Use of blood tests in the diagnosis of acute appendicitis

Acute appendicitis is frequently encountered by junior doctors in accident and emergency and on surgical wards. It is the commonest cause of persistent and progressive abdominal pain, and accounts for 10% of abdominal surgeries. Diagnosis, however, remains challenging, with up to 30% of operations performed for presumed appendicitis revealing a normal appendix (Bijnen et al, 2003). Diagnostic laparoscopy reduces negative appendicectomy rates, especially in women, when normal-looking specimens are left behind (van den Broeck et al, 2000). However, it should not be used as a substitute for good clinical judgement.

Introduction

History, examination and active observation of patients with right lower quadrant pain are the traditional means of diagnosing appendicitis (Ellis, 2012). Unfortunately, the clinical presentation may be atypical, resulting in diagnostic dilemmas. Clinicians therefore habitually resort to laboratory tests and imaging (as discussed in this issue by Ong et al) to make the call: 'appendicectomy or not'. Blood test results are frequently requested before making or accepting a surgical referral, but how much do they actually contribute to the diagnostic and clinical decision-making processes?

Basic inflammatory markers

Measurements of simple inflammatory markers (total leukocyte and neutrophil counts, and C-reactive protein) are easily performed and cheap 'on the shop floor', and the most commonly ordered. These indices are indeed elevated in the majority of patients with acute appendicitis, although their sensitivities vary markedly between different case series. Unfortunately, there is still a 3% chance of appendicitis even if all three are normal, and hence they cannot be relied upon to exclude the diagnosis (Andersson, 2004; Vaughan-Shaw et al, 2011).

They also falter on the grounds of specificity. Irrespective of aetiology, up to 70% of patients with right lower quadrant pain have an elevated white cell count (Calder and Gajraj, 1995). Leukocytosis cannot distinguish between the differential diagnoses of mesenteric adenitis, gastroenteritis, caecal diverticulitis, pelvic inflammatory disease (Rothrock and Pagane, 2000), tubo-ovarian abscess and ovarian cyst accident (Herlihy et al, 2011). Furthermore, a raised white cell count is seen in normal pregnancy (often with associated bandaemia) (Pastore et al, 2006), with concurrent use of corticosteroids, and as a response to high levels of stress or pain (Bøyum et al, 1996).

Use of C-reactive protein is similarly fraught: sensitivities range from 40–99% and specificities from 27–90%. Part of this variability relates to differences in timings of blood tests from symptom onset in different studies, as well as non-standardized threshold levels (5–25 mg/litre). A C-reactive protein level >35.5 mg/litre may be helpful in patients with confirmed acute appendicitis as it predicts a more complicated disease course (Vaughan-Shaw et al, 2011). Nonetheless routine measurement of inflammatory markers in the emergency setting can neither reliably exclude nor support the diagnosis.

Serial measurements of blood tests

The pathology of acute appendicitis proceeds through a series of stages: mucosal oedema, congestion and ulceration; phlegmonous inflammation with granulocyte invasion of the intestinal wall; gangrenous necrosis of the appendix; and perforation (leading to abscess formation or peritonitis). The time course of this evolution is extremely variable between patients, and in some cases spontaneous resolution occurs.

Levels of blood inflammatory markers in acute appendicitis correlate with its stage of development. Typically neutrophilia is seen first, followed by elevation in total white cell count within the first 24 hours. C-reactive protein starts to rise within 12 hours of the onset of symptoms, with a mean doubling time of 7.3±1.8 hours, and peaking at 24–48 hours (although there is greater variability in children) (Kharbanda et al, 2011). Persistent rise beyond this suggests perforation (Cole et al, 2008), whereas a sequentially falling leukocyte count with lymphopaenia is often seen once gangrene has set in (Jahangiri and Wyllie, 1990; Devuyst et al, 1991).

This explains much of the heterogeneity in studies based on single results obtained on first presentation to the emergency department, where patients have different lead times from symptom onset to attendance. However, further information can be gleaned from serial measurements of these variables: rises in white cell count, neutrophil ratio or C-reactive protein between measurements 6 hours apart are weak predictors of appendicitis, with likelihood ratios of 1.47, 1.92 and 2–3 respectively (Andersson et al, 2000). Nonetheless, these fare poorly in comparison to predictive power of repeated assessment by a surgeon, which is three times greater than any change in blood tests.

Use of blood tests in combination

Whereas the sensitivity and specificity of individual blood tests are poor, they have greater predictive power in combination, particularly alongside other clinical features (Andersson, 2004; *Table 1*). Scoring systems have been devised to help clinicians categorize patients into low, moder-

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ate and high probability. The Alvarado score is based on six clinical features and two laboratory markers (white cell count and neutrophil) (*Table 2*). A score <5 has sensitivity approaching 99% for excluding appendicitis across all patient groups (Ohle et al, 2011), and hence these patients can be safely discharged home. Those with a score ≥7 should generally be considered for emergency surgery, although this threshold may still over-predict appendicitis in women and children. Nevertheless, the scoring system provides a practical tool for junior doctors in diagnosing appendicitis, and is superior to the value of the C-reactive protein alone (Pruekprasert et al, 2004). A newer Appendicitis Inflammatory Response Score (AIRS; *Table 2*), which also includes C-reactive protein, appears to outperform the Alvarado criteria (Andersson and Andersson, 2008).

