


Laparoscopic appendectomy vs antibiotic therapy for acute appendicitis: a propensity score-matched analysis from a multicenter cohort study

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Abstract Acute appendicitis (AA) is among the most common causes of acute lower abdominal pain leading patients to the emergency department. Significant debate remains on whether AA should be operated or not. A propensity score-matched analysis was performed in seven Italian Hospitals, with the aim to assess safety and feasibility both nonoperative management with antibiotics (AT) and surgical therapy with appendectomy (ST) for patients with AA. Data regarding all patients discharged from the participating centers with a diagnosis of appendicitis from January 1st, 2014 to December 31st, 2014 were collected retrospectively. Follow-up data were collected from January 1st, 2015 to December 31st, 2016. The complication-free treatment success of AT (53.7%) was significantly inferior to that of ST (86.4%)

($P < 0.0001$). Patients initially treated with antibiotics reported an index admission AT failure rate of 20.9% and a recurrence rate at 1-year follow-up of 20.3%. No statistically significant difference was found when comparing AT and ST groups for the outcome of interest post-operative complications (13.5 vs 13.6%, $P = 0.834$). Patients treated with AT were discharged home earlier than patients in the ST group (3.38 ± 1.89 vs 4.84 ± 2.69 days, $P < 0.0001$). Due to the low rates of complications occurred in the ST group and the high efficacy of the surgical therapy, laparoscopic appendectomy still represents the most effective treatment for patients with AA. AT is associated with shorter hospital stay and faster return to normal activity, and may prevent from appendectomies around 80% of patients who leave the hospital with clinical recovery.

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Abbreviations

AA	Acute appendicitis
LA	Laparoscopic appendectomy
OA	Open appendectomy
AT	Antibiotic therapy
ST	Surgical therapy
AIR	Appendicitis inflammatory response
US	Ultrasound scan
CT	Computed tomography
MRI	Magnetic resonance imaging
RCTs	Randomized controlled trials

Introduction

Acute appendicitis (AA) is among the most common causes of acute lower abdominal pain leading patients to the emergency department, with a lifetime prevalence of about 7% and highest incidence in the second decade of life [1].

AA is heterogeneous in terms of presentation, clinical evolution, and pathological aspects. Most cases are uncomplicated. However, in about 20% of cases, AA is presenting on clinical onset with gangrene, abscesses, localized or diffuse peritonitis [2].

Despite all the improvements in the diagnostic process, significant debate remains on whether AA should be operated or not [3].

Since Lawson Tait performed successfully the first appendectomy in 1880, surgery has been the most widely accepted treatment of choice. Approximately 300,000 people undergo appendectomy each year in the US [4]. Current evidence suggests laparoscopic appendectomy (LA) be the most effective surgical treatment, being associated with lower incidence of wound infections and post-operative morbidity, a shorter hospital stay and better quality of life scores when compared to open surgery [5].

In 1886, Fitz reported that many autopsies specimens were showing pathologic signs consistent with AA, therefore, hypothesizing that in some patients, the disease could resolve without any surgery [6]. In 1953, Harrison reported 42 of 47 cases of AA being successfully treated using antibiotics and Coldrey in 1956 published the data on 471 patients with AA treated conservatively, with low morbidity, mortality (0.2%), and recurrence rates (14.4%) [7, 8].

Over the past 20 years, there has been a renewed interest in the conservative management both uncomplicated (non-perforated) and complicated (gangrenous and perforated) forms of AA, probably due to a more precise analysis of the incidence of post-operative complications and the increasing costs of surgical interventions, which are mostly related to the spreading use of laparoscopic approach [9–12].

Several studies have been published on conservative management of AA to date [10, 13–15]. However, in the

vast majority of cases, they compared outcomes achieved by either open appendectomy (OA) and antibiotic treatment (AT). Open procedures accounted for 81.4% of all appendectomies analyzed in the randomized controlled trials published to date [16].

As we are currently in the “laparoscopic era”, applying the findings of these studies in the daily practice would be difficult. In Italy, more than 75% of acute appendicitis are nowadays approached by laparoscopy, and the clinical outcomes achieved by an open approach (length of hospital stay, time to return to normal activities, complication rates, etc.) cannot be applied to our usual practice [17].

