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2022-06-14

Lastunen , K S , Leppäniemi , A K & Mentula , P J 2022 , ' DIAgnostic iMaging or Observation in early equivocal appeNDicitis (DIAMOND) : open-label, randomized clinical trial ' , British Journal of Surgery , vol. 109 , no. 7 , pp. 588-594 . https://doi.org/10.1093/bjs/znac120

http://hdl.handle.net/10138/353573
https://doi.org/10.1093/bjs/znac120

BJS, 2022, 109, 588–594
https://doi.org/10.1093/bjs/znac120
Advance Access Publication Date: 28 April 2022
Randomized Clinical Trial

DIAgnostic iMaging or Observation in early equivocal appeNDicitis (DIAMOND): open-label, randomized clinical trial

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Abstract

Background: Mild appendicitis may resolve spontaneously. The use of CT may lead to an overdiagnosis of uncomplicated appendicitis. The aims of this study were to examine whether early imaging results in more patients being diagnosed with acute appendicitis than initial observation, and to study the safety and feasibility of score-based observation compared with imaging in patients with equivocal signs of appendicitis.

Methods: Patients with suspected appendicitis with symptoms for fewer than 24 h and an Adult Appendicitis Score of 11–15 were eligible for this trial. After exclusions, patients were randomized openly into two equal-sized groups: imaging and observation. Patients in the imaging group had ultrasound imaging followed by CT when necessary, whereas those in the observation group were reassessed after 6–8 h with repeated scoring and managed accordingly. The primary outcome was the number of patients requiring treatment for acute appendicitis within 30 days.

Results: Ninety-three patients were randomized to imaging and 92 to observation; after exclusions, 93 and 88 patients respectively were analysed. In the imaging group, more patients underwent treatment for acute appendicitis than in the observation group: 72 *versus* 57 per cent (difference 15 (95 per cent c.i. 1 to 29) per cent). This suggests that patients with spontaneously resolving appendicitis were not diagnosed or treated in the observation group. Some 55 per cent of patients in the observation group did not need diagnostic imaging within 30 days after randomization. There was no difference in the number of patients diagnosed with complicated appendicitis (4 *versus* 2 per cent) or negative appendicectomies (1 *versus* 1 per cent) in the imaging and observation groups.

Conclusion: Score-based observation of patients with early equivocal appendicitis results in fewer patients requiring treatment for appendicitis. Registration number: NCT02742402 (http://www.clinicaltrials.gov).

Introduction

Traditionally, acute appendicitis has been treated by emergency appendicectomy, which was thought to avoid perforation and subsequent complications. However, not all cases of appendicitis will advance to gangrene and perforation; they may instead resolve spontaneously. Although CT can identify alternative diagnoses, it cannot predict the clinical course of the disease.

The introduction of CT into the diagnosis of appendicitis reduced the number of negative appendicectomies[1]. It also led to increased detection of uncomplicated appendicitis, which may overdiagnose appendicitis in patients with a resolving type[2,3].

There is a lot of high-quality evidence that appendicitis can resolve spontaneously[4–8], and a recent retrospective paediatric study[9] proposed that 9–93 per cent of patients with acute appendicitis can be managed safely without active treatment. In studies of conservative treatment of appendicitis with antibiotics, 73.5 per cent of those treated conservatively did not need an appendicectomy within 1 year after treatment[10]. Some of these patients might have had resolving appendicitis in the first place. This hypothesis is supported by a study[6] that showed similar treatment failure rates with antibiotics and placebo.

When the clinical diagnosis of acute appendicitis is not clear, diagnostic imaging is generally recommended. Some authors have proposed routine imaging for all patients with suspected appendicitis, and it has even been mandatory in some countries[11]. Ultrasound imaging is safe and readily available, but cannot reliably rule out appendicitis[12]. CT is very sensitive and specific[13], but incurs the risks associated with ionizing radiation[14]. Several scoring systems, such as the Appendicitis Inflammatory Response Score (AIRS)[15] and the Adult Appendicitis Score (AAS)[16], can be used to select patients requiring imaging. Patients are then managed according to their score; a high score leads to treatment without imaging, an intermediate score to imaging, and a low score to discharge[17]. Andersson and colleagues[7] conducted a randomized trial that compared early imaging with observation of patients with an intermediate AIRS, and reported that 69 per cent of these patients could be managed without imaging.

