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REVIEW ARTICLE

The role of endoscopy in the management of recurrent pyogenic cholangitis: a review

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Recurrent pyogenic cholangitis (RPC) is a clinical syndrome characterized by repeated episodes of suppurative cholangitis due to hepatolithiasis and extrahepatic stones in the biliary ducts. It is now recognized as a distinct syndrome with a different natural history and pathoetiology than spontaneously occurring liver abscesses. Most commonly seen in East Asian populations, this syndrome is growing increasingly common in Western Nations due to migration patterns. The exact pathogenesis of RPC remains elusive; although colonization of the biliary tract with particular enteric bacterial species, in combination with possible dietary factors, has been attributed as causative factors. Hepatobiliary surgery, in particular segmental hepatectomy, is often described as the definitive treatment of choice for RPC. The exact role of endoscopic intervention has been less clearly described in the literature. This review focuses on the management of RPC while highlighting situations in which endoscopic retrograde cholangiopancreatography may be preferred over surgery as an initial or salvage therapeutic measure.

Keywords: *recurrent pyogenic cholangitis*; *oriental cholangitis*; *hepatolithiasis*; *cholangitis*

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Recurrent pyogenic cholangitis (RPC) is a syndrome characterized by repeated episodes of cholangitis due to intra- and extrahepatic stones, biliary duct stricturing, and atrophy of the liver parenchyma. Unlike cholangitis due to common bile duct (CBD) stones, RPC is episodic due to persistent intrahepatic stones (1, 2). Spontaneous cholangitis associated with hepatolithiasis and RPC present similarly with regard to symptomatology and laboratory findings, but the pathoetiology of RPC as well as its natural history are unique (1–4). This condition predominantly affects lower socioeconomic groups in East Asian populations but is also seen among some Asian immigrants in Western countries (5, 6). RPC can lead to atrophy of the liver parenchyma, liver abscesses, and cholangiocarcinoma. Hepatectomy is an important measure in the definitive management of cases with high burden within third-order biliary ducts, and its role has been widely described in the surgical literature (7–10). Endoscopic retrograde cholangiopancreatography (ERCP) plays an important role when disease predominantly affects larger biliary ducts and to acutely relieve biliary obstruction in septic patients, but its indications in definitive management are less clearly defined (11).

Epidemiology

RPC is predominantly a disease of East Asian populations. Its incidence in East Asian countries has been reported to be between 4 and 52%, compared to 0.6–1.3% in the West (12–14). Men and women are affected in roughly equal proportions, with the disease manifesting in the fifth and sixth decades (12). The incidence of RPC in the East appears to be decreasing in recent decades based on national surveys from Taiwan and Japan, two countries with a high burden of disease (15–18). Meanwhile, the incidence of RPC is increasing in the West, largely due to migrations patterns (5, 19).

Methods

A thorough PubMed search of English-language publications was performed using the query keywords RECURRENT PYOGENIC CHOLANGITIS, ORIENTAL CHOLANGITIS, and PRIMARY HEPATOLITHIASIS without date restriction. This query resulted in a total of 157 publications, 4 of which are discussed in this review. At the time of writing, these were the only four cohort studies on the subject. The emphasis of this review is on management and classification systems.

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Pathogenesis

The inciting lesion in RPC is attributed to biliary stones. Some experts define RPC specifically as a syndrome resulting from hepatolithiasis, most of which are composed of calcium bilirubinate, or less commonly, cholesterol (7, 12, 13, 20). Other authors include less stringent criteria that do not explicitly rely on the presence of intrahepatic stones (11). Most authors, however, include intrahepatic stones as part of the syndrome. Over time, biliary stones cause fibrosis and stricturing of biliary ducts, leading to bile stasis and cholangitis. The left lateral segment and the posterior segment of the right lobe are most commonly affected (12, 13). Liver parenchyma may become atrophied and fibrotic. Sixty percent of cases are also associated with extrahepatic stones (10, 12, 13). The exact cause of these hepatolithiases remains unclear. The fact that anaerobic and Gram-negative bacterial species such as *Klebsiella* have been isolated from the bile of affected patients has led some authors to postulate a multifactorial model in which a low-protein diet, combined with biliary infection, leads to intrahepatic stone formation (7, 12, 13, 20). It is also unclear as to whether parasitic infections such as ascariasis and clonorchiasis, which can infect the biliary tract, contribute to pathogenesis (12, 20–23).

