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Conservative treatment of acute appendicitis: an overview

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ABSTRACT

Background. *Although the standard treatment for appendicitis (since 1883) is an appendectomy, this is not always possible in a maritime or military setting. To avoid relying on improvisation in such situations this study examines the evidence for conservative management of appendicitis.*

Material and methods. *PubMed was searched for studies on conservative treatment of appendicitis. Both prospective and retrospective studies with a well-defined description of the protocol were included.*

Results. *Finally, 5 publications (a total of 342 patients) were included in this overview. For these reports, the success rate for conservative treatment of appendicitis is 90.8% (88–95%) with a risk of relapse within 12 months of 15.9% (5–37%). For complicated appendicitis these mean rates decrease to 89% (67–100%) and 9.8% (0–39.6%), respectively.*

Discussion and conclusions. *This overview indicates that appendicitis can be safely and effectively treated conservatively. The studies differed in their treatment protocols. Appendicitis can best be treated with a third-generation cephalosporin and an imidazole derivative (2 days intravenously and 10 days orally). This is based on evidence from a combination of the studies presented here, and on expert opinion. Currently, this combination is the best available «evidence» on this topic.*

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Key words: appendicitis, conservative treatment, antibiotics, maritime medicine

INTRODUCTION

In western society, thanks to emergency services, helicopters, and a dense network of hospitals, medical facilities are easily accessible. In a military setting, however, such accessibility is not guaranteed. To care for the wounded and sick in the absence or delay of medical facilities, military medical ancillary services are used. These include the Combat Live Saver (CLS) and staff of the Medical Action Service. Similar problems are encountered in the maritime setting.

In some military situations, medical care is needed for a length of time without use of additional medical facilities such as an operating room (OR) and its staff. This applies to so-called “special operations”, also in the maritime setting. During this period there is no access to additional diagnostic, surgical, and/or medical facilities.

Until recently, improvisation was the main solution for these situations, with or without onshore advice. This model of onshore advice, provided by a maritime physician, is used by the navy and commercial ships.

The need to move to an evidence-based approach is great. Therefore, the Maritime Medical Expertise

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Centre (MMEC) of the Royal Netherlands Navy has formulated specific maritime questions in an attempt to address these questions, based on the best available clinical evidence, i.e. evidence-based medicine. This evidence is subsequently "translated" into the maritime and military setting.

The question discussed here is: Can a patient suspected of acute appendicitis, in a situation where surgical aid is not available or delayed, be treated conservatively?

The need for conservative treatment (as second best) is illustrated by the surgical adventures of a Russian physician and World War II American "pharmacist's mates".

In 1961 a Russian physician named Dr. Leonid Rogozov, stationed at the external Antarctic Novolazarevskaya base, performed an auto-appendectomy under local anaesthesia [1, 2]. After this event, prior to their deployment, the Soviet medical staff were required to undergo a prophylactic appendectomy.

The U.S. Navy has experienced similar problems. There are World War II reports of three appendectomies performed on board submarines. These were done by the so-called "pharmacist's mates" using non-surgical instruments. One of these interventions took longer than four hours [4]. These events led to the call for a new protocol. The Americans, unlike the Russians, did not choose prophylactic removal of the appendix, but instead chose conservative treatment. These non-surgical medical interventions of acute appendicitis have also been described by the U.S. Navy on board submarines.

Recent studies have shown that acute appendicitis in children can be treated with antibiotics [5–7]. For various research groups it is worth exploring the conservative treatment of acute appendicitis. For the Royal Netherlands Navy, and in particular for the MMEC, it is important to establish whether such conservative treatment is a safe and effective solution, in case there is suspected acute appendicitis in an isolated environment without medical facilities. These conclusions might also have implications for non-military maritime medical institutions.

HISTORY

Before examining the conservative treatment of acute appendicitis it is worth considering how the current surgical treatment became the standard care. Over 120 years have passed since the first appendectomy was conducted by Abraham Groves in August 1883. Reginald Fitz pronounced the appendectomy to be an effective treatment in early 1886 and published an article concerning 247 patients with perforated appendicitis [9]. In 1889 Samuel McBurney described eight patients with special emphasis on early appendectomy [10].

