The value of hyperbilirubinaemia in the diagnosis of acute appendicitis

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ABSTRACT

INTRODUCTION No reliably specific marker for acute appendicitis has been identified. Although recent studies have shown hyperbilirubinaemia to be a useful predictor of appendiceal perforation, they did not focus on the value of bilirubin as a marker for acute appendicitis. The aim of this study was to determine the value of hyperbilirubinaemia as a marker for acute appendicitis.

MATERIALS AND METHODS A retrospective analysis of appendicectomies performed in two hospitals ($n=472$). Data collected included laboratory and histological results. Patients were grouped according to histology findings and comparisons were made between the groups.

RESULTS The mean bilirubin levels were higher for patients with simple appendicitis compared to those with a non-inflamed appendix ($p<0.001$). More patients with simple appendicitis had hyperbilirubinaemia on admission (30% vs 12%) and the odds of these patients having appendicitis were over three times higher (odds ratio: 3.25, $p<0.001$). Hyperbilirubinaemia had a specificity of 88% and a positive predictive value of 91% for acute appendicitis. Patients with appendicitis who had a perforated or gangrenous appendix had higher mean bilirubin levels ($p=0.01$) and were more likely to have hyperbilirubinaemia ($p<0.001$). The specificity of hyperbilirubinaemia for perforation or gangrene was 70%. The specificities of white cell count and C-reactive protein were less than hyperbilirubinaemia for simple appendicitis (60% and 72%) and perforated or gangrenous appendicitis (19% and 36%).

CONCLUSIONS Hyperbilirubinaemia is a valuable marker for acute appendicitis. Patients with hyperbilirubinaemia are also more likely to have appendiceal perforation or gangrene. Bilirubin should be included in the assessment of patients with suspected appendicitis.

KEYWORDS

Appendicitis – Diagnosis – Bilirubin

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No reliably specific marker for acute appendicitis has been identified. A raised white cell count (WCC) is not specific for appendicitis and, although C-reactive protein (CRP) is commonly used in the assessment of suspected appendicitis, its specificity varies markedly between studies¹ and may only be significantly raised once appendiceal perforation takes place.^{2,3}

Jaundice has been associated with appendicitis⁴ and studies have shown hyperbilirubinaemia to be a useful predictor of appendiceal perforation.^{5,6} However, these studies did not focus on the value of bilirubin as a specific marker for acute appendicitis.

There is considerable debate about the optimal management of appendicitis with several studies suggesting that non-operative management with antibiotics may be feasible.^{7–10} In many hospitals the diagnosis of acute appendicitis is made on clinical grounds and patients in whom the diag-

nosis is uncertain or who do not have signs of peritonism are often managed with a trial of observation to avoid unnecessary surgery. A simple, cheap biochemical test that is specific for acute appendicitis may be useful in conjunction with clinical findings in deciding which patients are likely to have appendicitis and should be considered for surgery. The aim of this study was to determine the value of hyperbilirubinaemia as a marker for acute appendicitis.

Materials and Methods

We performed a retrospective review of all appendicectomies performed in two peripheral hospitals from 1 September 2008 to 31 May 2010. Patients were identified using an existing database (Lothian surgical audit system) and considered for inclusion in the study if they had an urgent appendicectomy performed by any method during the study

Table 1 Description of histology groupings and distributions of patients to groups

Group	Description	Number of patients (% of total)	Number of patients with hyperbilirubinaemia (% of group)
1	No acute inflammation	86 (18%)	10 (12%)
2	Acute appendicitis	294 (62%)	86 (29%)
3	Acute appendicitis with inflammatory infiltrate extending through full thickness of appendiceal wall	47 (10%)	17 (36%)
4	Perforated or gangrenous appendix	45 (10%)	27 (60%)
Total		472 (100%)	140

period. Data were collected on patient demographics, histological findings, results on admission of liver function tests (LFTs), WCC, CRP and blood cultures, and results of intra-abdominal fluid cultures obtained intraoperatively. Patients were excluded from the study if they did not have LFTs performed on admission, if they had a history of confirmed hepatitis or liver disease or if they were known to have persistently deranged LFTs.