Diagnosis

Clinical presentation

Hepatolithiasis in itself does not usually become symptomatic (4). One study of 311 asymptomatic patients with hepatolithiasis found 11.5% to eventually become symptomatic over the course of 17 years (4). Episodes of symptomatic hepatolithiasis frequently recurred (1, 4). This may be due to stricturing of biliary ducts as well the persistence of stones that may act as niduses of infection (12, 13). Both in its initial presentation as well as in its recurrences, RPC is characterized by signs and symptoms of suppurative cholangitis (24). The most common presenting symptoms are abdominal pain, nausea, vomiting, and fever. Patients are frequently febrile, jaundiced, and septic. Liver enzymes classically reflect a cholangitis picture. Liver abscesses may also be present. In one study, more than half (55%) of patients with hepatolithiases who presented with RPC had either transient or continuous symptoms of cholangitis (9). Particularly severe cases of RPC can present as Reynold's pentad, the constellation of altered mental status, fever, jaundice, right upper quadrant pain, and hypotension. Elderly patients with RPC may present atypically, with general clinical deterioration in the absence of pain and fever (12, 25).

Imaging

Due to its relative inexpensiveness, widespread availability, and lack of radiation, abdominal ultrasound is frequently the first diagnostic modality employed in making the diagnosis of RPC. On ultrasonography, extrahepatic biliary dilatation is generally more prominent than intrahepatic biliary dilatation (26, 27). One series of 48 patients with the diagnosis of oriental cholangitis revealed stones in 98% of cases, with 42% of cases having exclusively extrahepatic duct stones and 42% of cases having both intra- and extrahepatic duct involvement (26). Seven of 48 (15%) cases had exclusively intrahepatic duct stones (26). Ultrasonography can also be useful in evaluating complications of RPC, including intrahepatic abscesses, pneumobilia, and cholangiocarcinoma (27).

CT and MRCP have largely replaced direct cholangiography as first-line imaging modalities in the evaluation of hepatobiliary anatomy. However, direct cholangiography can be useful for preoperative planning due to its superior spatial resolution compared to CT and MR (13). Congruent with ultrasonography findings, CT may reveal dilatation of mostly extrahepatic biliary ducts (27). Non-contrast CT is better suited than contrast CT for the visualization of hepatolithiasis. Other common features observed in CT are lobar or segmental atrophy and possibly liver abscesses and cholangiocarcinoma. MRCP can detect approximately 10% of calculi that are non-calcified and are poorly visualized on CT (28). Atrophy of the left lobe and posterior right lobe is visualized more commonly than other liver segments (13, 27).

Classification

Given the lack of established guidelines on the management of RPC, the decision of how to manage RPC is made on a case-by-case basis, frequently in a multidisciplinary setting. A recent review from a group in Kashmir, a country with a relatively high burden of RPC relative to its geographic neighbors, proposes a classification system based on the affected anatomy (19). The authors used this classification system to guide perioperative decision-making. While this classification system has not been prospectively or retrospectively validated, it does offer a systematic approach to treating patients with RPC (Table 1). It should be noted, however, that the authors developed this classification system based on their experience with patients who were referred to them after failed ERCP and patients with severe disease, characterized by severe intrahepatic duct stricturing and liver parenchymal atrophy.

Another surgical group from Singapore stratified patients who underwent either surgical or endoscopic therapy for RPC based on whether the disease involved first-order ducts ('simple disease') or second- and/or third-order ducts ('complex disease') (11). These patients were further sub-classified according to laterality of disease.

