

Review Article

Inflammatory Markers in Acute Appendicitis: Are we Still Looking for the Philosopher's Stone?

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Citation: Alvarado A (2018) Inflammatory Markers in Acute Appendicitis: Are we Still Looking for the Philosopher's Stone?. J Surg: JSUR-1104. DOI: 10.29011/2575-9760.001104

Received Date: 29 January, 2018; **Accepted Date:** 04 February, 2018; **Published Date:** 12 February, 2018

Abstract

This article is an overview of the inflammatory markers that are presently used in the diagnosis of acute appendicitis in order to determine if they are useful or not in the early stages of the disease.

Keywords: Acute Appendicitis; Diagnosis; Inflammatory Markers

Background

Every year we find in the medical literature new tests related to inflammatory markers to confirm the diagnosis of acute appendicitis, and in many of these studies the investigators always mention the white blood cell count (WBC) which indicates that this is an important reference test that, in addition, has the great advantage of being available in all health facilities.

Overview of The Current Medical Literature

The most common biological markers that have been studied in the diagnosis of acute appendicitis, apart from the WBC, are: The Differential Leukocyte Count (DLC), the C-Reactive Protein (CRP), Erythrocyte Sedimentation Reaction (ESR), Tumor Necrosis Alpha (TNF-alpha), Alpha 1-Glycoprotein (alpha 1gp), leukocyte elastase complex (elastase), Interleukine-8 (IL-8), Interleukine-6 (IL-6), Interleukine-10 (IL-10), granulocyte colony stimulating factor, interferon gamma, soluble intercellular adhesion molecule-1, matrix metalloproteinase-9, tissue inhibitor metalloproteinase-1, serum amyloid A, plasma calprotectin, plasma serotonin serum Leucine-Rich Alpha Glycoprotein-1 (LRG), and procalcitonin [1].

However, none of these tests have been proved to be useful in the early diagnosis of acute appendicitis. Furthermore, all of these markers are non-specific because what they are measuring is the grade of an inflammatory process.

For instance, according to Jangioo [2], the most used inflammatory marker, the C-reactive protein, is not an ideal diagnostic tool for ruling out or for determination of acute appendicitis. Pruekprasert et al. compared the surgeon's clinical diagnosis of acute appendicitis with the Alvarado Score and measurement of the CRP, and demonstrated that the sensitivity of the surgeon's assessment was 96% versus 79% for the Alvarado score and 62% for the CRP [3]. The accuracy for the surgeon's assessment, the Alvarado score, and the CRP were 90%, 72%, and 61%, respectively. Atema [4], in a study to evaluate the accuracy of the WBC and C-reactive protein in relation to the duration of symptoms in patients suspected of acute appendicitis, found that none of these tests can safely and sufficiently confirm or exclude the diagnosis of acute appendicitis. They found that patients with symptoms of more than 48 hours, a WBC count of more than 20.000 cells/mm³ confirmed the presence of acute appendicitis with a PPV of 100%. He also found that the overall discriminatory capacity expressed as an AUC curve was 0.673 for WBC count, and 0.568 for CRP levels. They concluded that, in patients suspected of

acute appendicitis, normal inflammatory markers could not “rule out” acute appendicitis, regardless of the duration of symptoms. Based on these findings, they could not support the use of these biomarkers, either in isolation or in combination, to confirm or exclude a diagnosis of acute appendicitis.

Almaramhy [1], in a study of acute appendicitis in young children less than 5 years old, found that a normal WBC count cannot exclude the diagnosis, and that C-Reactive Protein (CRP) is more sensitive than the WBC count in diagnosing appendicular perforation and abscess formation. He recommended that an early diagnosis and prompt surgical intervention can reduce the morbidity and mortality rates. Craig and Dalton [5], in an evidence-based assessment of children with possible acute appendicitis, arrived at the conclusion that the best performing variables are rebound tenderness and a high WBC and CRP with short duration of symptoms. However, the test characteristics of these variables appear insufficient to reliably rule in or rule out the disease.

Kharbanda [6] showed that a WBC count was a more useful marker to predict appendicitis in children with pain for less than 24 hours, while CRP was a more useful test in those with pain for 24 to 48 hours. He also found that duration of symptoms may be an important variable to consider when interpreting laboratory values in patients with acute abdominal pain. In another study in children, Xharra [7] et al demonstrated that CRP was directly related to the severity of inflammation and that the diagnostic accuracy of CRP is not significantly greater than WBC count and neutrophil percentage. Also, in a study in children, Amalesh et al [8] concluded that neither raised nor normal CRP values are helpful in the diagnosis of acute appendicitis so CRP is not a good tool for helping the surgeon in making the diagnosis of acute appendicitis.

