

## **Form "EAST Multicenter Study Proposal"**

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**PROTOCOL TITLE:** Current Management of Suspected Retained Common Bile Duct Stones in Gallstone Pancreatitis and Choledocholithiasis

### **BACKGROUND AND SIGNIFICANCE**

Gallstones escaping the gallbladder into the common bile duct (CBD) may complicate gallstones disease in 5-10% of patients undergoing cholecystectomy for symptomatic cholelithiasis and 18-33% of patients with acute biliary pancreatitis. Despite its common occurrence and associated morbidity, the optimal management of patients at risk of a common duct stone in gallstone pancreatitis (GP) or choledocholithiasis (CDL) is controversial.

Acute GP and CDL with low suspicion of retained CBD stones have traditionally been managed by early cholecystectomy without further investigations. However, the management of patients with "intermediate to high" suspicion of retained CBD stones is more controversial. Patients may be managed with immediate laparoscopic cholecystectomy (with or without intraoperative cholangiogram (IOC)), preoperative MRCP, or preoperative ERCP followed by laparoscopic cholecystectomy. For patients with CBD stones discovered on IOC, options include laparoscopic versus open CBD exploration or postoperative ERCP.

No large multicenter studies to date have looked at whether or not patients with GP or CDL and intermediate to high risk of retained stones may benefit from routine preoperative ERCP or MRCP versus immediate cholecystectomy with or without IOC. We believe that preoperative studies should be limited to patients with high pre-test probability of common duct stones, as routine investigation may result in unnecessary procedures, increased hospital costs and delay to definitive management.

### **SPECIFIC AIMS**

**Aim #1:** *To determine what pretest risk factors (including ultrasound characteristics and laboratory trends) increase the probability of having retained CBD stones in patients with GP and CDL.*

Based on findings from a single-center study, age, laboratory findings and ultrasound results may help predict the presence of retained CBD stones and therefore may help minimize unnecessary procedures. A multi-institutional collaboration would be necessary to build a more robust predictive model to better

distinguish patients at “high-risk” versus “low-risk” for subsequently needing a cholangiogram or other preoperative investigation.

***Aim #2: To determine if immediate cholecystectomy without preoperative ERCP or MRCP is superior to routine preoperative ERCP or MRCP in patients with GP or CDL.***

In patients with GP or CDL, preoperative workup with ERCP or MRCP may not be necessary and patients may undergo laparoscopic cholecystectomy with selective postoperative ERCP or MRCP if they develop signs and symptoms of retained stones. In fact, ERCP is now progressively abandoned as a diagnostic tool as most cholangiograms end up being normal and it is associated with a non-negligible procedure-related morbidity and mortality. A strategy of restrictive preoperative ERCP or MRCP may decrease unnecessary procedures and shorten hospital LOS.

**Exploratory Aims:**

*Objective 1: To determine how often routine IOC is performed in patients presenting with evidence of GP or CDL.*

Historically, routine IOC has been advocated in patients presenting with GP or CDL. Recent literature, however, suggests that more selective use of IOC is an acceptable approach. Among patients at high-risk of having retained CBD stones, IOC is sensitive for detecting bile duct stones and guiding further treatment. A strategy of restrictive cholangiogram reserved only for these high-risk patients may improve value by decreasing unnecessary procedures and shortening hospital length of stay. This study will help to determine how often routine IOC is still being performed for the diagnosis and management of CBD stones in the setting of GP and CDL. Furthermore, in situations where IOC is positive, we will assess whether these patients are being managed with laparoscopic CBD explorations versus postoperative ERCP, with the risk of needing a third intervention if this fails.

*Objective 2: To assess the sensitivity and accuracy of MRCP for detecting CBD stones.*

For patients in whom pre- or postoperative workup is deemed necessary, is ERCP superior to MRCP for the detection of CBD stones? There are conflicting reports in the literature and questions remain as to the cost effectiveness of MRCP especially in the setting of hyperbilirubinemia but normal CBD on ultrasound. While the use of MRCP to rule out biliary obstruction may avoid the use of more invasive procedures, it is time consuming and not always readily available. Through this study we seek to evaluate whether ERCP is superior to MRCP for the initial diagnosis of CDL, especially among patients with moderate hyperbilirubinemia and/or hyperamylasemia without biliary dilation on ultrasound.

