

How do we make the (right) diagnosis of acute appendicitis?

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PROTOCOL STUDY

HOW DO WE MAKE THE (RIGHT) DIAGNOSIS OF ACUTE APPENDICITIS ?

Cèlia Caula Freixa, Ramon Farrés Coll

Abstract

Objectives: To evaluate the correct diagnosis in unselected patients presenting with suspected acute appendicitis in the Emergency Department in Hospital Trueta. To evaluate the different scenarios to achieve the correct diagnosis in patients with suspected acute appendicitis estimated by clinical evaluation without imaging, US only, CT only or US in all patients followed by CT after a non-diagnostic US.

Design: Cross-sectional study conducted between April 2014 and March 2015.

Settings: Medium-sized teaching hospital in Girona.

Participants: Consecutive adult patients, 14 years old or older, with clinically suspected acute appendicitis evaluated at the emergency department.

Main outcome: Correct diagnosis of acute appendicitis.

Key words: acute appendicitis; Alvarado score; US ; CT

Background

Acute Appendicitis (AA), an inflammation of the vestigial vermiform appendix, is one of the most common reasons for acute abdomen and for emergent surgery. The annual rate of AA increased from 7.62 to 9.38 per 10,000 between 1993 and 2008 in United States. No age group is exempt but AA rises to a peak incidence for a 10 to 19 year old subject [1].

Numerous hypotheses have been proposed to explain the aetiology of appendicitis. The most important hypotheses linked to appendicitis are: an obstruction, a specific infection and the hygiene hypothesis.

There is a widespread belief that appendicitis is caused by obstruction of the lumen followed by secondary bacterial invasion of the wall. However, the available data reveals little evidence that obstruction is the principal cause [2]. It is most likely to be several aetiologies of acute appendicitis, each of which leads to the final common pathway of invasion of the appendiceal wall by intraluminal bacteria. Most cases may be due to ulceration as a result of enteric infection. Other examples may be caused by foreign bodies or by ischemia due to blunt abdominal trauma or other circulatory disturbance. Diet may modulate the effect of these aetiologies, possibly by an effect on the gut flora. It is probable that obstruction is directly responsible for only a small minority of cases.

Clinical presentation may be influenced by the patient's age and the anatomical position of the appendix. Although, the primary feature used to be abdominal pain. Initially, the pain is commonly felt in the central abdomen but as the inflammatory process continues and involves the parietal peritoneum, the pain intensifies and localises towards the right iliac fossa. Usually, following the onset of pain, loss of appetite (anorexia) and nausea are frequent. Patients may have vomited, although persistence of this symptom is not a common feature. Patients tend to have a fever (up to 38°C) and a slight tachycardia. There is muscular rigidity and percussion tenderness following localization of the pain in the right iliac fossa.

The attachment of the appendix to the base of the cecum is constant. However, the tip may migrate and complicate the diagnosis. If the appendix migrates to retrocaecal/retrocolic, right loin pain is often present, with tenderness on examination. Muscular rigidity and tenderness to deep palpation are often absent because of protection from the overlying caecum. The psoas muscle may be irritated in this position, leading to hip flexion and exacerbation of the pain on hip extension (psoas stretch sign).

On the other hand, subcaecal and pelvic appendix could cause suprapubic pain and urinary frequency. Diarrhoea and tenesmus may be present as a result of irritation of the rectum. There may be a lack of abdominal tenderness, but rectal or vaginal tenderness may be present. Microscopic haematuria and leukocytes may also be present on urinalysis. Finally, diarrhoea may result from irritation of the distal ileum because of a pre-ileal or post-ileal appendix and a presumptive diagnosis of gastroenteritis may delay the diagnosis of appendicitis.

A constellation of history, physical signs, radiographic investigation, and laboratory analysis is used to diagnose an acute appendicitis as well as to balance the risk of delayed operative intervention against the removal of a normal appendix. A number of diagnostic modalities have been proposed including a clinical scoring system (e.g. Alvarado score), ultrasonography (US), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).

There are no physical findings, taken alone, that definitively confirm a diagnosis of appendicitis. The early signs of appendicitis are often subtle and unrevealing. However, as the inflammation progresses, involvement of the overlying parietal peritoneum causes localized tenderness in the right lower quadrant and can be detected on the abdominal examination. Rectal examination, although often advocated, has not been shown to provide additional diagnostic information in cases of appendicitis [3] Several findings on physical examination have been described to facilitate diagnosis of AA:

- McBurney's point tenderness is described as maximal tenderness at two-thirds of the way along a line drawn from the umbilicus to the anterior superior iliac spine.
- Rovsing's sign refers to pain in the right lower quadrant with palpation of the left lower quadrant. This sign is also called indirect tenderness and it is indicative of right-sided local peritoneal irritation.
- The psoas sign is associated with a retrocecal appendix. This is manifested by right lower quadrant pain with passive right hip extension. The inflamed appendix may lie against the right psoas muscle, causing the patient to shorten the muscle by drawing up the right knee. Passive extension of the iliopsoas muscle with hip extension causes right lower quadrant pain.
- The obturator sign is associated with a pelvic appendix. This test is based on the principle that the inflamed appendix may lay against the right obturator internus muscle. When the clinician flexes the patient's right hip and knee followed by internal rotation of the right hip, this elicits right lower quadrant pain.
- Dunphy's sign refers to pain in the right lower quadrant while coughing.

