The NOTA Study (Non Operative Treatment for Acute Appendicitis)

Prospective Study on the Efficacy and Safety of Antibiotics (Amoxicillin and Clavulanic Acid) for Treating Patients With Right Lower Quadrant Abdominal Pain and Long-Term Follow-up of Conservatively Treated Suspected Appendicitis

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Objectives: To assess the safety and efficacy of antibiotics treatment for suspected acute uncomplicated appendicitis and to monitor the long term follow-up of non-operated patients.

Background: Right lower quadrant abdominal pain is a common cause of emergency department admission. The natural history of acute appendicitis nonoperatively treated with antibiotics remains unclear.

Methods: In 2010, a total of 159 patients [mean AIR (Appendicitis Inflammatory Response) score = 4.9 and mean Alvarado score = 5.2] with suspected appendicitis were enrolled and underwent nonoperative management (NOM) with amoxicillin/clavulanate. The follow-up period was 2 years.

Results: Short-term (7 days) NOM failure rate was 11.9%. All patients with initial failures were operated within 7 days. At 15 days, no recurrences were recorded. After 2 years, the overall recurrence rate was 13.8% (22/159); 14 of 22 patients were successfully treated with further cycle of amoxicillin/clavulanate. No major side effects occurred. Abdominal pain assessed by the Numeric Rating Scale and the visual analog scale; median Numeric Rating Scale score was 3 at 5 days and 2 after 7 days. Mean length of stay of nonoperatively managed patients was 0.4 days, and mean sick leave period was 5.8 days. Long-term efficacy of NOM treatment was 83% (118 patients recurrence free and 14 patients with recurrence nonoperatively managed). None of the single factors forming the Alvarado or AIR score were independent predictors of failure of NOM or long-term recurrence. Alvarado and AIR scores were the only independent predictive factors of NOM failure after multivariate analysis, but both did not correlate with recurrences. Overall costs of NOM and antibiotics were €316.20 per patient.

Conclusions: Antibiotics for suspected acute appendicitis are safe and effective and may avoid unnecessary appendectomy, reducing operation rate, surgical risks, and overall costs. After 2 years of follow-up, recurrences of nonoperatively treated right lower quadrant abdominal pain are less than 14% and may be safely and effectively treated with further antibiotics.

Keywords: acute appendicitis, lower abdominal pain, natural history of conservatively treated appendicitis, non-operative antibiotic treatment, prospective study

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Acute appendicitis is one of the most common urgent conditions seen in general surgery practice. Complications can be severe and include perforation and generalized peritonitis. Traditionally, surgical appendectomy has been the primary treatment option even in cases of unconfirmed diagnosis, given the low incidence of major complications. However, in 15% to 30% of cases, the appendix is found to be free of disease upon resection.[1,2] As appendectomy is associated with short- and long-term complications such as surgical wound infection, pneumonia, and development of intraperitoneal adhesions with subsequent risk of intestinal obstruction due to adhesions and tubal infertility in females, the possibility of using conservative treatment deserves further investigation. Nonoperative management (NOM) of a suspected appendicitis has safety implications. However, delaying surgery may increase the risk of finding perforated appendicitis and development of intra-abdominal abscesses and/or localized or diffuse peritonitis before surgery, with a higher rate of wound infections, medical complications, and increased long-term risk of adhesions and subsequent adhesive small bowel obstruction and infertility after surgery. Surgery, however, is not without risks, and there are a variety of potential complications including anesthesia-related complications; notably, intraoperative (vascular lesions, enterotomies, urinary tract lesions, etc), early surgical postoperative (hematoma/bleeding, colonic fistula, surgical site infection, intra-abdominal abscess, adhesions, and ileus/obstruction) with subsequent reoperation, late surgical postoperative (adhesions and subsequent adhesive small bowel obstruction and tubal infertility, incisional hernias), and general postoperative complications may occur. However, NOM with antibiotics may be a cost-effective alternative to surgery in a large percentage of patients without increasing the risk and may reduce hospital stay and costs in both developed and third world countries.

There is considerable debate regarding the utility of NOM with antibiotics compared with surgical treatment in some cases of acute appendicitis, as few studies have addressed this issue to date.[3–5] If NOM with antibiotics is to be considered, it is very important to make an accurate diagnosis and assessment in every patient to select the most appropriate treatment option.

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The idea that appendicitis may resolve spontaneously is not new. In 1908, Alfred Stengel wrote: "Treated in a purely medical or tentative manner, the great majority of patients with appendicitis recover."[6(p428)] Restrained indications with few negative appendectomies are associated with a low incidence of diagnosed nonperforated appendicitis, with a secondary high proportion of perforated appendicitis, but no increase in the incidence of perforations.[7] This suggests that appendicitis in a significant number of patients may resolve undiagnosed. Resolving appendicitis may also be indicated by a history of recurrent appendicitis, which can be found in up to 6.5% of patients operated on for appendicitis.[8]

When perforation results from delayed treatment, the associated increase in morbidity and mortality must be weighed against the not negligible risks of negative appendectomy. The excess mortality associated with both nonperforated appendicitis and negative appendectomy with a discharge diagnosis of nonspecific abdominal pain suggests that appendectomy itself carries risks. The decrease in mortality achieved by a single prevented perforation may be therefore attenuated by an high incidence of negative appendectomy, especially in elderly and frail patients.[9,10] In fact, Andersson[11] recently showed from a population-based case-control study that appendicitis is only responsible for a small proportion of the deaths after appendectomy. Comorbidity and negative appendectomy were strongly associated with mortality, suggesting that comorbidity, diagnostic failure, and anesthesiosurgical trauma may play an important role.

