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Review

Conservative treatment of acute appendicitis

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Summary. Acute appendicitis has been considered by surgeons a progressive disease leading to perforation for more than 100 years. In the last decades the theories about this concept gained attention, especially in adults. However, appendectomy for acute appendicitis remains the most common urgent/emergent surgical procedure. At present, accumulating evidences are showing the changing in clinical practice towards the non-operative management of several cases of acute appendicitis either non-complicated or complicated. The present review aims to show the literature results regarding the non-operative management of acute appendicitis in non-complicated and in complicated cases. (www.actabiomedica.it)

Key words: appendicitis, conservative, complicated, uncomplicated, review, adult, children, treatment

Background

The acute appendicitis has been considered by surgeons a progressive disease leading to perforation for more than 100 years. In the last decade the theories challenging of this concept gained attention especially in adults. However appendectomy for acute appendicitis remains the most common urgent/emergent surgical procedure in children. The first report of operative treatment for AA has been reported in 1735 when Claudius Amyand treated an inflamed appendix during the course of a hernia operation in an 11-year-old boy. The perforated appendix was situated in the hernia sac. The abscess was opened, and the boy recovered and was discharged a month after the operation. Unfortunately, the hernia recurred (1). The first reported appendectomy for suspected AA was performed by the Scotsman Robert Lawson Tait in 1880 (2). His intervention precedes Charles McBurney who presented his first series in 1889 and Abraham Groves (3, 4). Five years later, McBurney published his article on the surgical procedure that bears his name. Some authors however suggested that the grid-iron incision was first performed by Louis L. McArthur (5, 6). The open appendectomy through a McBurney incision remained the method of choice to treat AA until Karl Semm in 1980 performed the first laparoscopic appendectomy (7). Successively Ure et al. published in 1991 the first series of laparoscopic appendectomies in children (8).

Conservative treatment of acute appendicitis during the years

Searching for the first case of nonoperative treatment of AA, it could be suggested that it is as old as man itself. The first report of a suspected spontaneous resolution of AA was published in 1910 by Smith and Wood Jones. They described the case of a young Nubian woman where the appendix was found attached with a thick adhesive band to the left pelvic wall suggesting that she had survived appendiceal rupture with abscess formation (9). The bizarre aspect of the report is that at the time of diagnosis, she was an uneviscerated mummy from the Byzantine era. In 1930 Bailey proposed his non-operative treatment algorithm (10) and in 1959 Coldrey described for the first time a large series of 471 patients treated non-operatively with intravenous antibiotics (11). The recurrence rate was 48/470 (10.2%) with 1 death, 9 patients requiring abscess drainage, and 48 cases requiring a subsequent appendectomy. Another series from China reported 500 patients with the clinical diagnosis of AA (12). Of these, 425 had conservative treatment with Chinese traditional medicine and antibiotics were given to some. 7 recurrences have been reported. Conservative treatment has also been reported from doctors in service aboard of the U.S. Navy and the Soviet fishing fleet ships (13, 14). The Russian one is a review of conservative treatment in 252 patients with AA on vessels of the Kalingrad fishing industry from 1975 to 1987. In this series Gurin et al. (14) reported a recovery rate of 84.1% with only the use of antibiotics. The authors found no difference in outcomes based on presenting symptoms or age, but they suggested that conservative treatment was as more effective as earlier it starts. In fact it showed to be most effective if administered within 12 h from symptom onset, ideally within the first 6 h. Moreover they reported the best effect when early intervention with antibiotics was combined with antihistamines and spasmolytics. All these aforementioned trials however dealed with a non-confirmed diagnosis, a poor follow-up. For these reasons these experiences did not receive much attention (15).

Reason for treating conservatively acute appendicitis

It is general opinion that the appendix has no significant function in humans. De Coppi et al. in 2006 showed that the vermiform appendix was capable of producing mesenchymal stem cells (16). They found that appendix-derived mesenchymal stem cells are present in the vermiform appendix. These cells can differentiate into osteoblasts, lipoblasts, and myoblasts, depending on the stimulation. They suggested the possibility that vermiform appendix acts like a reservoir for stem cells capable of bowel repair trough life. From North Carolina many articles have been published on this topic (17). Some authors moreover suggested the possibility that appendix deserve as a reservoir for bacteria of the gut flora, and it is necessary to recolonize the bowel after bacterial infections. Appendectomy either open either laparoscopic is still associated with a significant morbidity and mortality despite advances in surgery and care. Blomqvist et al. analyzed a Swedish cohort of 117,424 patients who underwent appendectomy (1987-1996) analyzing the 30-day postoperative mortality ratio (18). They reported a 3.5-fold excess mortality after surgical intervention for non-perforated appendicitis and a 6.5-fold excess mortality in perforated ones. In patients with a discharge diagnosis of nonspecific abdominal pain the mortality rate after negative appendectomy was increased by 9.1-fold. This mortality rate may only partially be explained by an underlying condition that was concealed by the appendectomy. Also Flum and Koepsell found a threefold increase in mortality after negative appendectomy compared with appendectomy for AA (19). Different studies reported an increased SBO (small bowel obstruction) rate in the years after appendectomy. During a 30-year follow a Swedish report showed that 1.3% of patients subjected to an appendectomy had a SBO compared with 0.2% of controls (20). Others have reported rates of SBO between 0.16 and 10.7% after appendectomy (21, 22). Leung et al recently reported as the incidence of SBO after appendectomy at 2.8%, and the incidence of reoperation for SBO after appendectomy to be 1.1% during the 5-year follow-up (23). Sakorafas et al. recently reported reduced cost, morbidity, and abdominal pain associated with non-operative treatment (15). Svensson et al. described that centers with restrictive indications for exploration have fewer patients with non-perforated appendicitis, compared with centers with a more active attitude to exploration (24). This could suggest that many patients with AA would potentially have spontaneous resolution of their disease. The experience of a hospital in which patients with suspected appendicitis were admitted to five units on a strict 24-hours rotation, three with a conservative approach and two with an active approach to exploration by Howie et al. in 1964. On one hand the active units removed a significantly greater average number of inflamed appendices per unit (72 vs. 46, $p<0.0001$). On the other hand the conservative units removed fewer normal appendices (16.7 compared with 34% for the radical units, p<0.0001). Luckman in 1989 suggested that perforated and non-perforated appendicitis could be two separate entities. Lastly a meta-analysis by Andersson et al showed as the incidence of perforated appendicitis did not correlate with the rate of negative appendectomy and as a counterpart that the incidence of uncomplicated appendicitis correlated directly with the rate of negative appendectomy and inversely with diagnostic accuracy.