A part from clinical examination, several scoring systems have been proposed to standardize the correlation of clinical and laboratory variables. The Alvarado score is the most widely used diagnostic aid for the diagnosis of appendicitis. The scoring system developed by Alvarado in 1986 was evolved in making an affirmative diagnosis of acute appendicitis. This 10 point clinical scoring system for the diagnosis of AA, also known by the acronym MANTRELS, is based on symptoms, signs and diagnostic

tests. It includes 3 symptoms (migratory pain in right lower quadrant, anorexia and vomiting/nausea), 3 physical signs (fever, tenderness and rebound tenderness in right iliac quadrant), and two laboratory findings (leukocytosis and shift to the left) [4]. This score tends to help physician about management of appendicitis. A patient with a score of 5 or 6 should be observed; a patient with a score of 7 or more requires surgery, as Alvarado indicated in his study in 1986. After this review was performed in Pennsylvania, a lot of research has been done in this area all over the world with new evidence supporting this first investigation [5]. Higher Alvarado scores are significantly associated with pathologically confirmed appendicitis (low [0-3 points], 87%; moderate [4-6 points], 92%; high [7-10 points], 96%) [6]. It has also a global sensitivity and specificity of 94.2 and 70% respectively [7]. As show in the previous data, a systematic review indicates that Alvarado score is a useful diagnostic score and supports the use of the score as a triage, however it should not be used as the sole criterion for ruling in surgery in any patient group [8].

Other models have been studied to identify patients with high or low likelihood of appendicitis before operative intervention. According to this likelihood model, patients have a high likelihood of appendicitis if they have a total white blood cell count higher than 13.000 with either rebound tenderness on physical examination or a neutrophil count higher than 82% and voluntary guarding on physical examination [9].

The Lintula score, a paediatric appendicitis score, has been tested in adults. It includes nine variables: gender (male, 2 points; female, 0 points), intensity of pain (severe, 2 points; mild or moderate, 0 points), relocation of pain (yes, 4 points; no, 0 points), pain in the right lower abdominal quadrant (yes, 4 points; no, 0 points), vomiting (yes, 2 points; no, 0 points), body temperature ($\geq 37.5^{\circ}\text{C}$, 3 points; $< 37.5^{\circ}\text{C}$, 0 points), guarding (yes, 4 points; no, 0 points), bowel sounds (absent, tinkling or high-pitched, 4 points; normal, 0 points) and rebound tenderness (yes, 7 points; no, 0 points). The Lintula score has a minimum of 0 points and a maximum of 32 points. The cut-off level to predict AA is more than 21 points, and the cut-off level for ruling out AA is less than 15 points. Patients with scores more than 21 points are recommended to undergo emergency appendectomy, and those with scores ≤ 15 points are amenable to discharge. Patients with the appendicitis score between 16 and 20 points are recommended to be observed. But this score does not seem to improve the diagnostic accuracy and the negative appendectomy rate in adults [10].

Some of these clinical scores include laboratory analysis a part from physical examination. Leukocytosis, left shift, and elevated markers of inflammation such as C-reactive protein (CRP) have been associated with acute appendicitis. As with the clinical symptoms and signs, each individual

laboratory test value is only weakly discriminatory and predictive of acute appendicitis. But some biochemical tests are markers of perforation in acute appendicitis: CRP has a higher sensitivity to predict a perforation than other blood test results (bilirubin, WBC, neutrophils) and it can improve specificity if it combines the results of CRP and bilirubin [11].

In addition to clinical examination and laboratory test, different image techniques could be done to diagnoses and acute appendicitis and rule out other diseases. First of all, a plain radiograph can show right lower quadrant appendicolith, localized right lower quadrant ileus, loss of the psoas shadow, free air, deformity of cecal outline and right lower quadrant soft tissue density. But this simple image test is usually not helpful for establishing the diagnosis of appendicitis despite its availability and its promptness. On the other hand, graded compression ultrasonography (US) can help physicians to the prompt diagnosis and early treatment of many cases of appendicitis. The most important benefit of this image technique is that it does not use radiation. However, US has some difficulties due to overweight, bowel obstruction or appendix localization. These conditions might difficult the complete visualization of the appendix. The experience of the radiologist plays a big role in the image interpretation process (operator-dependent technique) and consequently in the final treatment decision. The primary criteria of acute appendicitis are the evidence of a non-compressible appendix and a measured diameter greater than 7 mm. Other supporting criteria are echogenic periappendiceal mesenteric fat, peri-appendiceal fluid collection and mesenteric lymphadenopathy [12]. US has been studied in many trials and broad sensitivity and specificity has been described, a sensitivity between 55 and 94.7% and a specificity between 58 and 95% [12-15]. Another important imaging method for the diagnosis of AA is the CT scanner. The main signs on the CT that might help diagnose an acute appendicitis are: an enlarged appendiceal diameter more than 6 mm with an occluded lumen, appendiceal wall thickening (more than 2 mm), peri-appendiceal fat infiltration, peri-appendiceal free fluid and an appendicolith [16]. CT has been tested in various studies, alone or compared with clinical evaluation or other image techniques as ultrasonography. CT can decrease the negative appendectomy rate compared with a clinical evaluation alone [17] and it also demonstrates superior sensitivity 91% and specificity 90% versus ultrasonography [18]. In addition, it is associated with improved immediate postoperative complications and lower readmission rates in comparison with clinical evaluation. Nevertheless, CT represents a higher length of stay and increased cost of care [19]. Finally, Magnetic resonance imaging is a non-irradiating imaging technique but is not as widely or readily available as CT and US. It is more expensive and the

examination itself takes a longer time to perform. MRI can assist with the evaluation of acute abdominal and pelvic pain during pregnancy. In addition, it could be a potential replacement for CT without associated ionizing radiation and contrast medium administration [20]. A normal appendix is visualized as a tubular structure less than or equal to 6 mm in diameter and filled with air and/or oral contrast material. On MRI, a thickened appendix of more than 7 mm in diameter, an appendiceal wall thicker than 2 mm, signs of inflammatory changes surrounding the appendix or presence of a pelvic abscess are diagnostic signs of appendicitis.