Cheon et al. classified patients with symptomatic hepatolithiasis into one of three categories (Type A, B, and C) (8). Type A hepatolithiasis involves solitary or multiple stones in one lobe of the liver with or without

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Table 1. Classification systems used in the characterization of recurrent pyogenic cholangitis

Study	Year	Publication type	Description	Validated
Cheon et al.	2009	Retrospective	Type A: solitary or multiple hepatolithiasis in one lobe of the liver with or without intrahepatic dilatation and stenosis Type B: bilateral hepatolithiasis with unilateral stenosis of the intrahepatic duct Type C: bilateral hepatolithiasis and bilateral intrahepatic duct stenosis	No
Koh et al.	2013	Retrospective	Simple disease: only first-order biliary ducts affected Complex disease: second- and/or third-order biliary ducts affected. Further classified as unilateral or bilateral	No
Parray et al.	2014	Review	Grade 1: disease limited to extrahepatic ducts. No parenchymal liver disease, no stricturing. CBD size <1.5 cm Grade 2: disease limited to extrahepatic ducts. No parenchymal liver disease, no stricturing. CBD size >1.5 cm Grade 3: stones $\pm$ worms present in left or right intrahepatic bile ducts. No parenchymal disease. Dilatable strictures present Grade 4: stones $\pm$ worms present in left or right intrahepatic bile ducts. Severe, non-dilatable strictures present or parenchymal disease present on the affected side Grade 5: stones $\pm$ worms present in right and left intrahepatic bile ducts. Severe, non-dilatable strictures present or parenchymal disease present on the both sides	No

intrahepatic dilatation and stenosis. Type B hepatolithiasis involves bilateral stones with unilateral stenosis of the intrahepatic duct. Type C involves bilateral stones and bilateral intrahepatic ductal stenosis.

Management

In addition to the intra- versus extrahepatic burden of disease, the decision of how to manage RPC must also take into account the extent of biliary duct stricturing as well as the absence or presence of complications such as hepatic abscess or cholangiocarcinoma (7, 10, 29). When disease predominantly affects the CBD, ERCP is the preferred initial therapy due to stone clearance in 91.7% of patients in a 134-patient series (10, 30). In most other cases, however, the decision is much less clear-cut.

Koh et al. used the classification system described in Table 2 to develop a management algorithm based on the results from 80 patients with RPC with the goal of definitive therapy and compare the outcomes of operative versus non-operative management (11). Among patients with simple disease (limited to first-order ducts), 25 underwent ERCP-guided therapy versus 30 who underwent operative biliary drainage based on the surgeon's assessment. The authors distinguish the initial step of treating acute biliary sepsis from measures taken to prevent recurrence. In the acute setting of biliary sepsis, the primary goal is to relieve biliary obstruction and remove stones or other debris from biliary ducts accessible to the endoscopist. Particularly in the acute phase, ERCP has the advantage over surgery of being better tolerated in the septic patient and faster than interventions such as hepatectomy. Endoscopists can extract stones, perform balloon-sweeping of the CBD, perform sphincterotomy, and place CBD stents as temporizing measures to acutely relieve biliary obstruction. Once a patient is stabilized, they may undergo more definitive therapy. Among patients with complex disease involving higher-order ducts, perioperative decision-making was further based on laterality of disease, with most cases of bilateral disease (13 of 14) undergoing segmental hepatectomy. Unilateral complex

Table 2. Studies investigating the operative and/or non-operative management of recurrent pyogenic cholangitis

