

Long-term endoscopic management for primary recurrent pyogenic cholangitis

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Abstract

Background: Primary recurrent pyogenic cholangitis (RPC) is characterized by relentless suppurative cholangitis in those with a suspected parasitic injury of the biliary tree. Prior work has demonstrated that the infections recur following “definitive” biliary surgery and long-term percutaneous biliary catheters are poorly tolerated. The aim of this study was to assess whether scheduled surveillance endoscopic retrograde cholangiopancreatography (ERCP) prevents cholangitis in those with RPC. **Materials and Methods:** Following initial biliary decompression and stone clearance, patients with RPC were offered serial ERCP every 3-6 months to remove accumulating stony debris and to dilate incipient strictures. Review of a large series managed using this approach at the University of California, San Francisco Medical Center was performed. The principle outcome was the development of acute cholangitis requiring hospitalization and whether the episode occurred, while the RPC patient was in compliance with endoscopic surveillance recommendations. **Results:** Over a period of 10 years, 66 patients with primary RPC were managed for RPC at the University of California, San Francisco. The patients were comprised primarily of first-generation immigrants from Asia though one-quarter had migrated from Latin America and Russia. Episodes of cholangitis were significantly less likely to occur in those undergoing surveillance biliary endoscopy than in those who were not (odds ratio 5.3; $P = 0.005$). The mean follow-up was 36.1 months. **Conclusions:** Serial endoscopic treatment of RPC may be used to systematically clear biliary debris and decreases the risk of cholangitis requiring hospitalization. It represents a reasonable initial management strategy for these patients. Surgery and percutaneous management may also be required, but are best performed as part of a multidisciplinary approach.

Key words

Bile ducts, choledocholithiasis, endoscopic, intrahepatic, sphincterotomy

Introduction

During the first half of the 20th century, British surgeons operating in Hong Kong encountered an unfamiliar disease in Asian patients presenting with cholangitis.^[1] At the time of surgery, these patients did not have the cholelithiasis as was typically seen in cholangitic western patients but had

diffuse intrahepatic disease in the setting of an unremarkable gallbladder. It is now recognized that the Hong Kong disease or recurrent pyogenic cholangitis (RPC) is a chronic inflammatory disease of the entire biliary tree. Microbiological data suggests that it likely originates from parasitic injury to the biliary epithelium potentiated by a feed-forward cycle of bacterial infections, strictures, and stone disease.^[2] The prevalence in the developing world and the disappearance with industrialization further corroborate this hypothesis.^[3,4]

The surgical experience with RPC indicates that symptoms will generally recur following operative intervention. During the period from 1980 to 1994, Stain *et al.* encountered 20 patients with RPC at Los Angeles County Hospital.^[5] Among those who underwent partial liver resection or conventional

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hepaticojejunostomy, two-thirds developed recurrent biliary sepsis or obstruction. Most large surgical series report disabling symptom requiring further surgery and major interventions in at least 30-60% of patients.^[4,6] Surgery has a morbidity of 25% or greater given difficulty with perihepatic adhesions and may precipitate hepatic failure requiring transplantation.^[7,8]

Percutaneous intervention that may be supplemented with transcutaneous cholangioscopy has also been investigated in RPC. In a large series of patients with RPC, Huang, *et al.* were able to achieve ductal clearance in 85.3% of patients after a mean of 4.7 percutaneous sessions.^[9] Nonetheless, 50% develop subsequent disease requiring reintervention and procedures were associated with a risk of major complications in 1.6% including liver laceration. The placement of drainage catheters for long-term drainage is possible but met with poor patient acceptance as the transcatheter biliary tubes are reported by most patients to be very uncomfortable.^[6]

While biliary surgery and percutaneous approaches are options, the significant morbidity of the former and patient discomfort of the latter limit their applicability as a solution for this chronic disease. Endoscopic therapy represents a more ideal approach as the procedure has relatively low morbidity and following the sphincterotomy repeat biliary access is straight forward and well tolerated. The aim of this project was to assess whether scheduled endoscopic retrograde cholangiopancreatography (ERCP) (every 3-6 months) to survey and clear the biliary tree of debris decreases the frequency of acute cholangitis episodes in these patients.