Other authors suggest that appendectomy may not be necessary for the majority of patients with acute uncomplicated appendicitis, as the condition resolves spontaneously in many patients and may be treatable with antibiotics alone in other patients.[12] This approach has many advantages, including high success and low recurrence rates, reduced morbidity and mortality, less pain, shorter hospitalization and sick leave, and reduced costs.[13]

A meta-analysis comparing conservative treatment with acute appendectomy for complicated appendicitis (abscess or phlegmon) and including 1572 patients (847 patients received conservative treatment and 725 acute appendectomy) showed that conservative treatment was associated with significantly fewer overall complications, wound infections, abdominal/pelvic abscesses, ileus/bowel obstructions, and reoperations. Furthermore, there were significantly fewer overall complications in conservative treatment groups during sensitivity analysis of studies including only pediatric patients, high-quality studies, more recent studies, and studies with larger groups of patients.[14] In particular, a randomized clinical trial (RCT) of antibiotic therapy versus appendectomy as a primary treatment option for acute appendicitis in unselected patients showed that treatment efficacy was 90.8% for antibiotic therapy and 89.2% for surgery. In this trial, minor complications were similar between the groups whereas major complications were 3-fold higher in patients who underwent an appendectomy ($P < 0.050$). In total, 2.9% of the operated patients underwent a second operation, 3% of them developed abscesses, 2.4% postoperative small bowel obstruction (SBO), 1.8% wound rupture or wound hernia, 0.6% pulmonary embolism and 0.6% postoperative cardiac complications, and 1.2% underwent subsequent ileocecal resection. Wound infection occurred in 7.6%, and 1.2% of the patients had anesthesia-related problems.[15]

The cumulated risk of surgically treated SBO after appendectomy was 0.41% after 4 weeks, 0.63% after 1 year, and 1.30% after 30 years of follow-up, compared with 0.003% at 1 year and 0.21% after 30 years of follow-up among nonoperated controls, with perforated appendicitis, negative appendectomy, and high-age risk factors for developing subsequent SBO.[16]

A further article reviewing 1777 patients who underwent appendectomy for acute appendicitis showed the overall SBO rate to be 2.8% over an average 4.1-year follow-up period or 0.0069 cases per person-year.[17] The laparoscopic approach also carries risks, including intraoperative complications ranging from 3.1% to 0.7%, surgical postoperative complications ranging from 6.1% to 1.9%, general postoperative complications ranging from 4.9% to 1.5%, and rates of reoperations ranging from 3.4% to 0.7%.[18] A comparison of 3025 open versus 14,174 laparoscopic appendectomies showed that appendectomy may also be associated with a small risk of mortality (0.3% for open and 0.1% for laparoscopic).[19]

Another large population-based appraisal including 32,683 patients reported morbidity and mortality for both open and laparoscopic appendectomies.[20] The long-term follow-up of an RCT of open versus laparoscopic appendectomy showed a 42.3% incidence rate of overall complications in the open surgery group versus 12.8% in the laparoscopic group, with wound-related complications as high as 30.77% versus 4.2%.[21] After a mean follow-up of more than 9 years, 5.7% and 6.4% of patients, respectively, had adhesions or adhesion-related symptoms and 0.2% underwent another operation for adhesions. The risk of SBO after open appendectomy is between 0.33% and 1.51%. In addition, a liberal attitude to exploration among patients with suspected appendicitis does not prevent perforations.[22]

Hansson et al[15] conducted an RCT investigating the efficacy of conservative treatment compared with surgery for acute appendicitis. They reported that nonoperative treatment with antibiotics was efficacious in 91% of cases, with a 14% relapse rate at 12 months of follow-up.

One third of relapses occurred within the first 10 days of hospital discharge, whereas most of the remaining two-thirds occurred between 3 and 16 months after discharge. The incidence of major complications such as appendiceal abscess, paralytic ileus, and pulmonary embolism, however, was significantly higher in those treated surgically ($P < 0.05$).

A prospective randomized study conducted by Malik and Baris[2] compared antibiotic therapy with appendectomy for acute appendicitis. The authors reported that NOM with antibiotics was not only safe and efficacious but also caused the patients less pain than surgery, reducing the need for analgesics ($P < 0.001$). Ten percent of conservatively treated patients experienced relapse within 12 months of discharge.

A multicenter randomized trial conducted in Sweden[15] yielded similar results: the rate of relapse in antibiotics-treated patients was 14% at 1 year after discharge. Interestingly, this was equal to the rate of postoperative complications in patients treated surgically. On the basis of these reports, the diagnostic accuracy of acute appendicitis was as high as 71% to 87% with a combination of modern preoperative investigations.[23] More recent literature quote a negative appendectomy rate, dropping to 10% with ultrasonography (US) and 6% with computed tomography (CT). However, an increased use of preoperative imaging achieved a nonsignificant reduction of negative appendectomy rates (from 25.7% to 12.8%), and in the management of patients with acute appendicitis, it failed to reduce negative appendicectomy, perforation, and complication rates.[24] It is also known that CT scans may not reduce the negative appendectomy rate in children,[25] and increasing utilization of preoperative CT and advances in technology did not decrease appendectomy rate in men of any age or women older than 45 years.[26] Therefore, conservative treatment with antibiotics seems to be a viable alternative for cases of suspected or probable/proven acute appendicitis, as assessed on the basis of clinical scores. Relapse rate is low, and complications are no higher than the rate of surgical complications.