In conclusion, a diagnostic pathway using routine US, limited CT, and clinical re-evaluation for patients with acute abdominal pain can provide excellent results [21].

A variety of inflammatory and infectious conditions in the right lower quadrant can mimic the signs and symptoms of acute appendicitis. Gynaecological, urological and gastrointestinal conditions are included in a right lower quadrant pain differential diagnosis. In the gynaecological field we should think about a tubo-ovarian abscess, a pelvic inflammatory disease, ruptured ovarian cyst, a Fallopian tube torsion, an endometriosis, an ectopic pregnancy or other conditions. In the urological field we should rule out renal colic, pyelonephritis or urinary tract infection according to signs and symptoms. Finally, on the gastrointestinal area, we should rule out cecal diverticulitis, mesenteric adenitis, omental torsion, bowel perforation, Meckel's diverticulitis, acute ileitis and Crohn's disease. Some of these conditions may be surgical, but it is more important to recognize the non-surgical conditions at imaging such as mesenteric adenitis among others, thus avoiding unnecessary surgery.

The gold standard for a positive diagnosis of AA is the histopathologic confirmation. Acute appendicitis can be divided into a number of pathology patterns according to microscopic analysis: catarrhal appendicitis, suppurative/phlegmonous and gangrenous [2]. A catarrhal appendicitis is characterized by acute inflammation (neutrophils and ulceration) confined to the mucosa. A suppurative or phlegmonous appendicitis is characterized by a neutrophilic infiltrate involving the mucosa, submucosa and muscularis propria, generally circumferential. Transmural inflammation and extensive ulceration are found and other common changes include oedema, fibrinopurulent serositis, micro abscesses in the wall and vascular thrombi. A gangrenous appendicitis is defined by transmural inflammation with areas of necrosis, leading to perforation if untreated.

Most patients with acute appendicitis undergo appendectomy initially. Appendectomy for acute appendicitis is one of the most common surgical procedures performed [22]. In 1889, open appendectomy was accepted as the treatment standard. This surgical procedure could be done via laparoscopic technique, an open procedure or both (laparoscopic converted to open procedure). Delay of appendectomy for acute appendicitis in adults has been studied and it does not appear to adversely affect 30-day outcomes. The length of postoperative stay, the overall morbidity or serious morbidity/mortality is neither clinically meaningful nor statistically significant [23].

Some recent studies want to demonstrate evidence on antibiotic management of uncomplicated acute appendicitis. However, a Cochrane analysis cannot recommend this new treatment management nowadays because of its inconclusive outcomes and the low quality of studies analyzed [24]. Luckily, a new prospective randomized controlled multicenter trial wants to compare antibiotic therapy (ertapenem) with emergency appendectomy in the treatment of uncomplicated acute appendicitis [25]. This trial might demonstrate an alternative treatment option for uncomplicated acute appendicitis. For those treated nonoperatively, the recurrence rate of acute appendicitis is low, and for this reason a routine appendectomy after initial successful nonoperative treatment is not justified and should be abandoned [26].

In conclusion, we want to evaluate the prevalence of correct diagnosis of acute appendicitis and to analyse the current management of acute abdominal pain when it is suspected. This protocol wants to standardise data collection to obtain complete and update information about a very prevalent disease in the emergency department. Specific literature on this subject shows broad differences in sensitivity and specificity diagnosis tests and we still do not know the right way to manage acute appendicitis in order to avoid negative appendectomies and complications due to delayed surgery. Nowadays, the proportion of patients without appendicitis who had been submitted to appendectomy ranged from 5.2% to 42.2%, and it has decreased during the CT era but it still remains too high [3,17]. For the aforementioned reasons, our objective is to explore the likely utility of various diagnostic scenarios with respect to their ability to identify correctly patients with appendicitis. Thus, the current project could serve as a basis for clinical practice and further research projects on this topic.

Bibliography

1. Buckius MT, McGrath B, Monk J, Grim R, Bell T, Ahuja V. Changing epidemiology of acute appendicitis in the United States: study period 1993-2008. *J Surg Res* [Internet] 2012 [cited 2013 Dec 2];175(2):185–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22099604>
2. Carr NJ. The Pathology of Acute Appendicitis. *Ann Diagn Pathol* 2000;4:46–58.
3. Andersson REB. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg* [Internet] 2004 [cited 2013 Nov 20];91(1):28–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14716790>
4. Alvarado a. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med* [Internet] 1986 ;15(5):557–64. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3963537>
5. G V, Vv S, B V, Sateesh S, Bangla G, Rao P. Role of Alvarado score in the diagnosis of acute appendicitis. *Int J Res Med Sci* [Internet] 2013 [cited 2013 Dec 3];1(4):404. Available from: <http://www.scopemed.org/?mno=41051>
6. Nelson DW, Causey MW, Porta CR, McVay DP, Carnes AM, Johnson EK, et al. Examining the relevance of the physician’s clinical assessment and the reliance on computed tomography in diagnosing acute appendicitis. *Am J Surg* [Internet] 2013 [cited 2013 Nov 18];205(4):452–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23388421>
7. Dey S, Mohanta PK, Baruah AK, Kharga B, Bhutia KL, Singh VK. Alvarado scoring in acute appendicitis-a clinicopathological correlation. *Indian J Surg* [Internet] 2010 [cited 2013 Nov 20];72(4):290–3. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3002776&tool=pmcentrez&rendertype=abstract>
8. Ohle R, O’Reilly F, O’Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. *BMC Medicine* [Internet] 2011 [cited 2013 Nov 22];9(1):139. Available from:

- <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3299622&tool=pmcentrez&rendertype=abstract>
9. Birkhahn RH, Briggs M, Datillo P a, Van Deusen SK, Gaeta TJ. Classifying patients suspected of appendicitis with regard to likelihood. *Am J Surg* [Internet] 2006 [cited 2013 Nov 17];191(4):497–502. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16531143>
 10. Lintula H, Kokki H, Pulkkinen J, Kettunen R, Gröhn O, Eskelinen M. Diagnostic score in acute appendicitis. Validation of a diagnostic score (Lintula score) for adults with suspected appendicitis. *Langenbecks. Arch Surg* [Internet] 2010 [cited 2013 Nov 18];395(5):495–500. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20379739>
 11. McGowan DR, Sims HM, Zia K, Uheba M, Shaikh IA. The value of biochemical markers in predicting a perforation in acute appendicitis. *ANZ J Surg* [Internet] 2013 [cited 2013 Nov 20];83(1-2):79–83. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23231057>
 12. Memisoglu K, Karip B, Mestan M, Onur E. The value of preoperative diagnostic tests in acute appendicitis, retrospective analysis of 196 patients. *World J Emerg Surg* [Internet] 2010;5:5. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2834661&tool=pmcentrez&rendertype=abstract>
 13. Douglas CD, Macpherson NE, Davidson PM, Gani JS. Randomised controlled trial of ultrasonography in diagnosis of acute appendicitis, incorporating the Alvarado score. *BMJ*. 2000;321:1–7.
 14. Nasiri S, Mohebbi F, Sodagari N, Hedayat A. Diagnostic values of ultrasound and the Modified Alvarado Scoring System in acute appendicitis. *Int J Emerg Med* [Internet] 2012 ;5(1):26. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3410771&tool=pmcentrez&rendertype=abstract>
 15. Franke C, Böhner H, Yang Q, Ohmann C. Ultrasonography for Diagnosis of Acute Appendicitis : Results of a Prospective Multicenter Trial. *World J Surg* 1999;23:141–6.

16. Van Randen a, Laméris W, van Es HW, ten Hove W, Bouma WH, van Leeuwen MS, et al. Profiles of US and CT imaging features with a high probability of appendicitis. *Eur Radiol* [Internet] 2010 [cited 2013 Dec 2];20(7):1657–66. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2882051&tool=pmcentrez&rendertype=abstract>
17. Krajewski S. Impact of computed tomography of the abdomen on clinical outcomes in patients with acute right lower quadrant pain: a meta-analysis. *Can J Surg* [Internet] 2011 [cited 2013 Nov 6];54(1):43–53. Available from: <http://www.cma.ca/cjs/vol-54/issue-1/0043>
18. Randen A Van, Bipat S, Zwinderman AH, Ubbink DT, Stoker J, Boermeester MA. Acute Appendicitis : Meta-Analysis of Diagnostic Performance of CT and Graded Compression US Related to Prevalence of Disease. *Radiology* 2008;249(1):97–106.
19. Shaligram A, Pallati P, Simorov A, Meyer A, Oleynikov D. Do you need a computed tomographic scan to evaluate suspected appendicitis in young men: an administrative database review. *Am J Surg* [Internet]; 2012 [cited 2013 Nov 19];204(6):1025–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23022250>
20. Leeuwenburgh MMN, Laméris W, van Randen A, Bossuyt PMM, Boermeester M a, Stoker J. Optimizing imaging in suspected appendicitis (OPTIMAP-study): a multicenter diagnostic accuracy study of MRI in patients with suspected acute appendicitis. *Study Protocol. BMC Emerg Med* [Internet] 2010 [cited 2013 Dec 2];10:19. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2978143&tool=pmcentrez&rendertype=abstract>
21. Toorenvliet BR, Wiersma F, Bakker RFR, Merkus JWS, Breslau PJ, Hamming JF. Routine ultrasound and limited computed tomography for the diagnosis of acute appendicitis. *World J Surg* [Internet] 2010 [cited 2013 Nov 14];34(10):2278–85. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2936677&tool=pmcentrez&rendertype=abstract>
22. Centers for Disease Control and Prevention [Internet]. Hyattsville, MD; 2012 [cited 2014 Jan 12]. Table 115. Cost of hospital discharges with common hospital operating room procedures in

- nonfederal community hospitals , by age and selected principal procedure : United States , selected years 2000 – 2010. Available from: <http://www.cdc.gov/nchs/data/hus/2012/115.pdf>
23. Ingraham AM, Cohen ME, Bilimoria KY, Ko CY, Hall BL, Russell TR, et al. Effect of delay to operation on outcomes in adults with acute appendicitis. *Arch Surg* [Internet] 2010 ;145(9):886–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20855760>
 24. Wilms IMHA, de Hoog DENM, de Visser DC, Janzing HMJ. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database of Systematic Reviews* 2011, Issue 11.Art.No.:CD008359.DOI: 10.1002/14651858.CD008359.pub2.
 25. Paajanen H, Grönroos JM, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis (APPAC trial). *BMC Surg* [Internet] 2013 [cited 2013 Nov 25];13:3. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3585698&tool=pmcentrez&rendertype=abstract>
 26. Kaminski A, Liu I-LA, Applebaum H, Lee SL, Haigh PI. Routine interval appendectomy is not justified after initial nonoperative treatment of acute appendicitis. *Arch Surg* [Internet] 2005;140(9):897–901. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16175691>

Hypothesis

We expect to find a correct diagnosis of acute appendicitis of around 93%. We anticipate that there is broad variability on clinical criteria and image techniques used to diagnose acute appendicitis in patients with clinical suspicious of this pathology in the Emergency Department. This variability can affect the correct diagnosis of acute appendicitis.

