



## Hyperbilirubinemia And Perforated Appendicitis- A Review of Literatures

### KEYWORDS

Appendicitis; Serum Bilirubin; Hyperbilirubinemia; Perforation

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**ABSTRACT** *Hyperbilirubinemia is due to increased excretion of bilirubin by the liver. Bilirubin is elevated in many conditions like hepatocellular, cholestatic or haemolytic diseases. A special association of this raised Bilirubin has been seen in condition with perforated acute appendicitis. A systematic literature search of reports on hyperbilirubinemia in acute appendicitis was performed. After review and quality assessment of many studies the sensitivity, specificity and other measures of accuracy of hyperbilirubinemia as a predictor of perforation in acute appendicitis were established. The presence of hyperbilirubinemia does not alone distinguish a perforation in acute appendicitis. Serum bilirubin level is of some value as a predictor of appendiceal perforation. Patients with hyperbilirubinemia combined with symptoms and signs consistent with severe acute appendicitis should be considered for early appendectomy.*

### Medical Introduction-

Appendicitis is one of the commonest causes of pain in right iliac region which needs urgent surgery. Usually, it is difficult to diagnose. The lifetime risk for appendectomy is estimated to be 12% for males and 23% for females. Different clinical signs and symptoms always mimic the diagnosis of acute appendicitis, as there are a number of causes leading to pain in right iliac fossa particularly in female patients. Acute uncomplicated appendicitis can be difficult to distinguish clinically from perforated appendicitis, especially in the elderly and in children. Simple acute appendicitis can be a minor surgical procedure with limited complications; however, delayed diagnosis and subsequently appendiceal perforation can result in a potentially lethal condition. The mortality associated with simple acute appendicitis is reported to be 0.3% but increases to 6% in cases with perforation. Early diagnosis of appendiceal perforation is important to limit the associated abdominal sepsis. Moreover, where radiological modalities such as computed tomography (CT) scan and ultrasound (US) are effective in supplementing the diagnosis of acute appendicitis, both modalities have lower sensitivity in detecting perforated appendicitis. Development of supplementary tools besides clinical examination and radiology could be beneficial in the early diagnosis. Several studies have found bilirubin to be a useful serological marker for predicting acute appendicitis and appendiceal perforation. The purpose of this systematic review was to evaluate the current literature regarding elevated serum bilirubin as a diagnostic marker for appendiceal perforation.

Hyperbilirubinemia is a new diagnostic tool for perforation of appendix. Hyperbilirubinemia is the result of imbalance between production and excretion of bilirubin by the liver. It may be because of hepatocellular, cholestatic or hemolytic diseases. Liver receives blood mainly through the portal venous system, which receives blood from abdominal organs. Portal blood carries nutrients and other substances absorbed from gut including bacteria and its product (toxins). In a small percentage, even in normal healthy people, bacteria are found in portal blood. It is commonly cleared by detoxification and immunological action of the reticuloendothelial system of the liver that acts as first-line de-

fense in clearing toxic substances, bacteria and its products. But when bacterial load overwhelms the Kupffer cell function, it may cause dysfunction or damage to hepatocytes (liver parenchyma). It reflects a rise in serum bilirubin (SB) alone or in combination with liver enzymes depending upon the type, severity and site of the lesion. Recently, another substance known as cytokines e.g. interleukin (IL)-6, tumor necrosis factor (TNF), has also been considered to be responsible for depressed excretory function of the liver and may lead to increase in SB levels without a rise in liver enzymes. The association between the elevated SB levels and the variety of infectious diseases has been noted in few studies. This finding most commonly occurs in neonates with gram negative bacterial infection. It has also been described in patients with severe intra-abdominal infection. The pathogenesis is thought to be because of bacteremia or endotoxemia causing impaired excretion of bilirubin from the bile canaliculi. There are only a few reports in the literature that describe the finding of hyperbilirubinemia in patients with either severe post-operative infection after appendectomy or with complicated appendicitis. The establishment of a possible role of hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis has been stressed so that SB levels upon admission can be used in conjunction with other diagnostic tests such as ultrasonography and CT to help determine the presence of perforation and aid in proper clinical management.

### Discussion-

In this review of past literatures it was found that acute suppurative appendicitis and patients with gangrenous/perforated appendicitis has raised serum Bilirubin levels. This hyperbilirubinemia was mixed in type (both conjugated and unconjugated) in most of the patients and at the same time there was no elevation or minimal elevation (<100 U/L) in ALT and AST in most of the cases. Similarly, ALP was either within the normal range or was minimal to moderately elevated. The level of Serum Bilirubin was higher than 3 mg/dL in cases of gangrenous/perforated appendicitis while in cases with acute appendicitis it was lower than 3 mg/dL. Broadly, we can say that it was predominantly isolated hyperbilirubinemia in the majority of cases. These findings are almost similar to another reported study. Since these findings were documented at the

time of admission, it is unlikely that liver injury because of anesthetic agents, blood transfusion, or medication was the cause of elevated bilirubin levels.

The most likely explanation of the rise in SB is therefore circulating endotoxemia as a result of appendiceal infection. Utili et al has shown with in vitro infusion of endotoxin into the isolated rat liver that there is a dose-dependent decrease in bile salt excretion from the liver and that it is possible that *Escherichia coli* endotoxin exerts direct damage at the cholangiolar level.

It was demonstrated by Sisson et al in 1971 that in appendicitis mucosal ulceration occurs early and this facilitates invasion of bacteria into the muscularis propria of the appendix thereby causing classical acute suppurative appendicitis. Subsequent events lead to edema, elevated intraluminal pressure, and ischemic necrosis of mucosa, causing tissue gangrene and perforation. This process is associated with progressive bacterial invasion most likely facilitated by bacterial cytotoxins. The number of organisms isolated from patients with gangrenous appendicitis is five times greater than those with acute suppurative appendicitis. Estrada et al also found significantly higher peritoneal culture in patients with gangrenous/perforated appendicitis. This elevated load of bacteria in appendicitis causes either direct invasion or translocation into the portal venous system.

Thus, it is concluded that hepatocellular function is depressed during the early stage of sepsis despite the increased cardiac output and hepatic blood flow and decreased peripheral resistance. The depression of hepatocellular function in the early, hyper-dynamic stage of sepsis does not appear to be due to reduction in hepatic perfusion but is associated with elevated levels of circulating pro-inflammatory cytokines such as TNF and IL-6. Thus up regulation of TNF and/or IL-6 may be responsible for producing hepatocellular dysfunction during the early hyper-dynamic stage of sepsis.

Therefore, Serum Bilirubin estimation, a simple cheap and easily available test in every laboratory, can be added to the routine investigation list of clinically suspected case of acute appendicitis for the confirmation of diagnosis. Since the rise in SB level was significantly higher in patients with appendiceal perforation, it has a definite predictive potential in these cases. Therefore, obtaining SB values upon admission can be used in conjunction with more modern diagnostic tests such as CT scan, ultrasonography to help determine the presence of perforation and thus aid in prompt clinical management.

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