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ORIGINAL SCIENTIFIC REPORT

Acute Appendicitis: Still a Surgical Disease? Results from a Propensity Score-Based Outcome Analysis of Conservative Versus Surgical Management from a Prospective Database

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Abstract

Objective The aim of the present study was to compare the outcomes of conservative versus surgical treatment for acute appendicitis.

Background Although acute appendicitis is a common disease, great debate exists regarding the appropriate management of patients. Conservative treatment has shown positive results in several RCTs, eliciting questions about indications to surgery, therapeutic appropriateness and ethical conduct.

Methods Data were prospectively collected; a Propensity Score-based matching method was implemented in order to reduce bias arising from characteristics of the patients; a proportion of patients (69 in total) were excluded to obtain two comparable groups of study (1a). Main outcomes of the study were: failure rate, in-hospital length of stay (at first admission and cumulative), post-discharge absence from work. Within the medical group, failure was defined as the necessity for appendectomy after conservative treatment, while it was identified with complications and negative appendectomy within the surgical group (Failure 1). In parallel, an additional definition of failure was proposed (Failure 2) and excluded negative appendectomy from the reasons for failure within the surgical group (5b).

Results The failure rate for the conservative treatment resulted to be inferior, as compared to the surgical treatment (16.5 vs. 28.4%, OR 0.523 $p = 0.019$), considering negative appendectomy as a reason for failure. When excluding negative appendectomy from the definition of failure, medical and surgical treatment appeared to perform equally (failure rate: 16.5 vs. 18.3%, OR 1.014 $p = 0.965$). Patients managed conservatively showed to have a shorter length of stay at first admission than the patients who underwent appendectomy (3.11 vs. 4.11 days, $\beta = -0.628$ days, $p < 0.0001$). A lower number of lost work days after discharge resulted from a conservative approach (6 vs. 14.64 days, $\beta = -8.7$ days, $p < 0.0001$).

Conclusions Considering each outcome as part of a wide-angle analysis, the conservative management of acute appendicitis resulted to be safe and effective in the selected group of patients. In terms of failure rate, the medical treatment resulted to perform as effectively as surgical treatment, if negative appendectomy was excluded from failure, or better, when negative appendectomy was included in the definition of failure. A diminished length of stay during the first admission and a reduced number of lost work days were evident with a conservative approach. The comparison between medical and surgical treatment for acute appendicitis requires a change in perspective, from a spare 'effectiveness analysis' to a more thorough 'appropriateness analysis': in the present study, the conservative treatment showed to address the clinical requirements in terms of therapeutic appropriateness. Although acute appendicitis is considered a 'surgical disease', increasing evidence supports the effectiveness and safety of a conservative approach for selected groups of patients.

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Introduction

Acute appendicitis is one of the most common intra-abdominal emergencies; the annual incidence of acute appendicitis is 89 per 100,000 [1], and the overall lifetime risk of receiving a diagnosis of acute appendicitis is equal to 7–8% [2].

Appendectomy is considered to be the standard of care for acute appendicitis [3, 4]; however, increasing interest regarding the conservative treatment of this common condition is present in the medical literature: several randomized controlled studies and meta-analyses were conducted in the last two decades [5–13]. The main issues addressed by these studies are effectiveness, safety, therapeutic appropriateness and cost efficiency of the antibiotic treatment, as compared to surgical treatment of acute appendicitis. International guidelines, although still considering appendectomy as the treatment of choice, contemplate the antibiotic management as a possibility for uncomplicated acute appendicitis [3, 4].

The surgical procedure of appendectomy was introduced in medical practice during the pre-antibiotic era, and the vast diffusion of the technique prompted a significant decrease in mortality [14–16]. The conservative management of acute appendicitis has been firmly ostracized, because of the suspected risk of perforation due to a delayed surgical therapy. On the other hand, the use of a conservative approach to acute appendicitis, described in 1908—before the introduction of antibiotics—by Stengel [17] and in 1956 by Coldrey [18], showed an increase over the last decades [19], without a parallel rise of the appendix perforation rate [19, 20]. This has led to a revised pathophysiologic model of acute appendicitis, which describes how perforated and non-perforated acute appendicitis might represent two distinct entities [20, 21].