Objective

This study aims to evaluate the correct diagnosis in unselected patients presenting with suspected acute appendicitis in the Emergency Department in Hospital Josep Trueta in Girona.

We also aim to evaluate the different scenarios to achieve the correct diagnosis in patients with suspected acute appendicitis estimated by clinical evaluation without imaging, US only, CT only or US in all patients followed by CT after a non diagnostic US.

Methods/Design

Study Design

This cross-sectional study will be performed in a medium-sized teaching hospital in Girona with a 24 hr emergency service with surgery, radiology, intensive care, paediatrics, gynaecology and internal medicine.

Participants

Our population is based on consecutive adult patients, 14 year old or older, with clinically suspected acute appendicitis evaluated by a resident of the surgical department or an on-call surgeon or an emergency physician at the emergency department in Hospital Josep Trueta in Girona from April 2014 to March 2015.

Treating physicians in the emergency department will identify patients based on the anamnesis and physical examination prior to imaging. A patient will be included in this study if the subject explains acute abdominal pain (more than 2 hours and less than 7 days in duration) localized on the periumbilical region, suprapubic region or right low quadrant.

Patients who were evaluated at another hospital for the same complaint, patients with obvious cause of abdominal pain (e.g. penetrating trauma, postoperative pain), patients with history of appendectomy, and pregnant or lactating patients will be excluded.

Patients will be informed about the study and invited to participate.

Sample size

Sample size calculations are based on reported prevalence rates of Acute Appendicitis in Hospital Trueta in previous years. We calculate a sample size of 82 patients older than 14 years old, with an alpha risk of 0.05 for a precision of +/- 0.05 units in a two-sided test for an estimated proportion of 0.93, assuming that such population is equal to 300 subjects (data from previous years in our hospital). We also anticipate a replacement rate of 10%. Despite this calculation, we are going to include all patients with clinically suspected acute appendicitis.

Variables

The findings of anamnesis, clinical assessment, laboratory test and imaging will be prospectively documented by the treating physician in a case record form (Annex 1).

Three independent variables are considered:

- 1st) Alvarado score
- 2nd) Ultrasonography
- 3rd) CT

In the first place, the Alvarado score will be calculated according to the following eight points:

- Migratory pain in right lower quadrant (1 point)
- Anorexia (1 point)
- Vomiting/nausea (1 point)
- Fever (1 point)
- Tenderness in right lower quadrant (2 points)
- Rebound pain (1 point)
- Leukocytosis (2 points)
- Shift to the left (1 point).

According to the scores obtained with the Alvarado scale, the patients are going to be divided into three groups:

- Group I: score 7-10
- Group II: score 4-6
- Group III: score less than 3.

Apart from the score in Alvarado scale we are going to collect all data separately.

First, during the anamnesis the patient will be asked directly about the symptoms and every symptom will be managed as a qualitative variable: migratory pain in right lower quadrant, anorexia defined as a loss of normal appetite during the last few hours or days and vomiting and/or nausea.

Second, the signs are going to be evaluated by a resident of the surgery department, an on-call surgeon or an emergency physician. Fever will be measured in axillary and we will consider it as positive if it is more than 37.5°C checked in the Emergency Room by a nurse or an auxiliary nurse. We will also use the temperature as a continuous variable. The physical examination will include a complete abdominal exam and the tenderness and rebound tenderness in right lower quadrant will be noted in the case record form.

Third, the laboratory findings are going to be extracted from the first blood test performed upon arrival. We define the laboratory findings as normal or high depending on the standard values set by the Hospital Josep Trueta clinical analysis department. The leukocytosis will be considered as more than 12.500 WBC. The shift to the left will be considered as positive if the blood test shows earlier neutrophils precursors present (e.g. myelocytes, metamyelocytes, or promyelocytes). The C-reactive

protein will be managed as a continuous and a categorical variable. The categorical variable will be managed as positive if the C-reactive protein is higher than 0.5.

In the second place, a staff radiologist or a resident in the radiology department will perform an ultrasonography if the treating physician considers it necessary. This ultrasonography concerns a complete examination of the abdomen, including the use of the graded compression technique.

Graded compression ultrasonography results will be designated as the follow options [16]:

- Unperformed ultrasonography
- Highly suggestive ultrasonography for acute appendicitis when all of the following criteria are observed: transducer tenderness, a thickened appendix and a peri-appendiceal fat infiltration.
- Suggestive ultrasonography for acute appendicitis if two of the following criteria are observed: transducer tenderness, a thickened appendix or a peri-appendiceal fat infiltration.
- Negative ultrasonography if the appendix is identified and none of the above criteria are present.
- Inconclusive ultrasonography if the appendix is not identified with ultrasonography

Thirdly, an abdominal computed tomography (CT) of the complete abdomen will be performed if the treating physician considers it necessary.

This variable will be addressed as qualitative with five different options [16]:

- Unperformed CT
- Highly suggestive acute appendicitis CT if the appendix is completely visualised and there are thickened appendix, peri-appendiceal fat infiltration and appendiceal enhancement.
- Suggestive CT for acute appendicitis if two of the following criteria are observed: completely visualised appendix, thickened appendix, peri-appendiceal fat infiltration, appendicolith present or appendiceal enhancement.
- Non diagnosed acute appendicitis CT if none of the aforementioned criteria are observed
- Inconclusive if the appendix is not assessable with CT.