Since several relevant questions remain unanswered about nonoperative management of AA, we carried out a propensity score-matched analysis from the data of a multicenter retrospective cohort study, with the aim to assess safety and feasibility both nonoperative management with antibiotics (AT) and surgical therapy with appendectomy (ST) through the analysis of efficacy rates, incidence of recurrence, complications, length of hospital stay, and time to return to normal activity.

Methods

This propensity score-matched analysis comparing AT and ST for patients with acute appendicitis was performed in seven Italian Hospitals registered in the database of the Italian Ministry of Health.

Approval of Ethical Committee was obtained (Acceptance Code: Independent Ethical Committee of the University of Cagliari, PG/2016/7825, 31/05/2016).

The study has been approved by the board of all the hospitals involved and carried out in agreement with the Helsinki Declaration. All parts of the study and the present manuscript have been checked and presented according to the checklist for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [18]. A written informed consent for the treatment of personal and sensible data was obtained from all patients prior to the data collection and evaluation.

Data regarding all patients discharged from the participating centers with a diagnosis of appendicitis from January 1st, 2014 to December 31st, 2014 were collected retrospectively. Follow-up data were collected from January 1st, 2015 to December 31st, 2016.

Every patient with a clinical suspicion of AA was assessed first through physical examination performed by the on-call general surgeon, second through blood tests, including white blood cell count, polymorphonuclear cells count, C-Reactive Protein levels, and calculation of the Appendicitis Inflammatory Response (AIR) score [19]. Abdominal US and/or CT scan was performed in selected patients, depending on the on-call surgeon’s clinical judgement.

Patients without a direct surgical indication were initially managed conservatively with antibiotics, serial abdominal examinations, and blood tests. Patients were assigned to the surgical treatment group if they received immediate surgical treatment (laparoscopic or open appendectomy, depending on the on-call surgeon's decision) or were treated with a surgical approach within the first 12 h, based on clinical discretion of the on-call surgeon, according to current good surgical practice and availability of the operating theatre. Patients managed conservatively received one of the following parenteral antibiotic treatments: Piperacillin/Tazobactam (4.5 g) three intravenous administration per day; Ceftriaxone (2 g) once per day or Ciprofloxacin (500 mg) twice per day plus Metronidazole (500 mg) three times per day; Amoxicillin/Clavulanic acid (2 g) four times per day for a length depending on the clinical conditions; and Ertapenem (1 g) one administration per day for 3 days. Patients were discharged with oral antibiotics (amoxicillin/clavulanic acid or ciprofloxacin) for at least 4 days.

Inclusion criteria

- Signed informed consent for the treatment of personal and sensible data.
- Age range 18–65 years.
- Diagnosis of AA made using the appendicitis inflammatory response (AIR) score, eventually confirmed by ultrasound and/or CT scan in selected patients, depending on the on-call surgeon's judgement.

Exclusion criteria

- Pregnant or lactating.
- Non-consenting patients.
- Positive diagnosis for inflammatory bowel disease (IBD).
- Clinical diagnosis of diffuse peritonitis, confirmed by CT scan.
- Appendectomy performed as an elective procedure.
- Appendectomy performed during other abdominal surgical procedures.
- Previous hospitalization for acute appendicitis treated conservatively.

Definition of outcomes

Primary outcome

- Treatment efficacy was defined as “complication-free treatment success based on 1-year follow-up” (success of the initial treatment with uncomplicated course: no

post-operative complications, adverse events, or treatment failure occurring).

Secondary outcomes

- Index admission antibiotic therapy failure: failure of AT during initial hospitalization (lack of efficacy in the AT group intended as non-resolving AA).
- Recurrence at 1-year follow-up. Recurrence of AA was defined as an episode of appendicitis being diagnosed again after the initial antibiotic treatment was completed and the patient had been discharged home.
- Analysis of treatment modality for index admission antibiotic failures and recurrences (further cycles of AT or ST).
- Overall post-intervention complications, assessed by the Dindo–Clavien Classification. The number and rate of abscesses, post-operative peritonitis, surgical site infections, incisional hernias, incisional pain, or obstructive symptoms and other general complications. Complications were analyzed both for patients who underwent ST as primary treatment and for those who underwent surgery as second line approach, after the failure of AT.
- Length of primary hospital stay.
- Time to return to normal activities: rates of patients who returned to normal activities within 2 weeks from the treatment.

