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Predicting the likelihood of a persistent bile duct stone in patients with suspected choledocholithiasis: accuracy of existing guidelines and the impact of laboratory trends

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Abstract

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BACKGROUND—Existing guidelines aim to stratify the likelihood of choledocholithiasis in order to guide the use of ERCP versus a lower risk diagnostic study such as EUS, magnetic resonance cholangiopancreatography (MRCP), or intraoperative cholangiography.

OBJECTIVE—To assess the performance of existing guidelines in predicting choledocholithiasis and to determine if trends in laboratory parameters improve diagnostic accuracy.

DESIGN—Retrospective cohort study.

SETTING—Tertiary-care hospital.

PATIENTS—Hospitalized patients presenting with suspected choledocholithiasis over a 6 year period.

INTERVENTIONS—Assessment of the American Society for Gastrointestinal Endoscopy (ASGE) guidelines, its component variables, and laboratory trends in predicting choledocholithiasis.

MAIN OUTCOME MEASUREMENTS—The presence of choledocholithiasis confirmed by EUS, MRCP, or ERCP.

RESULTS—One hundred seventy-nine (35.9%) of the 498 eligible patients met ASGE high-probability criteria for choledocholithiasis on initial presentation. Of those, 99 subjects (56.3%) had stone/sludge on subsequent confirmatory test. Among cases not meeting high-probability criteria on presentation, 111 (34.8%) had a stone/sludge. The overall accuracy of the guidelines in detecting choledocholithiasis was 62.1% (47.4% sensitivity, 73% specificity) based upon data available at presentation. The accuracy was unchanged when incorporating the second set of liver chemistries obtained after admission (63.2%), suggesting that laboratory trends did not improve performance.

LIMITATIONS—retrospective study; inconsistent timing of second set of biochemical markers.

CONCLUSION—In our cohort of patients, existing choledocholithiasis guidelines lacked diagnostic accuracy, likely resulting in overuse of ERCP. Incorporation of laboratory trends did not improve performance. Additional research focused on risk stratification is necessary toward the goal of eliminating unnecessary diagnostic ERCP.

Introduction

Bile duct stones are a common clinical problem.^{1–3} ERCP is highly effective in relieving biliary obstruction, but carries up to a 15% risk of post-ERCP pancreatitis,⁴ a 1% to 2% risk of post-endoscopic sphincterotomy bleeding, as well as risks of perforation, infection, and anesthesia-related adverse events.⁵ Although the risk-benefit profile of ERCP is favorable in the setting of established choledocholithiasis, when the diagnosis is in question, endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) represent highly accurate, lower-risk alternatives for initial evaluation.^{6,7}

In order to restrict ERCP to patients with the highest probability of choledocholithiasis—in whom the risk-benefit ratio is most favorable—accurate and reproducible risk stratification strategies are necessary. In 2010, the American Society for Gastrointestinal Endoscopy (ASGE) published guidelines defining “very strong,” “strong,” and “moderate” clinical

predictors of choledocholithiasis.⁸ According to these guidelines, the presence of any “very strong” predictor (CBD stone on trans-abdominal ultrasound, clinical ascending cholangitis, serum bilirubin >4 mg/dL), or both “strong” predictors (dilated CBD >6mm on ultrasound with an intact gallbladder, serum bilirubin 1.8–4.0 mg/dL) indicate a high-probability of choledocholithiasis (defined as >50% likelihood), and ERCP is recommended. Patients classified as intermediate probability are best suited for a less-invasive initial test, such as EUS, MRCP, or intraoperative cholangiography (IOC).

Although these existing guidelines provide a straightforward algorithm for this common problem, their accuracy in predicting choledocholithiasis has not been widely validated, and the impact of the evolution of laboratory values is not addressed. Indeed, some clinicians believe that a comparison of liver function tests over time is highly informative, with decreasing values suggesting spontaneous stone passage and prompting a less invasive initial intervention.

Based on clinical experience, we hypothesized that current guidelines are not sufficiently accurate to minimize unnecessary ERCP, and that inclusion of laboratory trends would significantly improve accuracy. To test these hypotheses, we performed a retrospective cohort analysis in which we correlated patients’ ASGE risk classification with the presence of choledocholithiasis and assessed whether trends in liver chemistries improved the performance characteristics of the guidelines. Using this same cohort, we also evaluated the strength of association between common clinical and laboratory predictors and documented choledocholithiasis.