US and CT variables will be recoded in two categories: performed and unperformed. This variable will be compared with the outcome in order to analyze the influence of image techniques in the correct diagnosis of acute appendicitis.

Furthermore, we are going to consider a variable called diagnosis pathway. This variable will have four categories: clinical evaluation, ultrasonography, CT, ultrasonography + CT.

The outcome of this study is the correct diagnosis of acute appendicitis.

For those who undergo appendectomy, we will use the pathological report of the surgical specimen. Criteria of histological acute appendicitis will be an infiltration of the muscularis propria with polymorphonuclear cells and it will be classified as "correct diagnosis". Pathology results as appendix vermicularis without any additional finding will be accepted as negative appendectomy and it will be classified as "incorrect diagnosis".

For those who do not undergo appendectomy and histological examination, we will make a brief telephone interview to ensure the end of the episode as alternative outcome measure after 30 days of consultation. A resident of the surgical department will contact the patient by phone after 30 days of consultation. The telephonic interview will include questions about the resolution of their presenting symptoms, the need to revisit the emergency department or the hospital readmission for the same symptoms and the need for subsequent operation. These patients will be classified as "incorrect diagnosis" if the symptoms do not disappear after the 7-day period of observation after the first visit, or if the patient needs to revisit the emergency department, a readmission for the same complaint or needs an operation. If a patient does not require subsequent hospital admission or operation, it will be classified as "correct diagnosis". Patients who could not be contacted within this time frame will be considered lost to follow-up.

The final diagnosis will be included in the incorrect diagnosis. We are going to classify this variable in 7 categories: gynaecologic pathology, urological pathology, gastrointestinal pathology, Crohn disease, mesenteric lymphadenitis, no diagnosis (if any diagnosis could be done) or others (none of the above categories). We include this in order to know which are the most common pathologies that can mimic an acute appendicitis.

Besides this, we want to analyse different co-variables such as:

- Gender (male or female)
- Age (years)
- Weight (kilos)
- Body mass index (kilos/meter²)
- Vital signs on physical examination
 - o Temperature
 - o Heart rate
 - o Blood pressure
- Days of hospitalization
- Treatment:
 - o Laparoscopy appendectomy
 - o Open appendectomy
 - o Laparoscopy appendectomy converted to open procedure
 - o No surgery including drainage and/or antibiotic treatment
 - o Other treatments

These variables are included because we want to describe our population. We are also going to use them to make a multivariate analysis and its influence on the correct diagnosis.

Instrumentalization

An auxiliary nurse will measure the weight, the height, the temperature and the heart rate according to standard protocols in the emergency department.

Statistical analysis

Data analysis will primarily focus on the prevalence of correct diagnosis and the diagnostic pathway that identifies correctly patients with appendicitis. The association of the following scenarios with the correct diagnosis of acute appendicitis will be estimated: clinical evaluation without imaging, US after clinical evaluation, US in all patients followed by CT after a non diagnostic US and CT after clinical evaluation. Next, we will evaluate the diagnostic performance of stratified imaging strategies taking into account the patient's characteristics (e.g. age, gender) and presentation features (e.g. vomiting, fever). We will also investigate accuracy modifiers, such as body mass index, which are known to influence the diagnostic performance of some imaging modalities.

The mean and the standard deviation will be calculated for all quantitative variables (age, weight, body mass index, temperature, heart rate, blood pressure, white blood cells count and CRP) assuming a normal distribution and the percentage for all qualitative variables (gender, categories of BMI, migratory pain in right lower quadrant, anorexia, vomiting/nausea, fever, tenderness, rebound tenderness, leukocytosis, shift to the left, CRP, Alvarado score, ultrasounds record, CT record and treatment and diagnosis pathway) with a 95% confidence interval.

We will start with a bivariate analysis. Categorical variables will be compared using chi-square tests because our dependent variable is a binary dummy variable.

For each imaging feature we will calculate the corresponding diagnostic odds ratio using univariate logistic regression analysis. An odd ratio of 1 indicates no association with higher ratios pointing to stronger associations.

In addition, multivariate logistic regression analysis will be performed to evaluate the diagnostic accuracy association of a combination of features (clinical assessment, the ultrasound test and the CT test...), conditional on the presence or absence of other features and their contribution. Significance for all analyses will be set at a P value <0.05.

Ethical considerations

This study will be conducted according to the principles of the Helsinki Declaration and in accordance with the Medical Research Involving Human Subjects Act and other European guidelines, regulations and acts. The Clinical Research Ethical Committee (CEIC, Comitè d'Ètica d'Investigació Clínica) of Hospital Josep Trueta in Girona will approve our study protocol and we will take in consideration all their recommendations. We will respect confidentiality rules and we will inform all participants according to Article 5 in Organic Law 15/1999. All participants will receive an informative document (ANNEX 2) and they will have to sign the informed consent in order to be included in the study (ANNEX 3). All data will be managed anonymously.

Limitations

A limitation of this study is that it represents only a single centre experience. Furthermore, we know that research in the urgent pathology field is always more complicated due to the fast interventions required and the usual lack of time. Our goal is to compensate these lacks providing an excellent education for all the participants in the study (physicians in the emergency department, radiologist, pathologist and surgeons). Since this is not an interventionist study, but a mere descriptive one, we have a longer time span to research all data, which has not been compiled during early stages.