RATIONALE

Case-control studies that randomly assign patients with suspected acute appendicitis to either surgical or nonsurgical treatment group show a relapse rate of approximately 14% at 1 year. It would, therefore, be useful to determine the relapse rate of patients treated according to the results of a thorough clinical evaluation, including physical examination and laboratory results (all characteristics used to determine the Alvarado score[27]) and radiological evaluation. Only clinical signs and symptoms and laboratory values, as included in the Alvarado and Appendicitis Inflammatory Response (AIR)[28] scores, were routinely evaluated in patients with suspected acute appendicitis. If this clinical evaluation is effective, we would expect patient selection to be better than chance and the relapse rate to be below 14%. Once we have established the utility of this evaluation, we can begin to identify those components that have predictive value. This would be a first step toward developing an accurate diagnostic-therapeutic algorithm, possibly functional for avoiding the risks and costs of needless surgery.

Much research into the cause of diseases relies on cohort, case-control, or cross-sectional studies. Observational studies also have a role in research on the benefits and harms of medical interventions. Randomized trials cannot answer all-important questions about a given intervention. For example, observational studies are more suitable for detecting rare or late adverse effects of treatments and are more likely to provide an indication of what is achieved in daily medical practice.[29]

PATIENTS AND METHODS

This is a single-cohort, prospective, observational study. The study conformed to good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. It is also in keeping with accepted best practice guidelines of the STROBE statement for observational studies (cohort, case-control, or cross-sectional designs).[30]

The protocol was approved on November 2009 by Maggiore Hospital Ethical Review Board (ID CE09079). The study protocol has been registered on ClinicalTrials.gov database (identifier NCT01096927)[31] and published in the protocol form.[32]

Patients presented to the emergency department with right iliac fossa (RIF) pain and suspected acute appendicitis had the following tests: complete blood cell count with differential and C-reactive protein. An attending/consultant surgeon conducted an assessment of the right lower quadrant pain suspected of being appendicitis and rule out the presence of acute appendicitis and need for operation; they eventually underwent additional abdominal US and eventual completion with an abdominal CT scan if requested by the attending/consultant surgeon. Those patients not needing immediate surgery (see inclusion criteria later) were treated with a 5- to 7-day course of amoxicillin and clavulanate at dosage of 1 g orally thrice daily.

Study Aims

Main objective

The main objective was to evaluate the outcome of patients treated nonoperatively with antibiotics and to assess the reliability of the initial clinical evaluation in predicting which nonoperatively treated patients should have been treated surgically.

The primary outcomes were as follows:

1. Short-term efficacy of antibiotic treatment: failure of NOM with 7 days of amoxicillin and clavulanic acid therapy, defined as readmission due to lack of clinical improvement and/or worsening abdominal pain and/or localized/diffuse peritonitis.
2. Long-term efficacy of antibiotic treatment: efficacy of antibiotic therapy for right lower quadrant pain suspected of being appendicitis defined as an incidence of recurrences of clinical episodes of appendicitis up to follow-up at 2 years (at 7 days, 15 days, 6 months, 1 year, and 2 years).
3. Long-term efficacy of antibiotic treatment (no need for surgery): efficacy of antibiotic therapy for right lower quadrant pain suspected of being appendicitis defined as definite improvement without the need for surgery up to follow-up at 2 years (at 7 days, 15 days, 6 months, 1 year, and 2 years).
4. Safety of antibiotic treatment: major side effects/drug- or treatment-related complications (ie, allergy or other treatment-related complications such as abscess formation).

Secondary outcomes were as follows:

1. Minor complications: minor side effects/drug or treatment-related complications (ie, bloating, diarrhea, flatulence, headache, heartburn, nausea, and vomiting) (at 7 days, 15 days).
2. Abdominal pain after discharge: assessment of abdominal pain/discomfort evaluated by means of a Numeric Rating Scale (NRS)[33] (at 5, 7, and 15 days).
3. Length of hospital stay: length of clinical observation as an inpatient for nonoperated patients.
4. Outpatient clinic follow-up: number of follow-up appointments scheduled in the outpatient clinic.
5. Sick leave: number of days of sick leave needed by the patient.
6. Cost analysis: analysis of the costs of antibiotics, length of hospital stay, outpatient clinic follow-up appointments, and sick leave days.

Secondary Aims

An additional objective was to identify clinical, laboratory, and imaging findings that were predictive of failure of NOM with antibiotics and/or relapse of appendicitis and need for appendectomy within 2 years.

Inclusion and Exclusion Criteria

Any patient of both sexes, of nonpediatric age, who consented to participate in the study between January 1, 2010, and December 31, 2010, and underwent an initial trial of NOM with antibiotics (amoxicillin/clavulanate, 3 g/daily) and seen at a follow-up visit 5 days after an initial assessment in the emergency department was considered eligible for inclusion in the study (Table 1).

Specifically, the inclusion criteria were as follows:

1. Age more than 14 years.
2. Lower abdominal pain/RIF pain.
3. Clinical diagnosis/suspicion made by an attending general surgeon, of acute appendicitis, confirmed by at least 1 validated score (Alvarado and/or AIR scores; Table 2):
   - Alvarado score 5 to 6 (equivocal for acute appendicitis)
   - Alvarado score 7 to 8 (probable appendicitis)
   - Alvarado score 9 (highly probable appendicitis)
   - AIR score 3 to 4 (low probability)
   - AIR score 5 to 8 (indeterminate group)

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age >14 yr	Diffuse peritonitis
Right lower abdominal pain/RIF pain	Penicillin allergy
Clinical diagnosis/suspicion made by attending surgeon of acute appendicitis (Alvarado score >5 and <10 and/or AIR score >2 and <11)	Previously already started antibiotic therapy
Informed consent	Previous appendectomy
	Positive pregnancy test
	IBD history or suspicion of IBD recurrence