Uncomplicated acute appendicitis

Definition:

Uncomplicated appendicitis is defined as appendicitis without neither perforation nor appendiceal abscess nor mass formation.

Literature evidence:

Randomized controlled trials: Many different prospective and retrospective observational trials comparing conservative treatment of uncomplicated AA have been published during the years. A few randomized controlled trials have also been published increasing the data level of evidence. For this reason the present review will focus on higher level of evidence data.

The first prospective randomized trial on acute appendicitis was presented in 1995.

Eriksson and Granström randomized 40 patients to either operation or conservative treatment (25).

Methods: Randomization of patients admitted with history and clinical signs of acute appendicitis. Ultrasonography and laboratory tests: white blood cell count and C reactive protein to identify patients with a high probability for acute appendicitis.

Participants: Patients with typical history and clinical signs, positive findings at ultrasound, and either increased white blood cell count and C reactive protein values or high C reactive protein or white blood cell count on two occasions within a four hour interval. Initial randomization of 20 patients in each group, but one patient from the antibiotic group developed increased abdominal pain and generalized peritonitis and had surgery, and subsequent data were discounted.

Interventions: The conservative group underwent cefotaxime 2 g 12 hourly and tinidazole 800 mg for two days. Patients were discharged after two days with oral ofloxacin 200 mg twice daily and tinidazole 500 mg twice daily for eight days. Patients were excluded from the study in the event of increased abdominal pain and generalized peritonitis and this case they underwent surgical intervention. The surgery arm underwent antibiotics for 24 hours only in the event of bowel perforation or in cases of abdominal spillage. They were discharged when conditions were satisfactory and/or when patients wished to return home. Histology were obtained for all specimens. All patients were seen for a follow-up visit at 6th, 10th, and 30th day after admission and underwent blood tests for white blood cell count and C reactive protein, pain scores and temperature were evaluated and recorded. Abdominal and rectal examination were performed on days 6th and 10th. Stools were examined for *Clostridium difficile* toxin at day 30th. Ultrasonography was performed on days 10th and 30th.

Outcomes: Pain scores (every six hours using a VAS), morphine consumption, white blood cell count and temperature, positive diagnosis at surgery, hospital stay, wound infection, and recurrent appendicitis were evaluated.

Results: One out of 20 patients needed operation due to failure of conservative treatment, 3 out of 20 appendectomies were negative and 7 out of 19 patients treated conservatively had recurrence of symptoms and surgical intervention within 1 year. Non-operatively treated patients had a faster decrease of C-reactive protein, a lower morphine consumption, and a lower pain score compared with the patients who underwent initial operation. The authors state that 40 out of 45 consecutive patients (27 men and 13 women between 18 and 75 years of age) were included in the trial, and only 5 declined participation. In the surgery group, two had mesenteric lymphadenitis and one had *Campylobacter* enteritis. All patients in this trial had an ultrasound diagnosis of appendicitis but, despite this 17 out of 20 patients who underwent operation had AA.

Styrud et al. randomized 252 men: 128 to conservative treatment and 124 to open appendectomy (26).

Methods: Patients were randomized to either surgery or antibiotic treatment. Patients were monitored at the end of the first and sixth week and of the first year.

Participants: Male patients, between 18 and 50 years of age, admitted to six different hospitals. No women were enrolled by decision of the local ethics committee. All patients with suspected appendicitis with a C-reactive protein concentration >10 mg/L and with no clinical signs of perforation.

Interventions: The antibiotics arm underwent intravenous cefotaxime 2 g 12 hourly and tinidazole 800 mg daily for two days. Patients were discharged after two days with oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 10 days. If symptoms didn't improve within first the 24 hours, appendectomy was performed. All conservatively treated patients with a suspected recurrence of appendicitis underwent surgery. Patients randomized to surgery had open or laparoscopic operations at the surgeon's discretion. All removed specimens were sent for histology.

Outcomes: Hospital stay, sick leave, diagnosis at operation, recurrences, and complications were evaluated.