The aim of the present study is to compare the outcomes of medical and surgical therapy for acute appendicitis applying a Propensity Score-based matching method in order to minimize bias due to confounders in the outcome analysis. In particular, we compared length of stay, duration of absence from work and failure rates between the patients treated with conservative and operative therapy, aiming to evaluate safety, effectiveness and therapeutic appropriateness.

Methods

Inclusion and exclusion criteria

All adult patients (aged more than 18) admitted to the Surgical Department of the Papa Giovanni XXIII Hospital with a diagnosis of acute appendicitis in the period between September 2011 and December 2015 were initially considered for the current study, which represents an analytic extension of the randomized controlled trial Antibiotics versus Surgery in Acute Appendicitis (ASAA), approved by the ethics committee of Papa Giovanni XXIII Hospital in June 2011, prior to the beginning of the study [22]. The ASAA study unfortunately failed: the main adversity faced by our group was paucity of recruitment, a consequence of the frequent refusal to randomization expressed by the patients. The analytic structure of the current study is based on the comparison between patients treated conservatively and operatively, with the help of a Propensity Score matching model, implemented to reduce the bias arising from baseline characteristics.

Data were prospectively collected: every patient with a suspected diagnosis of acute appendicitis was assessed with a clinical protocol, which included three main steps: firstly, abdominal examination performed by the on-call General Surgeon; secondly, blood tests sampling, including C-reactive protein, white blood cell and polymorphonuclear cells count; thirdly, calculation of the appendicitis inflammatory response (AIR) Score [23]. Exclusion criteria were the following: appendectomy performed as an elective procedure, such as appendectomy during other abdominal surgical procedures (6a), previous hospitalization for acute appendicitis treated conservatively and pregnancy status (3b).

Radiological and long-term follow-up data were retrospectively reviewed from the hospital archive or via telephonic contact at a minimum time–distance of six months (5a) from discharge. The follow-up for the patients treated during the year 2015 was performed in June 2016.

Diagnosis of acute appendicitis

The diagnosis of acute appendicitis was made using the appendicitis inflammatory response (AIR) Score. Abdominal ultrasound and/or CT was performed as an adjunct in selected patients, depending on on-call surgeon's judgement. Within the group of patients who received surgical intervention, negative appendectomy was defined as the absence of acute inflammation on the basis of the histopathologic examination.

Conservative versus surgical treatment

Depending on the therapy received, patients were post hoc assigned either to the surgical group, if an initial surgical indication was present in the clinical notes, or to the medical group, otherwise. The totality of patient without a direct surgical indication was initially managed with a conservative approach, comprehensive of antibiotic treatment and serial abdominal examinations.

More specifically, patients were assigned to the surgical group if they received immediate surgical treatment or were treated with a surgical approach within the first 72 h; this was based on serial clinical examinations, clinical discretion of the on-call surgeon and availability of surgical facilities. Patients who did not receive surgery within 72 h represented the medical group (3b).

Patients who underwent surgical treatment received laparoscopic or laparotomic appendectomy, depending on the on-call surgeon's decision. Depending on the clinical presentation, patients managed conservatively received one of the following parenteral antibiotic treatment: Ertapenem (1 g) one intravenous administration per day for three days; Piperacillin/Tazobactam (4.5 g) four intravenous administration per day for a length depending on the clinical conditions; other antibiotic therapy, such as Ceftriaxone (1 g) once per day plus Metronidazole (500 mg) three times per day or Ciprofloxacin (500 mg) twice per day plus Metronidazole (500 mg) three times per day for a length depending on the clinical picture. Patients were discharged with oral amoxicillin/clavulanic acid (1 g) three times a day for five days. During the follow-up period, a colonoscopy was indicated for every patient aged more than 40 years and assigned to the medical group.

Statistical analysis

Continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range, IQR) and compared with Student's *t* test or Mann–Whitney U test as appropriate; categorical variables were expressed as percentages and were compared with the Pearson's Chi-square test.