Materials and Methods

We retrospectively reviewed the prospectively developed endoscopic database which was initiated in 1999. Patients were defined to have primary RPC if they had cholangiographic findings of extensive intrahepatic stones, strictures, and dilatation and a contributory clinical history of recurrent symptomatic choledocholithiasis or cholangitis. Patients with primary sclerosing cholangitis, ischemic biliary injury, and cystic fibrosis were classified as having secondary RPC and were excluded from the study. We reviewed the cholangiograms and entire medical records to characterize the disease pattern and detailed clinical course.

Patients with RPC at the University of California, San Francisco are managed in a uniform fashion. If not already present an endoscopic sphincterotomy is performed. All biliary strictures are treated using 4 mm and 6 mm dilatation balloons (Wilson Cook; Durham, NC). Stones are removed using a combination of basket lithotripsy and balloon passage (Wilson Cook). Repeat ERCP is performed every 1-3 months until ductal clearance and stricture resolution is achieved. Biliary stents (7Fr pigtail) (Boston Scientific; Natick, MA) are intermittently used in the initial management but not

during the long-term surveillance phase.

Upon clearance, patients are recommended to undergo serial ERCP every 3-6 months for removal of accumulating debris and dilatation of developing strictures. The suggested interval, in the range of 3-6 months, for the follow-up ERCP is made immediately after each procedure based on the cholangiographic findings and recent clinical symptoms. Patients compliant with recommendations undergo ERCP even if asymptomatic. Patients not adherent to surveillance ERCP recommendations only undergo ERCP for symptomatic obstruction or cholangitis. Prophylactic antibiotics are given prior to all ERCP as there is a high risk of cholangitis in patients with RPC, who undergo ERCP without peri-procedural antibiotics.^[10] Oral antibiotics were continued for 3 days following ERCP, but patients were not treated with rotating or long-term antibiotics.

Our principle endpoint was admission to the hospital for cholangitis and whether the patients were adherent to the recommended course of endoscopic surveillance prior to the event. Periods on surveillance proceeded periods off surveillance. For example, a patient advised to undergo ERCP within 6 months but did not comply and presented with cholangitis 12 months later was classified as off surveillance. A patient advised to undergo an ERCP within 6 months who presented with cholangitis within 5 months was classified as on surveillance. Cholangitis was defined as a temperature >38.5°C, acute worsening of liver tests, and abnormal biliary imaging. To compare whether there was an overall difference in the incidence of cholangitis occurring when patients were on and off surveillance, a Wilcoxon signed ranks test for paired datum was performed. Fisher's exact χ^2 tests were used to gauge whether other conditions were associated with cholangitis including bile duct features and comorbidities. We also recorded the necessity of any percutaneous or surgical interventions in this group of patients. The study was approved by the UCSF institutional review board.

Results

Patients

Since 1999 66 patients have undergone endoscopic management of primary RPC at the University of California, San Francisco. The mean age of the cohort was 58.8 years (standard deviation [SD] 18.5) and two-thirds were female [Table 1]. Asians comprised 74.5% of the population, and 10% were Hispanic; almost all were first-generation immigrants. The seven Caucasian patients were predominantly first-generation Russian immigrants. Most of the patients had undergone a prior cholecystectomy. We assessed the patients for eosinophilia that would suggest active parasitic infection, and it was not found in any of the cases. No parasites were identified during bile duct examination, and none of the patients required antihelminthics.

Management and complications

All the patients had intrahepatic stones and bile duct dilation [Figure 1a]. In 38 (58%) of cases, the disease predominantly involved the left intrahepatic biliary tree [Figure 1b]. High-grade strictures were seen in 24 (36%). Patients underwent a mean of 6 ERCP during which all intra and extrahepatic strictures were treated by hydrostatic balloon dilatation and stones removed by aggressive lithotripsy [Figure 1c and d]. Among the cohort 12 had undergone prior radiographic or surgical procedures. Eight patients subsequently required surgical or percutaneous management. Four patients underwent left lobectomy for left intrahepatic bile duct stones and atrophied liver. It was combined with biliary enteric diversion in all cases.