Results: Of the 128 patients treated non-operatively 18 required operation due to failure of antibiotic therapy. Of the 124 appendectomies, 4 were negative. 16 out of 110 conservatively treated patients had a recurrence within 1 year. 17 patients experienced complications in the open appendectomy group.

In 2009, Hansson et al. in a large randomized trial published the results of 369 patients where 202 were randomized to conservative treatment and 167 to surgical intervention (27). The trial protocol accepted a crossover after randomization, but before initiation of treatment. For this reason 119 patients were treated conservatively and 250 were operated.

Methods: Three centers participated to the study; one hospital enrolled patients to be used as a reference cohort for comparison and the other two centers enrolled patients into the study and control arms. Allocation were done by date of birth. Questionnaire was sent to all patients after one and 12 months. All patients who didn't answer to the questionnaire were contacted by telephone.

Participants: Patients were enrolled if they had positive history, clinical signs, laboratory tests, and, in some cases, ultrasonography, computed tomography, and gynecological examination.

Interventions: The conservative treatment arm underwent intravenous cefotaxime 1 g twice daily and metronidazole for at least 24 hours. Patients who improved were discharged 24 hours later with oral ciprofloxacin 500 mg twice a day and metronidazole 400 mg three times a day for 10 days. If there was no improvement the intravenous treatment was prolonged. The surgery arm underwent open or laparoscopic appendectomy with a single dose antibiotic prophylaxis, and postoperative antibiotic treatment when the appendix was gangrenous or perforated. All specimens were sent for histological examination.

Outcomes: Treatment efficacy, complications, recurrences and reoperations, length of antibiotic treatment, abdominal pain after discharge from hospital, length of hospital stay, and sick leave were evaluated. Moreover the total costs for the primary hospital stay were analyzed for each patient.

Results: Based on per-protocol analysis, 11 out of 119 patients in the conservative treatment arm needed early operation, 27 out of the 250 appendectomies were negative, and 15 out of the 108 conservatively treated patients had a recurrence within 1 year. Serious complications rate were three times more frequent in the surgery arm.

In 2011, a Vons et al. published the results of a randomized trial in which 239 adult patients were randomly assigned 120 to conservative treatment and 119 to surgical intervention (28).

Methods: The study is an open label, non-inferiority, randomized controlled trial to which participated six academic centers. Patients in both treatment groups were assessed twice a day after admission and were discharged after resolution of pain, fever, and any digestive symptoms. All patients were seen on days 15th, 30th, 90th, 180th, and 360th.

Participants: All included patients were adults over 18 years with suspected AA, who had diagnosis of uncomplicated appendicitis by computed tomography (CT). Included patients were randomized to appendectomy or antibiotic treatment. Patients who were allergic to antibiotics or iodine, had been on antibiotics before admission, were receiving steroid or anticoagulants, had a history of inflammatory bowel disease, were pregnant, had blood creatinine of ≥200 μmol/L, or were unable to understand the protocol or consent form were not included into the study.

Interventions: The patients included into the antibiotics arm underwent intravenous or oral amoxicillin plus clavulanic acid (3 g per day if <90 kg or 4 g for patients >90 kg) for 48 hours. If there was no resolution of symptoms after 48 hours patients underwent appendectomy. Patients were discharged with antibiotics and reviewed on day 8th if there was resolution of the symptoms. CT was done in presence of persistent pain or fever or if there was a suspicion for the necessity of appendectomy. If not, antibiotics continued for another 8 days. If symptoms persisted on day 15th, appendectomy was done. Patients enrolled in the surgery arm underwent open or laparoscopic appendectomy. Amoxicillin plus clavulanic acid 2 g was administered at the time of induction of general anesthesia. Antibiotics were given postoperatively only if the appendicitis was complicated. Histology was obtained for all specimens.

Outcomes: The primary endpoints was: occurrence of peritonitis within 30 days of initial treatment, diagnosed either at appendectomy or postoperatively by CT. The secondary endpoints were number of days with a post-intervention VAS pain score ≥4, length of stay, absence from work, incidence of complications other than peritonitis within one year, and recurrence of appendicitis after antibiotic treatment (considered as appendectomy done between 30 days and one year of follow-up, with a confirmed diagnosis of AA).

Results: There were 14 early failures and only 1 out of 119 negative appendectomy. Of 120 patients enrolled into the conservative treatment group 30 had an operation within the first year and 26 had appendicitis.

Malik and Bari published a trial where 80 patients were randomized 40 to conservative treatment and 40 to surgical intervention (29). This article was retracted from the Journal of Gastrointestinal Surgery in 2011 (31). The editors state that significant portions of the article were published earlier in other studies (25, 30).

Methods: This is a monocentric randomized controlled trial. Patients were evaluated during the follow-up at the 7th, 12th, 30th day, blood sample (WBC and CRP levels), pain (VAS) and oral temperature was registered. Patient with recurrent appendicitis within one year were readmitted.

