.

Postoperative complications

Any adverse event leading to a deviation from the normal postoperative course during a patient's hospitalization will be detected, recorded, described, and classified using the Dindo-Clavien scale [41].

Moreover, early and late complications after discharge will be detected from the medical records and analyzed:

- Postoperative bleeding (documented by clinical signs and symptoms or the need for transfusion, blood samples revealing acute anemia, reports of radiological investigations, reports of surgical procedures).
- Wound infection (superficial or deep surgical site infections, reported in medical records, according to the CDC classification) [23].
- Intra-abdominal abscess or fluid collection (confirmed by US or CT and reported in medical records).
- Small bowel obstruction and ileus due to adhesions (documented by clinical examination and signs of intestinal dilatation on abdominal X-ray and/or CT scan and reported in medical records).
- Incisional hernia (either from laparotomy or trocar sites, documented by clinical examination and eventually US and/or CT scan, and reported in medical records).
- Pulmonary embolism, cardiovascular complications, complications due to anesthesia.

Antibiotic treatment complications

Any antibiotic side effect (defined as an unwanted reaction occurring in addition to the desirable therapeutic action of the antibiotic), pulmonary embolism, and cardiovascular complications will be detected and recorded in the medical reports.

B. Ultrasound scan protocol

A collaborative group for the quality improvement in radiology, focalized on the diagnosis of AA, met on the September 15, 2015 in Oristano (Italy) to discuss a standardized ultrasound reporting template for appendicitis. The current literature was reviewed to design a template with high sensitivity and specificity [31, 39, 40, 42–47].

As result of the meeting, the following US diagnostic criteria were chosen to carry out the diagnosis of uncomplicated AA. Criteria have been divided into direct (primary) and indirect (secondary).

Primary criteria

- An outer diameter of the appendix of greater than 6 mm.
- An appendiceal wall thickness of greater than 3 mm with graded compression.

- The finding of peri-appendiceal abnormalities (hyperechogenic periappendiceal and or omental fat, augmented wall thickness of the cecum, augmented wall thickness of the ileal bowel loops in the right inferior fossa).
- The loss of compressibility of the appendix.
- The positivity of the US Blumberg sign (under direct ultrasound visualization of the appendix).
- The absence of gas into the appendiceal lumen.
- The presence of hypoechoic fluid-filled lumen.
- The presence of hypoechoic mucosa/submucosa.
- The presence of hypoechoic muscularis layer.
- The presence of hypervascularization of the appendiceal wall.

Secondary criteria

- Free fluid surrounding the appendix, not extended beyond the right iliac fossa and the Douglas pouch.
- Increased echogenicity of local mesenteric fat.
- Enlarged local mesenteric lymph nodes.

On the other hand, the following criteria were adopted by the experts to define the diagnosis of complicated acute appendicitis.

Primary criteria

- The loss of the submucosal layer.
- The finding of free peritoneal fluid extended beyond the right iliac fossa and the Douglas pouch, associated with the presence of the radiologic signs of acute appendicitis.
- The finding of a peri-appendiceal fluid collection consistent with an appendicular abscesses.
- Hypovascularity to avascularity in abscess and necrosis.
- The finding of a hypoechoic appendiceal mass.

Secondary criteria

- The finding of local dilatation and hypoperistalsis of the bowel consistent with focal peritonitis.
- Signs of secondary small bowel obstruction.
- Thickening of the peritoneum.

At least three of the abovementioned criteria are required for a compliant US report. Non-diagnostic exams are defined as US reports for which the description was insufficient to carry out or exclude the diagnosis of uncomplicated AA. Experts stated that US is read as negative only if a normal appendix is seen.

C. CT scan protocol

A collaborative group for the quality improvement in radiology, focalized on the diagnosis of AA, met on September 15, 2015 in Oristano (Italy) to discuss a standardized CT scan high resolution protocol for the diagnosis of appendicitis. The current literature was reviewed to design a template with high sensitivity and specificity [29–31, 39, 48–51].

Experts stated that all abdominal CT scans must be performed from the diaphragm to the pubic symphysis. A study series without contrast must be performed. Only if this study will be non-diagnostic, a study series with contrast will be performed during the porto-venous phase (70-s delay from the end of injection). Slice thickness and reconstruction interval values must be of 1.2 mm, collimation of $2 \times 128 \times 0.6$ mm^3, and rotation time of 0.28 s. The intravenous contrast medium (80–100 ml of iodinated contrast agent at 400 mg/ml concentration) is injected at 4 ml/s, followed by 20 ml of saline injected at 3 ml/s, in order to enhance the bowel walls and solid organs.

The following criteria were chosen to define the diagnosis of uncomplicated acute appendicitis at the CT scan:

- An outer diameter of the appendix of greater than 6 mm.
- An appendiceal wall thickness of greater than 3 mm.
- Thickening and contrast enhancement of the appendiceal wall.
- Inflammatory edema.
- Minor fluid collection around the appendix.
- "Dirty fat" sign (the adipose tissue surrounding the appendix is increased in density).

The final CT diagnosis of uncomplicated acute appendicitis requires a clear visualization of the appendix presenting with the above-listed characteristics and the absence of the following CT scan findings which make a shift in diagnosis from uncomplicated to complicated disease:

- Focal poor enhancement of the appendiceal wall.
- Destruction of the appendiceal wall.
- Periappendiceal abscess.
- Extraluminal gas closer to the appendix.
- Extraluminal free air.
- Free peritoneal fluid.
- Tumor of the appendix.
- Extraluminal faecalith.

At least three of the abovementioned criteria are required for a compliant CT scan report.

D. List of the involved surgical centers

1. Cagliari (General and Oncologic Surgical Unit, Santissima Trinità Hospital)
2. Nuoro (General, Emergency and Minimally Invasive Surgical Unit, San Francesco Hospital)
3. Lanusei (General Surgery Unit, Nostra Signora delle Mercede Hospital)
4. Cagliari (General and Endocrine Surgical Unit, University Hospital)
5. Cagliari (General and Emergency Surgery, University Hospital)
6. Voghera (General Surgery Unit, Civil Hospital)
7. Cavalese (General Surgery Unit, Civil Hospital)
8. Muravera (General Surgery Unit, San Marcellino Hospital)
9. Iglesias (General Surgery Unit, CTO Hospital)
10. Carbonia (General Surgery Unit, Sirai Hospital)
11. Napoli (Emergency Surgery Unit, Villa Betania Evangelic Hospital)
12. Cagliari (Emergency Surgery Unit, Brotzu Hospital)
13. Alghero (General Surgery Unit, Civil Hospital).

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