Feasibility

We had meetings with the radiologist team while we are writing this protocol because we want to agree on diagnostic criteria. And we did the same with the pathologist team.

Before we start with this study we will organize various meetings with all the professionals involved (auxiliary nurses, nurses, emergency physicians, radiologist, pathologist and surgeons). We will explain the objectives and the importance of recording all data on the case record forms. We want to train every professional involved in this project in order to homogenize the results recorded.

Timeline

All adult patients, 14 year old or older, admitted to the emergency department with a clinical suspicion of uncomplicated AA will be studied carefully by a physician at the Emergency department. An on-call surgeon or a resident of the surgery department will evaluate the patient if the physician in the emergency department requires it. Clinical history, physical investigation, laboratory blood test and image test are undertaken according to medical indications.

The treating physician will inform the patient and give the informed consent. After signed informed consent, all patients evaluated for study enrollment will be registered on a list and the same physician will fill in the case record form.

Once a month, two residents of the surgical department will analyse all case record forms filled in the emergency department and they will be in charge of introducing this data in the online form specially design for this study. At the end of the year, a statistician will analyse the results. These results will be included in an article and presented in different medical meetings.

Chronogram

		2013		2104												2015				
WHO? *		N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M
Stage 0.- Preparation																				
Prepare the protocol	MR																			
Train the physicians involved in this project	RS																			
Stage 1.- Data collection																				
Patients selection	MR+RS																			
Fill on-line case record form	RS																			
Follow-up patients	RS																			
Stage 2.- Data analysis and final evaluation																				
Statistical analysis	S + MR																			
Preparation of the article	MR+RS																			

* MR: main researcher
 RS: residents of surgery
 S: statistician

Budget

OUTCOMES		EUROS
1. Personal		
2. Executive outcomes		
Statistician	20h x 35€/h	700€
National meetings of <i>Spanish association of Surgeons</i>	200 € fee	700€
	300€ accommodation	
	200€ transport	
Article Publication	500€ Translation and design	1000€
	500€ fee for open access article	
TOTAL		2400€

ANNEX 1

Case record form.- HOW DO WE MAKE THE (RIGHT) DIAGNOSIS OF ACUTE APPENDICITIS ?

Demographic variables

- Gender
 - Male
 - Female
- Age (years):
- Date of consultation (DD/MM/YYYY): ___ / ___ / _____
- Days of hospitalization (days):
- Weight (Kilos):
- Body mass index (BMI) (kilos/meters²):
- Categories of BMI
 - Underweight: ≤ 18.5
 - Normal weight: 18.5 – 24.9
 - Overweight: 25 - 29.9
 - Obesity: ≥ 30

Vital signs:

- Temperature (Celsius):
- Heart rate (beats per minute):
- Blood pressure (mmHg):

Symptoms:

- Migratory pain in right lower quadrant
 - YES
 - NO
- Anorexia
 - YES
 - NO

- Vomiting/nausea

YES

NO

Physical signs

- Fever:

YES (more than 37.5°C)

NO

- Tenderness

YES

NO

- Rebound tenderness in right iliac quadrant

YES

NO

Laboratory findings

- Leukocytosis

YES (more than 12.500)

NO

- White blood cells count (value):

- Shift to the left

YES

NO

- CRP (value):

- CRP

YES (> 0.5)

NO (<0.5)

Alvarado score:

Group I: score 7-10

Group II: score 4-6

Group III: score less than 3.

Ultrasounds record

- Unperformed
- Highly suggestive acute appendicitis (transducer tenderness, a thickened appendix and a peri-appendiceal fat infiltration)
- Suggestive appendicitis (two of the following criteria: transducer tenderness, a thickened appendix or a peri-appendiceal fat infiltration)
- Negative ultrasonography (appendix is identified and none of the above criteria are present)
- Inconclusive ultrasonography if the appendix is not identified with ultrasonography

CT record

- Unperformed
- Highly suggestive acute appendicitis (completely visualised appendix, thickened appendix, peri-appendiceal fat infiltration and appendiceal enhancement)
- Suggestive appendicitis (two of the following criteria completely visualised appendix, thickened appendix, peri-appendiceal fat infiltration, appendicolith present or appendiceal enhancement)
- Negative CT (appendix is identified and none of the above criteria are present)
- Inconclusive if the appendix is not assessable with CT.

Treatment

- Appendectomy via Laparoscopy
- Open appendectomy
- Appendectomy via Laparoscopy reconverted to laparotomy
- No surgery (drainage and/or antibiotic treatment)
- Others (no treatment, other surgery...)

Diagnosis pathway

- Clinical evaluation
- Ultrasonography
- CT
- Ultrasonography + CT

Outcomes

- Correct diagnostic

Definition:

Pathological report of the specimen after surgery: infiltration of the muscularis propria with polymorphonuclear cells, perforation,

Brief telephone interview: end of the episode, no surgery or no reconsultation.

- Incorrect diagnostic

Pathological report of the specimen after surgery: appendix vermicularis without any additional finding.

Brief telephone interview: reconsultation, surgery or readmission.

Final diagnosis

- Gynaecologic pathology
- Urological pathology
- Gastrointestinal pathology
- Crohn disease
- Mesenteric lymphadenitis
- No diagnosis
- Others.

ANNEX 2

Full d'informació al pacient

Li agraïm que participi en el nostre estudi sobre els mètodes diagnòstics de l'apendicitis aguda.

Els objectius de l'estudi son: avaluar el correcte diagnòstic dels pacients que presentin clínica sospitosa d'apendicitis aguda a Urgències de l'Hospital Josep Trueta de Girona. Paral·lelament també volem avaluar el diversos escenaris que s'utilitzen per diagnosticar aquesta patologia: avaluació clínica, ecografia i/o tomografia computeritzada (TAC).