Study	Year	Publication type	Number of patients	Interventions
Tabrizian et al.	2012	Retrospective	30	Hepatectomy, Roux-en-Y hepaticojejunostomy
Cheon et al.	2009	Retrospective	311	Hepatectomy, percutaneous transhepatic cholangioscopy, peroral cholangioscopy, ERCP
Al-Sukhni et al.	2008	Retrospective	42	Hepatectomy, choledochojejunostomy, and Hutson loop, common bile duct exploration
Koh et al.	2013	Retrospective	80	Common bile duct exploration, hepatectomy, percutaneous transhepatic cholangiography-guided procedure, ERCP

disease was treated in nearly equal numbers by a percutaneous transhepatic cholangiography (PTC)-guided procedure (5 of 11) and hepatectomy (6 of 11). When attempted as definitive therapy, ERCP had higher rates of initial failure (36%, or 9/25) and long-term failure (68%, or 17/25) compared to hepatectomy alone (0/18 and 0/18 for initial and long-term failure, respectively). In comparison, hepatectomy with operative biliary drainage was associated with an initial and long-term failure rate of 18.2% (2/11) and 27.3% (3/11), respectively. Non-operative treatment was associated with failure with an odds ratio of 26.843 ($P = 0.001$). Bilateral disease was associated with failure of segmental hepatectomy and PTC-guided biliary drainage with an odds ratio of 8.101 ($P = 0.007$).

Experience in Western centers with the surgical management of RPC is considerably more limited than Asian centers, but available data support the conclusion that hepatic resection is effective in the definitive management of RPC associated with hepatolithiasis. Tabrizian et al. conducted a prospective study of 30 patients with RPC who underwent hepatic resection at Mount Sinai Medical Center. This retrospective study analyzes outcomes among patients with predominantly intrahepatic burden of disease defined by intrahepatic bile duct strictures, stones, abscesses, liver atrophy, and suspected cholangiocarcinoma (7). 66.6% (20/30) of patients had a stone(s) in the left lobe, 23.3% (7/30) had stones in the right lobe, and 10% (3/10) had bilateral stones (7). Notably, 7/30 patients had cholangiocarcinoma, in comparison to rates of 2.1–10% in previously published studies of patients undergoing hepatectomy or non-operative treatment for PHL (7, 10, 31–33). With the exception of one patient who required postoperative ERCP and two patients with cancer recurrence, the remaining patients remained disease-free at 21 months (7).

Cheon et al. conducted a retrospective survey of 236 patients who underwent either operative or non-operative therapy for hepatolithiasis. Among them, 23.7% of these patients (49/236) underwent ERCP, 38.1% (90/236) underwent hepatectomy, and 41.1% (97/236) underwent Percutaneous transhepatic cholangioscopic lithotomy (PTCSL) (8). A majority of these patients (62.7%) had stones in the left hepatic lobe, versus stones exclusively in the right lobe (13.6%) or bilateral stones (23.7%) (8). Patients underwent hepatectomy in the case of disease involving only one lobe, stones associated with biliary duct strictures, or when atrophy of an involved liver segment or lobe was observed. Cholangiocarcinoma, either confirmed or suspected, was another indication for hepatectomy. PTCSL was reserved for patients >80 years of age, patients who were deemed to be of high operative risk, and those who refused surgery. ERCP carried a 0% complication risk, compared to 1% in the hepatectomy group (8). The rate of complete stone clearance was highest in the hepatectomy group (83.3%) compared to the ERCP group (63.9%) (8). At 2–37 years post-procedure, similar rates of freedom from symptoms were observed among patients with complete stone removal from either of the three groups. Once again, ERCP was associated with higher rates of recurrence of hepatolithiasis and/or cholangitis (25% or 7/28) compared to hepatectomy with postoperative cholangiography (18% or 14/77) and PTCSL (21% or 13/62) (8). In contrast to the study by Koh et al., only patients with hepatolithiasis were included in this study.

Conclusion

Previously, a rare diagnosis in the West, that is, RPC, has grown increasingly common in North America and Europe with recent migration patterns. The decision of how to most effectively manage RPC in most extrahepatic disease or in cases of extensive intrahepatic disease is clear. Less well characterized, however, is the role of endoscopy as a first-line intervention outside the acute setting. Even in cases in which hepatectomy is ultimately indicated, ERCP frequently has an important role in the initial relief of biliary obstruction in the acute setting. All the studies reviewed here were retrospective in nature and are therefore subject to unknown biases. A disease classification schema validated through a prospective study could help guide future studies of the most appropriate management of this syndrome.

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