Received: November 22, 2021. **Revised:** February 08, 2022. **Accepted:** March 24, 2022

The aim of the present study was to test whether observation could be a safe and effective alternative to diagnostic imaging in patients with early equivocal appendicitis. The hypothesis underpinning the study was that a significant proportion of patients have resolving appendicitis, which does not demand treatment. Second, the observation period with repeated scoring could identify patients with progressive symptoms, thus reducing the need for imaging studies.

Methods

Trial design

This was an RCT with a parallel design. It was performed as a single-centre study in Helsinki University Hospital (HUS), Helsinki, Finland. The trial was registered in ClinicalTrials.gov before commencement (NCT02742402), and was approved by the institutional review board and the ethical committee of HUS (reference number 27/13/03/02/2016). The study was reported according to the CONSORT statement.

Patients

Adults (aged 18 years or older) with suspected acute appendicitis, an intermediate AAS (range 11–15), with symptom duration of less than 24 h, and C-reactive protein (CRP) level below 100 mg/l were eligible for the study (*Table S1*). The physicians on call recruited patients in the emergency department (ED), and all included patients provided written informed consent. Patients who were pregnant, who had received antibiotics during the previous 24 h, who did not give written consent, who were suspected of having some other illnesses requiring immediate intervention, or who had previously participated in this study, were excluded.

Randomization and masking

Patients were randomized into two groups in a 1 : 1 ratio to either an imaging or observation group. The randomization process was carried out using computer-based block randomization with randomly changing block sizes from four to eight. Randomization lists were generated using R statistical software with Blockrand 1.3 package (R Foundation for Statistical Computing, Vienna, Austria). The attending physician entered patient inclusion and exclusion criteria into a web-based system and received the allocation from the program if all the criteria were met.

Procedures

Patients in the imaging group first underwent ultrasound imaging, and then CT if no appendicitis was found. If acute appendicitis was found, patients were scheduled for urgent laparoscopic appendicectomy. If appendicitis was ruled out and no other illness requiring treatment was found, patients were discharged.

In the observation group, laboratory tests (white blood cell count, proportion of neutrophils, and CRP level) and clinical evaluation were repeated after 6–8 h, and a new AAS was calculated. Patients received analgesia during this observation period, but antibiotics were not permitted. A declining AAS led to discharge if no other illnesses requiring treatment were found, although gynaecological consultation or additional observation for 12–24 h on a hospital ward was also permitted. An unchanged or raised AAS of between 11 and 15 led to imaging with ultrasonography followed by CT when needed and, if acute appendicitis was found, patients were then scheduled for emergency laparoscopic appendicectomy. A raised AAS of 16 or higher led to the scheduling of emergency laparoscopic appendicectomy without imaging. All removed appendices were sent for histopathological evaluation, and the diagnosis of appendicitis was confirmed if the histopathological analysis showed transmural infiltration by neutrophils.

Patients were contacted by telephone 30 days after randomization. Additional contact with the ED or any physician, and any further imaging or treatment was recorded. When patients could not be reached by telephone, the HUS database of healthcare services was searched for these records. Patients were advised always to contact the surgical department in the event of any worsening of symptoms after discharge. As HUS is the only hospital in the region providing care for emergency general surgical patients covering a population of 1.7 million, it is very unlikely that those with recurrent appendicitis or complications requiring surgical care would not have been recorded in the database.

Outcomes

The primary outcome of the study was the number of patients requiring treatment for acute appendicitis during the 30 days after randomization. Secondary outcomes were the number of cases of complicated appendicitis (perforation or abscess formation) during the 30 days after randomization, number of delayed diagnoses of acute appendicitis over 24 h but less than 30 days after randomization, need for abdominal imaging during 30 days and 1 year after randomization, number of negative appendicectomies during the index hospital admission, number of other clinically significant findings, number of gynaecological consultations during the first ED visit, time from randomization to either treatment decision or discharge, number of repeat visits to the ED within 1 year, and cumulative number of cases of appendicitis requiring intervention within 1 year.

After the pilot phase of 50 patients, the proportion of patients referred for imaging in the observation group was evaluated to confirm the feasibility of the protocol. An interim analysis was conducted after recruitment of the first 100 patients to ensure that rates of complicated appendicitis would not have increased significantly. No changes were made to the study design, eligibility criteria, or outcomes after the trial commenced. No data monitoring committee was appointed.