Methods

The University of Michigan Medical Center Institutional Review Board approved this study. The study sample consisted of patients admitted to a large tertiary care academic medical center with suspected choledocholithiasis over a 6-year period, from January 1, 2007 through December 31, 2012. To identify study subjects, we reviewed all EUS and ERCP cases in our institution’s endoscopic reporting database (Provation MD—Provation Medical, Minneapolis, Minn.), which contains reports of all procedures performed at the University of Michigan, and used an institutionally developed search engine of all radiology reports generated by our radiology department (RadQuery – University of Michigan Department of Radiology, Ann Arbor, Mich.), which allows keyword searching of all institutional MRCP reports. One investigator (MA) manually reviewed the indications for all EUS, ERCPs, and MRCPs performed over the study period to generate a list of cases of suspected choledocholithiasis. Because the language denoting procedural indication was not standardized in Provation records, we initially cast a wide net and selected all patients with the procedural indications of pancreatitis, choledocholithiasis, biliary dilation, abdominal pain, abnormal liver function tests, or other symptoms that could suggest suspected choledocholithiasis. The RadQuery search was run using the following specific keywords: stone, stones, calculus, calculi, or choledocholithiasis, in combination with the terms biliary, bile duct, obstructing, or CBD. The records of potential cases were then reviewed in detail to evaluate for the presence of pre-specified eligibility criteria. Subjects were excluded if there was suspicion of ascending cholangitis based on the concurrent presence of fever or

leukocytosis (excluded because it is generally accepted that these patients require urgent ERCP for biliary decompression without antecedent bile duct evaluation), a history of liver transplantation or known liver disease, a history of biliary surgery, a history of primary sclerosing cholangitis, suspicion of pancreaticobiliary malignancy, previously placed endobiliary stent or sphincterotomy, a history of biliary stricture, or a history of cholecystectomy (excluded because post-cholecystectomy state can influence CBD diameter, and because the guidelines apply specifically to patients with "symptomatic cholelithiasis"). These exclusion criteria were applied because they confound the interpretation of liver biochemical markers and may therefore affect the performance of the guidelines.

The following data were abstracted for each eligible subject in independent and duplicate fashion (MA, AH) using a standardized data collection spreadsheet: age at time of procedure, gender, whether total bilirubin was >4 mg/dL or ≤ 4 mg/dL on initial or second set of labs, ultrasound findings (presence of visible stone, $\text{CBD} > 6\text{mm}$), presence of biliary pancreatitis, initial and second set of pre-intervention biochemical markers (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin), initial intervention chosen (EUS, MRCP, ERCP), presence of stone on computed tomography scan (if available), whether stone/sludge was found on initial EUS, MRCP, or ERCP, and occurrence of post-ERCP adverse events (if performed). Discrepancies were resolved by consensus.

From this information, we classified subjects' risk of choledocholithiasis according to ASGE guidelines based on initial laboratory values, and then again at the time of their subsequent laboratory evaluation (in the event liver chemistries were analyzed again before EUS, MRCP, or ERCP). For patients who initially presented to an outside hospital and were subsequently transferred to our institution, the outside facility blood draw was considered the initial laboratory evaluation. For cases in which the ERCP report documented stone(s) or sludge, two investigators (EW, BJE) independently verified the presence of clinically significant choledocholithiasis based on the presence of one or more of the following: (1) clear filling defect on cholangiogram, (2) photograph of stone/sludge within lumen of the duodenum after extraction, and/or (3) language in the body of the endoscopy report implying definitive visualization of stone/sludge by the endoscopist (ie, not "doubtful," "possible," "insignificant," "minimal" sludge, etc.) For the purpose of this study, we considered both stones and sludge as choledocholithiasis because both entities can cause clinically significant pain, cholangitis, and pancreatitis.