Theory/calculation

Statistical Package for the Social Sciences (SPSS), version 22 (SPSS Inc., Chicago, IL, USA) has been used to carry out the statistical analysis. Dichotomous variables have been expressed as numbers and percentages, while continuous variables as mean and standard deviation (SD). Student's *t* test or ANOVA have been used for comparisons of continuous variables between groups. Chi-square test or Fisher's exact test, as appropriate, have been used for analysis of categorical data. Results of univariate analysis were expressed as follows: odd ratios (OR) for dichotomous outcomes and β -coefficients for continuous outcomes, both with the correspondent 95% confidence intervals (95% CI). The Propensity Score (PS) model was calculated considering the following variables as covariates: age, sex, AIR score on admission and pre-intervention diagnosis [20]. Treated patients (AT group) and controls (ST group) were matched using “nearest neighbour 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 has been used to investigate clinical, laboratory, and radiologic variables

(independent variables) predictive of conservative treatment failure and success (dependent variable) using the STATA/SE, version 14 (StataCorp LP, College Station, TX, USA). A value of $P < 0.05$ was considered statistically significant.

Sample size calculation

Prior 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 [21]. We estimated that a minimum of 76 patients per group would yield a power of 0.90 ($1 - \beta$) to establish whether appendectomy was superior to antibiotic-first treatment using a one-sided significance α 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.

Results

A total of 502 clinical records were identified and reviewed. 46 patients had a diagnosis of diffuse peritonitis from ruptured appendicitis confirmed by CT scan, and were excluded from the analysis. Of the 456 patients who met the inclusion criteria, 78 (17.1%) were lost to follow-up or excluded because of incomplete/incongruous follow-up data availability. Mean follow-up period was 20 ± 4 months. According to our selection criteria, 378 patients were available in our database for complete follow-up. Matching was not possible for 32 patients of the surgical group.

The matched group was composed of 162 patients (46.8%) submitted to AT and 184 patients (53.2%) to ST. Within the latter group, 157 patients (85.6%) and 27 patients (14.4%) underwent LA and OA. No statistically significant difference was found in the rate of LA when comparing the surgical technique adopted in ST group and in the subgroup of patients who underwent surgery after failure of the antibiotic strategy (LA 80.3% and OA 19.7%).

The rate of complicated appendicitis identified at the time of surgical operation did not show any statistically significant difference between the two groups (29.4 and 23.8% in the AT and ST groups, respectively; $P = 0.519$).

The general characteristics of patients enrolled in the study (pre-matching and post-matching groups) are shown in Tables 1 and 2.

Treatment efficacy

A higher rate of efficacy was found in the ST group when compared with the AT group. Taking into account any kind

of post-interventional complication (post-operative complications, adverse events, and treatment failure), the post-matching analysis showed that the complication-free treatment success of AT (53.7%) was significantly inferior to that of ST (86.4%) (OR 5.482, 95% CI 3.250:9.247, $P < 0.0001$).

Patients initially treated with antibiotics reported an index admission AT failure rate of 20.9% and a recurrence rate at 1-year follow-up of 20.3%.

The post-matching analysis of treatment modality for index admission antibiotic failures and recurrences showed that all patients who reported an index admission failure were subsequently treated with surgery, whereas 33.3% of patients diagnosed with a recurrence was successfully managed with a further cycle of antibiotics. Results are shown in Table 3.

Post-operative complications

At the post-matching analysis, no statistically significant difference was found when comparing AT and ST groups for the outcome of interest post-operative complications (13.5 vs 13.6%, OR 1.06, 95% CI 0.449:2.502, $P = 0.834$). Complications after surgery for patients who experienced an index admission AT failure accounted for 2.9%, whereas 8.7% of patients reported a complication after appendectomy performed for a recurrence of acute appendicitis (Table 3). Complications following appendectomy as the first-line approach were 4 abscesses, 1 cardiovascular complication, 3 hemorrhages from the trocar sites insertion, 6 surgical site infections, and 11 other general complications. According to the Dindo–Clavien classification of surgical complications, 15 grade I (8.15%), 5 grade II (2.72%), 2 grade IIIa (1.09%), and 3 grade IIIb (1.63%) complications were reported. Conversely, in the AT group patients who were submitted to surgery, 3 grade I (3.57%), 2 grade II (1.78%), and 3 grade IIIb (3.57%) complications were recorded.