Statistical analysis

The primary outcome, number of patients requiring treatment for acute appendicitis, was used as the basis for the sample size calculation. The target sample size was based on the assumption that 50 per cent of patients with an intermediate AAS would have appendicitis, and 50 per cent of these patients would have a spontaneously resolving type. According to the research hypothesis, patients with spontaneously resolving appendicitis would never identify as having appendicitis in the observation group. This would result in a 50 per cent appendicitis rate in the diagnostic imaging group and a 25 per cent rate in the observation group. The absolute difference in proportions of the primary outcome between the groups took primacy in the sample size calculation. The sample size was calculated using G*Power 3.1[18] software with two-sided Fisher's exact test, with a power of 90 per cent, α of 0.05, and allocation ratio of 1 : 1. It was calculated that 170 patients would be needed to confirm the primary hypothesis statistically. Allowing for 15 per cent loss to follow-up, a recruitment target of a total of 200 patients was planned. For the number of imaging studies, it was computed that a sample size of 48 would be enough to achieve a statistically significant difference between groups. Many of the secondary outcomes were assumed to occur in too small numbers for this study to be adequately powered to detect statistically significant differences.

The results were analysed based on the intention-to-treat principle. For the primary outcome, the absolute difference between proportions with 95 per cent confidence interval served as the main result, but the odds ratio with 95 per cent confidence interval was also calculated. The confidence interval for the difference between proportions was computed using the traditional Wald confidence interval, which is based on the asymptotic normal distribution of the difference. The numbers of patients with different imaging, treatment, follow-up, and diagnoses were analysed, and differences in proportions with 95 per cent confidence intervals were calculated for the two groups. *P* values were calculated using Pearson's χ^2 test, except that Fisher's exact test was used instead when any of the cells contained a sample size below five. For analysis of time as a continuous variable, the mean, standard deviation, and the difference in means were calculated, and independent-samples *t* test was used. The statistical analysis was accomplished using SPSS® version 27 (IBM, Armonk, NY, USA).

Results

Recruitment took place from 3 May 2016 to 9 March 2020. It was terminated before the total of 200 patients was reached owing to uncertainty caused by the COVID-19 pandemic. A total of 571 patients with suspected appendicitis were assessed for eligibility for this trial, of whom 386 were excluded (*Fig. 1*). Of 185 patients randomized, 93 were allocated to the imaging group and 92 to the observation group. Four patients in the observation group were erroneously randomized without written consent, and were excluded from the analysis as they were treated outside the protocol. Therefore, 93 patients in the imaging group and 88 in the observation group were assessed for the primary and secondary endpoints. There were no missing data.

There were 99 women (54.7 per cent) and 82 men (45.3 per cent) among the participants. The median age was 30 (i.q.r. 25–39) years. Demographic and clinical characteristics are shown in *Table 1*.

