Significance of Bile Culture and Biliary Tract Pathology in Determining Severity of Cholangitis; Review of Current Literature

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Abstract

Introduction: Cholangitis is a serious clinical condition with significant morbidity and mortality. Biliary obstruction and stasis have traditionally been proposed as the factors responsible. However, more recently with the advent of immune-modulators and anti-inflammatory agents to target NF-κB, the balance has shifted towards exploring the role of immune-pathological factors in determining severity of cholangitis. We proposed to search current literature to assess significance of bile and blood cultures, severity of biliary obstruction and the role of immuno-pathological factors in determining severity of cholangitis.

Methods: We performed literature to assess the role of bile culture, biliary obstruction and impact of immuno-pathological factors on cholangitis. Relevant studies from January 1966 to October 2016 were identified from Medline, PubMed, Embase and Cochrane database search. Studies that reported influence of bile and blood cultures and impact of pathology on severity of cholangitis were included.

Results: A total of 173 abstracts were screened, 12 potential studies identified, only nine were included in the final study. All studies comprised of 2175 patients, of which cause of biliary obstruction was reported in 643 patients. Approximately 61% patients (n=394) presented with benign biliary obstruction resulting in cholangitis. Moreover, about 68% of patients with cholangitis had positive bile culture whereas 66% had positive blood cultures. None of the studies reported factors including immuno-pathological factors determining severity of cholangitis.

Conclusion: Current literature lacks evidence with regards to factors determining severity of cholangitis, including the role of immune-pathological factors. Further research into the role NF-κB, inflammatory pro-cytokines, interleukins, cellular mapping and immunoassay of bile is required to determine factors responsible for this benign but potentially malignant behaving disease.

INTRODUCTION

Cholangitis characterized by fever, abdominal pain and jaundice, is associated with significant morbidity and mortality [1-5]. Normal bile flow is sterile and biliary flora under these conditions bears no significance [1]. However, biliary obstruction and stasis resulting from biliary calculi, tumour, and or even endoscopic interventions predispose patients to cholangitis [1,2]. Othman M et al., revealed 8.8% bacteremia with 7% cholangitis following ERCP [2]. Cholangitis may at time be associated with negative blood cultures [2]. Almost 70% of cholangitis is associated with structural abnormalities in the biliary tract, including benign biliary problem or underlying loco-regional malignancy [3]. In addition, newly diagnosed common bile duct and pancreatic malignancies are sometime associated with cholangitis, suggestive of the fact that cholangitis may not always be compounded by complete biliary obstruction [3]. Additionally, it is apparent from previous studies that severe cholangitis associated with negative blood cultures may not response to empirical antibiotics, which not only render empirical treatment irrelevant but also could lead to serious consequences.

Although some animal studies had explained mechanisms of bacterial translocation from biliary tract to the blood this however has not been contemplated in human subjects [4]. Moreover, it has shown that prior biliary obstruction is not a significant factor...
in bacterial translocation [4]. Therefore, it would be completely logical to investigate those microbiological or pathological factors arguably responsible for severe cholangitis. The well-known organisms isolated from infected biliary systems are E. coli and Klebsiella Pneumonia [5]. These organisms usually ascend from GI tract prior to their translocation from bile into the blood [3-5]. Park et al., has however revealed isolation of varying microorganisms from bile and blood culture in some cholangitis patients [5]. Moreover it has also shown that various microorganisms do exist in the bile in the absence of biliary tract infection [5]. This poses serious concerns regarding instigation of anti-microbial based on empirical studies to target known organisms. These reports provide further ground to our current argument that severity of cholangitis not only determined by microbiological organisms but also underlying immuno-pathological modulators has some role in determining its intensity.

Furthermore, some studies have revealed that patients with the gallstone present with acute cholangitis more often than patients with underlying tumor in the biliary tract, however such studies reported outcome in very small number of patients [6]. Moreover these studies have not elaborated severity of cholangitis even though patients underwent endoscopic examination. The author of the current study believes that further research would be necessary to quantify the factors determining severity of cholangitis both microbiological as well as pathological.

The primary aim of this study is to evaluate the current literature to assess the impact of the bile and blood cultures and underlying immuno-pathological factors on severity of cholangitis.

METHODS

We performed a literature review to assess the impact of the bile and blood cultures as well as biliary pathology on the severity of cholangitis. Relevant studies from January 1966 to October 2016 were identified from Medline, PubMed, Embase and Cochrane database search. Studies that reported influence of bile and blood cultures and impact of pathology on severity of cholangitis due to biliary obstruction were included. Publications that did not report on bile and blood cultures, role of biliary pathology in cholangitis, or severity of cholangitis was not included in the study. The severity of cholangitis is difficult to define however it seem that white blood cell count greater than 20 000 cells/µl and total bilirubin greater than 10 mg/dl are two independent factors predicting adverse outcome in acute cholangitis [23].