Length of hospital stay and return to normal activity in 2 weeks

Data on length of primary hospital stay demonstrated that patients successfully treated with AT were discharged home earlier than patients in the ST group, with a statistically significant difference (3.38 ± 1.89 vs 4.84 ± 2.69 days, $\beta = 2.17$, 95% CI -2.60 : -1.73 , $P < 0.0001$). Conversely, the length of hospital stay in the subgroup of patients who underwent surgery for index admission antibiotic-first strategy failure was 5.32 ± 3.02 days, with no statistically significant difference when compared to the outcome in the ST group (5.32 ± 3.02 days, $\beta = 0.480$, 95% CI -1.489 : 0.529 , $P = 0.437$).

Table 1 General characteristics of the patients enrolled in the study

	Pre-matching sample			Post-matching sample		
	Antibiotic-first therapy	Surgery-first therapy	<i>P</i> value	Antibiotic-first therapy	Surgery-first therapy	<i>P</i> value
Demographic characteristics						
Patients enrolled: <i>n</i> (%)	162 (42.8)	216 (57.2)		162 (46.8)	184 (53.2)	
Age (mean ± SD)	33.6 ± 16.5	34.2 ± 16.8	0.346	33.6 ± 16.5	35.8 ± 17.2	0.892
Sex M:F (M% vs F%)	63:99 (38.9 vs 61.1)	113:103 (52.3 vs 47.7)	0.010	63:99 (38.9 vs 61.1)	86:98 (46.8 vs 53.2)	0.251
Diagnostic workup						
Clinical and laboratory alone: <i>n</i> (%)	64 (39.5)	73 (33.8)	0.280	64 (39.5)	64 (34.8)	0.435
Ultrasound scan: <i>n</i> (%)	90 (55.6)	108 (50)	0.299	90 (55.6)	94 (51.1)	0.516
CT scan: <i>n</i> (%)	3 (1.8)	21 (9.7)	0.002	3 (1.8)	14 (7.6)	0.013
Ultrasound scan + CT scan: <i>n</i> (%)	5 (3.1)	14 (6.5)	0.158	5 (3.1)	12 (6.5)	0.211
Pre-operative characteristics						
AIR score (mean ± SD)	6.1 ± 1.3	6.9 ± 1.9	0.002	6.1 ± 1.3	6.3 ± 1.5	0.188
AIR score range: <i>n</i> (%)						
AIR < 5	83 (51.2)	75 (34.7)	0.001	83 (51.2)	74 (40.2)	0.052
AIR 5–8	75 (46.3)	123 (56.9)	0.048	75 (46.3)	99 (53.8)	0.196
AIR > 8	4 (2.5)	18 (8.4)	0.024	4 (2.5)	11 (5.9)	0.121
Surgical treatment^a						
Total number: <i>n</i>	56 ^b	216		56	184	
Laparoscopic: <i>n</i> (%)	45 (80.3)	182 (84.3)	0.545	45 (80.3)	157 (85.6)	0.404
Open: <i>n</i> (%)	11 (19.7)	34 (15.7)		11 (19.7)	27 (14.4)	
Antibiotic administered						Number of patients (%)
<hr/>						
Antibiotic-first treatment group						
Piperacillin–Tazobactam						60 (37.0)
Ceftriaxone + Metronidazole						30 (18.5)
Ertapenem						29 (17.9)
Amoxicillin–Clavulanic acid						28 (17.3)
Ciprofloxacin + Metronidazole						15 (9.3)

SD standard deviation, AIR appendicitis inflammatory response, US ultrasound scan, CT computed tomography

^aIn the antibiotic-first therapy group after failure of primary treatment and subsequent surgery

^b34 index admission failures + 22 recurrences treated by surgical approach

Similarly, at the post-matching analysis, patients successfully treated with antibiotics had a faster return to normal daily life. In fact, 93.7% of them returned to normal activities in 2 weeks, whereas only 76.1% of patients in the ST did (OR 5, 95% CI 3.146:7.945, *P* < 0.0001), as shown in Table 3.

Multiple logistic regression analysis

Age, sex, AIR score, classification of the disease (uncomplicated or complicated), time from the onset of symptoms to the administration of antibiotic therapy, and the type of antibiotics used were included as variables in a multiple logistic

model. Among these variables, it was possible to include only age and AIR score (in two classes: < 5 and ≥ 5). Sex, classification of the disease, and duration of the symptoms considered individually were not associated with the identified outcome variable (success vs failure of antibiotic therapy). The results of the multiple logistic regression analysis showed that the risk of the antibiotic-first strategy failure increased with increasing age (OR 1.027; *P* = 0.018; 95% CI 1.004–1.049), and with AIR scores ≥ 5 (OR 3.236; *P* = 0.006; 95% CI 1.405–7.458), although a specific age interval related to an augmented risk of AT failure was not identified.