The performance characteristics (sensitivity, specificity, and accuracy) of the ASGE high-probability classification upon initial presentation and the second set of liver tests, and the performance characteristics of the individual component predictors were calculated. The association between each component predictor included in the ASGE guidelines and the presence of choledocholithiasis was explored by performing a multivariable logistic regression analysis including choledocholithiasis (sludge or stone) as the dependent variable and the following independent variables: age, gender, bilirubin > 4 mg/dL, bilirubin 1.8–4 mg/dL, visible stone in the bile duct on trans-abdominal US, dilated bile duct on US, and presence of gallstone pancreatitis. We also included an independent variable defined as a

decrease in both ALT and total bilirubin by 30% each between the first and second set of liver chemistries. All statistical analyses were performed using the STATA 12 statistical package (StataCorp LP, College Station, Tex).

Results

498 patients were included in this study. One hundred and seventy-nine (35.9%) met ASGE high-probability criteria at the time of presentation. Of these, 99 (55.3%) had a stone or sludge on subsequent MRCP, EUS, or ERCP and 80 (44.7%) had a negative evaluation. Among cases not meeting high-probability criteria on presentation, 208 (65.2%) had no stone/sludge on subsequent diagnostic study, and 111 (34.8%) had stone/sludge present. Taken together, as applied to our cohort, the guidelines had an accuracy of 62.1% (47.4% sensitivity; 73% specificity) [Table 1].

Impact of laboratory trends

480 (96.6%) of the 498 subjects had a second set of labs drawn before their confirmatory study (EUS, MRCP or ERCP), either intentionally or due to a delay in intervention. Among the 171 (of 480) patients who were high-probability on initial presentation, 132 (77.2%) maintained this classification based on their second set of biochemical markers. Conversely, 39 high-probability patients (22.8%) were re-classified as intermediate or low probability based on the second set of lab tests. Among the 310 patients at intermediate or low probability for choledocholithiasis on initial presentation, 31 (10%) were re-classified as high-probability based on repeat laboratory values (279 remained in the intermediate or low-probability group).

Among the 161 patients classified as high-probability based on the second set of labs, 93 (57.8%) had a stone or sludge, whereas 68 (42.2%) had no choledocholithiasis. Of the 317 patients who were classified as intermediate or low probability based on the second set of labs (due to a drop in total bilirubin), 209 (65.9%) had no stone or sludge, whereas 108 (34.1%) did have choledocholithiasis. In sum, as applied to our cohort at the time of repeat laboratory evaluation, the guidelines had a sensitivity of 46.3% and a specificity of 75.5% in detecting choledocholithiasis. [Table 1] The accuracy of the guidelines, when applied to the second set of biochemical markers, was 63.2%.

Performance characteristics of very strong predictors: bilirubin > 4 mg/dL

113 patients (23.1%) had a bilirubin >4 mg/dL on initial presentation. Of these, 63 (55.8%) had a stone or sludge present on EUS, MRCP, or ERCP, whereas 50 (44.3%) did not have choledocholithiasis. Conversely, 381 patients (76.9%) had a bilirubin ≤ 4 mg/dL on presentation. Of these, 235 (61.7%) had no stone or sludge, whereas 146 (38.3%) had choledocholithiasis. When applied to our cohort, a bilirubin >4 mg/dL on initial presentation had a sensitivity of 30.1% and a specificity of 82.5% in detecting choledocholithiasis [Table 2]. The overall accuracy of this predictor was 60.3%.

Focusing on the second set of liver function tests, 85 patients had a bilirubin >4 mg/dL. Forty-five of these (53%) had choledocholithiasis and 40 (47%) had a negative evaluation. Three hundred and ninety-five patients had a bilirubin ≤ 4 mg/dL on the second set of labs,

238 (60.3%) of whom had no stone or sludge and 157 (39.8%) did. When applied to our cohort, a bilirubin >4 mg/dL on the second set of labs had a sensitivity of 22.3% and a specificity of 85.6% in detecting choledocholithiasis. The overall accuracy of this predictor when applied on the second set of biochemical markers was 59.0%.

Performance characteristic of very strong predictors: CBD stone present on trans-abdominal ultrasound

65 patients (13%) had a CBD stone present on initial ultrasound. Of these, 46 (70.8%) had a stone or sludge present on subsequent confirmatory examination, whereas 19 (29.2%) did not. Conversely, 438 patients (87%) had no stone present on US. Of these, 273 (62.3%) had no stone or sludge on EUS, MRCP, or ERCP, and 165 (37.7%) did have choledocholithiasis. When applied to our cohort, the presence of a stone on trans-abdominal ultrasound had a sensitivity of 21.8%, a specificity of 93.5%, and an accuracy of 63.4% in diagnosing choledocholithiasis.