All the abstracts were identified by the first author (S.R.) and were then reviewed by a senior author (R.C). Any differences in the opinion about selection and interpretation of data were discussed with the senior author (R.C) whose decision was deemed final. The main outcome was to quantify the impact of bile and blood cultures as well biliary pathology on severity of cholangitis. In addition, other aspects of cholangitis management including its complications were also assessed. The data were tabulated and analyzed where necessary however no metanlysis was performed.

RESULTS

Some 173 abstracts were reviewed and although 12 potential studies were initially identified, only 9 were included in the final review [5,7-9,16,19-22]. All included studies were retrospective case series except one [15] and none of them were case reports. The included studies comprised a total of 2175 patients who were diagnosed with acute cholangitis and had both bile and blood culture obtained. The bile cultures were positive in 68% (n=1488) patients. The most commonly occurring organisms found in the bile culture from acute cholangitis were Enterobacter species i.e. E. Coli, Enterococcus sp., Klebsiella, Pseudomonas aeruginosa, Proteus and some cultures grew Candida species. Moreover, contemporaneous positive blood cultures were found in 66% (n=1412) of patients. The organisms isolated were almost similar to the ones obtained from bile culture. This corresponds to the similar reports in the literature [7-12] (Table 1).

Benign diseases notably Gall stones and common bile duct stones were by far the most common reason for obstruction of the biliary tree (n=394). Only small number of patients was having either benign biliary stricture as the cause of cholangitis or primary sclerosing cholangitis. Malignant stricture of the biliary tract or other underlying pancreatic or loco-regional malignant conditions causing biliary obstruction leading to cholangitis was seen in 249 patients. It is apparent from these figures that by far the benign biliary obstruction is the most common cause of this dreadful condition of cholangitis, which in severe form could lead to deleterious consequences and associated with significant mortality.

In addition, only small percentage of the studies actually reported regarding severe cholangitis, this however in most of the case was associated with either benign biliary obstruction or in cases where patients with malignant biliary stricture undergoing invasive biliary intervention [10-15]. Moreover, none of the studies reported on degree of biliary obstruction caused by underlying pathological condition and its impact on the development of cholangitis and its severity.

DISCUSSION

Cholangitis is undoubtedly a serious clinical condition associated with significant morbidity and mortality [1-3,5-9]. Its incidence varies in the literature and has been reported between 5-25% [10-13]. Our study has shown that the bile culture was positive in 68% of the cases whereas almost similar percentage of cases (66%) has positive blood cultures. This potentiates the importance of both blood and bile cultures earlier on in the management of acute cholangitis. This will not only help us to treat this hostile condition but also prevent further deterioration and halt its progress to more severe form of cholangitis.

The most common organisms isolated from the bile were Escherichia coli, Klebsiella species, Enterococcus species, Streptococcus species, Enterobacter species, and Pseudomonas aeruginosa [7-9]. Organisms isolated from blood cultures are similar to those found in the bile. The most common pathogens...
isolated in blood cultures are E coli, Klebsiella species, Pseudomonas auroginosa, and Enterococcus species.

The most common cause for biliary obstructions in our review were benign conditions secondary to either galls stones or biliary stricture (n=394). Gallstones can slip into the common bile duct causing biliary stasis, which in turns attract gut microbial. Englesbe M et al., in their study of 30-patients reported 23 patients with benign biliary conditions resulting cholangitis whereas remaining seven patients developed cholangitis only after endoscopic biliary intervention [7]. Similarly Goo C et al., reported 320-patients having cholangitis caused by biliary obstruction due to benign biliary conditions [8]. It can be easily concluded from these reports that cholangitis, a benign biliary condition behaves more like a malignant disease and is associated with significant morbidity and mortality [9-14]. Prompt instigation of appropriate treatment could halt deleterious consequences of cholangitis [15].

Various theories have been proposed to elicit exact pathophysiological phenomenon of cholangitis [7-15]. Most common theory is that biliary tract obstruction leads to elevated intraluminal pressure, resulting in infection of bile [9-16]. It is believed that biliary obstruction diminishes host antibacterial defenses, causes immune dysfunction, and subsequently increases small bowel bacterial colonization [14]. Although the exact mechanism is unclear, it is believed that bacteria gain access to the biliary tree by retrograde ascent from the duodenum or from portal venous blood [10-12]. Increased biliary pressure pushes the infection into the biliary canaliculi, hepatic veins, and perihepatic lymphatics, leading to bacteremia [11-13]. Such hypotheses have been augmented by various studies where gut bacteria (E Coli, Enterococcus) have been isolated from biliary tract in patients with cholangitis [9-13]. However, the most obvious objection to this theory is lack of evidence as to how bacteria could ascend from gut into biliary tree in the presence of severe biliary obstruction. One possibility is by cholangiovenous reflux of microorganisms, which is however not a fully established phenomenon. Moreover, bacteria grown by bile and blood cultures are identical only in 70% of the cases reported in majority of the studies [6-12] whilst remaining 30% could not be explained by this mechanism. Furthermore, current literature falls short of providing enough evidence as to what factors play role in potentiating severe cholangitis. Could this be severity of biliary obstruction, or inflammatory cytokines, interleukins or immunological factors (underlying tumor stem cells provoking sinister immune-modulatory response) determining intensity of cholangitis? In addition, with more and more sophisticated endoscopic techniques available, it would not be inconvenient to conduct research into gauging correlation between biliary obstruction and severity of cholangitis. Furthermore, moving away from traditional thinking of microbiological as well as biliary obstruction to fetch microbial hypothesis towards role of tumor stem cells or provocation of immunological cascade would then be area to explore in the future studies. In addition,