Interventions: The patients enrolled to conservative treatment arm underwent intravenous ciprofloxacin 500 mg every 12 h and 500 mg of metronidazole administered intravenously every 8 h for a period of 2 days. After the discharge were administered a 7-day oral therapy with 500 mg of ciprofloxacin twice a day, and 600 mg of tinidazole twice a day. Patients randomized to the surgery arm received a preoperative antibiotic prophylaxis with cephalosporin and tinidazole that was protracted for 48 hours in the event of bowel perforation or abdominal spillage. cephalosporins and imidazole. For each patient the pain was registered every 6 hours using VAS and oral temperature was measured twice daily. Histology was obtained for all specimens. Patients from both groups were discharged once conditions were satisfactory.

Outcomes: hospital stay, complications, pain, analgesic consumption, inflammatory laboratory tests, and body temperature were evaluated.

Results: In the conservative treatment group the 85.0% and in the surgical treatment group 92.5% patients were successfully cured within two weeks without major complications. The mean duration of pain was 23 hours in antibiotic arm and 21.3 hours in surgery arm. The mean hospital stay was 2.3 days in antibiotic arm and 1.2 days in surgery arm. 2 out of 40 patients in the conservative treatment arm failed and undergone surgery during the first admission and 4 out of the remaining 38 undergone appendectomy during the first year.

Systematic reviews and meta-analyses:

There are several systematic reviews with meta-analysis published about the comparison between conservative and surgical treatment of AA.

Varadhan et al analyzed three trials (25-27, 32). Their analysis showed a trend toward a reduced risk of complications in the antibiotic-treated group [RR (95%CI): 0.43 (0.16, 1.18) p=0.10], without prolonging the length of hospital stay [mean difference (inverse variance, random, 95% CI): 0.11 (-0.22, 0.43) p=0.53]. In their analysis 350 patients were randomized to the antibiotic group, among them the 68% (238 patients) were treated successfully with antibiotics alone and the 15% (38 patients) were readmitted. The remaining 112 patients (32%) who were randomized to conservative treatment crossed over to surgery. At 1 year follow-up analysis, 200 patients in the conservative treatment group remained asymptomatic. Authors concluded that "that although antibiotics may be used as primary treatment for selected patients with suspected uncomplicated appendicitis, this is unlikely to supersede appendectomy at present".

Ansaloni et al. included four trials in their study, including the discussed Malik and Bari's trial (25-29, 33). Efficacy was significantly higher for surgery (OR=6.01, 95% CI=4.27-8.46). No differences were found in the numbers of perforated appendix (OR=0.73, 95% CI=0.29-1.84) and patients treated with antibiotics (OR=0.04, 95% CI=0.00-3.27). Complication rates were significantly higher for surgery (OR=1.92, 95% CI=1.30-2.85). They conclude that "although a nonsurgical approach in AA can reduce the complications rate, the lower efficacy prevents antibiotic treatment from being a viable alternative to surgery".

Liu and Fogg included six trials in their meta-analysis (25-29, 33-35). They found a non-operative management failure rate of 6.9% and a 14.2% recurrence rate. They conclude that appears to be safe to treat AA with antibiotics. One appendectomy patient had a recurrence. A normal appendix was found in 7.3% of patients at appendectomy. Complications rate was lower with antibiotic treatment than with appendectomy (OR 0.31; 95% CI 0.19-0.49, p<0.05).

The Cochrane collaboration published its review in December 2011 (36). The authors included five trials (25, 26, 28, 29, 34) excluding the Hansson et al. trial as it was considered a low quality trial. The primary reason was the cross-over between the groups driven by patient or surgeon preference. Malik and Bari and Turhan et al trials were included in the review (34, 29). It should be mentioned that the Turhan et al trial is difficult to be considered a real randomized trial.

Authors found that the 73.4% (95% CI 62.7 and 81.9) of patients who underwent conservative treatment and the 97.4% (95% CI 94.4 and 98.8) of patients who underwent surgical intervention were successfully treated within two weeks and had no major complications (including recurrence) within the first year. Patients who undergone surgical intervention experienced a shorter hospital admission OR 0.66 (95% CI 0.44 to 0.87). However the duration of sick leave periods is significantly shorter in patients treated with antibiotics with an OR of 0,69 (95%CI -1.65 to 0.27). The authors concluded that appendectomy remains the gold standard, as a counterpart initial antibiotic therapy was not inferior to operation based on a 20% non-inferiority margin.

Fitzmaurice et al. published their systematic review with the aim to evaluate the evidence to challenge initial operation as the gold standard treatment for AA in adults (37). By searching in the literature they found 13 trials (1999-2009). Most of them were considered of low level of evidence. They included four randomized controlled trials (26-29, 38). Fitzmaurice et al did not find enough evidence to challenge initial operation as the gold standard treatment for AA in adults.

Mason et al. published their meta-analysis of five randomized trials (25-29, 39). In 2008 Mason has already published a review supporting the conservative treatment of AA showing as many of the treated patients (up to 70%) would not require surgical intervention (40). The aforementioned meta-analysis revaluate the evidence of the necessity of a blind assessment of the outcome. Authors proposed as the most important factor is the choice of treating AA with antibiotic is the safety of treatment. They focused on the lower complication rate of patients treated with antibiotics with an OR of 0.54 (95% CI 0.37-0.78, p=0.001). Patients treated with antibiotics experienced a reduction in sick leave/disability SMD -0.19 (95% CI -0.33, -0.06, p=0.005) and in pain medication utilization SMD -1.55 (95% CI -1.96, -1.14, p<0.0001). The failure rate is higher in conservative treatment with an OR of 6.72 (95% CI 0.08, 12.99, p<0.0001). Author conclude that "the conservative treatment is associated to fewer complication, better pain control and shorter sick leave disease, but has inferior efficacy because of the high rate of recurrence".