The Propensity Score (PS) model [24, 25] was calculated considering the following variables as covariates: age, sex, AIR Score, presence of Blumberg sign at admission, C-reactive protein (CRP) and white blood cells (WBC) at admission, antibiotic therapy prescription (Ertapenem, Piperacillin/Tazobactam, and other antibiotic therapy). Patients were matched with the PS matching software [26]. Treated patients (antibiotics group) and controls (surgery 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. In order to correct imbalance in the outcome analysis, weight adjustment was used. A more detailed description of PS analysis performed in this study is reported in the document supplied as Appendix. Results of univariate and multivariate analyses were expressed as follows: odd ratios (OR) for binary outcomes and beta coefficients for continuous outcomes variables, both presented along with the correspondent 95% confidence intervals (95% CI). At multivariate analysis, we adjusted for the covariates included in the PS model. The results regarding the failure rates were expressed also as absolute and relative risk reduction. Results showing a p value < 0.05 were considered to be statistically significant.

Outcome analysis

The outcome analysis was computed exclusively for matched patients. Six main outcomes were considered (see Table 1 for definitions): in-hospital length of stay at first admission, cumulative individual length of stay (sum of hospitalization days for every patient), number of post-discharge lost work days (absence from work), failure rate (variables Failure 1 and Failure 2) and length of stay of more than 3 days.

The failure rate was evaluated using two different outcome variables ('Failure 1' and 'Failure 2'). Within the surgical group, both variables considered peri- and post-operative complications as a failure of the surgical approach; moreover, for the computation of the variable 'Failure 1' negative appendectomy was considered as failure. Complications were categorized according to the Clavien–Dindo classification [27]. With regard to failure within the medical group, all patients who needed surgical intervention after 72 h of conservative management were accounted for as failure cases. In our opinion, the limit of 72 h represents a satisfactory compromise, considering the necessity of a correct diagnosis, the possibility of resolution of the disease with a medical approach and the logistic requirements at a tertiary surgical centre.

Concerning the outcome variable 'LOS > 3 days', this threshold was chosen because this figure corresponds to the overall median cumulative length of stay in our sample.

Results

Four hundred sixty-two patients met the inclusion criteria: 178 (38.53%) were assigned to the surgical group and 284 (61.47%) to the medical group. The mean age was 37.5 ± 16.2; 218 patients (47.2% of the total) were female. Table 2 describes results before and after matching.

Matching was not possible for 69 patients, and all of them belong to the surgical group (Table 3): mean age was 37.61 years and 27.5% were female; they presented with worse signs of peritonitis and higher AIR Score, CRP and WBC, as compared to matched patients.

The matched group was composed of 284 patients treated with medical therapy, and 109 patients underwent surgical management. Regarding the antibiotic therapy (Table 2), 90.5% of the patients managed conservatively

Table 1 Definitions of outcome variables

Outcome variable	Surgical group	Medical group
Failure 1	Peri- and post-operative complications (SSI, fascial dehiscence, post-operative ileus >48 h, medical complications) Negative appendectomy	Necessity of appendectomy during index admission (acute failure) New episode of suspected acute appendicitis requiring surgical treatment, within one year from discharge (delayed failure)
Failure 2	Peri- and post-operative complications (SSI, fascial dehiscence, post-operative ileus >48 h, medical complications)	Necessity of appendectomy during the index admission (acute failure) New episode of suspected acute appendicitis requiring surgical treatment within one year from discharge (delayed failure)
LOS > 3 days	In-hospital length of stay exceeding 3 days	
LOS—first admission	Individual in-hospital length of stay at first admission for acute appendicitis	
LOS—cumulative	Individual cumulative days of hospitalization, including the first admission for acute appendicitis and subsequent hospitalization due to complications	
Lost work days	Number of days of sickness leave (from date of discharge to date of first day of work). Students and retired patients were not considered	

LOS Length of stay

Table 2 Covariates distribution between medical and surgical groups, before and after matching