Table 2 Pre-operative vs intra-operative diagnoses

	Pre-matching sample			Post-matching sample		
	Antibiotic-first therapy	Surgery-first therapy	<i>P</i> value	Antibiotic-first therapy	Surgery-first therapy	<i>P</i> value
Pre-operative diagnosis: <i>n</i> (%)						
Uncomplicated acute appendicitis ^a	148 (91.3)	179 (82.8)	0.021	148 (91.3)	158 (85.9)	0.130
Complicated acute appendicitis ^b	14 (8.7)	37 (17.2)		14 (8.7)	26 (14.1)	
Intra-operative diagnosis ^c						
Uncomplicated acute appendicitis ^d	24 (70.6)	157 (72.7)	0.001	24 (70.6)	140 (76.2)	0.519
Complicated acute appendicitis ^e	10 (29.4)	59 (27.3)		10 (29.4)	44 (23.8)	

^aWithout gangrene or localized abscess

^bWith gangrene or localized abscess

^cIn the antibiotic-first therapy group after index admission failure of primary treatment and subsequent surgery

^dWithout gangrene, localized abscess, or diffuse peritonitis

^eWith gangrene, localized abscess, or diffuse peritonitis

Discussion

Several questions remain unanswered when talking about safety and feasibility of nonoperative treatment with antibiotics for patients with acute appendicitis.

The first question concerns efficacy.

The choice of the primary outcome measure used to compare such different treatment strategies may represent a difficult step.

In the trial published by Hansson et al., efficacy for AT was defined as achieving a definitive improvement without requiring surgery within a median follow-up of 1 year. Lack of efficacy in the AT group included both index admission treatment failure of antibiotic therapy during the hospitalization and recurrences. On the other hand, efficacy for the ST was defined as AA confirmed at the time of the surgical operation and resolution of symptoms after surgical treatment [22]. Allievi et al. recently published the results from a propensity score-based outcome analysis of conservative vs surgical management for patients with AA in which the primary outcome (failure rate) was evaluated using different definitions for the two groups of treatment. For the surgical group, failure was defined as the occurrence of pre- and post-operative complications, eventually associated with negative appendectomy. With regard to failure within the medical group, all patients who needed surgical therapy after 72 h of conservative management were accounted for as failure cases [23].

However, to allow a reliable analysis of the efficacy of the two therapeutic strategies, in our personal opinion, the primary outcome should be identical for both the branches of treatment, and combine endpoints of efficacy and safety at the same time.

The definitions of “Efficacy” and “Safety” provided by Harnoss et al. in their recent systematic review and

meta-analysis met the above-mentioned criteria. “Efficacy” was defined by the success of the initial treatment with uncomplicated course (no post-intervention complications, adverse events, or treatment failure occurring); “Safety” was defined by the absence of post-operative complications, adverse events of antibiotic treatment, and complicated progress of the disease [21].

Although in the past, the common behavior suggested that the proportion of perforations increased with the duration of symptoms and progression from an uncomplicated form of AA to perforation was considered dogmatic, an increasing amount of evidence suggests not only that not all patients with appendicitis will progress to perforation, but even that the resolution may be a common event [24]. The increasing proportion of perforations with duration of symptoms may at least partly be explained by selection of patients with perforated appendicitis because of spontaneous resolution of the non-perforated cases [25].

Regarding efficacy outcomes, the results of the present study, conducted on 346 patients with acute appendicitis, have confirmed the superiority of the ST approach, which has shown a complication-free treatment success rate of 86.4% at the post-matching analysis. Conversely, AT resulted in a 53.7% of cases successfully treated ($P < 0.0001$). 20.9% of patients initially treated with antibiotics experienced an index admission failure of the conservative treatment, whereas 20.3% presented with an episode of recurrence during the follow-up period.

It is worth noting that around 80% of patients who left the hospital with clinical recovery did not experience appendectomy within a median follow-up time close to 2 years. The same results have been recently published by Lundholm et al. in a large series of 710 patients with a mean follow-up of over 9 years [26].