A total of 555 patients had urgent appendicectomies performed during the study period and 472 were included in the study. Patients were divided into four groups according to their histology findings. Group 1 comprised patients with non-inflamed appendices, group 2 comprised those with acute appendicitis, group 3 included patients with appendicitis with an inflammatory infiltrate extending through the full thickness of the appendiceal wall to the serosa and group 4 comprised patients with a perforated or gangrenous appendix.

Comparisons were made between three broad groups of patients: those with non-inflamed appendices were compared with those with acute but not perforated or gangrenous appendicitis (simple acute appendicitis) and those with appendiceal perforation or gangrene were compared with those with simple acute appendicitis. Mean levels of bilirubin, WCC, CRP and other LFTs were compared between groups. The presence of raised levels of these potential markers was also compared. The sensitivities, specificities and positive predictive values of hyperbilirubinaemia and

raised CRP and WCC for both simple acute appendicitis and perforated or gangrenous appendicitis were calculated. The receiver operating characteristic (ROC) curve for bilirubin was calculated to determine its optimum threshold value for sensitivity and specificity for acute appendicitis.

Hyperbilirubinaemia was defined as a bilirubin level greater than 20.5µmol/l, a raised WCC as greater than $10 \times 10^9/l$ for patients over 12 years old and greater than $15 \times 10^9/l$ for those under 12 years old, and a raised CRP as greater than 10mg/l. These values corresponded to the upper limits of normal of the reference ranges used by the laboratory services in both institutions.

Statistical analysis was performed using Epi Info™ 3.0 (Centers for Disease Control and Prevention, Atlanta, Georgia, US). Means were compared using a one-way analysis of variance or a Mann-Whitney U test for non-parametric data and categorical data were compared using chi-square or Fisher exact tests where appropriate.

Results

Of the 472 patients included in the study, 254 patients (53.8%) were male. The mean age was 27 years (median 23, range: 5–82). Table 1 shows the distribution of patients by histology group. Eighty-six patients (18%) had a non-inflamed appendix.

The mean bilirubin levels were higher for patients with simple acute appendicitis compared to those with a non-

Table 2 Values of raised bilirubin, white cell count (WCC) and C-reactive protein (CRP) for differentiating simple acute appendicitis from non-inflamed appendices

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio positive (95% CI)	Likelihood ratio negative (95% CI)
Bilirubin <i>n</i> =426	30%	88%	91%	24%	2.57 (1.40–4.70)	0.79 (0.71–0.88)
WCC <i>n</i> =426	82%	60%	90%	42%	2.05 (1.57–2.67)	0.30 (0.23–0.40)
CRP <i>n</i> =127	64%	71%	93%	23%	2.16 (1.02–4.58)	0.52 (0.35–0.76)

Table 3 Values of raised bilirubin, white cell count (WCC) and C-reactive protein (CRP) for differentiating perforated or gangrenous appendicitis from simple acute appendicitis

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio positive (95% CI)	Likelihood ratio negative (95% CI)
Bilirubin <i>n</i> =384	60%	70%	21%	92%	1.99 (1.49–2.65)	0.57 (0.40–0.83)
WCC <i>n</i> =384	93%	19%	13%	96%	1.16 (1.05–1.27)	0.34 (0.11–1.05)
CRP <i>n</i> =120	91%	36%	13%	98%	1.43 (1.13–1.81)	0.25 (0.04–1.65)

inflamed appendix (18.7µmol/l vs 14.5µmol/l, $p<0.001$) and significantly more patients in this group had hyperbilirubinaemia on admission (30% vs 12%, $p<0.001$). The odds of a patient with hyperbilirubinaemia having simple acute appendicitis were over three times higher than those without hyperbilirubinaemia (odds ratio [OR]: 3.25). The specificity of hyperbilirubinaemia for simple acute appendicitis was 88% and its positive predictive value was 91% (Table 2).