Over the course of 387 total ERCP, there were three episodes of minor bleeding that did not require intervention and two episodes of mild pancreatitis requiring >3 days of hospitalization.^[11] One of the patients who underwent percutaneous biliary drainage had a fatal bleed during the percutaneous procedure and one of the patients who

underwent subsequent biliary surgery developed a wound infection.

Impact of surveillance endoscopic retrograde cholangiopancreatography

The mean follow-up period was 36.1 months (SD 44.5). The mean period on surveillance of 18.5 (SD 22.8) months and period off surveillance was 17.9 (SD 30.4) months. During the course of the study, 21 admissions for cholangitis occurred; 17 occurred while patients were not on endoscopic surveillance and four occurred while patients were compliant with the recommended biliary therapy. Patients who were off surveillance were significantly more likely to develop cholangitis than those who were on surveillance odds ratio (OR = 5.3, $P = 0.005$) [Figure 2].

Endoscopic biliary access following hepaticojejunostomy may be very difficult, and these patients may not be comparable to those with conventional anatomy. Therefore, analysis for the impact of surveillance on the development of cholangitis was also performed with exclusion of those who underwent hepaticojejunostomy, and the results remained significant (OR = 3.7, $P = 0.018$). In addition, to account for the possibility that multiple episodes of cholangitis in individual patients could skew the results the analysis was also performed to compare the number of patients (rather than the number of episodes) who developed cholangitis on- and off-surveillance. The results remained significant; four patients developed cholangitis on and 14 off surveillance ($P = 0.021$).

Other predictors of cholangitis

Of interest biliary strictures and the pattern of intrahepatic dilatation was not significantly associated with cholangitis. Prior hepaticojejunostomy, but neither choledochoduodenostomy nor hepatic resection were significantly associated with cholangitis ($P = 0.002$). Nephrolithiasis was associated with RPC ($P < 0.001$) but tophaceous gout was not. Age and sex were not associated with cholangitis, but ethnicity was ($P = 0.032$). Among Asian patients 16 of 49 (32.7%) had cholangitis as well as three of seven (42.9%) of Caucasians. None of the Hispanic patients had cholangitis during the study period.

Discussion

Recurrent pyogenic cholangitis is a complex biliary disease increasingly encountered in the west, particularly in Pacific Rim cities, consequent to immigration patterns. While biliary surgery and percutaneous intervention may be used to treat strictures and stones, the disease inexorably recurs given its diffuse nature. In this report, we present the most comprehensive long-term endoscopic management strategy for RPC to date.

The crucial principle is that RPC is a chronic process impacting the entire biliary system. The genesis of the

Table 1: Demographics and cholangiographic features

| | |
|--|-----------|
| Age | |
| Range | 14-93 |
| Mean±SD | 58.8±18.5 |
| Gender <i>n</i> (%) | |
| Male | 22 (33.3) |
| Female | 44 (66.7) |
| Race <i>n</i> (%) | |
| Asian | 49 (74.2) |
| Hispanic | 10 (15.2) |
| Caucasian | 7 (10.6) |
| Cholangiographic features <i>n</i> (%) | |
| High grade strictures | 24 (36) |
| Left greater than right dilatation | 38 (58) |

