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Inflammatory markers for acute appendicitis in children: are they helpful?

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Abstract

Background/Purpose: Diagnosis of acute appendicitis in children remains challenging, and the role of blood tests in the decision-making process is still unclear. We prospectively evaluated if routine inflammatory markers could contribute to exclude the presence of acute appendicitis in children.

Methods: Preoperative white blood cell count (WBCC) and C-reactive protein (CRP) were prospectively tested in children undergoing surgery for suspected appendicitis. Surgery was indicated on the basis of clinical findings and/or ultrasound scan, but WBCC and CRP values were ignored during the decision-making process. Sensitivity of individual markers and their combinations were assessed.

Results: One hundred children (55 males) with a mean age of 9.34 years (SD, 3.54 years) had pathologically confirmed diagnosis of appendicitis. A perforated appendix was found in 23% of cases. Elevated WBCC alone had a sensitivity of 0.6 (confidence interval [CI], 0.506-0.694). Sensitivity of elevated CRP alone was 0.86 (CI, 0.926-0.793). Elevation of either WBCC or CRP or both had a sensitivity of 0.98 (CI, 1.0-0.953).

Conclusions: White blood cell count or CRP values alone do not appear to provide any useful additional information to the surgeon. However, the sensitivity of the 2 combined tests is extremely high, and normal values of both WBCC and CRP are very unlikely in pathologically confirmed appendicitis.

Acute appendicitis represents the most common abdominal emergency in children [1], and clinical diagnosis in pediatric patients is often challenging even for experienced surgeons. In particular, children may present with different and nonspecific symptoms. Furthermore, the risk of progression to perforation in children is higher than in adults, ranging from 20% to 50% [2], whereas the rate of unnecessary appendectomies is as high as 40% [3].

Despite the introduction of sonography and computed tomography, the accuracy of diagnosis has improved only marginally in recent years [4], highlighting the need for better diagnostic tools. Laboratory tests such as white blood cell count (WBCC) and C-reactive protein (CRP) have long been used to support clinical data in the decision-making process, but the considerable overlap with other inflammatory conditions mimicking acute appendicitis accounts for the low specificity and positive predictive value of these tests [4-6]. However, recent studies on adult [7-10] and elderly [11] patients have shown that although clinical history and examination are highly suggestive for acute appendicitis, the need for surgery can be excluded if both WBCC and CRP are within normal reference values. It has indeed been suggested that measuring both WBCC and CRP could avoid up to one quarter of negative appendectomies in adult patients [7].

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Table 1 Normal reference values for WBCC according to patient age [13]

Age	Reference WBCC (10^9/L)
0-3 d	9.0-30.0
4-7 d	5.0-21.0
8-30 d	5.0-19.5
2-12 mo	6.0-17.5
2-4 y	5.0-15.5
5-6 y	5.0-13.5
7-10 y	4.5-12.0
11-18 y	4.5-11.0

However, only a few studies have been reported in pediatric patients [4,12], and the role of WBCC and CRP in excluding acute appendicitis in children has not been confirmed.

The aim of this prospective study was to evaluate the diagnostic role of preoperative WBCC and CRP in acute appendicitis in children and, particularly, its accuracy in excluding the presence of appendicitis.

1. Patients and methods

A prospective study was performed on children (maximum age, 14 years) who underwent surgery for suspected acute appendicitis at the Paediatric Surgery Unit of the University of Padova, Italy, between March 2003 and December 2005. The diagnosis of suspected appendicitis was established preoperatively by one of the consultant pediatric surgeons on the basis of clinical history and physical examination. Abdominal ultrasound scan was performed when a gynecologic condition was suspected or when the diagnosis of appendicitis was uncertain. Laboratory tests were not prescribed by the surgeon before the diagnosis of acute appendicitis was made, and results of laboratory tests prescribed by the family doctor or the attending pediatrician were not considered by the surgeon for the diagnosis. Once the diagnosis was made and surgery was indicated, informed consent was obtained from parents and a blood sample was collected from all patients at the time of venous line insertion and before intravenous antibiotics were administered.

Total WBCC was measured by an automated hematology analyzer (Advia 120 Hematology System; Bayer Diagnostics, Dublin, Ireland). C-reactive protein levels were measured by a highly sensitive immunonephelometric method (DABE Behring, Milan, Italy) on a BN II Analyser (analytical sensitivity, 0.04 mg/L). Reference intervals for WBCC were dependent on the age of patients as previously reported [13] (Table 1), whereas the upper reference limit for CRP was 6.0 mg/L for all age groups.