Table 3 Clinical outcomes in antibiotic-first and surgery-first therapy groups for all the patients included in the study

	Pre-matching sample				Post-matching sample			
	Antibiotic-first therapy	Surgery-first therapy	OR/ β -COEFF (95% CI)	<i>P</i> value	Antibiotic-first therapy	Surgery-first therapy	OR/ β -COEFF (95% CI)	<i>P</i> value
Patients enrolled: <i>n</i> (%)	162	216	–	–	162 (46.8)	184 (53.2)	–	–
Treatment efficacy: Complication-free treatment success: <i>n</i> (%)	87 (53.7)	183 (84.8)	4.780 (2.124:2.950)	< 0.0001	87 (53.7)	159 (86.4)	5.482 (3.250:9.247)	< 0.0001
Index admission failure: <i>n</i> (%)	34 (20.9)	0 (0)	–	–	34 (20.9)	0 (0)	–	–
Recurrence at follow-up: <i>n</i> (%)	33 (20.3)	0(0)	–	–	33 (20.3)	0 (0)	–	–
Length of primary hospital stay in days (mean \pm SD) ^a	3.38 \pm 1.89	4.91 \pm 2.83	– 1.530 (– 2.035:– 1.024)	< 0.0001	3.38 \pm 1.89	4.84 \pm 2.69	– 2.17 (– 2.60:– 1.73)	< 0.0001
Length of primary hospital stay in days (mean \pm SD) ^b	5.32 \pm 3.02	4.91 \pm 2.83	– 0.410 (– 1.447:0.627)	0.437	5.32 \pm 3.02	4.84 \pm 2.69	– 0.480 (– 1.489:0.529)	0.349
Return to normal activity in 2 weeks: <i>n</i> (%)	63 (93.7)	162 (75.2)	4.714 (3.032:7.328)	< 0.0001	63 (93.7)	140 (76.1)	5 (3.146:7.945)	< 0.0001
Total number of complications (%) ^c	8 (13.5)	31 (14.3)	1.05 (0.432:2.327)	0.841	8 (13.5)	25 (13.6)	1.06 (0.449:2.502)	0.834
Complications after surgery for patients with index admission AT failure	1 (2.9)	–	–	–	1 (2.9)	–	–	–
Complications after surgery for patients with recurrent appendicitis	3 (8.7)	–	–	–	3 (8.7)	–	–	–
		Index admission failure		Recurrence		OR/ β -COEFF (95% CI)		<i>P</i> value
Treatment modality of AT failures								
Further cycles of AT		0 (0)		11 (33.3)		–		< 0.0001
Appendectomy		34 (100%)		22 (66.7)		–		

AT antibiotic therapy, SD standard deviation

^aIn the antibiotic-first therapy group for patients successfully treated with antibiotics

^bIn the antibiotic-first therapy group after failure of antibiotic strategy and subsequent index admission appendectomy

^cIn the antibiotic-first therapy group after failure of primary treatment and subsequent surgery

To date, several meta-analyses, randomized controlled trials, and propensity score-based analysis comparing AT and ST for AA have been published in the literature [10, 12, 15,

21, 23, 27, 28]. Although these studies support the evidence that the majority of patients can be treated with an antibiotic-first therapy avoiding appendectomy, contrasting data about

rates of the efficacy of antibiotic therapy, especially regarding long-term outcomes, have been obtained [22, 29].

When performing a pooled analysis of the trials published up to the current date, our group found that AT management was associated with a significantly lower treatment efficacy based on the 1-year follow-up when compared to ST (75.9 vs 98.3%). In particular, the recurrence rate was 22.5% with a mean length of time to recurrence of 4.65 months [16].

However, each trial published in the literature shows limitations in terms of patient selection bias, definition of primary endpoints, lack of a standardized computed tomography, or ultrasound scan diagnosis. Furthermore, the majority of the appendectomies performed for patients enrolled in RCTs 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 [5, 17].

Recently, the ACTUAA study has been launched, with the aim to test the hypothesis that surgical treatment with appendectomy is superior to the conservative approach with antibiotics for patients with uncomplicated acute appendicitis. It is designed as a prospective, non-randomized, controlled, open label, superiority multi-institutional trial to compare conservative treatment with antibiotics and appendectomy for patients with uncomplicated acute appendicitis confirmed by US and/or CT or MRI scan [30].