Varadhan et al published their meta-analysis as an update to their previous review (32, 41). They excluded the trial by Malik and Bari and Turhan et al included on an intention to treat basis data by Hasson et al. excluding the cross-over of patients (27, 29, 34). They showed as non operative management was associated with a significantly lower complication rate (RR 0.69; 95% CI 0.54-0.89; P=0.004). A secondary analysis, excluding the crossover of patients between the two interventions after randomization from Hasson et al, confirmed the relative risk reduction RR 0.61 95% CI 0.40-0.92; P=0.02). The authors found no differences neither in the duration of hospital stay nor in the incidence of complicated appendicitis. This is the only of the published meta-analysis concluding that: "Antibiotics are both effective and safe as primary treatment for patients with uncomplicated acute appendicitis. Initial antibiotic treatment merits consideration as a primary treatment option for early uncomplicated appendicitis".

An interesting prospective non-randomized study recently published by Di Saverio et al. evaluate the question from a different point of view (95). Randomized trials that assign patients with suspected AA to either surgical or nonsurgical treatment group show a relapse rate of approximately 14% at 1 year. Authors suggested that would 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 (101)) and radiological evaluation. Only clinical signs and symptoms and laboratory values, as included in the Alvarado and Appendicitis Inflammatory Response (AIR) (96) scores, were routinely evaluated in patients with suspected AA. If this clinical evaluation is effective, authors would expect patient selection to be better than chance and the relapse rate to be below 14%. Authors suggested that once established the utility of this evaluation, it would be possible to 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. Authors also suggest that observational studies 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 (97). This single-cohort, prospective, observational study has been registered on ClinicalTrials.gov database (identifier NCT01096927) (98) and published in the protocol form (99). All patients presented to the emergency department with right iliac fossa (RIF) pain and suspected AA 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 were treated with a 5- to 7-day course of amoxicillin and clavulanate at dosage of 1 g orally thrice daily.

The aim of the study were to evaluate the outcome of patients treated non-operatively with antibiotics and to assess the reliability of the initial clinical evaluation in predicting which non-operatively treated patients should have been treated surgically. The primary outcomes were 1- Short-term efficacy of antibiotic treatment evaluated as failure of non-operative management with 7 days of amoxicillin and clavulanic acid therapy and 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 defined as the efficacy of antibiotic therapy for right lower quadrant pain suspected of being AA 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) defined as the efficacy of antibiotic therapy for right lower quadrant pain suspected of being AA 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 defined as the incidence of major side effects/drug- or treatment-related complications (i.e., allergy or other treatment related complications such as abscess formation).

Secondary outcomes were as follows:

1- Minor complications 2- Abdominal pain after discharge: assessed at 5, 7, and 15 days. 3- Length of hospital stay. 4- Outpatient clinic follow-up defined as the number of follow-up appointments scheduled in the outpatient clinic. 5- Sick leave. 6- Cost analysis. An additional objective was to identify clinical, laboratory, and imaging findings that were predictive of failure of non operative management with antibiotics and/or relapse of appendicitis and need for appendectomy within 2 years.

The inclusion criteria were as follows: age more than 14 years, lower abdominal pain/RIF pain, clinical diagnosis/suspicion made by an attending general surgeon, of AA, confirmed by at least 1 validated score (Alvarado and/or AIR scores):

- Alvarado score 5 to 6 (equivocal for AA)
- Alvarado score 7 to 8 (probable AA)
- Alvarado score 9 (highly probable AA)
- AIR score 3 to 4 (low probability)
- AIR score 5 to 8 (indeterminate group)

Exclusion criteria: diffuse peritonitis, antibiotic (penicillin) documented allergy, ongoing/previously started antibiotic therapy, previous appendectomy, positive pregnancy test, inflammatory bowel disease history or suspicion of it recurrence.

Clinical diagnosis or clinical suspicion of non perforated AA not requiring immediate surgery was made by an attending surgeon and rigorously assessed and validated on the basis of routine use of clinical scores. Suspected AA was defined as patient presenting with RIF pain and the absence of a definite alternative diagnosis of a gastrointestinal disease, urinary tract disease or an obstetric-gynecological cause. Patients needing immediate surgery were defined as those with diffuse peritonitis and/or signs of severe abdominal sepsis and also those with clinic-radiological (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 (100) 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. This study gave interesting results. In 2010, a total of 159 patients with a mean AIR (Appendicitis Inflammatory Response) score of 4.9 and a mean Alvarado score of 5.2. The follow-up period was 2 years. The study showed a short-term (7 days) non operative management failure rate of 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 was assessed by the Numeric Rating Scale and the visual analog scale with a median score of 3 at 5 days and 2 after 7 days. Mean length of stay of non operatively managed patients was 0.4 days, and mean sick leave period was 5.8 days. Long-term efficacy of non operative management was 83% (118 patients recurrence free and 14 patients with recurrence non operatively managed). None of the single factors forming the Alvarado or AIR score were independent predictors of failure of non operative management or long-term recurrence. Alvarado and AIR scores were the only independent predictive factors of non operative management failure after multivariate analysis, but both did not correlate with recurrences. Overall costs of non operative management and antibiotics were €316.20 per patient. Authors concluded that antibiotics for suspected AA 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 non operatively treated right lower quarter abdominal pain are less than 14% and may be safely and effectively treated with further antibiotics.