Variable	Pre-matching sample		p value	Post-matching sample		p value
	Medical ($N = 284$)	Surgical ($N = 178$)		Medical ($N = 284$)	Surgical ($N = 109$)	
Sex (female)	149 (52.5%)	69 (38.8%)	0.004	149 (52.5%)	50 (45.9%)	0.242
Age (mean, years ± SD)	36.69 ± 16.68	38.84 ± 15.73	0.239	36.85 ± 16.68	39.63 ± 15.92	0.135
AIR score (mean ± SD)	6.26 ± 1.67	7.26 ± 1.88	<0.0001	6.26 ± 1.67	6.83 ± 1.82	0.005
AIR score						
0–4	45 (15.8%)	14 (7.9%)	<0.0001	45 (15.8%)	12 (11%)	0.244
5–8	217 (76.4%)	124 (69.7%)		217 (76.4%)	84 (77.1%)	
9–12	22 (7.7%)	40 (22.5%)		22 (7.7%)	13 (11.9%)	
Blumberg score						
0	95 (33.5%)	38 (21.3%)	<0.0001	95 (33.5%)	27 (24.8%)	0.171
1	113 (39.8%)	60 (33.7%)		113 (39.8%)	44 (40.4%)	
2	66 (23.2%)	66 (37.1%)		66 (23.2%)	30 (27.5%)	
3	10 (3.5%)	14 (7.9%)		10 (3.5%)	8 (7.3%)	
CRP (mean, mg/dl ± SD)	5.29 ± 4.25	7.0 ± 6.51	0.22	5.29 ± 4.25	6.52 ± 5.03	0.113
WBC (mean, $\times 10^9$/uL ± SD)	13.03 ± 4.01	14.77 ± 4.44	<0.0001	13.03 ± 4.01	13.87 ± 4.23	0.08
Antibiotic therapy						
Ertapenem	257 (90.5%)	121 (68%)	<0.0001	257 (90.5%)	87 (79.8%)	0.012
Piperacillin/Tazobactam	3 (1.1%)	18 (10.1%)		3 (1.1%)	4 (2.7%)	
Other antibiotics	24 (8.5%)	39 (21.9%)		24 (8.5%)	18 (16.5%)	
Imaging performed						
Abdominal ultrasound	254 (89.4%)	150 (84.3%)	0.103	254 (89.4%)	95 (87.2%)	0.512
Abdominal CT scan	33 (11.6%)	21 (11.8%)	0.954	33 (11.6%)	12 (11%)	0.865

SD Standard deviation

and 79.8% of those in the surgical group received Ertapenem as a first-line therapy. The remaining patients were administered Piperacillin/Tazobactam (3 patients within the medical group and 4 within the surgical group) or another antibiotic treatment (24 and 18 patients, respectively).

Table 3 Characteristics of unmatched patients

Variable	Matched ($N = 393$)	Unmatched ($N = 69$)	p value
Sex (female)	199 (50.6%)	19 (27.5%)	<0.0001
Age (mean, years)	37.2	37.61	0.877
AIR score (mean)	6.42	7.93	<0.0001
AIR score			
0–4	57 (14.5%)	2 (2.9%)	<0.0001
5–8	301 (76.6%)	40 (58%)	
9–12	35 (8.9%)	27 (39.1%)	
Blumberg score			
0–1	279 (71%)	27 (39.1%)	<0.0001
2–3	114 (29%)	42 (60.9%)	
CRP (mean, mg/dl)	5.63	7.68	0.083
WBC (mean, $\times 10^9$/uL)	13.27	16.19	<0.0001
Ertapenem	344 (87.5%)	34 (49.3%)	<0.0001
Piperacillin/Tazobactam	7 (1.8%)	14 (20.3%)	<0.0001
Other antibiotics	42 (10.7%)	21 (10.4%)	<0.0001
Imaging performed			
Abdominal ultrasound	349 (88.8%)	55 (79.7%)	0.035
Abdominal CT scan	45 (11.5%)	9 (13%)	0.704
LOS first admission (days)	3.39	4.44	<0.0001
LOS cumulative (days)	3.97	4.87	0.893
Failure 1	78 (19.8%)	22 (31.9%)	0.025
Failure 2	67 (17%)	17 (24.6%)	0.132
LOS > 3 days	160 (40.7%)	43 (62.3%)	0.001