SD=Standard deviation

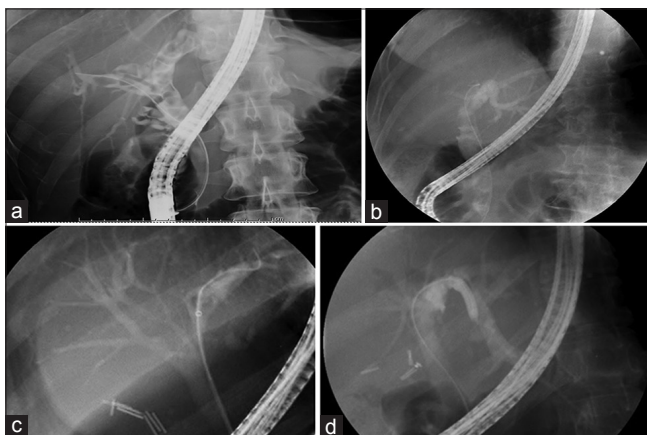


Figure 1: Characteristic features of recurrent pyogenic cholangitis (RPC). (a) Cholangiography in RPC reveals intrahepatic bile duct stones and (b) Predominantly left sided dilatation. (c) Endoscopic therapy requires aggressive stone removal and (d) Treatment of intrahepatic strictures

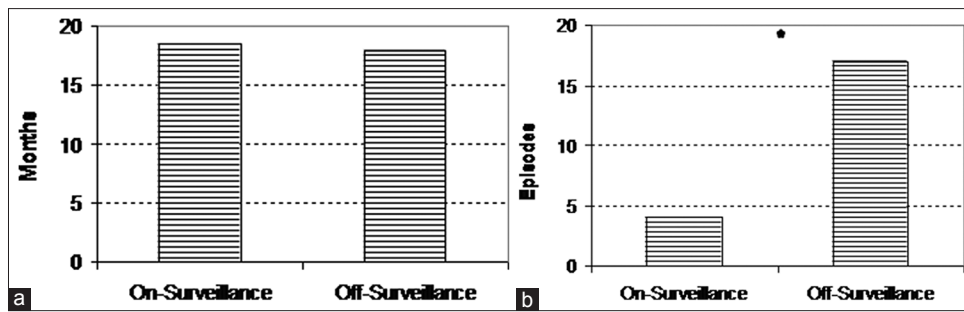


Figure 2: Impact of surveillance endoscopic retrograde cholangiopancreatography on episodes of recurrent cholangitis. (a) While the time on and off endoscopic surveillance was similar. (b) Episodes of cholangitis were significantly more likely to occur in those off endoscopic surveillance * $P = 0.005$

disease is proposed to be a past infection of the biliary tree with *Clonorchis sinensis*, *Ascaris lumbricoides*, and related pathogens.^[1,2] Most series propose that this parasitic infection occurs long before the presentation with chronic biliary complications. Consistently, in our cohort we did not encounter evidence of active helminthic infection. Diffuse parasitic injury to the ducts renders them susceptible to infection by Gram-negative organisms of the gut including *Escherichia coli*. Bacterial B-glucuronidase results in deconjugation of bile with crystallizes with calcium and amalgamates with pus and desquamated ductal epithelium to form brown stones and casts. Consequent inflammation of the biliary tree and surrounding tissue results in strictures and thrombophlebitis.^[12] Long-term complications include abscess in up to 20% of patients, secondary biliary cirrhosis in 7-10%, and cholangiocarcinoma in 2-10%.^[13]

Lam *et al.* reported the first series of patients who underwent endoscopic management of RPC.^[10] Their initial diagnostic studies helped to define the classic pattern of left side predominant intrahepatic strictures, stones, and dilatation used to define RPC in the current series. They subsequently demonstrated that the sphincterotomy and endoscopic methods could be used with success to clear intrahepatic stones.^[14] In a series of therapeutic ERCP in 12 patients, Sperling, *et al.* demonstrated that intrahepatic strictures could be successfully treated, and intrahepatic stones removed in more than two-thirds of patients.^[15] However, data on long-term endoscopic management are scarce.

Our strategy is to halt recurrence at an early stage in which it is manageable in order to facilitate bile duct drainage via its natural route into the duodenum. Upon achieving endoscopic clearance of stones and resolution of strictures, we brought back patients serially so that small stones, biliary mud, and early recurrent strictures could be treated by endoscopic toilet and dilatation. Our aim is to remove biliary debris and dilate incipient strictures to prevent the development of high-grade strictures and hardened casts of biliary stones that may require surgical management. In patients compliant with serial endoscopic therapy, we rarely encountered complex stones or high-grade strictures. However, when the same individuals and in others who were noncompliant we encountered casts of hard

faceted pigment stones, casts, and difficult intrahepatic strictures. Statistical analysis of the cohort demonstrated that surveillance ERCP was significantly associated with less hospital admissions for cholangitis. Favorably, we had close long-term follow-up of a large group of patients with well characterized disease.