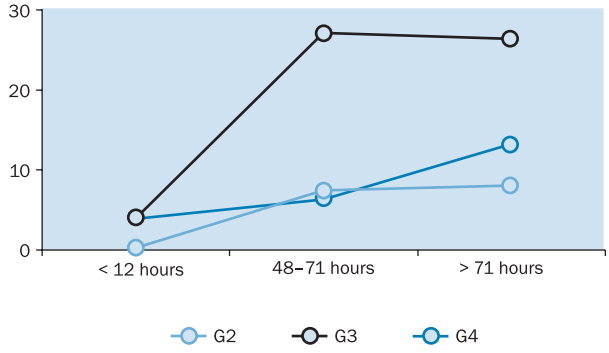

Figure 1. Complications of delaying treatment for appendicitis over time (range G1–G4; where G1 — mild and G4 — serious complications). On the Y-axis, complications are expressed in percentages; on the X-axis, time is expressed in hours. The more serious complications increase as time progresses. For reasons of clarity, G1 complications are omitted from this figure

An exception to the more accepted treatment modality was proposed by Coldrey, who wrote an article on conservative treatment [11]. In 1959 he treated 471 patients in a conservative manner, with low mortality and morbidity. The idea was as controversial then as it is today.

DELAY OF THE OPERATION

One could argue that, for a patient with acute appendicitis on board ship, the best policy is to transfer the patient to the nearest surgical facility. In the maritime context, however, such a transfer can take longer than 12–24 h. If treatment is delayed, a question arises concerning the consequences for the patient.

The study of Ditillo et al. [12] indicates that the severity of pathology and complications in adult patients with acute appendix worsens by delaying the operation. The authors conclude that delaying an appendectomy is unsafe. For example, when the total interval is less than 12 h, the risk of developing G1, G2, G3, and G4 complications (G1–G4 indicates the severity of the complication as defined in the original article, with G1 indicating mild complications and G4 indicating the serious complications) is 94%, 0%, 3%, and 3%, respectively. These values change to 60%, 7%, 27%, and 6%, respectively, when the total interval increases to 48–71 h, and to 54%, 7%, 26%, and 13% for longer than 71 h (Figure 1).

The odds ratio for progressive pathology was 13 times higher when a total interval of 71 h was exceeded, compared with a total interval of less than 12 h.

These figures show that watchful waiting, or delaying an appendectomy in a patient with acute appendicitis on board ship, cannot be justified. Because an appendectomy aboard ship is undesirable, it is important to explore the possibility of conservative treatment.

METHODS

For this study a systematic search of the literature was made in PubMed (from inception of the database to June 2010), using the search term "conservative treatment of appendicitis". We scrutinized the titles and read the summaries of the articles that appeared to best fit our research goal. After reading the summary, it was decided whether the article would be included in the present study.

Inclusion criteria were a direct comparison between conservative treatment and surgery for appendicitis; both prospective and retrospective studies were included. Another requirement was that the article clearly describe the treatment protocol. Decisions about inclusion were made by the first author (KHW). The list of articles compiled by PubMed, and the reference lists of all the articles, was also consulted. These lists were scanned in the same manner as described above.

RESULTS

The search term "conservative treatment of appendicitis" yielded 198 hits. After reading the titles and summaries, 8 articles appeared to be relevant. Only one article directly compared appendectomy with conservative treatment of appendicitis *and* described a clear protocol [13], the remaining articles were contemplative or were published ≥ 50 years ago [11].

Via the list of related articles compiled by PubMed, another four articles were included. Two articles were prospective randomized controlled trials (RCTs) [14, 15], one a review [16], and one a current practice article [17]. After searching the reference lists of all included articles, another four articles were added which had a clear protocol [11, 18–20], and five other articles that compared conservative treatment of appendicitis versus appendectomy but did not clearly describe their treatment protocol [17, 21–24].