Use of blood tests to predict success of conservative management

White cell count and C-reactive protein may help identify patients with appendicitis who can be managed non-operatively with antibiotics alone. For example, patients with probable appendicitis under the age of 60 years with white cell count <12 x 10^9/litre and C-reactive protein <60 mg/litre had an 89% chance of recovery when managed conservatively. However, the tests failed to identify all of the potential antibiotic responders at these cut-off values, achieving high specificity at the expense of low sensitivity (Hansson et al, 2012). The prospective NOTA study will evaluate the efficacy of biochemical markers in conjunction with the Alvarado score and imaging for predicting uncomplicated appendicitis that can be managed conservatively with antibiotics (Tugnoli et al, 2011).

Novel inflammatory markers

A number of novel serum markers of acute inflammation have been assessed for their diagnostic and prognostic utility, particularly the cytokine interleukin-6 (Groselj-Grenc et al, 2007) and procalcitonin (Gavela et al, 2012). While these tend to be elevated in acute appendicitis, and their levels correlate with disease complications, they are not routinely available, none outperforms the neutrophil count or C-reactive protein, and they have yet to be incorporated into predictive multivariate models.

Using blood tests correctly: reflection on case scenarios

Case scenario 1

A 25-year-old man presents with a 24-hour history of vomiting and abdominal pain, starting in the peri-umbilical region then migrating to the right iliac fossa. On examination, his temperature is 37.5°C and there is tenderness in the right lower quadrant but no guarding or rebound. Should the accident and emergency senior house officer wait for blood test results before deciding on whether to refer to the surgical team?

Table 1. Likelihood ratios for acute appendicitis

	Positive likelihood ratio	Negative likelihood ratio
White cell count ≥10x10^9/litre	2.47	0.26
Polymorphonucleocyte ratio ≥75%	2.44	0.24
C-reactive protein ≥ 10 mg/litre	1.97	0.32
White cell count ≥10x10^9/litre and guarding or rebound	11.34	0.14
White cell count ≥10x10^9/litre and polymorphonucleocyte ratio ≥75% and C-reactive protein ≥12 mg/litre	20.85	0.03

Data from Andersson (2004)

Table 2. Alvarado and Appendicitis Inflammatory Response Score

	Alvarado score		Appendicitis Inflammatory Response Score		
Symptoms	Migration of pain to right iliac fossa	1	Pain in the right iliac fossa		1
	Anorexia or ketonuria	1	Vomiting		1
	Nausea or vomiting	1	–		
Signs	Elevated temperature >37.5°C	1	Elevated temperature ≥38.5°C		1
	Rebound tenderness	1	Rebound tenderness or guarding	Light	1
				Medium	2
				Strong	3
	Tenderness right lower quadrant	2	–		
Lab findings	Leukocytosis ≥10.0x10^9/litre	2	Leukocytosis	10.0–14.9 x 10^9/litre	1
				≥15.0 x 10^9/litre	2
	Neutrophilia ≥ 75%	1	Neutrophilia	70–84%	1
				≥85%	2
	–		C-reactive protein	10–49 g/litre	1
				≥50 g/litre	2
Total		10			12

Score	Recommended action	Score	Recommended action
≤ 4	Discharge and review in 24 hours	≤ 4	Discharge and review as outpatient if unaltered general condition
5–6	Admit and observe with or without imaging	5–8	Admit and observe with or without imaging or diagnostic laparoscopy
7–10	Consider surgery	9–12	Surgical exploration

From Andersson and Andersson (2008), Ohle et al (2011)

This demonstrates a typical presentation of acute appendicitis to accident and emergency. The patient already scores >4 points according to the Alvarado system, based on the history of vomiting, migration of pain to the right iliac fossa, fever and tenderness in the right iliac fossa. Thus blood tests would not change the decision to admit and surgical referral should be made immediately, but the results may determine whether the surgeons organize imaging or proceed direct to surgery.

Case scenario 2

A 25-year-old sexually active woman presents with a 6-hour history of right lower quadrant pain, associated with pyrexia, nausea and diarrhoea. There are no gynaecological symptoms and her beta-human chorionic gonadotrophin level is negative. Her observations are stable and her abdomen is diffusely tender, with guarding but no rebound. Urinalysis is positive for leukocytes and blood. She has a white cell count of $11x10^9$/litre (50% neutrophils) and C-reactive protein level of 10 mg/litre. The surgical senior house officer wonders whether the blood test results change the diagnosis and further management.

In scenario 2 the patient also has a high Alvarado score. However, this does tend to over-predict appendicitis in this patient demographic, and there are gynaecological differential diagnoses that need to be excluded. The blood test results neither confirm nor exclude acute appendicitis, and hence admission for observation and monitoring, careful repeated clinical examinations by both surgical and gynaecological teams, and further investigations are warranted.

Conclusions

This article is not questioning whether routine blood tests should be requested in all potential surgical patients; rather it highlights that absolute values of inflammatory markers are of limited use with respect to diagnosing acute appendicitis. Individual parameters lack sensitivity and specificity, and although these are somewhat improved by serial measurements, they cannot be used as the basis to confirm or exclude the diagnosis. In combination, they contribute to risk stratification scores that guide management alongside other clinical criteria. Nonetheless, they do not replace clinical acumen and the physical examination. BJHM

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TOP TIPS

- Diagnosis of appendicitis is largely clinical and pending laboratory tests should not delay referral to surgeons.
- White cell count can be normal, high or low depending on the stage of appendicitis at presentation.
- Alvarado and Appendicitis Inflammatory Response Scores can be used to guide clinical management of suspected acute appendicitis, although more cautiously in women and children.

KEY POINTS

- A diagnosis of acute appendicitis cannot be excluded on the basis of normal inflammatory markers alone.
- In combination, blood tests contribute to risk stratification scores that guide further management.
- Even in combination, blood tests lack specificity, particularly in women and children.
- Blood tests are most useful as adjuncts in equivocal cases. They do not replace a thorough history and clinical examination, nor devalue a period of observation.