Significance of a decrease in both ALT and total bilirubin by 30% or more

In 72 subjects, both the ALT and the total bilirubin each decreased by 30% or more between the first and second set of labs. Of these subjects, 28 (38.9%) had choledocholithiasis, whereas 44 (61.1%) had no stone or sludge. Conversely, in 438 patients, ALT and total bilirubin did not each decrease by 30% or more on the second set of labs. Of these, 251 (57.3%) had no stone or sludge, and 187 (42.7%) did. When applied to our cohort, the presence of a decreased ALT and total bilirubin by at least 30% by the second set of labs had an overall accuracy of 45.3% for predicting a spontaneously passed stone.

Significance of biliary pancreatitis

Of the subset of patients who had suspected choledocholithiasis because of the presence of biliary pancreatitis, 34.8% (57 of 164) met high-probability criteria on presentation (based on having either one very strong predictor, or both strong predictors), and 107 were at intermediate or low-probability. Among the high-probability patients with biliary pancreatitis, 25 (43.9%) had a stone/sludge present, and 32 (56.1%) did not. Of the 106 low and intermediate-probability patients with biliary pancreatitis, 71 (67%) had no stone and 35 (33%) had a stone present. When applied to our cohort of patients with biliary pancreatitis the guidelines had a sensitivity of 41.7% and a specificity of 68.9% in diagnosing choledocholithiasis, with an overall accuracy of 58.9%.

Of the 164 patients with biliary pancreatitis, 156 (95.1%) had a second set of labs drawn before the confirmatory diagnostic test, either intentionally or due to a delay in intervention. Forty-eight (31.4%) were classified as high-probability based on the second set of biochemical markers. Of these 48 high-probability patients, 22 (45.8%) had choledocholithiasis, and 26 (54.2%) did not. Of the 108 low or intermediate-probability patients, 74 (68.5%) had a stone and 34 (31.5%) had no stone. In sum, among patients with biliary pancreatitis, the guidelines had a sensitivity of 39.3%, a specificity of 74.0%, and an accuracy of 61.5% when applied to the second set of laboratory tests.

Logistic regression model

Multivariable logistic regression analysis revealed that a bilirubin > 4 mg/dL (odds ratio (OR) 2.03; 95% confidence interval (CI), 1.27–3.24), bilirubin 1.8–4 mg/dL (OR 1.97; 95% CI, 1.31–2.98), and a stone visualized on ultrasound (OR 5.47; 95% CI, 2.69–11.09) were independently associated with the presence of a stone on ERCP, EUS, or MRCP.

Discussion

The optimal approach to suspected choledocholithiasis remains uncertain. Ideally, clinical risk stratification tools would allow highly accurate selection of patients appropriate for ERCP, limiting the risks of this procedure to those who are most likely to benefit and minimizing healthcare resource utilization. However, as we hypothesized, the accuracy of existing risk-stratification guidelines was low in our cohort of patients (62.1%; sensitivity 46.7% and specificity 73%), leading to overutilization of ERCP. Laboratory trends did not appear to improve accuracy, and among guideline predictors, only visualization of a stone on trans-abdominal US—which occurred in only 13% of patients—was predictive enough to potentially drive clinical decision-making.

These findings are generally congruent with the results of a prior validation study of the ASGE guidelines, wherein 71.5% of high-probability patients and 41% of intermediate probability patients were confirmed to have a bile duct stone during ERCP.⁹ In this study, the presence of one very strong or both strong predictors increased the odds of choledocholithiasis, but could not obviate the need for non-invasive testing. The impact of laboratory trends was not assessed.

Ultimately, the acceptable rate of negative ERCP in patients with suspected choledocholithiasis is a value judgment based on the pre-test probability of a stone, the risks of the procedure, and the availability, cost, and performance characteristics of alternative diagnostic modalities. Indeed, the ASGE guidelines themselves define "high probability" as having a greater than 50% likelihood of persistent choledocholithiasis. However, given the morbidity and costs associated with ERCP-related adverse events, the risk of occasional catastrophic outcomes, the growing medico-legal perception that ERCP should be a near-exclusively therapeutic intervention, and the increasing availability of EUS and MRCP, it is reasonable to strive toward the elimination of most (>80%) diagnostic ERCP. Toward this goal, the 50% likelihood threshold for defining a patient as "high-risk" should be revised and continued research focusing on the development of highly accurate and reliable risk-stratification strategies is justified.