SELECTED STUDIES

Finally, we examined the following 5 studies, with a total of 342 patients (Table 1).

1. In a pilot study of 40 patients, Eriksson and Granström showed that 19/20 (95%) patients were successfully treated with antibiotics, but with a high rate of recurrence (7/9; 37%) [18]. Seven patients were admitted within 1 year due to recurrent appendicitis and underwent an appendectomy, confirming the diagnosis of acute appendicitis. The authors concluded that antibiotic treatment in patients with acute appendicitis is as effective as appendectomy. The patients who were treated conservatively had less pain and less pain medication was required, but the recurrence rate was high. The treatment began with two days of intravenous (IV) cefotaxime (Claforan, Aventis Pharma, Stockholm, Sweden) 2 g/12 h, and tinidazole (Fasigyn, Pfizer, Täby, Sweden) 0.8 g per day. Patients received IV fluid during the first 24 h and were allowed to eat during the second day of hospitalization. If their symptoms did not improve within the first 24 h, an appendectomy was performed. Participants who received antibiotics alone were discharged after 2 days of IV treatment and treatment was continued with oral ofloxacin (Tarivid, Aventis Pharma, Stockholm, Sweden) 200 mg twice daily and tinidazole (Fasigyn, Pfizer, Täby, Sweden) 500 mg twice daily for 10 days.
2. Later, the same research group (Styrud et al.) conducted a randomized trial (using the same protocol as the Eriksson and Granström study [18]) in which, again, antibiotic treatment of acute appendicitis was compared with an appendectomy in men (aged 18–50 years) [15]. A total of 128 men were enrolled in the antibiotic group. The results of this showed that 88% recovered without surgery, with a recurrence rate of 15% within 1 year. As many as 18 patients still underwent surgery within 24 h. Of these, 17 had an acute appendicitis, with 7 having a perforated appendicitis and 1 patient with terminal ileitis. In this study, only men were included. The researchers explained that this was because women have a more extensive differential diagnosis for these complaints and have a significant chance that the diagnosis of appendicitis is adjusted to a gynaecological diagnosis. The authors assume that the results obtained in this study can be stratified for women. A study that examined the natural course of appendicitis suggests that there is even a slightly higher risk of recurrence in male patients (16 of 39 patients) than in female patients (7 of 21 patients) [25]. However, this was not confirmed in a study by Kaminski et al. [26].

Table 1. Overview of the protocols used for conservative treatment of acute appendicitis

Author	Year	n	Type	Antibiotics	Extra	Escape	D	Med	F	S	R
Eriksson & Granström [18]	1995	20	Pilot study	Cefotaxime 2 g 12 hourly + Tinidazole 0.8 g daily	IV fluids; oral intake 2nd day	No improvement 24 h append-ectomy	2	Ofloxacin 200 mg 2 dd; Tinidazole 500 mg 2 dd	10	95%	37%
Winn et al. [19]	2004	48	Treatment based on the Alvarado score	Gentamicin IV 6 mg/kg one dose Metronidazol 1500 mg one dose	None documented	Review in 24 h	1	Augmentin 875/ /125 mg 2 dd	7	92%	5%
Styrud et al. [15]	2006	128	Prospective RCT	Cefotaxime 2 g 12 hourly + Tinidazole 0.8 g daily	IV fluids; oral intake 2nd day	No improvement 24 h appendectomy	2	Ofloxacin 200 mg 2 dd; Tinidazole 500 mg 2 dd	10	88%	15%
Hansson et al. [14]	2009	106	Prospective modified RCT	Cefotaxime 1g 2 dd + Metronidazol 500 mg 1 dd	IV fluids; no oral intake	Prolonged IV treatment	1	Ciprofloxacin 500 mg 2 dd; Metronidazol 400 mg 3 dd	10	91%	14%
Malik & Bari [13]	2009	40	Prospective RCT	Ciprofloxacin 500 mg 12 hourly + Metronidazole 500 mg 8 hourly	IV fluids		2	Ciprofloxacin 500 mg 2 dd; Tinidazole 600 mg 2 dd	7	95%	10%
5 studies		**342**								**90,8%**	**15,9%**