Shogilev et al [9] found that a White Blood Cell Count (WBC) is not a specific marker and is commonly elevated in patients with other inflammatory conditions. In their meta-analysis they found a representative approximation of the true sensitivity and specificity of a WBC $>10,000$ cells/mm³ of 83% and 67%, respectively. The discriminatory power of an elevated WBC count, expressed as an Area Under the Curve (AUC), ranges from 0.72 to 0.80 which represents a modest discriminatory power. The likelihood ratio values were not clinically significant because they were lower than 10 or higher than 0.1. In response to the difficulty of making the accurate diagnosis of appendicitis and to decrease CT utilization and negative appendectomy rates, they discussed a number of novel markers as follows:

a) Interleukine 6 (IL-6) is a cytokine that plays a focal role in the activation of acute inflammatory response. Paajamen, et al. [10] found the sensitivity, specificity and accuracy of IL-6 to be higher than that of WBC or CRP. However, they did not show that IL-6 improved the diagnosis of appendicitis.

- b) Serum Amyloid A (SAA) is a non-specific inflammatory marker that may be useful in early appendicitis. Muenzer, et al. [11] studied leukocyte gene expression (Riboleukogram) and cytokines profiles in children being evaluated for appendicitis and found that riboleukograms had potential for being sensitive markers.
- c) Allister, et al. [12] tested the utility of Granulocyte Colony-Stimulating Factor (G-CSF) in the diagnosis of acute appendicitis in 32 patients with a mean age of 12 years. Using a cut-off 28.3 pg./ml yielded a sensitivity of 91% and a specificity 51%, respectively.
- d) Another promising novel marker in acute appendicitis is urine Leucine-Rich 16 α -2 Glycoprotein (LRG) that is believed to be shed earlier in the urine than locally activated neutrophils.
- e) Calprotectin (also known as S100A8/A9) is a calcium binding protein associated with acute inflammation, specifically of gastrointestinal origin. This test is a promising new marker of appendicitis that may help differentiate acute appendicitis from non-inflammatory causes of acute abdominal pain.

In conclusion, according to the Shogilev group, in adults, an Alvarado score up to five shows promise at ruling out appendicitis. Laboratory markers all contribute to the presentation of appendicitis but are unable to change the diagnostic management of suspected appendicitis on their own. Leeuwenburgh, et al. [13], in a study related to Clinical Decision Rule (CDR), found that CRP was not associated with acute appendicitis in univariable and multivariable logistic regression. Furthermore, the addition of CRP to the rule with four predictors did not increase its performance. These results suggest that CRP is not a strong additional predictor in patients suspected of appendicitis who have elevated WBC count. Farooki, et al. [14] found that combining blood markers was useful in predicting appendicitis and perforated appendicitis. Patients with perforated appendicitis had significantly higher levels of white blood cells, bilirubin, and C-reactive protein than patients with non-perforated appendicitis. Acharya, et al. [15], in a systematic review, found that white cell blood count and bilirubin performed best overall with the latter scoring marginally higher. They also found that interleukine-6 have been shown to have higher diagnostic benefit, but is associated with significant costs. In fact, no single biomarker had all the desired characteristics for the diagnosis of acute appendicitis but they are of poor diagnostic accuracy when used in isolation. Alternatively, the use of a biomarker in conjunction with a consistent clinical history and examination may improve diagnostic accuracy in a more feasible manner. This could be achieved by utilization of stratification scores such as the Alvarado, which is a 10-point scoring system incorporating the typical signs and symptoms seen in appendicitis. With a cutoff of 7, this diagnostic algorithm has been shown to

have a reported specificity as 100%]. Furthermore, a surgeon's clinical impression has in some cases shown to be of equivalent diagnostic value as the scoring systems.

Vaughan-Shaw, et al. [16] al, in a meta-analysis, found that patients with normal inflammatory markers can still have appendicitis and that the negative predictive value of CRP, WBC and NC is poor. They believed that the diagnosis of appendicitis remains a multifactorial process and should still rely on clinical suspicion even if inflammatory markers are normal. They advised that patients with clinical history and examination consistent with appendicitis but normal inflammatory markers should not be discharged. In patients where there is clinical doubt there should be a prompt and appropriate use of imaging modalities or surgery. Cicot, et al. [17] found that plasma calprotectin and C-reactive protein values were significantly higher in patients with a complicated acute appendicitis group than those with uncomplicated acute appendicitis whereas white blood cell counts did not differ significantly between the two groups.

Kartal, et al. [18] found that WBC count and CRP level were higher in patients with acute appendicitis, but these findings alone were insufficient for definitive diagnosis. They concluded that US should be combined with laboratory tests and used as standard initial imaging in the diagnostic pathway of patients with clinically suspected appendicitis.

Shin et al. [19] studied the Delta Neutrophil Index (DNI) as an early predictor of acute appendicitis and acute complicated appendicitis in adults. They found that DNI independently predicted acute complicated appendicitis. However, in their multivariate logistic regression analysis, they found that the Odds Ratio for the WBC count and for the DNI was 2.64 and 2.62, respectively which is essentially the same. The predictive value of DNI for acute complicated appendicitis was fair (AUC 0.727) and lower than that of CRP (AUC 0.842). They concluded that DNI may be better biomarker than other previously known markers, such as WBC, Neutrophil-To-Lymphocyte Ratio (NLR) and Platelet-To-Lymphocyte Ratio (PLR).