TABLE 2. Alvarado and AIR Score Comparison

Diagnosis	Alvarado Score	AIR Score
Vomiting		1
Nausea or vomiting	1	
Anorexia	1	
Pain in RLQ	2	1
Migration of pain to the RLQ	1	
Rebound tenderness or muscular defense	1	
Light		1
Medium		2
Strong		3
Body temperature >37.5°C	1	
Body temperature >38.5°C		1
Leukocytosis shift	1	
Polymorphonuclear leukocytes		
70%–84%		1
≥85%		2
White blood cell count		
$>10.0 \times 10^9$/L	2	
$(10.0–14.9) \times 10^9$/L		1
$\geq 15.0 \times 10^9$/L		2
C-reactive protein concentration		
10–49 g/L		1
≥50 g/L		2
Total score	10	12

Alvarado score: sum 0–4 = not likely appendicitis; sum 5–6 = equivocal; sum 7–8 = probably appendicitis; sum 9–10 = highly likely appendicitis. Acute appendicitis response score (AIR): sum 0–4 = low probability; sum 5–8 = indeterminate; sum 9–12 = high probability.
RLQ indicates right lower quadrant.
Modified from de Castro et al.[43]

- ○ AIR score 9 to 10 (high probability)

4. Informed consent (patient or legal representative).

Exclusion criteria were as follows:

1. Diffuse peritonitis
2. Antibiotic (penicillin) documented allergy
3. Ongoing/previously started antibiotic therapy
4. Previous appendectomy
5. Positive pregnancy test
6. Inflammatory bowel disease (IBD) history or suspicion of IBD recurrence.

Clinical diagnosis or clinical suspicion of nonperforated acute appendicitis not requiring immediate surgery was made by an attending surgeon and rigorously assessed and validated on the basis of routine use of clinical scores (Alvarado and AIR scores; Table 2). Patients with Alvarado scores of 5 or more and less than 10 and/or AIR scores of more than 2 and less than 11 were considered eligible. These patients with right lower abdominal pain and suspicion of acute appendicitis not requiring immediate surgery were offered nonoperative treatment with antibiotic therapy (amoxicillin and clavulanic acid) and requested to provide informed consent to undergo clinical observation.

Suspected acute appendicitis was defined as patient presenting with RIF pain and the absence of a definite alternative diagnosis of a gastrointestinal disease (such as IBD, irritable bowel syndrome, colitis, etc), urinary tract disease (such as urinary tract infection, renal colic, urinary tract stones, etc), or an obstetric-gynecological cause (such as pregnancy, pelvic inflammatory disease, ovulation, etc).

Patients needing immediate surgery were defined as those with diffuse peritonitis and/or signs of severe abdominal sepsis and also those with clinicoradiological (US or CT scan) evidence of an intra-abdominal collection/abscess or free perforation.

Sepsis was defined by the presence of systemic inflammatory response syndrome[34] in the presence of a known or strongly suspected intra-abdominal infection/collection or free perforation.

Patients who did not undergo surgery were physically examined 5 days later. If their condition did not improve or worsened, they were admitted for surgical appendectomy. If they improved, they were given further information and invited to participate in a further follow-up and asked to sign an informed consent form. If the patient was younger than 18 years, consent was obtained from a parent or other legal guardian.

Abdominal pain was assessed by the NRS (range, 0–10)[33] and the visual analog scale (VAS) (range, 0–10).[35] Telephone (or e-mail) follow-up was conducted at 7 and 15 days, 6 months, and 1 and 2 years (see Fig. 1 for tempogram of the study). In the case of patients younger than 18 years, telephone interview was conducted

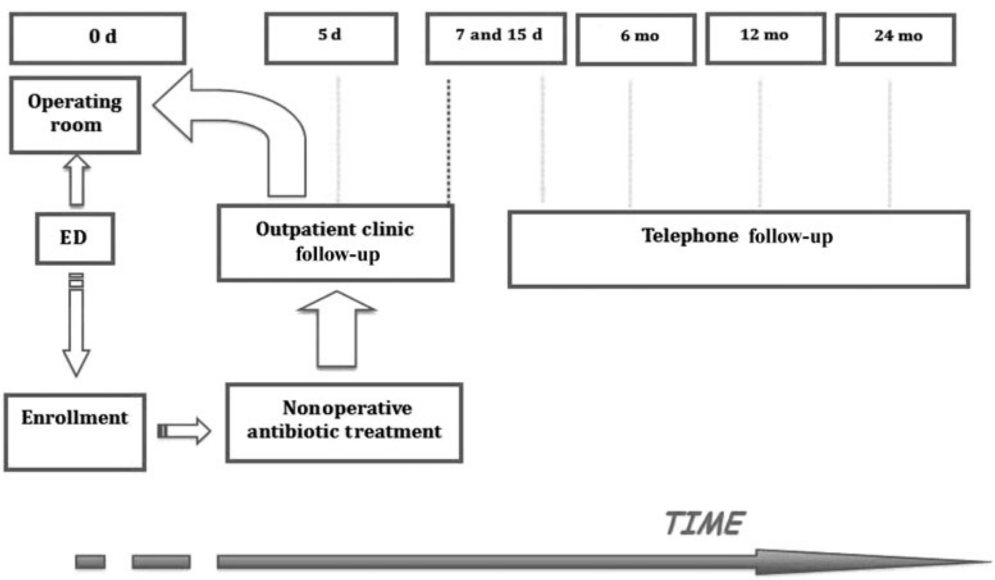

FIGURE 1. Tempogram of the study. ED indicates emergency department.

with a parent or legal guardian. Patients were asked whether they had undergone surgery since the first visit (5 days after presenting to the emergency department). If not, the patients were asked the following:

1. Has your illness improved, stayed the same, or worsened since its onset?
2. Have you undergone any further tests or had additional doctor's visits for your illness?
3. After your initial emergency department visit, how long did it take to return to your normal activities (physical activity, work, etc)?