Table 4 Complications within the surgical group according to Clavien–Dindo classification

Clavien–Dindo classification	N (%)
1	10 (50%)
2	6 (30%)
3a	0 (0%)
3b	4 (20%)
4	0 (0%)
Total	20

Comparing the medical and surgical groups, the proportions of patient who received abdominal ultrasound examination and abdominal CT tomography resulted to be similar (89.4 vs. 87.2%, $p = 0.512$ and 11.6 vs. 11%, $p = 0.865$, respectively).

Within the surgical group, the majority of patients received laparoscopic appendectomy (94.5% of the cases) and the conversion rate was equal to 11.7%. In the surgical group, 78 patients (71.6%) did not present complications; 18 (16.5%) and 2 (1.8%) developed superficial surgical site infection (SSI) and deep SSI, respectively (Table 4); 3 patients (2.7%) had fascial dehiscence (leading to evisceration in one case and to incisional hernia in two other cases); 5 (4.6%) had post-operative ileus lasting more than 48 h or presented with bowel occlusion during the follow-up period; 3 (2.7%) had post-operative medical complication, such as pneumonia (1), urinary tract infection (1) and cardiovascular complications (1).

Table 5 shows the results of the outcome analysis. Among the 284 patients who received medical therapy 5 (1.8%) required appendectomy during the first hospitalization, because of the worsening clinical condition despite antibiotic therapy (acute failure), and 47 (16.5%) required surgery within 1 year from hospital discharge (late failure); the average time to failure in the medical group was 171 days, with a median of 84 days (IQR 33–186 days).

Regarding failures in the surgical group, 31 (28.4%) and 20 (18.3%) patients failed according to the definitions of Failure 1 and Failure 2, respectively. The absolute risk reduction of failure for the medical group, as compared to the surgical group, is 11.89% (95% CI 11.86–11.92)—considering Failure 1—and 1.8% (95% CI 1.77–1.83)—considering Failure 2; the relative risk reduction is equal to 41.81% (95% CI 41.73–41.88) and 9.81% (95% CI

Table 5 Outcome analysis (failure, length of stay, lost work days)

Outcome variable	Medical group (284)	Surgical group (109)	*p* value	Unadjusted OR (weighted univariate analysis)	*p* value	Adjusted OR (weighted multivariate analysis)	*p* value
Failure 1 *n* (%)	47 (16.5%)	31 (28.4%)	0.008	0.499 (0.296:0.84)	0.009	0.523 (0.305–0.899)	0.019
Failure 2 *n* (%)	47 (16.5%)	20 (18.3%)	0.671	0.882 (0.495:1.572)	0.671	1.014 (0.558:1.1914)	0.965
LOS > 3 days *n* (%)	98 (34.5%)	62 (56.9%)	<0.0001	0.399 (0.254:0.627)	<0.001	0.468 (0.287:0.763)	0.002
Outcome variable	Medical group mean (days ± SD)	Surgical group mean (days ± SD)	*p* value	Unadjusted beta (WLS univariate analysis)	*p* value	Adjusted beta (WLS multivariate analysis)	*p* value
LOS first admission	3.11 ± 1.42	4.11 ± 1.63	<0.0001	−0.693 (−0.916:−0.670)	<0.0001	−0.628 (−1.912:−0.345)	<0.0001
LOS cumulative	3.68 ± 1.96	4.88 ± 7.28	0.011	−0.500 (−1.162:−0.162)	0.138	−0.442 (−1.094:−0.209)	0.183
Lost work days	6 ± 5.21	14.64 ± 10.2	<0.0001	−9.05 (−11:−7)	<0.0001	−8.7 (−10.78:−6.62)	<0.0001

LOS Length of stay

9.67–9.94), respectively. At multivariate analysis, the conservative management resulted in a significantly reduced failure rate (considering Failure 1), a shorter length of stay at first admission and a diminished number of lost work days after discharge, as compared to surgical treatment (Table 5).