Tind, et al. [20] investigated if the results of C-Reactive Protein (CRP) and White Blood Cell count (WBC) had any positive or negative influence on the decision-making of the surgeons handling patients with acute appendicitis. Based on clinical findings alone, 76.1% of the diagnosis were correct and this was only marginally improved to 78.3% after taking into consideration the results of the blood samples. ROC curves showed an Area Under the Curve (AUC) of 0.71 and 0.75 for different values of CRP and WBC counts, respectively. This group found that 28.9% of the patients operated on suspicion of acute appendicitis had normal findings and alternative diagnostic tools are still warranted for this most common condition. Routine measurement of conventional inflammatory markers is not the answer when diagnosing patients

suspected of acute appendicitis. Schellekens, et al. [21] made an evaluation of two novel markers, Calprotectin (CP) and Serum Amyloid A (SAA), along with the more traditional inflammatory markers, C-Reactive Protein (CRP) and White Blood Count (WBC), in patients suspected of having acute appendicitis. In this study, all the patients that underwent surgery had imaging of the abdomen using US or CT.

The clinical information was used to retrospectively calculate the Alvarado score. A total of 233 consecutive patients were seen in the ED with suspected appendicitis (101 males and 132 females) and from this group, 86 patients underwent appendectomy finding 16 patients with perforated appendicitis (20.1%) and 9 patients with a normal appendix (10.4%). These findings prove that imaging tests could not eliminate the perforation and negative appendectomy rates. The diagnostic accuracy, using the ROC curves, revealed that the Alvarado score of 7-10 points had an AUC of 0.79 points as opposed to 0.67 for the CP, 0.76 for SAA and 0.71 for CRP. Combining all the laboratory variables, revealed that WBC together with SAA-1 had the best overall accuracy, resulting in an AUC of 0.80, and the combination of WBC and CRP led to an AUC of 0.80 also. The WBC (at cutoff of 8.850 cells/mm³) performed better than the newer biomarkers (CP and LRG) for the purpose of diagnosing acute appendicitis. They also determined that a WBC < 10.000 cells/mm³, with a low level of clinical suspicion, can identify a subgroup of patients who may be sent home without further evaluation, but whom should have available next-day follow-up. Because of this, they proposed that WBC is the preferred biomarker for patients suspected of acute appendicitis.

Panagiotopoulou, et al. [22] made a retrospective analysis of 1.169 appendectomies to determine the diagnostic accuracy of white blood cell count, C-reactive protein and bilirubin in acute appendicitis and its complications. Using the Area Under the Curve (AUC), they found that no independent variable was diagnostic of acute appendicitis. But, when all variables were combined, a good accuracy was seen. In perforated appendicitis the median CRP level was significantly higher than that of simple acute appendicitis. On the other hand, normal levels of WBC, CRP and bilirubin could not rule out appendicitis. Sonmez, et al. [23] evaluated the value of SCUBE1 and routine parameters used in patients diagnosed with acute appendicitis. They found a positive correlation between SCUBE1 values and appendicular diameter as measured on CT. They also found that patients with an Alvarado score of 9-10 points had an appendicular diameter greater than 10 mm. In conclusion, they determined that SCUBE1 is not a diagnostic biomarker for acute appendicitis.

Muzaffar and Bhatti [24] carried out a study to determine the value of a preoperative Total Leukocyte Count (TLC) and C-Reactive Protein (CRP) in the diagnosis of acute appendicitis. They found that TLC and CRP are better predictors of the presence or absence of acute appendicitis when both are considered together

rather than individually.

Andersson [25], in a meta-analysis of the clinical and laboratory diagnosis of appendicitis, concluded that the discriminatory power of the inflammatory variables was particularly strong for perforated appendicitis with a ROC area of 0.85 to 0.87. Appendicitis was likely when two or more inflammatory variables were increased, and unlikely when all were normal. Although all clinical and laboratory variables are weak individually, they achieve a high discriminatory power when combined [26]. Laboratory examination of the inflammatory response plus clinical descriptors of peritoneal irritation, and a history of migration of pain, yield the most important information and should be included in any diagnostic study.

Conclusion

After a careful examination of this overview, we can arrive at the conclusion that a few well-known inflammatory markers, alone or combined, perform well to confirm the diagnosis of acute appendicitis in the late stages. However, they are not superior to the clinical assessment of patients suspected of acute appendicitis. The duration of symptoms can always indicate us if we are dealing with an early or a late inflammatory process. In other words, if we see the patient during the first 24 hours after the onset of symptoms, we can assume that we are dealing with a case of uncomplicated appendicitis, but if we see the patient with symptoms of more than 24 hours duration, we can assume that we are dealing with a complicated appendicitis, more probably with signs and symptoms of an acute abdomen and with a leukocytosis of more than 15.000 cells/mm³. In this case the patient will require surgery as soon as possible. That is why the clinician has to use his clinical experience and common sense in order to arrive at a correct diagnosis.

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