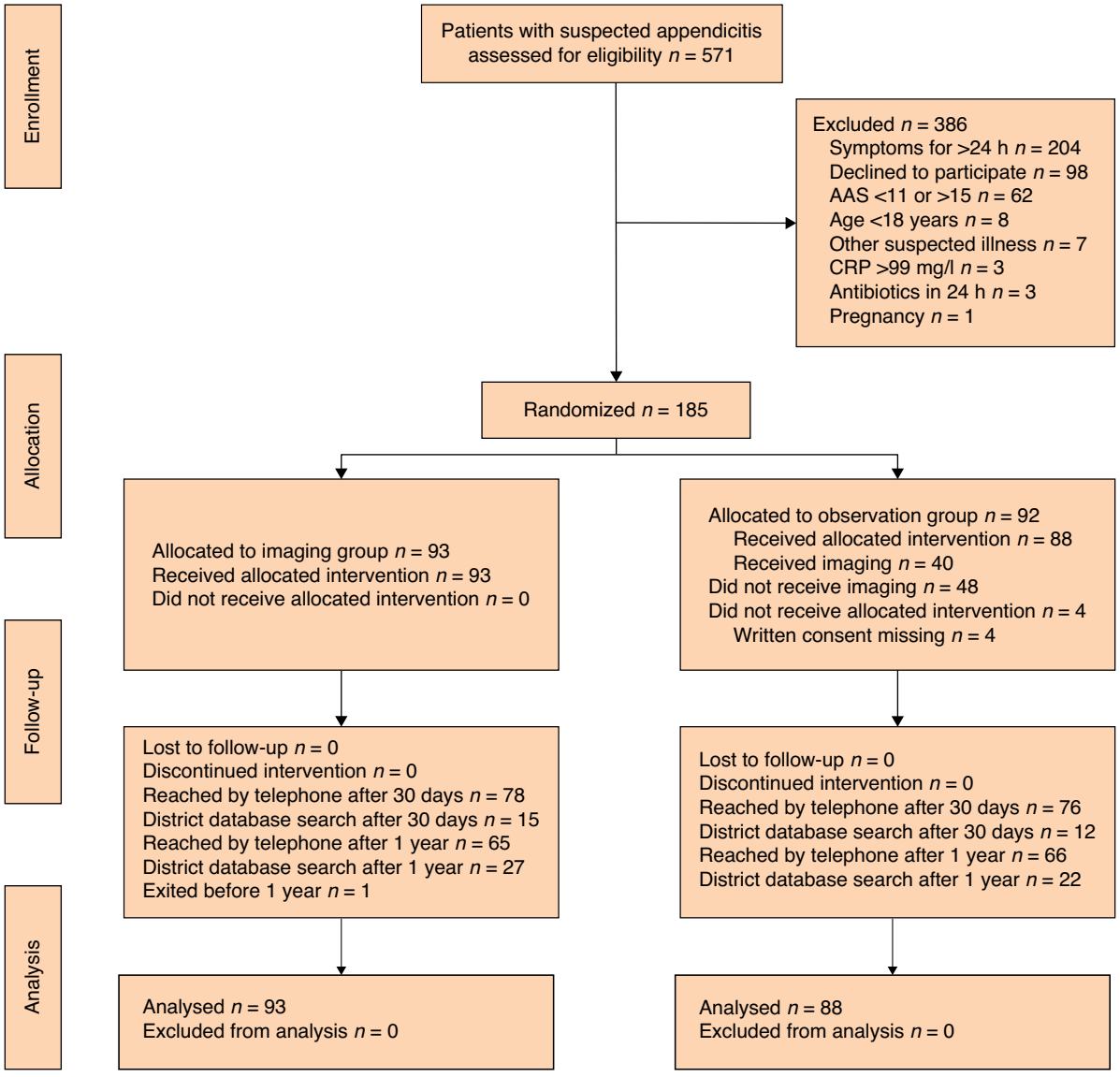

Fig. 1 CONSORT diagram for the trial

AAS, Adult Appendicitis Score; CRP, C-reactive protein.

Table 1 Demographics and clinical characteristics

	Imaging group ($n = 93$)	Observation group ($n = 88$)
Age (years)*	30.0 (24.0–38.5)	30.0 (25.0–39.8)
Women	53 (57)	46 (52)
Duration of symptoms (h)†	12.5 (5.4)	12.8 (5.7)
C-reactive protein (mg/l)*	6.0 (3.0–19.0)	6.0 (3.0–14.0)
White blood cell count ($\times 10^9$/l)*	13.0 (10.3–15.3)	12.1 (9.9–14.9)
Adult Appendicitis Score at start*	13.0 (12.0–14.0)	13.0 (12.0–14.0)

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r.) and †mean (s.d.).