Patients with a perforated or gangrenous appendix had higher mean bilirubin levels than those with simple acute appendicitis (25.1µmol/l vs 18.7µmol/l, $p=0.01$). Significantly more patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute appendicitis (60% vs 30%, $p<0.001$) and the odds of a patient with hyperbilirubinaemia having a perforated or gangrenous appendix were over three times higher (OR: 3.47). The specificity of hyperbilirubinaemia for a perforated or gangrenous appendix was 70% (Table 3).

The specificity of WCC for simple acute appendicitis was 60% and for appendiceal perforation or gangrene it was 19%. Limited numbers of patients had CRP levels measured on admission ($n=138$). Although patients with simple acute appendicitis had higher mean CRP levels than those with non-inflamed appendices (55.6mg/l vs 13.4mg/l, $p=0.006$), the specificity of a raised CRP for appendicitis (71%) was lower than that of hyperbilirubinaemia. More patients with perforated or gangrenous appendicitis had elevated CRP levels than patients with simple acute appendicitis. However, this result was not significant ($p=0.10$). Mean CRP levels in those with perforated or gangrenous appendices were significantly higher than those with simple acute appendicitis (130.0mg/l vs 55.6mg/l, $p=0.02$). Nevertheless, the specificity of an elevated CRP for appendiceal perforation or gangrene was only 36%.

There was no significant difference between patients with appendicitis with an inflammatory infiltrate extending through the full thickness of the appendiceal wall (group 3) and those without extension through the wall (group 2) in mean bilirubin levels ($p=0.15$) or in the proportion of patients with hyperbilirubinaemia ($p=0.21$).

There was no significant difference in the mean levels of any of the other LFTs between patients with simple acute appendicitis and those with non-inflamed appendices, or between patients with a perforated or gangrenous appendix

and those with simple acute appendicitis.

A total of 61 patients had swabs of intraperitoneal fluid taken intraoperatively for bacterial culture, of which 37 (60.7%) yielded a positive culture. The most common organisms cultured were *Escherichia coli* and mixed anaerobes, present in 46% and 36% of positive cultures respectively. Forty-seven patients had blood cultures taken on admission, none of which yielded significant positive cultures. There was no significant difference in mean bilirubin levels between patients with positive and negative intraperitoneal fluid cultures ($p=0.34$) or the number of patients in each group with hyperbilirubinaemia ($p=0.34$).

The ROC curve for bilirubin levels in patients with simple acute appendicitis showed the optimal threshold bilirubin level with the highest sum of sensitivity and specificity was 15µmol/l. At this level hyperbilirubinaemia would have a sensitivity of 57% and a specificity of 72%, approaching similar levels to CRP in this study. However, the laboratory standard threshold for hyperbilirubinaemia yields a much better specificity of 88%.

Logistic regression analysis showed hyperbilirubinaemia to be significantly associated with simple acute appendicitis ($p=0.01$, OR: 2.65, 95% confidence interval [CI]: 1.27–5.47), along with WCC ($p<0.001$). Neither age nor any of the other LFTs were found to be significantly associated with acute appendicitis. Hyperbilirubinaemia in appendicitis was also associated with a perforated or gangrenous appendix ($p<0.001$) but WBC was not ($p=0.12$).