Year — publication year; n — number of patients in the antibiotics arm; type — type of study; Antibiotics — choice of antibiotics at admission; Extra — other measures taken during admission; Escape — policy if antibiotics were not successful; D — Discharge, or number of days after which patients were discharged; Med — medication; F — follow-up, number of days the patients were taking antibiotics after discharge; S — rate of successfully treated patients; R — recurrence rate; IV — intravenous; RCT — randomized clinical trial

3. Winn et al. [19] divided their study population into three groups based on the Alvarado score (Table 2): Group 1 — Alvarado score 4 or less: Resignation, no follow-up. Group 2 — Alvarado score 5–7: Antibiotics and observation (if possible outpatient). Group 3 — Alvarado score 8–10: Urgent surgery. In the antibiotic group, 48 patients were enrolled with an efficiency of 91.7%. The risk of recurrence was 4.8% with a median follow-up of 11 months. The antibiotic group received IV gentamicin (6 mg/kg) and metronidazole (500 mg for adults or 15 mg/kg as loading dose for children). If not contraindicated by pain, vomiting, or social circumstances, the patients in this group were sent home with a 7-day course of amoxicillin (875 mg) and clavulanate (125 mg) twice daily (Augmentin Duo Forte; Glaxo Smith Klein, Melbourne, Australia), 22 mg/kg for children, and were seen again within 24 h at the surgical clinic.
4. The study of Hansson et al. shows that conservative treatment with antibiotics was effective in 90.8% of the cases, with a 13.9% chance for a recurrence within 1 year [14]. The protocol consists of cefotaxime 1 g twice and metronidazole 500 mg once, for at least 24 h. During this time, patients received IV fluids and nil by mouth. Patients whose clinical condition had improved by the following morning were released to continue with oral antibiotics (ciprofloxacin 500 mg twice daily and metronidazole 400 mg three times daily) for a total of 10 days. In patients whose clinical condition did not improve, the IV therapy was prolonged. The analysis showed that the risk of serious complications was three times higher in patients who underwent an appendectomy than in those who received antibiotics. Patients in the antibiotic group reported significantly less pain, although the pain lasted longer. This study is widely criticized because the ethics committee allowed use of a modified randomization procedure. All patients with suspected acute appendicitis were included. The randomization was

Table 2. Alvarado's score indicating the probability of acute appendicitis. The scores are summed, with 0 indicating the lowest probability and 10 the highest probability of acute appendicitis

Symptoms & signs	Score
Migratory right iliac fossa pain	2
Nausea/vomiting	1
Tenderness in right iliac fossa	2
Rebound tenderness in right iliac fossa	1
Elevated temperature	1
Rovsing's sign/positive cough sign/ /rectal tenderness	1
Leucocytosis	2

based on the birth date. If the patient was born on a date which was an odd number, he/she was allocated to the antibiotic group, if born on a date which was an even number, allocation was to the surgical group. Both surgeon and patient had the possibility of changing the group for any reason. Of the 202 patients allocated for treatment with antibiotics, only 106 (52.5%) patients completed their treatment. It is doubtful whether these results are a correct reflection of reality. On the other hand, given this form of randomization, almost all patients with suspected acute appendicitis were included in the study. The study included 99.2% of all patients who presented with suspected acute appendicitis [14].