Table 2 Primary and secondary outcomes

	Imaging group ($n = 93$)	Observation group ($n = 88$)	Difference†‡	P††
Appendicitis diagnosis	67 (72)	50 (57)	15 (1, 29)	0.032
Operated	67 (72)	49 (56)	16 (3, 30)	0.022
Uncomplicated acute appendicitis	63 (68)	47 (53)	14 (0, 28)	0.048
Complicated acute appendicitis	4 (4)	2 (2)	2 (−3, 7)	0.683‡‡
Antibiotic-treated	0 (0)	1 (1)	1 (−1, 3)	0.486‡‡
Non-appendicitis diagnoses	26 (28)	38 (43)	15 (1, 29)	0.032
Operated for suspected appendicitis	2 (2)	2 (2)	0 (−4, 4)	1.000‡‡
Negative appendicectomy	1 (1)	1 (1)	0 (−3, 3)	1.000‡‡
Neoplasia of appendix	1 (1)	0 (0)	1 (−1, 3)	1.000‡‡
Necrosis of caecum	0 (0)	1 (1)	1 (−1, 3)	0.486‡‡
Operated for other reasons	2 (2)	2 (2)	0 (−4, 4)	1.000‡‡
Appendiceal mucocele	0 (0)	1 (1)	1 (−1, 3)	0.486‡‡
Ruptured ovarian cyst	1 (1)	0 (0)	1 (−1, 3)	1.000‡‡
Femoral hernia	0 (0)	1 (1)	1 (−1, 3)	0.486‡‡
Crafting needle in subcutis	1 (1)	0 (0)	1 (−1, 3)	1.000‡‡
Non-operated	22 (24)	34 (39)	15 (2, 28)	0.029
Non-specific abdominal pain	13 (14)	31 (35)	21 (9, 34)	0.001
Ruptured ovarian cyst	4 (4)	0 (0)	4 (0, 8)	0.121‡‡
Other	5 (5)¶	3 (3)#	2 (−4, 8)	0.721‡‡
Any operation	71 (76)	53 (60)	16 (3, 30)	0.020
Relevant finding other than appendicitis	12 (13)	6 (7)	6 (−3, 15)	0.172
Gynaecological consultations	10 (11)	4 (5)	6 (−1, 14)	0.165‡‡
Patients having diagnostic imaging within 30 days	93 (100)	40 (46)	55 (44, 65)	<0.001
Ultrasonography only	26 (28)	10 (11)	17 (5, 28)	0.005
CT only	6 (7)	12 (14)	7 (−2, 16)	0.106
US and CT	61 (66)	17 (19)	46 (34, 59)	<0.001
CT and MRI	0 (0)	1 (1)	1 (−1, 3)	0.486‡‡
CT	67 (72)	30 (34)	38 (25, 51)	<0.001
Patients having diagnostic imaging within 1 year	93 (100)	44 (50)	50 (40, 60)	<0.001
CT	67 (72)	34 (39)	33 (20, 47)	<0.001
Time from randomization to treatment decision (h)*	3.9 (2.8)	8.5 (3.3)	4.5 (3.6, 5.5)§	<0.001§§
Time from randomization to discharge (days)*	1.2 (0.8)	1.2 (0.9)	0.01 (−0.2, 0.3)§	0.930§§
Time off work (days)*,**	9.5 (4.3)	10.0 (7.0)	0.6 (−1.4, 2.5)§	0.559§§
30-day follow-up				
ED visits	6 (7)	7 (8)	2 (−6, 9)	0.695
Visit to any physician	17 (18)	13 (15)	4 (−7, 14)	0.526
Delayed diagnosis of appendicitis	0 (0)	0 (0)		
1-year follow-up				
ED visits	7 (8)	10 (11)	4 (−5, 12)	0.376
Visits to any physician	20 (22)	19 (22)	0 (−12, 12)	0.989
Cumulative no. of patients requiring intervention for appendicitis	67 (72)	53 (60)	12 (−2, 26)	0.093

Values in parentheses are percentages unless indicated otherwise; ∗values are mean(s.d.); †values in parentheses are 95 per cent confidence intervals. ‡Percentage difference in proportions, except §difference in means. ¶One patient with urinary tract infection, one with ureterolithiasis, one with ovarian cyst haemorrhage, one with endometritis, and one with diverticulitis. #One patient with urinary tract infection, one with ureterolithiasis, and one with rectus sheath haemorrhage. **76 and 58 patients in imaging and observation groups respectively. ††Pearson's χ^2 test, except ‡‡two-sided Fisher's exact test, and §§independent-samples *t* test. ED, emergency department.

Management

In the imaging group, 28 per cent of patients had abdominal ultrasonography only, 66 per cent had ultrasound imaging and CT, and 6 per cent had CT alone. In this group, 69 patients (74 per cent) underwent operation for suspected appendicitis, of whom two had a non-inflamed appendix, and four had complicated appendicitis.