**RESEARCH DESIGN AND METHODS**

### Study Population

This will be a multicenter prospective observational study of patients undergoing cholecystectomy for gallstone pancreatitis with or without choledocholithiasis over the next two years. All patients >18 years of age who undergo cholecystectomy on the same hospital admission will be eligible for inclusion. Exclusion criteria will include history of prior ERCP or biliary instrumentation, or a diagnosis of cholangitis. We anticipate enrolling a total of 1200 patients across all centers, with 200 being enrolled at Emory.

IRB approval will be obtained at all participating sites and Data Transfer Agreements will be completed where applicable. Data will then be collected at each site. All data will be de-identified and entered in to a secure RedCap database by each participating center. The complete database will only be accessed via a password protected computer in the PI's locked office at Emory.

### Intervention

No interventions will be performed solely for the purpose of the study. Patients will undergo their workup as deemed necessary by their respective surgeon. Data will be collected from chart review.

### Informed Consent

This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers.

### Data Collection

Demographic data, as well as information on presenting laboratory values, preoperative imaging results (including ultrasound, MRCP, ERCP, CBD diameter, presence of CBD stones and size of stones if available), intraoperative cholangiography data, and complications will be collected.

The primary outcome measure will be the retained CBD stone rate among patients managed with preoperative ERCP and/or MRCP versus those managed with surgery and no further preoperative testing. Secondary outcome measures will include unnecessary procedure rate (%) of ERCP and IOC as well as any complications such as post-ERCP pancreatitis, bleeding complications, leak rates, 30-day readmission rates for choledocholithiasis, hospital length of stay (preoperative and postoperative), and rates of secondary intervention.

### Specific Variables

1. Demographics: age, gender, weight, comorbid medical conditions
2. Admission physiology: temperature, heart rate, blood pressure, initial laboratory values, duration of symptoms

3. Hospital management: imaging, preoperative interventions (MRCP, ERCP), laparoscopy versus open surgery, use of intra-operative IOC, postoperative interventions (MRCP, ERCP)

5. Outcomes: hospital LOS, ICU LOS, ventilator days, mortality, complications, retained stones

### Data Analysis

Standardized data will be collected for each patient. Patients will be divided into groups according to the presence or absence of previously defined biochemical test and ultrasound results. Continuous variables will be compared using Student's t-test and the Mann Whitney U test. The Chi-squared tests or Fisher's exact test will be used to compare categorical variables. Univariate and multivariate regression analysis will be used to determine independent predictors of common bile duct stones. These predictors will be used to develop a scoring model. Various measures for the assessment of risk prediction models will be determined, such as predictive ability, accuracy, and the area under the receiver operating characteristic curve (AUC). Data will be reported as adjusted odds ratios with 95% confidence intervals. Statistical significance will be set at a  $p < 0.05$ .

### Sample Size & Power Estimates

Based on a sample size of 600 and assuming 50% of the cohort will have certain lab results and ultrasound characteristics, the study will have 84% power to detect a 12% difference in the rate of CBD stone presence between those with and without the characteristics of interest. Given that this is a multicenter study, we do anticipate enrolling up to 1200 patients during the study period.

### **RISK/BENEFIT ANALYSIS**

This study involves no more than minimal risk to patients, as it is an observational study. A potential risk is a breach of confidentiality. There is a potential future benefit if we can accurately define patients at "high risk" of having retained CBD stones, and determine the optimal management strategy for suspected CBD stones in these patients. This would help minimize the complications associated with invasive procedures and improve outcomes.

### **STUDY LIMITATIONS**

The primary limitation of this study will be the chance that accurate pre- or intra-operative data is not captured in patient records but the prospective design of the study will help prevent this. Every effort will be made to perform detailed data extraction and only patients with complete datasets will be included in this study.

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