5. Malik et al. included patients for conservative treatment when they had an Alvarado Score ≤ 6; a total of 40 patients were enrolled [13]. The protocol consisted of ciprofloxacin 500 mg/12 h and metronidazole 500 mg/8 h in the first 2 days. Patients received IV fluids only during this period. They were discharged within 3 days and treatment was continued with oral ciprofloxacin 500 mg twice daily and tinidazole 600 mg twice daily for 7 days. The protocol was effective in 95% of the cases, with a recurrence rate of 10% within 1 year. There was a significant decrease in the consumption of analgesics in patients treated with antibiotics ($p < 0.001$) and significantly less pain was observed after 12 h of conservative treatment ($p < 0.001$). The white blood cell count decreased significantly faster in patients treated with antibiotics, and the average temperature was significantly lower on days 1 and 2 ($p < 0.05$) with no more than 0.5°C difference. However, in both groups the C-reactive protein levels were the same. A note regarding this study is the low Alvarado score that Malik et al. used to include patients in the antibiotic group. An Alvarado score ≤ 4 indicated that an acute appendicitis was unlikely, 5–7 doubtful, and 8–10 almost certainly acute appendicitis. Their study included only those patients in whom it was doubtful whether (or not) they had an acute appendicitis [13].

When looking beyond the clinic, we see that after World War II the U.S. Navy reported 127 cases of acute appendicitis, of which 14 (11.1%) failed with conservative treatment [17]. These failed attempts either ended in an evacuation or in a very difficult appendectomy aboard the vessel. The current U.S. naval protocol for suspected acute appendicitis consists of bowel rest (nasogastric suction), semi-Fowler position, IV fluids, and parenteral administration of Cefoxitin, gentamicin, and metronidazole [27]. An early study using a similar protocol was conducted by Adams [20]; this is the only known study investigating the protocol of the U.S. Army for conservative treatment of acute appendicitis. It includes 9 patients, with a success rate of 55.6%.

MANAGEMENT OF COMPLICATED ACUTE APPENDICITIS

Approximately 2–6% of patients with appendicitis will present with an appendicular infiltrate with or without an abscess [16]. In the setting of acute appendicitis with abscess or phlegmon, initial conservative management has been proven to be safe and effective [28]. Some even claim that conservative management is considered the gold standard for patients with complicated appendicitis [16, 26, 29–54]. Appendectomy may be technically difficult if, at the time of presentation, inflammation is associated with abscesses or phlegmon. Therefore, an operation could lead to damage of the adjacent loops of the small intestine [55].

Studies show that conservative treatment of complicated acute appendicitis fails in 0–33% of cases, with an average of 11% [16, 46, 52, 56, 57] and with recurrence rates ranging from 0 to 39.6% with an average of 9.8% [36, 43 , 46, 48, 49, 56].

CHOICE OF ANTIBIOTICS

In this overview, it is noteworthy that different protocols are used. Almost every study uses a different protocol concerning the choice of antibiotics. There is consensus regarding the start of IV antibiotics and then proceeding to oral medication. In each

study, an imidazole derivative in combination with fluoroquinolone, aminoglycoside, cephalosporin, or a penicillin preparation was given.

Perhaps a choice could be made for one of these protocols, based on a clear understanding of the pathophysiology of acute appendicitis. Unfortunately, the exact pathophysiology of appendicitis is not entirely clear. It was first thought that luminal obstruction by external (lymphoid hyperplasia) or internal compression (compressed faecal material, a stone in the appendix called appendicolith) plays an important pathogenic role [12, 13].

Other researchers (such as Carr [58]) contest this general approach by showing that it is unlikely that obstruction of the appendix is the primary cause. The study by Arnbjornsson et al. [59] is the only one to measure intraluminal pressure in the appendix, and showed that 90% of patients with phlegmonous appendicitis (19/21) had no evidence of increased intraluminal pressure or signs of luminal obstruction. Six patients with gangrenous appendicitis showed signs of obstruction of the lumen resulting in increased intraluminal pressure, while this was only the case in two patients with phlegmonous appendicitis [59]. These data suggest that obstruction is not an important factor in the pathophysiology of acute appendicitis, but the cause may be related to the inflammatory process. Some believe that perforated and non-perforated appendicitis are separate entities [60].

The numerous different theories show that much can be gained by exploring the pathophysiology of acute appendicitis. The various studies clearly illustrate that the first steps to acute appendicitis are non-bacterial changes. Only later does bacterial infection play a role.