None of the patients included in both groups had a fatal complication; mortality was 0% at 1-year follow-up in both groups.

Discussion

In the present study, the conservative treatment of acute appendicitis appeared to be (9b) safe and effective. If we consider negative appendectomy as a failure, the medical therapy was associated (9b) with a smaller number of failures, as compared to the surgical treatment, demonstrating also a shorter length of stay during the first admission and a reduced period of absence from work after hospitalization.

The current understanding of the exact aetiology and pathophysiology of acute appendicitis is not exhaustive (7a). These uncertainties are mirrored by the several obscure points that surgeons and emergency physicians face when managing a patient with acute appendicitis: unclear indications to surgery or conservative treatment, uncertain long- and short-term effects of surgical and medical management.

In such an unsecure environment, the choice of the outcome variables used to compare the results of medical and surgical therapy, though a focal issue, may represent a difficult task. In the current study, we considered a flexible and multi-faced set of outcome variables, with the aim of analysing the results of medical and surgical therapies under multiple perspectives.

Although appendectomy is considered the first-line therapy for acute appendicitis [3, 4], increasing evidence of safety and effectiveness of the antibiotic therapy for acute appendicitis is present in the literature [5–13, 28]. The dogmatic assumption identifying appendectomy as the only effective and safe therapeutic choice for acute appendicitis should be revisited on the basis of both pathophysiologic and historical considerations. First, the knowledge of the exact natural history of acute appendicitis is still debated; complicated and uncomplicated acute appendicitis is likely to be two different entities [20, 21, 29].

Furthermore, in some cases, acute appendicitis may present with a self-limiting behaviour, with a benign development even without the administration of antibiotics [20, 30]. Second, the absolute necessity of a surgical intervention for acute appendicitis was established in the pre-antibiotic era. This concept needs to be filtered in order to evaluate the role of the medical therapy for acute appendicitis, especially when uncomplicated: several studies, including the present one, support the evidence that conservative management for acute appendicitis may be considered safe and effective in selected groups of patients [5–13, 20, 28, 30].

Analysing the characteristics of unmatched cases, it is evident that these patients presented with higher AIR Score, CPR and WBC; they were more likely to receive Piperacillin/Tazobactam as a first-line therapy [4] than the matched patients, due to the worse clinical conditions at presentation. These patients were not eligible for a conservative approach ‘ab initio’ and were excluded from matching and from the subsequent outcome analysis. The matched sample therefore represents a clinically homogeneous group including patients with less severe acute appendicitis.

In the present study, we aimed to consider both therapeutic effectiveness and therapeutic appropriateness in the outcome analysis of the matched sample. The problem of therapeutic appropriateness is strictly related to the theme of outcome measures choice. In our view, the risks intrinsically related to a negative appendectomy should be taken into consideration (4a): a negative appendectomy represents therefore a failure to direct the patient to the pertinent therapeutic choice (Failure 1). In the current study, the conservative treatment showed fewer complications as compared to surgical therapy (16.5 vs. 28.4%, OR 0.523 at multivariate analysis) with statistical significance. Excluding negative appendectomies as a failure (‘Failure 2’), the difference of failure rate (16.5 vs. 18.3%) did not result statistically significant underlying a substantial equality between the two groups. Two hundred thirty-seven patients (83.5%) were successfully treated with a conservative approach and did not need re-intervention within 1 year. An indirect but considerable advantage of the conservative approach is represented by the avoidance of the morbidity [30–34] and mortality [35] related to appendectomy. This element is of great interest, especially if one considers the relevant number of appendectomies performed throughout the world annually, ranging between 250,000 and 300,000 interventions per year only in the USA [36].

As confirmed by univariate and multivariate analysis, the average length of stay at first admission was significantly shorter in the medical group than in the surgical group (3 vs. 4 days), while the cumulative length of stay did not differ significantly between the two groups, highlighting an element of long-term equivalence between these two lines of treatment.