Histologically, the appendices were categorized as *acute appendicitis* or *normal appendix*. Depending on surgical findings, pathologically confirmed appendicitis was defined as *complicated* if a perforated appendix with either diffuse peritonitis or abscess was found, and as *uncomplicated* if there were no signs of perforation or abscess.

Data analysis was performed using Prism 4 (GraphPad Software Inc, San Diego, CA). Results are shown as mean ± SD unless specified and were compared by χ^2 test and Mann-Whitney U test as appropriate. Results showing P values less than .05 were considered significant.

2. Results

One hundred children had a pathologically confirmed appendicitis during the study period. There were 55 males and 45 females, with a mean age of 9.34 ± 3.54 years. During the same period, 8 children who underwent surgery for suspected acute appendicitis had a normal appendix at histopathologic examination (7.40% of total appendectomies). There were 5 males and 3 females, and the mean age was 11.82 ± 1.94 years. At surgery, 23 patients had complicated appendicitis (diffuse peritonitis in 19 children and abscess in 4).

Values of WBCC and CRP in children undergoing appendectomy for suspected appendicitis according to surgical and pathologic findings are shown in Table 2. Not surprisingly, patients with complicated appendicitis had higher values of WBCC and CRP, as compared with those with uncomplicated appendicitis.

The number of children with WBCC and CRP levels within reference values according to surgical and histopathologic findings is shown in Table 3.

The estimated sensitivity of elevation of WBCC, elevation of CRP, and elevation of at least one inflammatory marker (WBCC or CRP) in pathologically confirmed acute appendicitis is shown in Table 4. In particular, elevated

Table 2 White blood cell count and CRP values in children undergoing appendectomy for suspected appendicitis according to surgical and histopathologic findings

	Pathologically confirmed appendicitis (n = 100)			Normal appendix (n = 8)
	Uncomplicated (n = 77)	Complicated (n = 23)	Total	
WBCC ($\times 10^9$/L)	14.527 ± 5.750	17.118 ± 5.381[a]	15.123 ± 5.746	10.909 ± 6.163
CRP (mg/L)	55.2 ± 63.8	104.4 ± 68.6[b]	66.5 ± 69.1	20.2 ± 28.9

Data are shown as mean ± SD and were compared by Mann-Whitney U test.

[a] P = .050 vs uncomplicated.

[b] P = .0002 vs uncomplicated.

Table 3 Number (%) of children with WBCC and CRP levels within reference range according to surgical and histopathologic findings

	Pathologically confirmed appendicitis			Normal appendix (n = 8)
	Uncomplicated (n = 77)	Complicated (n = 23)	Total (n = 100)	
Elevated WBCC Elevated CRP	31 (40.2%)	17 (73.9%)[a]	48 (48%)	2 (25%)
Elevated WBCC Normal CRP	12 (15.6%)	0 (0%)	12 (12%)	0 (0%)
Normal WBCC Elevated CRP	32 (41.6%)	6 (26.1%)	38 (38%)	2 (25%)
Normal WBCC Normal CRP	2 (2.6%)	0 (0%)	2 (2%)	4 (50%)

Data are shown as number of patients (%) and were compared by χ^2 test.
[a] $P = .041$ vs uncomplicated.

WBCC had a relatively low sensitivity in both complicated and uncomplicated appendicitis, whereas the sensitivity of elevated CRP was higher and equalled 1.0 in patients with complicated appendicitis. However, an elevation of at least one inflammatory marker (WBCC of CRP) appeared to be the most sensitive indicator of acute appendicitis, with values between 0.95 and 1.0 in all patients with appendicitis, and between 0.93 and 1.0 in uncomplicated cases.

3. Discussion

Acute appendicitis is characterized by the development of inflammation at a local level, followed by a more generalized inflammatory response. The rationale of laboratory tests in the diagnosis of acute appendicitis is based on the possibility of detecting signs of systemic inflammation with a diagnostic tool that is widely available and easy to perform, is minimally invasive, has limited costs, and can be repeated if necessary [14]. Although, over the last few decades, several markers of inflammation have been proposed to increase diagnostic accuracy in acute appendicitis (including phospholipase A_2 [15], serum amyloid A, [12], leukocyte elastase[16], neutrophil count [9], and several interleukins and cytokines [6]), WBCC and CRP are certainly the most widely used. They can also provide complementary information, with WBCC rising in the early phases of the inflammatory response and CRP increasing in advanced appendicitis [17].