Doubtful issues:

It has already been observed by Fitz that AA may takes various different clinical courses, mainly three: spontaneous resolution, persistent inflammation without perforation and perforation. With the advent of ultrasonography and CT, spontaneous resolution rate has been reported in the range of 3.6% to 20.0% in many cases reports, (42-44) and in large case series (45-50, 52). Case reported demonstrate as the typical symptoms of AA corroborated by imaging studies, appear to resolve completely in 24 to 48 hours without treatment. So on it could be speculated as the real challenge is to differentiate since the beginning those patients who are likely to resolve spontaneously the AA episode and those who will not. If an appendectomy results in a inflamed appendix that is considered sufficient to justify the surgical intervention (45). We must keep in mind however that the absence of inflammatory infiltrate extending into the *muscularis* *propria*, with only mucosal or sub-mucosal involvement has no definitive significance. This inflammatory pattern in fact is commonly observed in the incidentally removed appendix (45, 53). So on the appendix reported as inflamed would comprise a lot of not "really inflamed" appendix (53) giving partial and incorrect results and leading sometimes to misinterpretation of data. Livingston et al showed that "there was a sudden reversal of the long term decreasing trend in the rate of nonperforating appendicitis coincident with more frequent use of CT imaging and laparoscopic appendectomy" (54). Anderson corroborated this statement by demonstrating that the increment in use of CT scan has leaded in last decade to an increase in the number of detected appendicitis (55). Moreover Petrosyan et al evaluated the direct correlation between appendectomy and CT scan. In fact at the increase of the number of patients with a CT scan increased also the number of patients who undergone appendectomy, and this phenomenon was especially pronounced in patients with low Alvarado scores (56). As a counterpart patients without CT scan are more likely to be treated without appendectomy. This confirm the trend toward overdiagnosis of AA by CT scan. Kirshenbaum et al. in fact reported an highest spontaneous resolution rate (up to 20%) if AA is diagnosed by CT scan (52).

As a consequence of all the aforementioned data, Liu et al suggested that the idea that appendicitis could be a condition that has a continuous spectrum from non-perforated to perforated, and from uncomplicated to complicated appendicitis, may be incorrect. They suggested the existence of several distinct types of appendicitis, each with varied pathophysiology and clinical courses (35).

Ongoing randomized trials:

The APPAC trial:

The APPAC trial aims to provide level I evidence to support the hypothesis that approximately 75-85% of patients with uncomplicated AA can be treated with effective antibiotic therapy avoiding unnecessary appendectomies and the related operative morbidity, also resulting in major cost savings (registration: Clinicaltrials.gov NCT01022567) (57). The APPAC trial is designed to be a randomized prospective controlled, open label, non-inferiority multicenter trial to compare antibiotic therapy (ertapenem) with emergency appendectomy in the treatment of uncomplicated AA.

Inclusion criteria are: signed informed consent, age between 18 and 60 years. CT scan diagnosis of uncomplicated AA. Exclusion criteria are: age <18 years or >60 years, pregnancy or lactating, allergy to contrast media or iodine, renal insufficiency, serum creatinine > 150 μmol/l, metformin medication, peritonitis, inability to co-operate and give informed consent, serious systemic illness, complicated AA in a CT scan (appendicolith, perforation, peri appendicular abscess or suspicion of a tumor).

The primary endpoint is the success of the randomized treatment. In the antibiotic treatment arm successful treatment is defined as the resolution of AA resulting in hospital discharge without the need for surgical intervention and no recurrent appendicitis during a minimum follow-up of one-year (treatment efficacy). Treatment efficacy in the operative treatment arm is defined as successful appendectomy evaluated to be 100%. Secondary endpoints are post-intervention complications, overall morbidity and mortality, the length of hospital stay and sick leave, treatment costs and pain scores (VAS, visual analogue scale). 610 adult patients (aged 18-60 years) with a CT scan confirmed uncomplicated AA will be enrolled from six hospitals and randomized by a closed envelope method in a 1:1 ratio either to undergo emergency appendectomy or to receive ertapenem (1 g per day) for three days continued by oral levofloxacin (500 mg per day) plus metronidazole (1.5 g per day) for seven days. Follow-up will be performed by a telephone interview at 1 week, 2 months and 1, 3, 5 and 10 years. Both the primary and secondary endpoints will be evaluated at each time point.

The ASAA trial:

The ASAA-Study (Antibiotics vs. Surgery in Acute Appendicitis) is an intention to treat prospective randomized controlled study which aims to compare the antibiotic therapy and the surgery in the treatment of uncomplicated acute appendicitis (registration: EudraCT 2011-002977-44). Preliminary agreement has been reached over Andersson's score as the most comprehensive diagnostic tool for patients suspected to suffer of AA. According to the Andersson's score 3 groups have been individuated. Group 1: patients with very low probability to suffer from AA and group 3: patients with very high probability to suffer from AA. The group 2 includes patients with intermediate probability to suffer from AA; in this group we added ultrasound to better discern the presence of AA. Patients which require immediate surgery and group 1 or 2 patients with negative ultrasound and/or positive gynecological consultation are excluded. Of the remaining patients, those who meet the inclusion criteria are randomized. In order to perform a non-inferiority analysis between antibiotics and surgery the population size was calculated as 110 patients in each arm.