Discussion

The development of jaundice in sepsis is well recognised and has been associated with a variety of causative bacteria, gram-negative bacteria being most commonly implicated.^{11,12} Several mechanisms leading to hyperbilirubinaemia in systemic infections have been described. Haemolysis causes an increased bilirubin load and has been associated with several bacteria including *Escherichia coli*.^{12,15} Another mechanism is reduced hepatic uptake and canalicular excretion of bilirubin caused by endotoxaemia.^{14,15} Bacterial endotoxin causes a cytokine mediated inhibition of bile salt transport mechanisms, leading to cholestasis.^{16,17} *Escherichia coli* is associated with the endotoxin lipopolysaccharide and is the most common organism cultured from intraperitoneal

fluid in appendicitis,^{18,19} as was the case in this study. Hyperbilirubinaemia presumably occurs in appendicitis as a result of bacteraemia or endotoxaemia, which could occur both in simple appendicitis and perforated or gangrenous appendicitis albeit more commonly in the latter group.

There have been several reports of hyperbilirubinaemia in appendicitis.^{20–22} Estrada *et al* hypothesised that hyperbilirubinaemia may be associated with appendiceal perforation and showed that more patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute appendicitis.⁵ Sand *et al* showed that hyperbilirubinaemia had a specificity of 86% for appendiceal perforation or gangrene, compared with a specificity of only 35% for CRP.⁶

However, neither of these studies mentions the value of hyperbilirubinaemia as a predictive factor for simple acute appendicitis. Our study shows that hyperbilirubinaemia is a significant marker for simple acute appendicitis and not only appendiceal perforation. Patients with hyperbilirubinaemia were significantly more likely to have simple acute appendicitis than those with a normal bilirubin. The specificity of hyperbilirubinaemia for appendiceal perforation or gangrene was 70%, which was lower than in other studies.^{16,23} However, we found that hyperbilirubinaemia had a high specificity of 88% and positive predictive value of 91% for simple acute appendicitis. Although only a limited number of patients had CRP levels measured on admission, the specificity of hyperbilirubinaemia for simple acute appendicitis was higher than that of CRP, which was only 71%.

No single clinical or laboratory test is able to reliably predict acute appendicitis.²⁴ Rather, a combination of history, clinical examination and laboratory and radiological investigations is used to make the diagnosis and decide appropriate management. Although abdominal computed tomography is accurate in diagnosing acute appendicitis,²⁵ in several studies its routine use has not been shown to improve diagnostic accuracy or reduce the rate of negative appendicectomies.^{26–28} Furthermore, it may result in delays in definitive treatment with more postoperative complications, longer emergency department and hospital stays, and increased costs.^{27,29,30} Moreover, it is not always immediately available for such use in all hospitals at any hour.

In a patient with a typical history of migrating pain and right lower quadrant tenderness, the diagnostic accuracy may be sufficiently high to perform an appendicectomy directly.³¹ Those with less typical symptoms or signs warrant a period of observation and re-evaluation,^{32,33} a 'watch-and-wait' approach employed by many clinicians. However, this approach could result in unnecessarily prolonging patients' hospital stays and delaying their definitive treatment. This study shows bilirubin can help identify patients who are more likely to have appendicitis. It could be used together with clinical findings and other routine laboratory tests to definitively manage patients with acute appendicitis earlier. In addition to its specificity for acute appendicitis, hyperbilirubinaemia in patients with appendicitis indicates a higher likelihood of a perforated or gangrenous appendix. It may therefore be prudent to consider early appendicectomy for patients presenting with suspected appendicitis who have

hyperbilirubinaemia.

This study is limited by its retrospective design, which meant that not all patients had full data available, and detailed histories and investigations to exclude all patients with pre-existing liver or haemolytic diseases were not taken. There was no way of reliably detecting patients with Gilbert's syndrome although the small number of patients with this condition would likely have been distributed evenly between histology groups. Furthermore, only patients who underwent appendicectomy were included in the study, which could result in elevated specificities for the various inflammatory markers.

Conclusions

Bilirubin is a specific marker for acute appendicitis with a good positive predictive value. It is also a valuable indicator of patients more likely to have appendiceal perforation or gangrene. Bilirubin should be used together with clinical examination and other laboratory investigations in the assessment of patients with suspected acute appendicitis.

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