One potential strategy is the routine use of EUS before ERCP in cases of suspected choledocholithiasis without signs of cholangitis.¹⁰ A focused endosonographic evaluation of the bile duct is highly accurate, extremely safe, and can be accomplished in a short period of time while the patient is in the endoscopy suite for possible ERCP. A pilot randomized controlled trial comparing an EUS-guided management strategy to up-front ERCP in all-comers with suspected choledocholithiasis (but no concern for cholangitis) revealed that the EUS strategy reduced procedure time and adverse events without compromising stone-related outcomes.¹¹ In this study, the characteristics of patients who were and were not

converted to ERCP on the basis of the EUS examination did not differ, consistent with our finding that clinical and laboratory predictors (with the possible exception of a stone seen during trans-abdominal ultrasound) are inadequate to accurately select patients for ERCP. If the findings of our study are reproduced in other settings, additional research focused on the EUS-guided strategy may be warranted.

Novel predictive modeling techniques may also hold promise. In a recent study of 291 patients undergoing ERCP for suspected choledocholithiasis, an artificial neural network model was found to accurately predict 92.3% of patients with positive findings on ERCP and 69.6% of patients with negative findings on ERCP (AUROC 0.884; 95% CI, 0.831–0.938; $p < 0.001$).¹² This, as well as other machine learning techniques, warrant further investigation in this context.

There are a number of important limitations to our study. First, given the retrospective design, there was significant variation in the timing of repeat laboratory testing although in the large majority of cases, at least 6 hours passed between the first two laboratory assessments. Therefore, we were unable to assess for a threshold length of time after which laboratory trends become more informative, for example after the period in which liver chemistries are affected by hydration. Second, we did not evaluate the impact of clinical symptoms on the likelihood of choledocholithiasis, although in practice, symptom resolution is confounded by administration of pain medication and the presence of concurrent pancreatitis. Third, to maximize internal validity we restricted our study sample to patients who did not have any concurrent biliary conditions or pathologies that often confound evaluation in clinical practice. Therefore, our findings are best generalized to healthy, non-cirrhotic patients without a history of cholecystectomy or strong suspicion of alternate pancreaticobiliary conditions. Finally, there may exist selection bias relating to not capturing patients who were triaged directly to cholecystectomy with IOC and therefore never underwent pre-operative EUS, ERCP, or MRCP. However, at our center, IOC as a primary method of evaluating for choledocholithiasis is very infrequently performed due to local surgeon practices. Thus, we expect this potential source of bias to have a very limited impact on the study results.

In summary, when applied to our patient cohort, existing guidelines demonstrated suboptimal diagnostic accuracy, likely resulting in overuse of ERCP. Contrary to our hypothesis, incorporation of laboratory trends did not appear to improve performance of the guidelines within the limitations of the study. Additional research focusing on alternative diagnostic strategies, especially involving early use of EUS, appears justified.

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Acronyms

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASGE	American Society for Gastrointestinal Endoscopy
CBD	common bile duct
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
MRCP	magnetic resonance cholangiopancreatography
IOC	intraoperative cholangiography

Table 1

Sensitivity, specificity, PPV, and NPV of ASGE guidelines in accurately predicting presence of persistent choledocholithiasis using first and second set of biochemical markers

	Sensitivity	Specificity	PPV	NPV
First Set Labs	.474	.730	.563	.654
Second Set Labs	.463	.755	.578	.659

Table 2

Sensitivity, specificity, PPV, and NPV of various clinical and biochemical predictors in accurately predicting presence of persistent choledocholithiasis

	Sensitivity	Specificity	PPV	NPV
Bili >4 mg/dL (first set)	.301	.825	.558	.603
Bili >4 mg/dL (second set)	.223	.856	.529	.603
Stone on ultrasound	.218	.935	.708	.623
Decrease in ALT and bilirubin >30% each on second set labs	.870	.150	.427	.611
Biliary pancreatitis	.417	.689	.439	.670