Inclusion criteria are: all the patients between 18 and 65 years old admitted to the hospital with a first episode of suspected AA diagnosed by Andersson's score combined with abdominal ultrasound (see below, at the population study section, for details). Exclusion criteria are: patients with any potential immunodeficiency status (diseases or syndromes, neoplasm in the last five years), diabetes, assumption of antibiotics for different infectious disease or surgery in the last 30 days, allergy to antibiotics established in the study protocol, no acceptance of study protocol, pregnancy or delivery in the last 6 months, ASA IV or V, no Italian or English fluently speakers.

The primary endpoints are: absence of symptoms and normalization of laboratory test after 2 weeks, no major complications or recurrence within 1 year. The secondary endpoints are: reintervention for bowel occlusion or intraperitoneal abscess, bowel occlusion longer than 48 hours, incisional hernia or wound dehiscence, recurrence of AA, wound infection, negative appendectomy, hospital stay, work absence and evaluation of pain (VAS at admission time, twice a day during the entire admission beginning since 24 hours from the intervention or the first antibiotic dose).

In the antibiotic arm will be administered to the patients Ertapenem e.v. infusion 1g for day for 3 consecutive days followed by Amoxicillin plus Clavulanic acid per os 1gr 3 times day for seven days. In the surgery arm will be administered Amoxicillin plus Clavulanic acid e.v. 2 gr followed by surgery.

Complicated acute appendicitis

Introduction and definition:

Complicated appendicitis is defined as appendicitis complicated by a local or contained perforation with an appendiceal abscess or mass formation.

Literature evidence:

Conservative treatment of complicated AA may include radiologic-guided drainage of a peri-appendiceal abscess. After successful conservative management, some centers are used to proceed with elective interval appendectomy. At present no consensus exists among surgeons regarding the optimal treatment for patients with complicated AA (58).

Randomized controlled trials: at the best of our knowledge no randomized trials exist comparing conservative and surgical treatment of complicated AA in adults.

Systematic review and meta-analysis: one systematic review with meta-analysis have been published by Similis et al. (58). The following outcomes were evaluated to compare patients in the conservative treatment group and those in the surgery one: 1 - duration of hospital which means the mean duration of hospital stay during the first hospital admission and the overall duration of hospital stay. The overall duration of hospital stay included hospitalizations for interval appendectomy and eventual complications. 2 - duration of antibiotic therapy which means the average number of days the patient had intravenous antibiotic therapy as an inpatient but excluded any oral courses completed after discharge. 3 - complications rate divided into overall complications rate and wound infection rate. Wound infection is defined as superficial or deep after wound closure but excluded any abscess formation. Abdominal/pelvic abscess defined as a collection of fluid in the pelvis or abdomen diagnosed on radiologic imaging or at reoperation or at interval appendectomy, ileus or bowel obstruction diagnosed after CT or postoperatively, pneumonia, sepsis/diffuse peritonitis, deep venous thrombosis/pulmonary embolism, death, adhesions, and fistula formation. The authors choose these particular complications because they were the most commonly reported by the different studies to compare the 2 groups. 4 – reoperation rate considers all the reoperations needed as a result of postoperative complications after interval appendectomy or acute appendicitis during the same and/or during any other hospital readmissions (58).

This review included a total of 17 studies published between 1969 and 2007 (59-75) considering the management either of adult either of pediatric patients. 16 non-randomized retrospective trials (59-75) and 1 non-randomized prospective trials (74). The analysis was performed on 1,572 patients, of which 847 (53.9%) patients received conservative treatment and 725 (46.1%) patients underwent acute appendectomy for complicated appendicitis. Of the 847 patients who received conservative treatment, 483 proceeded to have interval appendectomy. The duration of intravenous antibiotics given to patients, which was found to be similar between conservative treatment and acute appendectomy (WMD, 1.02; 95% CI, --1.30--3.34; P =.39). No difference was found in the duration of first hospitalization (WMD, 0.49; 95% CI, --2.70--3.69; P =.76). No difference was found in the overall duration of hospitalization (WMD, 0.04; 95%CI, --3.87--3.95; P = .98). Complications comparing the 2 treatment approaches were found to be more common in the acute appendectomy group compared with the conservative treatment group (OR, 0.24; 95% CI, 0.13--0.44; P<.001). A greater incidence of ileus/bowel obstruction was found in the acute appendectomy group (OR, 0.35; 95% CI, 0.17--0.71; P=.004). The acute appendectomy group was found to have a greater rate of abdominal/pelvic abscess formation (OR, 0.19; 95% CI, 0.07--0.58; P = .003). Wound infection was found to be more common in the acute appendectomy group (OR, 0.28; 95% CI, 0.13-- 0.60; P=.001). No difference was shown between the 2 groups when comparing pneumonia (OR, 1.11; P=.89), sepsis/diffuse peritonitis (OR, 0.54; P=.36), deep venous thrombosis/pulmonary embolism (OR, 0.37; P=.20), mortality (OR, 0.70; P=.67), adhesions (OR, 3.35; P=.39), and fistula formation (OR, 0.22; P=.07). Reoperation was found to be greater in the acute appendectomy group (OR 0.17; 95% CI, 0.04--0.75; P=.02).