Regarding the short-term results, the conservative treatment appears to be more efficient than surgery as shown by the reduced length of stay: this is of great interest for the economic sphere of clinical governance. Previous studies had explored the cost efficiency of antibiotic versus surgical treatment of acute appendicitis and the results supported a conservative management [10, 28]. Patients who underwent a surgical intervention had longer absence from work than patients treated with medical therapy; these results are in line with previous studies [9, 11, 28]. Therefore, medical therapy for uncomplicated acute appendicitis may be considered advantageous from a socio-economic point of view.

The current study presents a great limitation in its non-randomized nature: although we attempted to reduce the selection bias using the Propensity Score to implement a matching method, some residual confounding may be present, regarding for example the inclusion criteria or the indications to imaging, which are not standardized at our centre. The main drawback in the application of a PS-based matching procedure regards the validity of the outcome analysis. Results should be considered valid inside the matched group, which is likely to identify the patients with acute appendicitis, not requiring urgent laparotomy and therefore amenable to initial conservative approach. Consequently, we can state that medical treatment for acute appendicitis is safe and effective but only for a selected group of patients, presenting with uncomplicated acute appendicitis. However, the borders and exact definitions of this group of patients are currently unclear. Further studies regarding the definition of patients with ‘clearly uncomplicated appendicitis’ [13] probably represent the keystone which can lead to the creation of evidence-based stratified therapeutic pathways.

Unfortunately, it is impossible to obtain histological confirmation of diagnosis within the medical group. At the same time, an estimation of the rate of patients who does not present cute appendicitis within the medical group is unattainable (3a) and this may create imbalance in the analysis of the failure outcomes. To obviate this, we created a pair of complementary outcome variable, namely Failure 1 and Failure 2, which should be considered simultaneously.

Notwithstanding the pathophysiologic and diagnostic complexities, the aims of clinical effectiveness, therapeutic appropriateness and cost efficiency in the treatment of acute appendicitis can be addressed with a conservative approach.

Antibiotics play a major role in the conservative treatment of acute appendicitis; the increasing risk of development of bacterial resistance represents a challenge in current surgical practice. This possibility needs to be appropriately weighed against the necessity of appropriate antibiotic treatment for the intra-abdominal septic source. Previous studies have shown how the prevalence of extended-spectrum beta-lactamase (ESBL) producing enterobacteriaceae represents a relevant issue in both community-acquired and nosocomial intra-abdominal infections [37]. Vons et al. hypothesized that a proportion of failures to medical therapy were caused by resistance to amoxicillin–clavulanate in their sample; in a more recent RCT [9], Ertapenem was chosen for his broad spectrum of activity and efficacy in intra-abdominal infections. The World Society of Emergency Surgery guidelines recommend the use of Ertapenem in case of community-acquired extra-biliary sepsis, in the presence of risk factors for ESBL-producing bacteria (2a) [4].

New approaches for the treatment of uncomplicated acute appendicitis, including a case-to-case evaluation and discussion with the patient regarding the different therapeutic choices, have been proposed [38]. A step-up management could be considered [20, 39], but definite and broadly accepted guidelines or diagnostic-therapeutic pathways are not present in the literature. A change in perspective, from a bare 'effectiveness analysis' to a more thorough 'appropriateness analysis', is essential for the interpretation of comparison between medical and surgical treatment for acute appendicitis.

In conclusion, considering each outcome as part of a wide-angle analysis, we may state that within the considered group of patients, antibiotic treatment can be considered effective and safe for acute appendicitis. Furthermore, the conservative approach represents an appropriate treatment as the clinical presentation is often well controlled by antibiotic therapy in selected cases. When excluding negative appendectomy from the reasons of failure, surgical and antibiotic therapy performed equally in terms of failure rate; however, the failure rate of the conservative treatment appeared to be smaller, as compared to surgical approach, when negative appendectomy is included in the failure count. Furthermore, the conservative treatment demonstrated to reduce the length of stay at first admission and the absence from work, showing a good profile of appropriateness at the same time. The main disadvantage of this approach is represented by the possible recurrence of acute appendicitis. The risk of recurrence appears to be an acceptable price to pay, given the relatively low incidence and the absence of major complication at time of surgery.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interests.

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