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Number</th>
<th>Bile Culture</th>
<th>Blood Culture</th>
<th>Pathology/Severity if reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupp C et al.</td>
<td>1150</td>
<td>823</td>
<td>E.Coli, Klebsella, pseudomonas</td>
<td>823</td>
</tr>
<tr>
<td>Park JW et al.</td>
<td>266</td>
<td>258</td>
<td>Gram Negative Cocci&gt;Gram+</td>
<td>258</td>
</tr>
<tr>
<td>Goo JC et al.</td>
<td>346</td>
<td>256</td>
<td>71% pt had same blood and bile cs organisms</td>
<td>266</td>
</tr>
<tr>
<td>Kaya M et al.</td>
<td>91</td>
<td>46</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Englesbe MJ et al</td>
<td>30</td>
<td>10</td>
<td>Ecoli, Klebsella, pseudomonas auroginosa</td>
<td>15</td>
</tr>
<tr>
<td>Neve R et al</td>
<td>15</td>
<td>4</td>
<td>E. Coli Enterococcus, Klebsella</td>
<td>3</td>
</tr>
<tr>
<td>Keisslich R et al</td>
<td>80</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Thompson J et al</td>
<td>127</td>
<td>28</td>
<td>Enterobacter, enterococcus sp. Candida species</td>
<td>28</td>
</tr>
<tr>
<td>Seigman-Igra Y</td>
<td>70</td>
<td>10</td>
<td>Enterococcus, E Coli, Klebsella, proteus</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2175</td>
<td>1488(68%)</td>
<td>1412(66%)</td>
<td>Benign n=394 Malignant n=249</td>
</tr>
</tbody>
</table>

Table 1: Included studies with their data and outcome.
cellular mapping of biliary fluid to assess their significance in determining intensity of cholangitis could be explored in more laboratory-controlled environment. The authors of the current study hypothesize that the further research in to the latter two hypotheses would provide groundbreaking information in to the assessment and management of this potentially malignant disease with significant mortality.

The authors of the current study are well aware of the previous work done in connection with role of pro-inflammatory markers such as tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), in the pathophysiology of organ injury from severs cholangitis [14]. Increases in the levels of these proinflammatory cytokines have been shown to correlate strongly with the severity of multiple organ failure and with the mortality from Cholangitis [15]. Moreover, production of these cytokines could lead to complications of cholangitis such as liver injury, and release of transcription factors for example nuclear factor-kappa B (NF-kappa B) [16,17]. However, the role of these pro-inflammatory markers has not been fully assessed to determine intensity of cholangitis. In addition, some studies have reported high levels of intestinal oxidative stress with significant increase in lipid peroxidation in patients with obstructive jaundice [12]. Increased oxidative stress induces intestinal barrier failure leading to development of septic complications in patients with obstructive jaundice [12]. However, most of these studies have been performed on animals and their contemplation to human being has yet to be proven [12]. In addition, Watanabe et al reported activation of NF-κB inducing inflammatory cytokines such as TNF-α and IL-6, which in turn may cause neutrophil overreaction leading to organ failure [13]. Their study on the role of 15-Deoxy-Δ12, 14-prostaglandin J2 in preventing inflammatory reaction by down regulating the release of inflammatory cytokines and interleukins paved the different pathway of treating cholangitis other than anti-microbial and biliary drainage [13]. The evaluation of the gravity of a cholangitis is a real problem. It seems that white blood cell count greater than 20 000 cells/μl and total bilirubin greater than 10 mg/dl are two independent factors predicting adverse outcome in acute cholangitis [22].

It is therefore apparent from all these and various other reports that severity of cholangitis in biliary obstruction is determined by multiple factors and the role immune-pathological factors is yet to be explained. We strongly believe that it is unlikely the extent of biliary obstruction determining intensity of cholangitis, rather cellular and immunological entities present in the biliary fluid which determine the intensity of cholangitis as well as its related complications. The authors strongly recommend further research in this area to explore factors responsible for promoting cholangitis in order to prevent extensive morbidity and mortality associated with this potentially malignant condition.

REFERENCES