This meta-analysis showed that conservative management of complicated AA, with or without interval appendectomy, is associated with a decreased complication and reoperation rate. Moreover the conservative treatment of AA has similar duration of hospital stay and duration of intravenous antibiotics. The authors however suggest the needing for subsequent studies (58).

Conservative treatment acute appendicitis in pediatric patients

Uncomplicated acute appendicitis

A different discussion should be reserved to the management of AA in pediatric patients. The vast majority of published data presented discussed almost exclusively about adult patients. Only one pilot randomized controlled trial exists (102) comparing appendectomy with non-operative treatment in children with uncomplicated AA. In this trial, 92% of patients treated with antibiotics had initial resolution of symptoms and only 1 patient (5%) had recurrence of AA during follow-up. These results suggested that non-operative treatment of AA in children is feasible and safe. Some other randomized controlled trial about this topics are in progress (103-106). Similarly, some meta-analysis and cohort studies (76, 77, 107-109) suggested the possibility to successfully use the non-operative treatment of uncomplicated AA with a reported success rate ranged from 74% to 97% and a recurrence rate of 14%. These studies reported the same complications rate in the surgery group and in the non-operative group. The reported long term efficacy of non-operative management ranged from 73 and 82%. Although scarce, present literature supports the feasibility of non-operative management of acute uncomplicated appendicitis in children. Higher quality prospective randomized controlled trials with larger sample sizes are required to establish its utility.

Complicated acute appendicitis

No consensus exists among pediatric surgeons regarding the optimal treatment complicated AA in children (78). The advent of broad-spectrum antibiotics leads some surgeons to suggest the possibility to try to apply the non-operative management in cohort of children (79-87). As a counterpart a little evidence exists about the possibility to determine which children are most likely to benefit from this approach. In fact, the term "complicated acute appendicitis" includes different clinical entities: the gangrenous appendicitis, the perforated appendicitis, the phlegmon and the appendicular abscess.

The existing literature that try to determine the real efficacy of the non-operative management in patients with perforated AA has no possibility to reduce the heterogeneity of data and the incompleteness of them. For this it's impossible to differentiate the real clinical status of patients treated with conservative management and those treated with appendectomy and no definitive data could be obtained.

Literature reports that 30 to 60% of children with AA have already developed appendicular perforation at the moment of the child presentation to the surgeon (88, 89). The surgeon at that moment could choose between three main options: immediate appendectomy and non-operative management with or without drainage of a peri-appendiceal abscess. After successful conservative management, once the child is returned to normal activity many surgeons suggest interval appendectomy.. Several reports demonstrated good outcomes in series of children with perforated appendicitis, without abscess, phlegmon, or mass, treated non-operatively with intravenous broad-spectrum antibiotics (79, 80, 82, 84, 87, 90-92). As already stated before the majority of these series are affected by significant selection bias, most commonly due to the undefined clinical status at presentation which has determined the treatment choice. All the published series proposed retrospectively collected data where diagnosis was based on different combinations of clinical suspicion, abdominal US and CT scan. The success rate of non-operative is reported in 62 to 100% of cases. To overcome some of the limitations of these retrospective studies, Blakely et al. performed a prospective, randomized controlled trial comparing non-operative treatment to early appendectomy in 131 unselected children with perforated AA without evidence of abscess or mass (93). The protocol fixed the date of interval appendectomy following successful non-operative treatment after 6 to 8 weeks. The 89% of the children who underwent early appendectomy for suspected perforated appendicitis had this as a final diagnosis. The primary outcome was time away from normal activities. It has been demonstrated to be significantly shorter in the group who underwent early appendectomy compared with those who underwent non-operative management and who returned for interval appendectomy. The adverse events rate were significantly more common in the non-operative management arm. On the basis of these findings the authors propose a clear preference for early appendectomy for perforated AA. A subsequent paper with a cost-analysis based on this trial showed a significant cost-benefit to early appendectomy (94).

Another randomized controlled trial (110) focusing on children with appendicitis with abscess, didn't find advantages between initial laparoscopic appendectomy versus initial non-operative management and interval appendectomy in terms of total hospitalization, recurrent abscess rate or total charges. An analysis of the studies that included only pediatric patients in a meta-analysis about appendicitis complicated with abscess or phlegmon revealed that, compared with the non-operative group, the early appendectomy group had a greater rate of overall complications, wound infections and abdominal/pelvic abscess formation. No differences were found between the two groups in the duration of first hospitalization, ileus/bowel obstruction and reoperations. Similar results emerged in another recent meta-analysis (111) about pediatric patients with complicated appendicitis.

Finally a meta-analysis (112) of the two randomized controlled trials about complicated acute appendicitis found that for children with perforated appendicitis and no abscess at presentation, it appears that early appendectomy is favored, while for children with an intra-abdominal abscess at presentation, the controversial question of early versus interval appendectomy is still alive because there is no convincing evidence suggesting major differences between the two surgical approaches. More high quality randomized studies are needed to demonstrate the risks and benefits of operative and nonoperative approaches to complicated appendicitis.

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