Vostè seguirà el procediment diagnòstic que el metge d'urgències consideri més oportú basat en els seus coneixements mèdics. Aquest estudi per tant, no pretén modificar ni introduir cap pràctica nova sinó que vol analitzar el maneig actual de les apendicitis agudes a Urgències i és per això que vostè ha estat seleccionat per participar en aquest estudi.

No obtindrà cap benefici ni cap perjudici durant la participació en aquest estudi.

Si no és operat durant el transcurs del seu ingrés contactarem amb vostè via telefònica un mes després de l'alta per tal d'avaluar l'episodi que va presentar inicialment. Li preguntaran sobre els símptomes que presenta i si ha necessitat més atenció mèdica després d'aquest episodi.

Li garantim que les seves dades es tractaran amb absoluta confidencialitat segons la Llei Orgànica que regula la confidencialitat de dades informatitzades (Llei Orgànica 15/1999), també es respectarà la llei d'investigació biomèdica 14/2007 i qualsevol altre que resulti aplicable. Les dades recollides seran utilitzades només amb finalitat d'investigació.

Per dur a terme aquest projecte i atenent a les disposicions legals vigents li sol·licitem la seva autorització. Abans i després de firmar el document de consentiment informat, pot preguntar tot el que cregui convenient als metges i personal sanitari responsable de l'estudi.

En tot moment podrà consultar amb altres professionals si ho considera oportú.

Si renuncia a participar en l'estudi, no suposarà cap càstig ni pèrdua de beneficis per vostè.

Hoja de información al paciente

Le agradecemos su participación en nuestro estudio sobre los métodos diagnósticos de la apendicitis aguda.

Los objetivos de nuestro estudio son: evaluar el correcto diagnóstico de los pacientes que presentan clínica sospechosa de apendicitis aguda en Urgencias del Hospital Josep Trueta de Girona. Paralelamente queremos evaluar los diferentes escenarios que se utilizan para diagnosticar esta patología: evaluación clínica, ecografía y/o tomografía computerizada (TAC).

Usted seguirá el procedimiento diagnóstico que el médico de urgencias considere más oportuno basado en sus conocimientos médicos. Este estudio, por lo tanto, no pretende modificar ni introducir ninguna prueba nueva sino que quiere analizar el manejo actual de las apendicitis en Urgencias y es por esta razón que usted ha sido seleccionado.

No obtendrá ningún beneficio ni perjuicio durante la participación en este estudio.

Si no es operado durante el transcurso de su ingreso, contactaremos con usted vía telefónica un mes después del alta para evaluar el episodio que presentó inicialmente. Le preguntaremos sobre los síntomas que presenta y si necesitó más atención médica después del episodio.

Le garantizamos que sus datos serán tratados con absoluta confidencialidad según la Ley Orgánica que regula la confidencialidad de datos informatizados (Ley Orgánica 15/1999), también se respetará la ley de investigación biomédica 14/2007 y cualquier otra ley aplicable. Los datos recogidos se utilizarán solo para la investigación.

Para llevar a cabo este proyecto y atendiendo a las disposiciones legales vigentes le solicitamos su autorización. Antes y después de firmar el documento de consentimiento informado puede preguntar todo lo que crea conveniente a los médicos y personal sanitario responsable del estudio.

En todo momento podrá consultar con otros profesionales si lo considera oportuno.

Si renuncia a participar en este estudio, no supondrá ningún castigo ni pérdida de beneficios para usted.

ANNEX 3

Consentiment informat de l'estudi "How do we make the (right) diagnosis of acute appendicitis?"

Declaració del participant:

He estat informat pel professional de la salut citat a continuació de les finalitats i les implicacions de l'estudi, sobre el procés d'obtenció, emmagatzematge i processament de les meves dades personals; que les dades obtingudes tenen com a objectiu la investigació científica; que la participació és voluntària i que la retirada pot ser en qualsevol moment, i que puc sol·licitar l'eliminació de les meves dades personal sense cap repercussió en l'atenció sanitària posterior. A més, he pogut fer totes les preguntes que he considerat oportunes.

Per altra banda, accepto que el personal de l'estudi es posi en contacte amb mi si cal per avaluar el meu estat de salut.

Nom:

Firma:

Data:

Declaració del professional de salut que ha informat al pacient.

Nom:

Firma:

Data:

Apartat per la revocació del consentiment

Jo,, revoco el consentiment de participar en l'estudi indicat anteriorment.

Firma:

Data:

Consentimiento informado del estudio: "How do we make the (right) diagnosis of acute appendicitis?"

Declaración del participante:

He sido informado por el profesional de salud citado a continuación de las finalidades e implicaciones del estudio, sobre el proceso de obtención, almacenaje y procesamiento de mis datos personales; que los datos obtenidos tienen como objetivo la investigación científica; que la participación es voluntaria y que la retirada puede ser en cualquier momento, y que puedo solicitar la eliminación de mis datos personales sin ninguna repercusión en la atención sanitaria posterior.

He podido hacer todas las preguntas que he considerado oportunas.

Por otro lado, acepto que el personal del estudio se ponga en contacto conmigo si hace falta para evaluar mi estado de salud.

Nombre:

Firma:

Fecha:

Declaración del profesional de salud que ha informado al paciente.

Nombre:

Firma:

Fecha:

Apartado de revocación del consentimiento

Yo,, revoco el consentimiento a participar en el estudio indicado anteriormente.

Firma:

Fecha:
