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# Appendicitis diagnosis and management in emergency medicine- A systematic review

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### **ABSTRACT**

Noticeably, Acute appendicitis is the most common abdominal emergency requiring emergency department diagnosis and further treatment later on by surgery. However, the diagnosis is usually hard and the decision to either admit the patient or discharge from the emergency room. The utility of clinical scoring systems (namely the Alvarado score), laboratory markers, and the development of novel markers in the diagnosis of appendicitis considered acceptable so far. This article presents an update on the diagnostic approach to appendicitis through an evidence-based review.

#### **Methods and Materials:**

We used a wide range of databases, PubMed and Medline search engines for diagnosis and management options of appendicitis. Radiological imaging, the Alvarado score, common laboratory markers, and markers in patients with suspected appendicitis also have been addressed.

#### **Results:**

To sum up we found that CT-scan is the most accurate option of imaging for suspected cases of appendicitis, but the problem remains in the radiation. The Alvarado score is a clinical scoring system that is used to predict the likelihood of appendicitis based on signs, symptoms and laboratory data. It can help risk stratify patients with suspected appendicitis and potentially decrease the use of CT imaging in patients with certain Alvarado scores. White blood cell (WBC), C-reactive protein (CRP), granulocyte count and proportion of polymorphonuclear (PMN) cells are frequently elevated in patients with appendicitis but are insufficient on their own as a diagnostic modality.

### **Conclusion:**

However, CT-scan is the most accurate option of imaging in suspected appendicitis, the hazardous radiation is a matter for us. Ultrasound help in the diagnosis while decreasing the need for CT in certain circumstances. The Alvarado Score has better diagnostic utility at specific cutoff points. Laboratory markers have very limited diagnostic utility on their own but show promise when used in combination. Further studies are warranted for laboratory markers in combination and to validate potential novel markers.

**Keywords: NIL** 

### INTRODUCTION

The classical signs and symptoms of acute appendicitis were first reported by Fitz in 1887. [1] Acute appendicitis remained the most common diagnosis for hospital admission requiring laparotomy. [2],[3] Appendicitis is the most common abdominal condition requiring surgery in children accounting for over 320,000 operations per year in the United States. [4] The diagnosis of acute

appendicitis in children remains challenging, occasionally taxing the diagnostic skills of even the most experienced surgeon because not all patients present with the classic symptoms. It is also more difficult to obtain a clear history in children. Furthermore, many disorders in the gastrointestinal tract can mimic acute appendicitis. [5]So the diagnosis of acute appendicitis can be difficult,

Acute appendicitis is the most common abdominal emergency requiring surgery with an estimated lifetime prevalence of 9%.1 Despite its high prevalence, the diagnosis of appendicitis remains challenging. The diagnosis of appendicitis embodies Sir William Osler's spirit when he stated, "Medicine is a science of uncertainty and an art of probability." The clinical presentation is often atypical and the diagnosis is especially difficult because symptoms often overlap with other conditions.2 fundamental clinical decision in the diagnosis of a patient with suspected appendicitis is whether to operate or not. Ideally, the goal is to expeditiously treat all cases of appendicitis without unnecessary surgical interventions. A 2009 study reported negative appendectomy rates between 15% and 34% with approximately 15% being commonly accepted appropriate to reduce the incidence perforation.3,4

The meaningful evaluation of acute appendicitis balances early operative intervention in hopes of preventing perforation against a more restricted approach with the hope of reducing the risk of unnecessary surgery. Additionally, physicians must consider the accuracy, delay-to-surgery, and radiation risks of using computed tomography (CT) imaging, as well as the reliability of laboratory results and clinical scoring systems. Lastly, physicians' actions are often unfortunately influenced by malpractice litigation as appendicitis is one of the most frequent medical conditions associated with litigation against emergency department (ED) physicians with claims paid to patients in up to one third of cases.5,6 The goal of this article is to present the reader with an update on the diagnostic approach to appendicitis by providing an evidence-based review of radiological imaging, clinical scoring systems, laboratory testing, and novel biomarkers for appendicitis.

### **Methods and Materials:**

We used a wide range of databases, PubMed and Medline search engines for diagnosis and management options of appendicitis. Radiological imaging, the Alvarado score, common laboratory markers, and markers in patients with suspected appendicitis also have been addressed.

We searched meta-analysis, systematic reviews, reviews and clinical trials dating back to 2005. Only published research was used in our paper. We also conducted a secondary source search on the most relevant articles. Since many meta-analyses are available, we focus on these, but also include relevant single publication data. Our focus is on bringing the reader up to date in this rapidly developing field.

# **Radiological Imaging**

Technological advances and an increase availability of CT have fundamentally changed the approach to appendicitis. In a 2011 study of 2,871 patients, multi-detector CT had a sensitivity of 98.5% and a specificity of 98%.7 Similarly, another 2006 meta-analysis consisting of data from 31 studies and 4341 patients yielded both a sensitivity specificity of 94%.8 A 2011 meta-analysis made up of 28 studies comprising 9,330 patients found that the negative appendectomy rate was 8.7% when using CT compared to 16.7% when using clinical evaluation alone.9 Similarly, this study demonstrated a significantly higher negative appendectomy rate during the pre-CT era compared to the post-CT era (10% vs. 21.5%).9Interestingly, the incidence of appendiceal perforation, the most significant complication of appendicitis, was reported as unchanged by the use of CT.9

A 2007 systematic review (25 studies and 9,121 patients) examining ultrasound (US) in the diagnosis of equivocal acute appendicitis yielded a sensitivity of 83.7% and a specificity of 95.9%.10 Similarly, a 2006 meta-analysis found similar results in both children and adults.8 A long-standing criticism of US use in the diagnosis of appendicitis is that it is less accurate than CT and user-dependent. This criticism was evident in a pooled study of surgeon-performed US imaging in cases of suspected appendicitis where considerable inter- and intra-observer heterogeneity was seen. While this was largely attributed to the operator-dependent variability of US, it also likely

reflected the resolution spectrum seen in bedside ultrasound machines compared to higher-resolution machines in radiology departments.11

The improvement in diagnostic accuracy with widespread adoption of CT for appendicitis comes with the concerns over increased radiation exposure and long-term cancer risks. One study estimated that there would be approximately 29,000 future cancers related to CTs performed in the year 2007, alone, with the largest proportion coming from scans of the abdomen/pelvis, the scan of choice in suspected appendicitis.12Another study estimated that there would be the development of a radiation-associated cancer for every 620 males and every 470 females who received abdomen/pelvic CT with contrast at the age of 20. For those undergoing this type of CT at the age of 60, it was estimated that 1 in 1,250 males and 1 in 1,320 females would develop CT radiationassociated cancers.1

### **Discussion:**

Efforts have also been made to limit CT's high radiation levels with low-dose CT imaging. Kim et al. examined the use of this low-dose abdominal CT for evaluating suspected appendicitis. In their single-center study of 891 adolescents and young adults, they demonstrated that low dose CT (which used 1/4th of the standard radiation) and standard CT had a similar negative appendectomy rates and no major differences in perforation rates.17 Other smaller studies have yielded similar results,18,19 and there is currently at least one large, multicenter randomized control trial underway.20

### The Alvarado Scoring System

The Alvarado score is a clinical scoring system used to stratify the risk of appendicitis in patients presenting with abdominal pain. Alvarado's original work was published in 1988 and is based on his retrospective data analysis of 305 patients presenting with abdominal pain suggestive of acute appendicitis. This study found eight predictive factors of diagnostic value in acute appendicitis and assigned each factor a value of 1 or 2 based on their diagnostic weight. A score of 1 was given for each of the following: elevated temperature >37.3°C, rebound tenderness, migration of pain to right lower quadrant (RLQ), anorexia, nausea or vomiting, and leukocyte left shift. A score of 2 was given for RLQ tenderness

and leukocytosis >10 000. The likelihood of appendicitis and specific management recommendations are given based on the total score. A score of 5 or 6 is "compatible" with the diagnosis of acute appendicitis and recommends the clinician observe or serially examine the patient. A score of 7 or 8 is "probable" appendicitis and a score of 9 or 10 is "very probable" appendicitis and recommends surgical intervention.21

Ironically, the results in subsequent validation studies of the Alvarado score largely outperform the original study's findings and provide the major support for consideration of the rule in clinical practice. In a meta-analysis by Ohle et al.22 conducted in 2011, a review of 29 studies including 5,960 subjects revealed that for a cutoff of 5 (criteria to observe/admit) there was a sensitivity of 99% (95% CI: 97–99%) and specificity of 43% (36–51%). At a cutoff of 7 (criteria to proceed directly to surgery) sensitivity was 82% (76-86%) and specificity was 81% (76–85%). Based on these results, the authors argue that using a cutoff score of 5 or lower provides a good "ruling out" score, while a cutoff of 7 is not sufficiently specific enough to provide an adequate "ruling in" score.22 However, several other smaller studies did not find such a high sensitivity. A 2007 retrospective study of 150 patients aged 7 and older who presented to the ED with abdominal pain found that 5% of patients with a score of 3 or less had appendicitis, as did 36% of patients with a score between 4-6.23 Similarly, in a retrospective study of 215 adults and children who presented with acute abdominal pain, Gwynn et al.1 found that 8.4% (12 of 143) of subjects with appendicitis had an Alvarado score below 5. Another retrospective study of 156 children found that 9% of subjects with complicated appendicitis would have been overlooked with the use of the Alvarado score.24

What can we conclude from this? Based on the results of the aforementioned 2011 meta-analysis we can conclude that since an Alvarado score of ≥5 had a sensitivity of 99%, this is a promising strategy for ruling out patients who are clinically at low risk for appendicitis. These patients may be observed clinically or with outpatient warnings as opposed to receiving an ED CT. Conversely, the specificity of the Alvarado score does not reliably determine the need for surgery without further clinical assessment and testing. While some smaller studies call into

question the accuracy of the Alvarado score, this approach does seem to be a reasonable starting point in the assessment of a patient with suspected appendicitis.

One main critique of the Alvarado score is its applicability in pediatric populations. A meta-analysis revealed that at a cutoff of 5 (observe/admit criteria) for 1,635 pediatric patients there was a sensitivity of 99% and specificity of 57%, similar to that of the adult subjects. At a cutoff of 7 (surgery criteria) sensitivity was 87% and specificity was 76%.22 Thus, similar clinical prediction rules can be prescribed as above. This meta-analysis did not give a clear definition of what constitutes a "child," and thus, it is not clear whether these results apply to all pediatric populations. The Alvarado score requires children to identify migration of pain, nausea and anorexia, variables that are not easily identified by very young children.25

## **Laboratory Markers**

Acute appendicitis is a common surgical emergency that the emergency physician faces. It causes a problem when the patient presents with pain in right iliac fossa with equivocal signs. In such questionable cases the decision making for admission or discharge of these patients is always difficult, especially if the examining doctor is a junior staff with little experience. [13] Although there has been some improvement in the diagnosis of acute appendicitis over the paste several decades, the percentage of normal appendices reported in various series varies from 8-33%. [14],[15] The Alvarado score, is a simple scoring system that can be instituted easily in out-patient setting to decrease high false-positive appendectomy. In a prospective study of children in Gradiff, use of Alvarado score decreased an unusually high false-positive appendectomy of 44-14%. [16] These results match with our statistics as with cut off at score of 6 (either > 6 or  $\le 6$ ), sensitivity will be 86.4%, specificity will be 26%, positive predictive value of 75.5% and negative predictive value of 41.9% and total accuracy of 69.8%

### White Blood Cells (WBCs)

The degree of white blood cell (WBC) elevation in acute appendicitis has been extensively studied. It is very commonly elevated in patients with acute

appendicitis. However, it is not a specific marker and is commonly elevated in patients with other inflammatory conditions included in the differential diagnosis. lists 19 publications including two metaanalyses of WBC sensitivity, specificity, likelihood ratios and accuracy. Part of the difficulty in drawing precise conclusions from these data is that there is great variability in the WBC concentration cut-offs. A WBC cut-off of greater than 10-12 000 cell/mm3 yielded a range of sensitivity between 65-85% and specificity between 32-82%.2,25,27-36A 2003 metaanalysis including 14 studies (3,382 patients) likely gives a representative approximation of the true sensitivity and specificity of a WBC>10 000 cell/mm3 measured at 83% and 67%, with a positive and negative likelihood ratio of 2.52 and 0.26.2 Thus, on its own, a WBC>10 000 cell/mm3 is insufficient as a diagnostic modality. The discriminatory power of an elevated WBC count, expressed as area under the curve (AUC). The AUC values range from 0.72 to 0.8 reflecting WBC's modest discriminatory power.28,31,34,36-42 The likelihood ratio values are also shown in . While these values are statistically significant, it is generally agreed that clinically significant values for likelihood ratios are either greater than 10 or under 0.1. Thus, these values only alter the probability of the diagnosis to a modest degree, and thus, do not change the diagnostic workup on its own.

### **C-Reactive Protein (CRP)**

CRP is an acute phase reactant. Its diagnostic significance is largely based on both its kinetic properties and its utility as a marker for complicated/advanced appendicitis. CRP levels show an increase between 8-12 hours after the onset of inflammatory processes with a peak between 24 and 48 hours, which is later than that of WBC.43,44 Consequently, CRP contributes little diagnostic utility early in the case of simple appendicitis. 12 studies including two large meta-analyses on CRP levels in appendicitis. A CRP cut-off of >10 mg/L yielded a range of sensitivity between 65-85% and a specificity between 59-73%.2,28,33,34,36,45 In a study of 542 people the AUC of CRP on day 1 was only 0.60 compared to 0.77 on day 2 and 0.88 day 3. In cases of perforated appendicitis, the AUC was 0.90 on day 1, 0.92 on day 2 and 0.96 on day 3.44 Thus, CRP serves as a strong predictor for appendiceal perforation but is quite limited for appendicitis in general.44,46

Granulocyte Count **Proportion** of and Polymorphonuclear (PMN) Cells 10 publications including one meta-analysis of granulocyte count and proportion of polymorphonuclear (PMN) document their sensitivity, specificity, likelihood ratios and accuracy. A normal granulocyte count ranges between 2500-6000 cells. A modestly elevated PMN greater than 7-7.5 ×109 cells/L vielded a range of sensitivity of 71-89% and a specificity of 48-80% in diagnosis of acute appendicitis.2,28,37,39,45 Andersson's 2003 metaanalysis of several laboratory variables in acute appendicitis showed that a granulocyte count greater than 11×109/L had a larger likelihood ratio than any other lab marker measured and was one of the strongest laboratory discriminators of appendicitis.2 Yet, the likelihood ratios were not even increased to near clinically significant levels unless the PMN was very elevated to  $>13 \times 109$  cells/L. At this level, 2 studies of 502 and 1013 patients found a likelihood ratio of 7.09 and 6.67, respectively.2,39

Similarly, as detailed, PMN ratio>75%, was also a discriminator of acute appendicitis but had limited clinical significance due to a sensitivity of 66–87% and specificity of 33–84%.2,28,32,34,39,41,47Again, the likelihood ratios were not high enough to significantly change the probability of appendicitis.

Assessing "left shift," defined as a band form count >700/microL, a 2002 retrospective study of 1013 subjects found a sensitivity of 28%, a specificity of 87%, and an AUC of 0.58.39 In this study the presence of "left shift" provided a likelihood ratio of 2.17 which has limited clinical significance. In another study of 722 patients with a mean age of 9.7 years who presented to the pediatric ED, a "left shift" had a total sensitivity of 59% and a specificity 90%.48 Here the likelihood ratio was 5.7. Thus, while possibly providing some diagnostic clues, "left shift" did not yield any absolute conclusions.

# **Temperature**

History of fever provides very little diagnostic significance in acute appendicitis.2,28,38,49 In a study of 492 patients, a temperature of greater than 37.7°C had a sensitivity of 70% and a specificity of 65%.28 In a meta-analysis consisting of 570 patients

with suspected appendicitis, history of fever only gave a likelihood ratio of 1.64.2 A meta-analysis of 502 patients reported that the average measured temperature in non-surgical abdominal pain was 37.7°C versus 37.8°C in cases of appendicitis on first measurement.28However, the diagnostic significance of the variable increased significantly on serial examination and was an important discriminator of advanced appendicitis. The receiver operating characteristic (ROC) curve for all appendicitis on primary examination was 0.56 increasing to 0.77 after serial assessment.28 Thus, although initial temperature does not provide much diagnostic value initially, it still remains a parameter worth looking at observing someone suspected when with appendicitis.

### **Lab Values in Combination**

Perhaps a multi-marker approach is necessary for the diagnosis of appendicitis. While the individual elements of clinical and laboratory data carry limited diagnostic value, many studies show an exponential increase in the predictive and discriminatory power when multiple markers are combined.35,41,50–54 The major limitation of these publications is that some of the data may have been over-fit and the product of post-hoc analyses.

Many of the different combinations of lab markers evaluated. A study of 502 patients over the age of 10 years found that the combined inflammatory parameters (including WBC, PMN cells, PMN ratio, body temperature and CRP) had an accuracy of 0.85, which was similar to the total accuracy of clinical findings (0.87) and greater than all elements of disease history (0.78).28 The largest study identified included 897 patients and gave a sensitivity of 99% and specificity of 6% when any one of CRP>8 mg/L, WBC≥10.4 × 103 cells/mm3 or PMN Ratio >74% was present, and a sensitivity of 98% and specificity of 12% when either WBC or CRP was elevated.47 Thus, while the absence of all of these laboratory markers can potentially "rule out" the diagnosis of appendicitis, the complete lack of specificity severely limits its application. In a smaller study of 98 patients, Sengupta et al.33 calculated a sensitivity of 100%, a specificity of 50% and a NPV of 100% when either CRP≥10 mg/L or WBC≥11 × 103 cells/mm3. Vaughn-Shaw et al.45 replicated Sengupta's study in 297 patients and found a lower sensitivity of 92–94%

The sensitivities and specificities when both CRP and WBC or CRP, WBC and PMN ratio are all elevated. Again, different combinations and cut-off values were used making it difficult to compare individual studies. The data show a specificity that ranges from 77–99%.33–35,45,55 Thus, because of this wide range of measured values, the current studies do not show a consistently high enough specificity to "rule in" appendicitis and warrant surgery without further clinical and/or imaging workup.

Interestingly, in a 1999 study by Gronroos et al.,52 none of the 200 consecutive adult patients with acute appendicitis had both CRP and WBC within normal range. However, Gronroos53 also reported that in the same study done on children, normal values of both WBC and CRP were found in 7 of 100 consecutive children. Therefore, the sensitivity and specificity of combined laboratory markers may vary in different age demographics.

This analysis is limited by the relative scarcity and small sample sizes of the literature examining the combined use of markers. Small studies have shown enhanced diagnostic potential and utility but much larger sample sizes are needed before any absolute recommendations can be made. Furthermore, evaluation of this multi-marker approach in different patient demographic groups, most notably children, adults and the elderly is warranted.

### **Diagnostic Markers of the Future**

In response to the difficulty of making the accurate diagnosis of appendicitis and to decrease CT utilization and negative appendectomy rates, there has been much effort to search for novel markers. Several of these markers, which we will now briefly discuss. While some of these markers have shown early promise, the power of these studies is limited due to the small sample size.

Interleukin 6 (IL-6) is a cytokine that plays a focal role in the activation of the acute inflammatory response.40,56,57 A 2011 prospective study of 280 patients aged 3–18 with suspected appendicitis showed the IL-6 levels increase early appendicitis, and mean concentration also increases with the degree of inflammation.40,56,57 The sensitivity and specificity at different cut-off points. In a small prospective study of 80 patients, Paajanen et al.43 found the sensitivity, specificity and accuracy of IL-6 to be higher than that of WBC or CRP. While these studies show a clear relationship between IL-6 levels and acute appendicitis, they did not show that IL-6 improved the diagnosis of appendicitis.40,43,58,59

Serum Amyloid A (SAA) is a non-specific inflammatory marker. A small 2005 study of 42 patients with a mean age of 10.6 years and confirmed appendicitis on surgery calculated a sensitivity of 86%, a specificity of 83% and an AUC of 0.96 at a cutoff of SAA>45 mg/L. All 42 patients with acute appendicitis had elevated SAA levels, whereas only 14/42 had normal WBC values and 9/42 had normal CRP values.60They also found that SAA had an early and more dynamic increase in inflammatory conditions compared to that of WBC and CRP. Thus, SAA may be useful in early appendicitis.

Muenzer et al..61 studied leukocyte gene expression (Riboleukograms) and cytokine profiles in children being evaluated for appendicitis. In a training cohort of 20 patients, they first identified 28 genes and five cytokines that were strongly associated with the diagnosis of appendicitis. They subsequently tested the diagnostic potential of these genes and cytokines in eight patients. Four out of the five patients with confirmed appendicitis would have been correctly diagnosed using riboleukograms alone. Out of the three patients without appendicitis, there would have been one false-positive result. Using the five identified plasma cytokines alone, only one out of four patients with appendicitis was correctly

identified. However, all three patients without appendicitis were correctly identified here. Thus, riboleukograms showed potential for being a sensitive marker and plasma cytokines as a specific marker for acute appendicitis. Some of the major limitations of this study are the very small sample size, cost and real-time technical feasibility.

Calprotectin (also known as S100A8/A9) is a calcium-binding protein associated with acute inflammation, specifically of gastrointestinal origin. The relationship between Calprotectin as a diagnostic tool in acute appendicitis was first studied by Bealer et al.65 in 2010. In a preliminary study of 181 patients, Bealer found a sensitivity of 93% and a specificity of 54% at a cut-off of 20 Elisa units. Their promising results persuaded the investigators to undergo a larger ongoing study examining this relationship. In 2012, Mills et al.66 conducted a similar study with 843 patients. Using a cut-off of 14 Elisa units yielded a sensitivity of 96% and a specificity of 16%. One major problem in this study was that the measured value of ELISA for Calprotectin showed a 13-43% increase in actual levels due to a shipping effect whereby the test values were inflated due to delay in analysis. Thus, the next step in development of Calprotectin as a lab marker for acute appendicitis is to create an accurate realtime laboratory analyzer. In short, Calprotectin is a promising new marker of appendicitis that may help differentiate acute appendicitis from noninflammatory causes of acute abdominal pain.

### **Conclusion**

Patients with equivocal signs can present a diagnostic challenge and are very often admitted to the surgical department for observation. The Alvarado score can be used as a scoring system that help in taking the decision for admission of cases with suspected acute appendicitis especially by primary healthcare providers.

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