Jindal et al. [61] investigated the bacterial flora of 105 patients with acute appendicitis. An acute inflammation was confirmed in 101 of them. A total of 121 anaerobes and 149 aerobes were isolated, with an average of 1.15 anaerobes and 1.41 aerobes per specimen, respectively. Mixed flora were observed in 100 (95.2%) specimens. Bacteroides fragilis and Escherichia coli were the most predominant aerobic and anaerobic bacteria, respectively, and this combination was most commonly seen. There were no significant differences in the degree of isolation of B. fragilis between the perforated/non-perforated and inflamed/normal appendix.

Based on the above details, in our opinion the best available evidence for the choice of an antibiotic is a combination of expert opinion and the studies discussed above. The department of internal medicine advises adherence to the policy of various studies regarding metronidazole. To complement the metronidazole, ciprofloxacin may be the best option given the coverage of aerobic gram-positive and gram-negative bacteria.

Gentamicin is an excellent alternative for the hospital. However, this drug can be severely oto-, neuro-, and/or nephrotoxic in cases of overdose. In the maritime setting, the levels cannot be monitored and thus it is not recommended that this particular drug be used.

DISCUSSION

The success rate for conservative treatment of appendicitis in the studies presented here is 88––95% (average 90.8%) with a recurrence risk of 5–37% (average 15.9%). The only military study (known to us) achieved a success rate of 55.6% in the conservative treatment arm; however, this latter study was based on only 9 patients [20]. In 1959, Coldrey [11] showed that the conservative treatment of acute appendicitis can be successful in 91.8% of cases.

An important point is the fact that the possibility to treat acute appendicitis conservatively should not give a false sense of security. The therapy should be seen as an emergency solution in situations in which an appendectomy cannot be performed within 12 h. Even at the start of conservative treatment, an evacuation should be pursued, given the 9.2% risk of treatment failure.

A point of discussion is the policy after the successful conservative treatment of appendicitis; there is a 15.9% chance of recurrence. We believe that a “number needed to treat” of 6.3 is acceptable in the military setting to perform an appendectomy, even after initial successful conservative treatment. In a non-military setting, the chance that the patient will work again in a non-surgical environment and suffer an acute appendicitis should definitely be assessed.

Finally, it should be noted that the possibility of conservative treatment of appendicitis should not affect the diagnostic process. Knowledge of conservative treatment of an acute appendicitis brings the risk that one will over-diagnose appendicitis in the case of a simple “stomach ache”. Even with the success rates for conservative treatment of appendicitis, diagnosis based on history and physical examination is extremely important. The Alvarado score may prove to be a useful addition to the onboard diagnostic tools.

CONCLUSIONS

Since the late 19th century, the gold standard for acute appendicitis is an appendectomy. However, an appendectomy is not always possible in a non-surgical setting. Delaying treatment appears to have adverse consequences for the patient. A MedEvac (medical evacuation, usually by helicopter) is not always possible, and choosing this option may delay surgery in a way that it is not desirable. Clearly, an alternative has to be found.

An alternative policy is the conservative treatment of appendicitis, which is an effective and responsible policy. Our search of the literature revealed five studies, of varying quality, which propose a protocol for uncomplicated acute appendicitis which has a very high rate of success.

To achieve this success rate, treatment has to start with IV administration of imidazole combined with fluoroquinolone or a third-generation cephalosporin. Preference is given to the combination of metronidazole and ciprofloxacin. From the group of third-generation cephalosporins, ceftazidime can also be selected. During IV treatment maintain nil by mouth. If there is clinical improvement after 2 days, treatment can be switched to oral administration of antibiotics for an additional 10 days.

Although studies on the conservative treatment of appendicitis vary in quality, there is agreement regarding the percentage of successful treatment and recurrence within 1 year. If appendectomy cannot be performed within 12 h, the above-described policy can be safely applied to treat acute appendicitis. Given the relatively high risk of recurrence of acute appendicitis, consideration should be given to performing an appendectomy when in the vicinity of a surgical facility.

CONFLICT OF INTERESTS

There is no potential or real conflict of interest for any of the authors of this study.

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