However, there are several important limitations of this study. No cost effectiveness analysis of the strategy was performed although the cost of inpatient admissions for cholangitis potentially outweighs the cost of out-patient surveillance ERCP. Furthermore, while our approach suggests that endoscopic management is a good primary strategy, the study was retrospective that introduces bias. In addition, the crossover of patients to other therapeutic modalities makes it more difficult to account for the independent effects of endoscopic surveillance, though we did perform the analysis to exclude patients who had undergone hepaticojejunostomy and confirmed the impact of surveillance ERCP.

In practice, the management of recurrent primary cholangitis requires multiple therapeutic modalities. Patients with RPC may develop a severe disease in the left lateral segment due to the sharp angulation with the trunk of the biliary tree. Chronic obstruction results in the formation of large stones and parenchymal atrophy.^[12] These patients may benefit from left lateral segmentectomy [Figure 3a].^[7] Similarly, right posterior ducts may be difficult to access using endoscopic approaches and management may be facilitated by percutaneous intervention [Figure 3b]. Additionally, biliary diversion surgery may become necessary. Given the chronicity of the disease, operations that allow subsequent endoscopic therapy including choledochoduodenostomy and hepaticojejunostomy with creation of a side-to-side duodenjejunostomy are preferable. Another option for difficult cases is the creation of a hepaticocutaneous jejunostomy (Hutson loop) in which the afferent jejunal limb is positioned near the skin or stomatized to enable prompt endoscopic access to the intrahepatic biliary tree [Figure 3c and d].

There are several considerations for further research. In addition to a prospective randomized design to minimize bias, future work could assess the role of evolving technology for bile duct stones including modern single operator

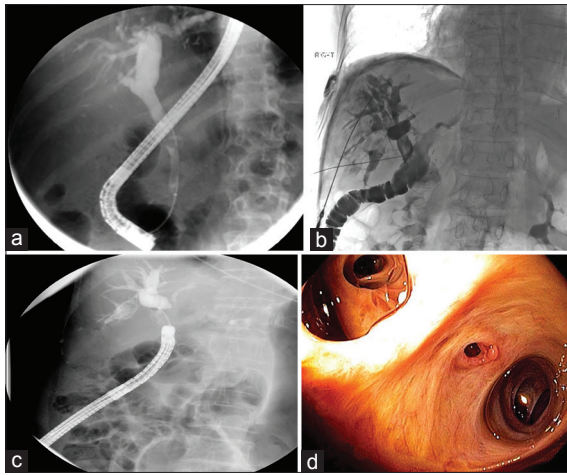


Figure 3: Management of complicated cases of recurrent pyogenic cholangitis. (a) The disease tends to recur post operatively, patients who have undergone left segmentectomy may subsequently develop large stones elsewhere in the biliary tree (b). High grade narrowing and oblique angulation may necessitate percutaneous drainage (c and d). The Hutson loop is a jejunostomy which enables the endoscope to be advanced directly into the proximal biliary tree for evaluation and toilet

choledochoscopes and device assisted enteroscopy systems to manage those with surgically altered anatomy.^[16,17]

Recurrent pyogenic cholangitis is a relentless, diffuse biliary disease. Given low morbidity and good patient tolerance, endoscopic therapy is the favored initial management strategies. Our series suggests that scheduled, serial endoscopic toilet of the biliary tree results in less significant complications of the disease and represents a potential long-term management strategy. Surgery and percutaneous intervention have roles particularly for several left lateral segmental disease and oblique strictures, but care is best coordinated in a multidisciplinary manner to optimize the long-term outcome. Further prospective studies are needed to more precisely quantify the role of serial endoscopic management.

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