Statistics

Data were entered into a spreadsheet using Epi-Info (version 6.04d; Centers for Disease Control and Prevention) and analyzed using SPSS software (version 15.0, SPSS Inc., Chicago, IL). Descriptive statistics were reported as mean (SD) for normally distributed variables and median (interquartile range) for variables not normally distributed. The χ^2 analysis of variance was used to compare differences for categorical variables. Odds ratio with 95% confidence interval were calculated.

The Student paired-samples *t* test was used to compare mean differences between continuous variables. The Mann-Whitney *U* test was used to compare nonparametric continuous variables (eg, age, white blood cell count). Statistical significance was defined as $P < 0.05$.

Variables with clinically relevant cutoff points were dichotomized. To determine independent predictors of the short- and long-term efficacy of antibiotic treatment (in terms of failure rate of NOM with antibiotics, recurrence rate of clinical episodes of acute appendicitis, and definite improvement without the need for surgery within 1 year of follow-up) in the general study population, numerous variables were assessed including demographic characteristics (sex, age), clinical features (medical history, gynecological status, IBD history), clinical status (body temperature), laboratory studies (white blood cell count, neutrophil count, C-reactive protein), whether or not empirical antibiotics were previously administered, and time to administration and duration of treatment with amoxicillin and clavulanic acid.

Univariate analyses were used to identify which variables with a *P* value less than 0.05 had to be included in the multivariate models. Stepwise backward logistic regression was used to determine whether these covariates were independent predictors of treatment efficacy; covariates were eliminated when *P* values were 0.05 or greater.

The same methods were used to assess predictors of abdominal pain after discharge, length of hospital stay, number of outpatient clinic follow-up appointments, and sick leave. Finally, cost analysis was carried out on antibiotic course, length of hospital stay, outpatient clinic follow-up appointments, and sick leave days.

RESULTS

Catchment population of Bologna urban area is half a million people. The number of patients aged older than 14 years admitted to the emergency department with RIF pain and/or suspected appendicitis have been monitored in our hospital for the last 3 years and range from 328 to 443 cases per year.

Two-hundred forty-eight patients with suspected appendicitis, due to right lower abdominal pain, were assessed as potentially eligible (Fig. 2); of these potentially eligible patients, 89 patients were excluded because they did not meet the inclusion criteria (n = 58) or because they declined to participate (n = 14) or for other reasons (n = 17). Overall, 159 patients (118 females) were enrolled. All underwent a full blood cell count and C-reactive protein; diagnostic imaging (abdominal US and/or CT scan) was requested at physician discretion.

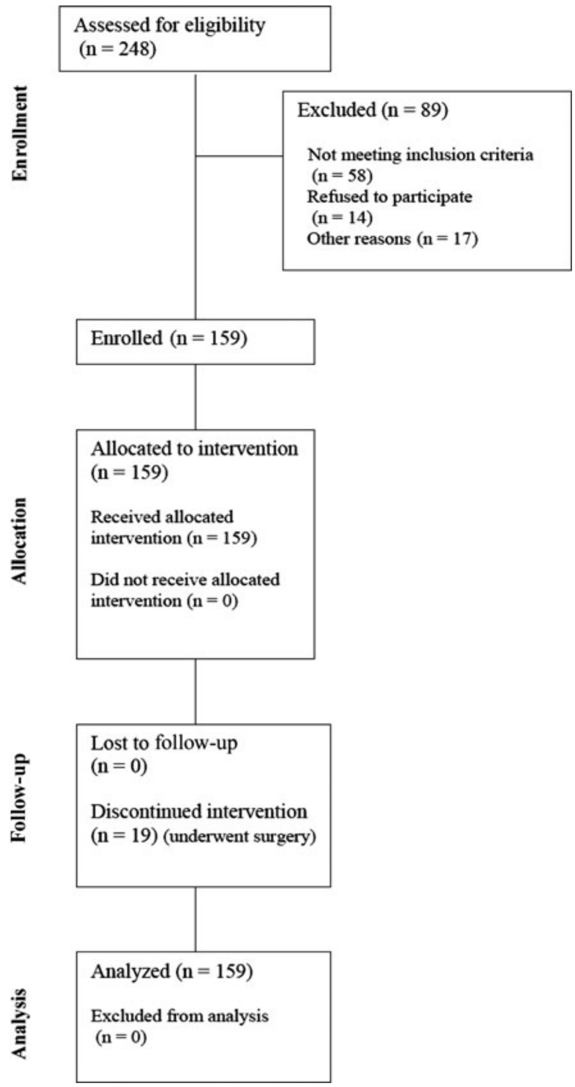

FIGURE 2. Consort diagram and flowchart of the study.

Mean AIR score was 4.9 (range, 3–10), and mean Alvarado score was 5.2 (range, 5–9).

One hundred sixteen patients (73%) were assessed by US, and for 88 patients (76%), US scans were positive for at least one of the following findings: enlarged appendix more than 6 mm, fluid-filled appendix, loculated pericecal fluid, free intraperitoneal fluid, appendicolith, increased periappendiceal echogenicity, hypoechoic appendix, echogenic submucosa, lack of compressibility, and inflamed periappendiceal fat. In 27 patients (17%), a completion CT scan was requested and 21 (78%) had a CT finding consistent with inflamed but not perforated appendix. CT findings suggestive of acute appendicitis included direct signs such as thickened appendiceal diameter, thickened appendiceal wall, and distended appendiceal luminal diameter and indirect signs such as the presence of periappendiceal inflammatory changes (fat stranding, fluid collection, phlegmon, or abscess formation), appendicolith, adjacent adenopathy, and adjacent bowel wall thickening.

To obtain a CT scan was the decision of the consultant surgeon, and this was usually requested as a second-level diagnostic tool to rule out free perforation or large abscesses in patients who had high scores, or in case of persisting diagnostic doubts and for differential diagnosis, especially in older patients to rule out masses or intra-abdominal collections of extra-appendiceal origin (ie, colonic or gynecological cancer, diverticulitis with or without abscesses, Hinchey II pelvic collections), which may need surgical treatment.

All 159 patients underwent observation and NOM with amoxicillin/clavulanate. Reassessment and enrollment for further follow-up were performed 5 days later as outpatient. Long-term follow-up was done at 7, 15 days, 6 months, and 1 and 2 years (see Fig. 1 for tempogram). Patient characteristics, Alvarado and AIR score distribution of included patients, incidence of diagnostic imaging use, and sensitivity of US/CT are shown in Table 3.

Short-term (<7 days) NOM failure rate was 11.9%; 68.5% of these patients (n = 13) who failed NOM with amoxicillin/clavulanate were defined at admission as having probable appendicitis (according to Alvarado score of 7–8) and 31.5% (n = 6) as equivocal for acute appendicitis (Alvarado score 5–6). All patients with initial failures were operated on within 7 days. At 15 days, no early recurrence was recorded. At 6 months, 17 additional recurrence episodes (10.7%) were recorded; 10 of these were successfully treated with a further antibiotic cycle. At 1 year, only 3 further recurrence episodes later than 6 months from the index episode occurred (meaning a recurrence rate at 1 year of follow-up of 12.6% or 20/159). Two years of follow-up showed a recurrence rate of 13.8% (22/159 patients) (Table 4); overall, 14 of 22 patients who experienced recurrence were again nonoperatively treated with a further cycle of amoxicillin/clavulanate with successful outcome, whereas 8 patients who developed a recurrence needed surgery. Antibiotic treatment proved to be safe because no major side effects, such as allergic reactions, were registered. Minor treatment-related side effects (ie, bloating, diarrhea, flatulence, nausea, vomiting) were reported by only 19 patients (11.9%) during the first 15 days after beginning the antibiotic treatment.

Abdominal pain was assessed by NRS and VAS scores; median NRS score was 3 at 5 days and 2 after 7 days. Mean VAS score after 15 days was 1.3 (SD = 0.6). Long-term efficacy was 83% (no need for surgery after 1 year of follow-up: 120 patients recurrence free and 12 patients who experienced recurrence were conservatively managed). Long-term efficacy after 2 years still remained 83%, because 118 patients did not experience recurrence whereas 14 of these overall were conservatively treated. Mean length of hospital stay of nonoperatively managed patients was 0.4 days. Mean sick leave period 5.8 days. Mean number of outpatient follow-up appointments was 1.3 (Table 3). Cost analysis showed overall costs of NOM and antibiotics to be €316.20 per patient (antibiotic: €14.80/patient; length of hospital stay: €180/patient, outpatient clinic follow-up: €4.20/patient, sick leave days: €117.20/patient) (Table 5). None of the single factors forming Alvarado or AIR score was an independent predictor of either NOM failure or long-term recurrence after multivariate analysis. Alvarado and AIR scores were the only independent predictive factors of NOM failure after multivariate analysis, with the latter performing much better in terms of statistical significance ($P < 0.005$ and $P < 0.001$, respectively), but neither one did correlate with recurrences (Table 6).

The outcomes of the patients who underwent surgery for failure or recurrence were as follows: 17 of 19 patients who had early failure of NOM presented at surgery with a variable degree of acute appendiceal inflammation (phlegmonous/gangrenous/perforated appendicitis). Two female patients had pelvic inflammatory disease and complicated tubo-ovarian abscess in contiguity with secondary inflamed appendix, respectively. No major complications were observed after surgery (appendectomy) in these 19 patients failing NOM. Incidence of intra-abdominal abscess was 1 of 19 and that of surgical site infection 6 of 19. No excessive incidence of complication after surgery was observed in this subset of patients compared with

TABLE 3. Characteristics of Included Patients

Characteristics of included patients	
Male vs female	41 vs 118
US done	116 (73%)
US positive*	88 (76%)
CT scan done	27 (17%)
CT scan positive (NPA†)	21 (78%)
Clinical diagnosis *only* of acute appendicitis	16 (10%)
Alvarado score 5–6 (62 patients)	40.2%
Alvarado score 7–8 (81 patients)	51%
Alvarado score 9 (14 patients)	8.8%
AIR score 3–4 (61 patients)	38.3%
AIR score 5–8 (80 patients)	50.3%
AIR score 9–10 (18 patients)	11.3%
Minor side effects (eg, bloating, diarrhea, flatulence, nausea, or vomiting)	11.9%
Results	
Long-term efficacy after 1 yr	83%
Long-term efficacy after 2 yr	83%
Abdominal pain at 5 d (median NRS score)	3
Abdominal pain at 5 d (median NRS score)	2
Abdominal pain at 5 d (mean VAS score)	1.3
Length of hospital stay‡	0.4
Sick leave period‡	5.8
No. follow-up (outpatient) appointments‡	1.3

*US positive for at least one of the following: **enlarged appendix >6 mm, fluid-filled appendix, loculated pericecal fluid, free intraperitoneal fluid, appendicolith, increased periappendiceal echogenicity, hypoechoic appendix, echogenic submucosa,** lack of compressibility, inflamed periappendiceal fat.
†Nonperforated appendicitis with CT findings consistent with inflamed but not perforated appendix.
‡Mean value (days).

TABLE 5. Cost Analysis

	Cost Analysis of NOM per Patient
Overall costs	€316.20
Antibiotics	€14.80
Length of hospital stay	€180
Outpatient follow-up	€4.20
Sick leave days	€117.20

TABLE 4. Results: 2 Years of Follow-up With Failure (Within 7 Days) and Relapse Rates

Time	7 d	15 d	6 mo	1 yr	2 yr
Rate	11.9%*	0%	10.7%	12.6%	13.8%
No. patients	19/159 failures	0/159 recurrences	17/159 recurrences	20/159 recurrences	22/159 recurrences
Therapy	19 O.R. <7 d†	—	7/17 O.R. 10/17 NOM	8/20 O.R. 12/20 NOM	8/22 O.R. 14/22 NOM

*68.5% had an Alvarado score of 7–8 (probably appendicitis) and 31.5% had Alvarado score of 5–6 (equivocal for acute appendicitis).
†All patients with initial failures underwent surgery within 7 days.
O.R., indicates operating room.

TABLE 6. Univariate and Multivariate Analyses of Prognostic Factors Predictive of NOM Failure

	Univariate Analysis, *P*	Multivariate Analysis, *P*
Vomiting	0.515	ns
Nausea or vomiting	0.423	ns
Anorexia	0.652	ns
Pain in RLQ	0.098	ns
Migration of pain to the RLQ	0.125	ns
Rebound tenderness/muscular defense	0.076	ns
Body temperature	0.085	ns
Leukocytosis shift	0.152	ns
Polymorphonuclear leukocytes	0.058	ns
White blood cell $>10 \times 10^9$ /L	0.239	ns
C-reactive protein	0.071	ns
Sex	0.186	ns
Age	0.240	ns
Alvarado score	0.003	<0.05
AIR (Andersson) score	0.001	<0.01

those patients who were not included in the study and treated by immediate appendectomy. Among the 8 of 22 patients who developed recurrences during follow-up and underwent surgery, 6 had acute appendicitis and 2 female patients had pelvic inflammatory disease.

DISCUSSION

Different meta-analyses have been published in the past few years concerning NOM of acute appendicitis. Varadhan et al,[36] in a meta-analysis of RCTs of antibiotic therapy versus surgery for acute appendicitis, examined 350 patients treated with antibiotic therapy for suspected acute appendicitis and found a 68% success rate with antibiotics alone and a trend toward a reduced risk of complications while the recurrence rate was 15%. Another meta-analysis and systematic review about the use of antibiotics alone for treatment of uncomplicated acute appendicitis[37] included a total of 1201 patients reported a failure rate in patients treated with antibiotics alone of 6.9% ± 4.4% and a rate of recurrent appendicitis of 14.2% ± 10.6%. However, in 2011, another systematic review concluded that appendectomy remains the standard of treatment of acute appendicitis because the reported rate of success for patients treated with antibiotics alone was 73.4% versus 97.4% for those treated with appendectomy.[38] A meta-analysis of RCTs published by Mason et al[12] showed that NOM of uncomplicated appendicitis with antibiotics was associated with a significantly fewer complications, better pain control, and shorter sick leave, but overall had an inferior efficacy, due to the higher rate of recurrence than appendectomy (failure rate 40.2% vs 8.5%). Most recent meta-analysis published in 2012 by Varadhan et al, concerning safety and efficacy of antibiotics compared with appendectomy for the treatment of uncomplicated acute appendicitis, concluded that an early trial of antibiotics merits consideration as the initial treatment option for uncomplicated appendicitis, reporting a success rate at 1 year for antibiotics of 63%.[39] When the issue moves to appendicitis complicated by abscess or phlegmon, the data support the practice of nonsurgical treatment without interval appendectomy, with a failure rate of 7.2% and a risk of recurrence of 7.4%.[40]

Our group has also published a meta-analysis of RCTs in 2011, analyzing the efficacy of antibiotic treatment of acute appendicitis compared with surgery, and the conclusion was that although preliminary results suggested that a nonsurgical approach can be safe and practical, thereby reducing complications, posttreatment pain, recovery time, and expenses, the low efficacy made evident by the treatment failure rates and acute appendicitis recurrences meant that antibiotic regimens cannot be recommended as a viable alternative to surgery.[41]

Given that this topic represents a significant matter of debate, application of all these results to the daily clinical practice might be an issue of relevant importance. This is the reason why using this observational study and a standardized diagnostic approach (Alvarado/AIR score), we aim to take a first step toward the development of more accurate diagnostic-therapeutic algorithm, which can be used to avoid risks, complications, and costs of needless surgery.

Considering our main objective, which was to analyze the utility of a thorough clinical evaluation, performed by Alvarado and AIR scores, in diagnosing acute appendicitis and addressing it to the correct therapeutic pathway, our relapse rates of 12.6% at 1 year and of 13.8% at 2 years proved to be better than chance. A success rate of 87.4% highly supports the effectiveness of these scores.

The use of Alvarado score may be a bias of our study, given the preponderance of females in our population (74%), because Alvarado score has been noted to significantly overpredict appendicitis in females.[42] However in our experience, the combination of Alvarado and AIR scores may significantly reduce the risk of overpredicting acute appendicitis and reach a diagnostic performance as highly reliable as a CT scan, thus avoiding the routine use of CT and reducing costs and utilization of hospital resources and the potential risks of radiation/contrast exposure. In a study including 941 consecutive patients with a suspicion of acute appendicitis, the AIR score with an area under the receiver operating characteristic curve of 0.96 performed significantly better than the area under the curve of 0.82 of the Alvarado score ($P < 0.05$).[43] Another study including 664 patients with a suspicion of appendicitis (37% females) showed that higher Alvarado scores were significantly associated with pathologically confirmed appendicitis (high scores 96%), but even the low and moderate likelihood score groups were associated with an 87% to 92% probability of pathologically confirmed appendicitis.[44]