The second question is how to distinguish during patients' assessment those who might respond well to AT alone from those who would require surgery. Our attempt to identify a subgroup of patients who might be treated with antibiotics through a multivariate analysis showed that the risk of the AT strategy failure increased with increasing age and AIR scores ≥ 5 , although a specific age interval related to an increased risk of AT failure was not identified. Sex, classification of the disease (uncomplicated or complicated), time from the onset of symptoms to the administration of antibiotic therapy, and the type of antibiotics were not directly related to failure or success of the conservative treatment.

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 < $12 \times 10^9/L$, and age < 60 years had 89% of chance to recover with antibiotics without surgery [31].

A further issue concerns the treatment modality of recurrent episodes of appendicitis for patients previously treated with antibiotics. The NOTA study stated that a second attempt with AT could be a successful option for over 60% of patients who present with a recurrent episode of appendicitis at follow-up [32]. In our experience, 33.3% of patients who presented with a recurrence at follow-up were successfully treated with a further cycle of antibiotics, whereas 66.7% underwent surgery.

A further matter of debate is whether the diagnosis of AA should be necessarily performed by the US or CT scan. The WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis stated that the use of imaging techniques in the diagnostic workup should be linked to risk stratification such as AIR or Alvarado scores. Intermediate-risk classification identifies patients likely to benefit from systematic diagnostic imaging, whereas high-risk patients may not require pre-operative imaging [5].

In our study, the great majority of patients were classified with an AIR score of 5–8 (intermediate), and the diagnosis was carried out via diagnostic imaging in 63% of the patients enrolled in the study.

In the EU, only around 13% of patients undergo pre-operative 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 [33]. 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 [34].

The most common post-operative complications following an appendectomy, such as wound infections, intra-abdominal abscess, and ileus caused by adhesions may vary in frequency between open (overall complication rates 11.1%) and laparoscopic (8.7%) appendectomy [35, 36].

No statistically significant difference was found when comparing patients submitted to surgery after AT and ST for post-operative complications in our study (13.5 vs 13.6). Complications after surgery for patients who experienced an index admission AT failure accounted for 2.9%, whereas 8.7% of patients reported a complication after appendectomy performed for a recurrence of acute appendicitis.

The shorter length of hospital stay and early return to daily normal activity are two well-known advantages of the antibiotic-first management, especially in terms of cost-effectiveness. In our study, patients successfully treated with AT were discharged much earlier, with a mean length of primary hospital stay of 3.38 ± 1.89 vs 4.84 ± 2.69 of the ST group, with a statistically significant difference. In the same way, patients treated with antibiotics without surgery returned earlier to normal activity. Indeed, our results demonstrated that 93.7% of patients successfully treated conservatively returned to normal activity in 2 weeks, whereas only 76.1% of the ST group achieved the same result. Therefore, the conservative treatment may be considered advantageous from a socio-economic point of view.

Possible limitations of this study are related to its retrospective design, which carries a high risk of selection bias. In fact, we cannot exclude that AT was preferred for selected patients expected to have better chances of successful conservative treatment and better outcomes.

Moreover, although CT and US scans are thought to be the best tools, not only to diagnose acute appendicitis, but even to distinguish between uncomplicated and complicated forms, only 60 and 65% of patients in the AT and ST groups, respectively, underwent diagnostic imaging before the treatment choice. Therefore, the question is whether the rate of patients, initially treated with antibiotics and subsequently operated on during the index admission for the persistence of symptoms, was affected by a complicated form *ab initio*, or the natural history of the disease was more aggressive in this subgroup of patients. However, to overcome this limitation, a propensity score analysis with a “nearest neighbour” matching allowed us to obtain two balanced groups in terms of age, sex, laboratory variables, and pre-intervention diagnosis.

Based on this study, due to the low rates of complications occurred in the ST group and the high efficacy of the surgical therapy, laparoscopic appendectomy still represents the most effective treatment for patients with AA. However, AT is associated with shorter hospital stay and faster return to normal activity, and may prevent from appendectomies around 80% of patients who leave the hospital with clinical recovery. When a conservative treatment is attempted, surgeons must appropriately inform patients about the current evidence of the efficacy related to an antibiotic-first strategy, as well as inform about the uncertainties.

Further large prospective multicenter trials with adequate multivariate analysis are needed to identify a subgroup of patients with AA for whom antibiotic treatment can be highly effective.

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Compliance with ethical standards

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Research involving human participants and/or animals All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Independent Ethical Committee of the University of Cagliari) and with the Helsinki Declaration of 1975, as revised in 2008.

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