Inflammatory markers such as WBCC and CRP are poorly reliable in confirming the presence of an acute appendicitis because of their low specificity in adults as well as in children [4,5,7,8]. This is not surprising because many conditions mimicking acute appendicitis are also associated with an inflammatory response. On the other hand, several studies have reported that if the values of both WBCC and CRP are normal, the presence of a clinically suspected acute appendicitis can be excluded with high accuracy in adult patients [7-10]. However, serum inflammatory markers are known to be age dependent [5], and the results described in adults have not been confirmed in children. Gronroos [4] reported that normal values of both WBCC and CRP were found in 7 of 100 consecutive children but in none of the 200 adults with pathologically confirmed acute appendicitis [7], and concluded that normal inflammatory markers can reliably exclude appendicitis in adults but not in children. Similarly, in a study by Lycopoulou et al [12] the sensitivity of elevated WBCC was 76%, and of elevated CRP only 62%, in 260 children with histologically confirmed appendicitis.

Results from our study also confirm that the sensitivity of elevated WBCC or elevated CRP alone for acute appendicitis is inadequate in offering reliable support to the surgeon in the diagnostic pathway. Overall, 40% of patients (95% confidence interval [CI], 31%-49%) with pathologically confirmed diagnosis of appendicitis had a normal WBCC, and 14% (95% CI, 7%-21%) had normal CRP levels. However, 98% (95% CI, 95%-100%; Table 3) of our patients with appendicitis had either an increased WBCC or increased CRP levels, or both. The probability of patients with acute appendicitis to have both of these inflammatory markers within normal values is therefore, in our experience, extremely low and is estimated to be between 0% and

Table 4 Sensitivity of elevation of WBCC, elevation of CRP, and elevation of at least one inflammatory marker (WBCC or CRP) according to surgical and histopathologic findings

	Pathologically confirmed appendicitis		
	Uncomplicated (n = 77)	Complicated (n = 23)	Total (n = 100)
Elevated WBCC	0.558 (0.355-0.761)	0.739 (0.559-0.918)	0.60 (0.506-0.694)
Elevated CRP	0.818 (0.732-0.904)	1.0 (1.0-1.0)	0.86 (0.793-0.926)
Elevated WBCC or CRP	0.974 (0.938-1.0)	1.0 (1.0-1.0)	0.98 (0.953-1.0)

Data are shown as estimate (95% CI).

5%. All of our patients with complicated appendicitis had an increase of either CRP or both CRP and WBCC, suggesting that, in children with normal inflammatory markers, the presence of an abscess or a diffuse peritonitis can be excluded with accuracy.

The different cutoff values used for inflammatory markers may explain the different results observed in our study as compared with others. Our reference range for WBCC (Table 1) is age dependent and based on values from an age-matched reference population, whereas most pediatric studies use 10.0×10^9 cells/L as the upper limit regardless of patient age [4,12]. In addition, we used 6.0 mg/L as the upper reference value for CRP as opposed to 10.0 as reported by others [12]. This could contribute to an increased sensitivity of this test. Alternatively, the variability observed between our study and others might be based on a difference in sampling time. We performed laboratory tests at the end of the diagnostic pathway when the decision to proceed to surgery was already made, whereas inflammatory markers were measured at an earlier stage of the decision-making process in other reports [4,5,12,17,18].

Our results suggest that when performed at the end of the diagnostic pathway in patients with a high clinical suspicion of acute appendicitis, WBCC and CRP might play a role in increasing diagnostic accuracy. In particular, patients with an inflamed appendix are extremely unlikely to have both WBCC and CRP within reference values. A sensible approach to these patients would therefore be to reconsider the need for surgery if both WBCC and CRP are within reference range, and to repeat clinical and laboratory examinations as needed, as has been suggested for adults [10,11,19]. Although such a strategy carries a theoretical risk of delayed diagnosis and progression to complicated appendicitis, in our experience, normal WBCC and CRP almost certainly excludes an advanced appendicitis. In these cases, it might be more reasonable and safer to defer surgery and reevaluate the patient over time; repeated measurements of inflammatory markers could be performed to minimize the risk of progression to perforation.

The results of laboratory tests were not taken into account by the surgeon in the decision-making process. Interestingly, patients who underwent appendectomy but had a histologically normal appendix presented with both normal preoperative WBCC and CRP levels in 50% of cases (4 of 8 patients, Table 3). It seems reasonable to speculate that if the results of laboratory tests were considered by the surgeon, and if the decision to operate were postponed and patients were reevaluated when levels of inflammatory markers were within reference values, unnecessary appendectomies would have been reduced by up to 50%. However, patients with abdominal pain who did not undergo surgery were not included in our study, and a precise estimate of negative predicted values of markers of inflammation could therefore not be performed.

Our study suggests that if both WBCC and CRP levels are normal in a child with a high suspicion of appendicitis, the presence of an inflamed appendix is extremely unlikely, and reevaluating the patient over time is perhaps a better option than proceeding to operation.

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