To our knowledge, radiological imaging has never proven a comparable reliability. Abdominal US, as we all know, is a subjective examination and is not usually necessary for diagnosing appendicitis and deciding its further treatment. More recently, Vons et al[45] tried to introduce an emergency routine CT scan as a standard procedure to address an uncomplicated acute appendicitis to the correct therapeutic pathway; this randomized control trial evaluated noninferiority of antibiotic therapy (amoxicillin plus clavulanic acid) to emergency appendectomy for the treatment of uncomplicated acute appendicitis to identify predictive markers on CT scans that could enable improved targeting of antibiotic treatment. The first concern is the method of choice for diagnosing acute appendicitis, which in this study was a CT scan. Diagnosis of appendicitis was made exclusively by an emergency radiologist based only on CT imaging and not on any clinical finding and/or physical examination. Several patients may present CT findings suggesting appendicitis but not have a real acute appendicitis, or on the contrary, patients with a clinically clear acute appendicitis may not have a visible appendix on a CT scan. To diagnose acute appendicitis by a CT scan may represent a dangerous attitude. Furthermore, one of the exclusion criteria considered by the authors was the presence on a CT scan of periappendiceal fluid, which might appear questionable because periappendiceal fluid can be a common radiological finding in acute appendicitis even in uncomplicated cases. A further word of caution should also be raised when interpreting the incidence of postoperative peritonitis in the group of antibiotics-treated patients who failed and underwent secondary appendectomy and subsequently developed postoperative peritonitis. The incidence of postoperative peritonitis in this latter group should not be considered as 2% but rather as high as 22.2% (2/9 patients who had complicated appendicitis with peritonitis identified at surgery), and this risk represents in our opinion a relevant expression of concern.

A further criticism is the longer hospital stay of the NOM patients. It is relevant that patients treated with antibiotics had a mean length of hospital stay of 4 days, and the appendectomy group stayed in the hospital on average for 3 days ($P = 0.08$). If these are the results of NOM, antibiotic treatment does not seem a cost-effective treatment option for acute appendicitis.

Other authors have also criticized the main criterion of inclusion of this study, which was an appendix diameter of more than 6 mm on the CT scan, which can be found in a large proportion of a control population[46] and also the fact that for females recruited in this study, the diagnosis of uncomplicated appendicitis based on clinical and CT appearance, without a diagnostic laparoscopy, was unreliable.[47] Nonetheless, a CT scan remains an expensive examination and its routine application in an emergency department for a simple RIF pain from suspected appendicitis remains matter of debate. A CT scan is not without risks and potential drawbacks, related to the risks of contrast administration, exposure to ionizing radiation, and costs. An estimated 2% incidence of future cancers has been reported as being caused just by CT scans, and this potential risk can not be neglected.[48] Many patients in whom appendicitis is suspected are children or young adults,[49] and radiation exposure from CT scans is of particular concern in this population, especially in females of childbearing age. Although the issue is debatable, concern that even a single typical abdominal CT examination may confer a small but real risk of carcinogenesis is increasing.[50,51]

An interesting recent series of 664 patients assessed using the Alvarado score from the study of Nelson et al[44] demonstrated that the negative appendectomy rate for patients with clinical assessments consistent with appendicitis was 4%, compared with 3% associated with CT. The authors conclude that that multiple studies have shown that surgeons' clinical assessments alone are not only highly accurate at diagnosing acute appendicitis but comparable with CT and, given the increasing evidence that CT is not without its own associated risks, only when scores are between 4 and 6 should admission and observation or complementary tests such as US or CT be performed. CT may be useful only in cases of diagnostic uncertainty or those with atypical presentations, as commonly occurs with older patients.

Once the clinical evaluation proved to address patients to the correct therapeutic pathway and NOM proved to be effective, we performed a multivariate analysis for identifying those components with a predictive value, but none of the factors included within the Alvarado or AIR score, analyzed alone, was an independent predictor of failure of NOM or of long-term recurrence, whereas when combined together within both the clinical scores, they were the only independent predictor of NOM failure.

Given a strict respect of inclusion and exclusion criteria combined together with a good clinical practice based on a careful surgeon's judgment and use of validated clinical scores, a reliable diagnosis can be made with acceptable accuracy and without need of further costs and time in imaging tests. This can also avoid radiation exposure and un-necessary operations. Based on this premises, the present study moved a first step toward the development of an accurate diagnostic-therapeutic algorithm, which may be applied to avoid unnecessary appendectomies, thus reducing operation rate, surgical risks, and overall costs.

CONCLUSIONS

These results demonstrate that if patients are correctly addressed to the proper treatment option, starting from correct clinical evaluation, antibiotic therapy for suspected acute appendicitis is safe and effective. After 2 years of follow-up, recurrences of suspected acute appendicitis NOM with antibiotics are lower than 14% and may be safely and effectively treated with further antibiotics. NOM seems therefore to be safe and cost-effective and associated with a short sick leave time (5.8 days in our study vs average sick leave after appendectomy of 10 days). Reducing operative rate of such a common condition may also have an additional impact on human and surgical operating room resource utilization and have a further positive impact on social and health care costs.

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Author contribution is as follows: Study conception and design: Tugnoli, Di Saverio; acquisition of data: Tugnoli, Sibilio, Giorgini, Biscardi, Villani, Di Saverio; analysis and interpretation of data: Di Saverio, Giorgini, Sibilio, Tugnoli, Smerieri, Biscardi, Villani, Coccolini, Pisano, Sartelli, Catena, Ansaloni; drafting of manuscript: Di Saverio, Sibilio, Tugnoli, Giorgini; critical revision: Di Saverio, Sibilio, Tugnoli, Smerieri, Giorgini, Biscardi, Villani, Coccolini, Pisano, Catena, Sartelli, Ansaloni; final approval of the version to be submitted; Di Saverio, Tugnoli, Sibilio, Giorgini, Biscardi, Villani, Coccolini, Smerieri, Pisano, Sartelli, Catena, Ansaloni.

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