Observation was interrupted in two patients in the observation group because of worsening symptoms: one had CT and later underwent surgery for uncomplicated appendicitis; the other had surgery without imaging owing to signs of peritonitis, and necrosis of the caecum was found at the subsequent emergency laparotomy. One patient with resolving symptoms discontinued participation during the observation period and left the hospital. A total of 85 patients (97 per cent) finished the observation period. After observation, 25 patients (28 per cent) had an AAS of 16 or higher, and were scheduled for surgery, resulting in 23 patients with uncomplicated and two with complicated

appendicitis. In 23 patients (26 per cent), the AAS was below 16 and not declining, and imaging followed. Such imaging resulted in 19 patients being diagnosed with uncomplicated appendicitis. A declining AAS was observed in 36 patients (41 per cent), of whom 24 were discharged with a diagnosis of non-specific abdominal pain. Five were kept in hospital for an additional observation period, during which two patients underwent imaging; in this group, the final diagnoses were uncomplicated appendicitis (1 patient), non-specific abdominal pain (3), and urinary tract infection (1). The remaining seven patients had imaging against the protocol, resulting in a diagnosis of uncomplicated appendicitis (4), negative appendicectomy (1), ureterolithiasis (1), and non-specific abdominal pain (1). One patient did not have the second score registered, but was imaged with CT and underwent surgery for a strangulated femoral hernia. One patient in the observation group had histological appendicitis only, whereas all other patients had appendicitis identified both clinically and histologically. Patient management is described in detail in *Table S2*.

Primary outcome

There were fewer patients requiring treatment for acute appendicitis during the 30 days after randomization in the observation group: 50 (57 per cent) *versus* 67 (72 per cent) in the imaging group (odds ratio 0.51, 95 per cent c.i. 0.27 to 0.95; $P = 0.032$) (*Table 2*). The number needed to treat with the observation protocol was 6.6 to avoid one patient being diagnosed with appendicitis.

Secondary outcomes

These results are, in most part, detailed in *Table 2*. The number of patients with complicated appendicitis was low, and no statistical difference was found between the groups: four (4 per cent) in the imaging group *versus* two (2 per cent) in the observation group. No delayed diagnoses of acute appendicitis were made during the interval between 24 h and 30 days after randomization in either group. In the observation group, 40 patients (46 per cent) required imaging within 30 days and 44 (50 per cent) within 1 year after randomization. Fewer CT scans were performed in the observation group: 34 *versus* 72 per cent within 30 days, and 39 *versus* 72 per cent within 1 year. There was one negative appendicectomy in each group, both resulting from false-positive findings in the imaging study. In the observation group, 35 per cent of patients left hospital with a diagnosis of non-specific abdominal pain compared with 14 per cent in the imaging group. There was no marked difference in the number of other clinically relevant diagnoses or gynaecological consultations between groups. The treatment decision was made on average 4.5 h later in the observation group than in the imaging group ($P < 0.001$), but the overall duration of hospital stay was similar in the two groups. For patients with acute appendicitis, the median treatment decision time in the imaging and observation groups was 3.0 (i.q.r. 1.9–4.0) *versus* 7.7 (6.5–9.4) h respectively. For patients without acute appendicitis, the median treatment decision time in the imaging and observation groups was 4.4 (2.8–7.4) *versus* 7.9 (6.4–10.1) h respectively. There was no relevant difference in the number of missed work days between groups. Regardless of the diagnosis, non-operative treatment was more common in the observation group than in the imaging group: 40 *versus* 24 per cent. A similar proportion of patients revisited doctors for abdominal pain within the first year. Three non-operated patients, all in the observation group, were later diagnosed with acute appendicitis during the 1-year follow-up and underwent laparoscopic appendicectomy for uncomplicated appendicitis. In addition, one patient in the observation group had recurrent symptoms of appendicitis 6 weeks after primary appendicectomy, and an inflamed appendiceal stump was resected during the exploratory laparotomy. At the end of the 1-year follow-up, a total of 67 patients (72 per cent) in the imaging group and 53 (60 per cent) in the observation group had been treated for acute appendicitis, with no statistical difference between groups.

Discussion

In this study, approximately half of the patients with an intermediate AAS and symptoms for less than 24 h could be managed without radiological imaging. Observation led to fewer diagnoses of appendicitis than early imaging, presumably because of symptom improvement or resolution during the observation period. Complicated appendicitis was rare in both groups, suggesting that an observation protocol can be implemented safely in clinical practice.

Observation of patients with suspected appendicitis is not a novel idea; it has merely been superseded in recent times by radiological imaging, particularly CT. During observation, both spontaneous resolution and progression of symptoms can occur. Patients with decreasing symptoms can avoid treatment for appendicitis, whereas those with intensifying symptoms can often be diagnosed and treated without imaging. Treatment of appendicitis predisposes patients to complications, and has an economic impact on both patients and society; avoiding excess treatment is therefore advantageous.

The non-operative management of appendicitis has been an area of interest for more than a decade[19,20]; studies in this area rely on CT to select patients suitable for conservative management. However, routine imaging with CT may increase the incidence of appendicitis[1,3], as the present study has confirmed. Similarly, early laparoscopy has been noted to increase the number of patients diagnosed with appendicitis compared with observation[4,5]. A prospective, randomized trial[4] of women presenting with acute non-specific abdominal pain found acute appendicitis in 30.2 per cent in the early laparoscopy group compared with only 6.0 per cent in the observation group. Both CT and early laparoscopy are therefore sensitive in making a diagnosis, but may expose patients with resolving appendicitis to unnecessary treatment.

The AAS stratifies patients into three groups: low risk (score 10 or less), intermediate risk (11–15), and high risk (16 or higher). In the prospective external validation study[21], 38.9 per cent of patients with suspected appendicitis fell into the intermediate-risk group. In the present study, observation with repeated scoring using the AAS led to a decline in the need for diagnostic imaging, which benefited not only patients by reducing exposure to ionizing radiation but also released diagnostic imaging resources for other patient groups. Ionizing radiation used in CT is a known risk factor for subsequent cancer[22]. The results of a population-based cohort study[14] of over 800 000 patients with appendicitis showed that abdominopelvic CT was associated with a higher subsequent incidence of haematological malignant neoplasms. As adolescents and young adults are at higher risk of developing both appendicitis[23] and side-effects of radiation[24], avoiding unnecessary CT is particularly attractive.

A recent RCT[25] of non-operative management of appendicitis reported that 11 per cent of patients initially treated with

antibiotics underwent appendicectomy within 48 h and 20 per cent within 30 days of presentation. In the present study, no missed appendicitis or new appendicitis was noted within the first 30 days in the observation group. However, within 1 year, three patients developed appendicitis. It is estimated that 13 patients in the observation group had non-diagnosed resolving appendicitis, which would mean that the recurrence rate of appendicitis after spontaneous resolution is similar to the recurrence rate after successful conservative treatment with antibiotics at 1 year (23 per cent)[19].

The decline in negative appendicectomy rates in recent decades has mainly been explained by improved diagnostic accuracy, especially the use of abdominal CT[1,26–29]. In the present study, there were equally few negative appendicectomies in the two groups, indicating that the specificity of the observation protocol was as good as that of imaging in these patients.

There are several scoring systems to aid the diagnosis of acute appendicitis. In a randomized trial by Andersson and colleagues[7], a reduction of only 9.1 per cent in the diagnosis of appendicitis with observation of 4–8 h compared with early imaging was found using the AIRS. In the present study, which used the AAS, 15.2 per cent of patients were found to have spontaneously resolving appendicitis. The difference could in part be explained by different inclusion criteria and also by the fact that the aim of that study was to show the equality of the two management approaches. More research is needed to determine which scoring or protocol performs best during observation. The observation protocol used in this study could be improved. Because the risk of complicated appendicitis was low, an even longer observation period may be appropriate. In addition, the feasibility of observation in patients with a longer duration of symptoms should be studied. Furthermore, the indication for imaging after a period of observation may require adjustment. Some caution should be used when patients are managed according to protocols. As shown in this study, not all patients can be managed exactly according to the protocol. There should always be room for clinical judgement and deviation from the protocol when deemed necessary.

This study has some limitations. Recruitment was at times slow, stretching to 4 years. All patients with symptom duration over 24 h and a CRP level over 100 mg/l were excluded, limiting the applicability of this practice to a very precise proportion of patients with suspected appendicitis. Observation lengthened hospital stay and ultimately resulted in additional crowding in the ED. This study lacked the power to show statistically meaningful differences between the groups for the majority of the secondary outcomes, including the 1-year cumulative appendicitis count.

The reduction in appendicitis diagnoses, together with the increase in non-specific abdominal pain diagnoses in the observation group, validates the theory that appendicitis can resolve spontaneously. Observation of patients with early equivocal signs of appendicitis with repeated scoring is a safe and effective strategy to reduce imaging, and results in fewer patients being diagnosed with appendicitis and fewer interventions for acute appendicitis.

Funding

This study was supported financially by HUS Research Funds, Finland (Government Research Funds). The funder had no role in study design, data collection, data analysis, data interpretation, or report writing.

Acknowledgements

The authors thank all participating clinicians for recruiting patients at the ED of Meilahti hospital.

Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

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