Antibiotic prophylaxis and post-procedure infectious complications in endoscopic retrograde cholangio-pancreatography with peroral cholangioscopy

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ABSTRACT

Background and study aims Single-operator peroral cholangioscopy (SOC) has gained increasing attention in modern biliary and pancreatic therapy and diagnosis. This procedure has shown higher rates of infectious complications than conventional endoscopic retrograde cholangiopancreatography (ERCP); therefore, many guidelines recommend antibiotic prophylaxis (AP). However, whether AP administration decreases infectious or overall adverse events (AEs) has been little studied. We aimed to study whether AP affects post-procedure infectious or overall AEs in ERCP with SOC.

Patients and methods We collected data from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks). Of the 124,921 extracted ERCP procedures performed between 2008 and 2021, 1,605 included SOC and represented the study population. Exclusion criteria were incomplete 30-day follow-up, ongoing antibiotic use, and procedures with unspecified indication. Type and dose of antibiotics were not reported. Post-procedure infectious complications and AEs at 30-day follow-up were the main outcomes.

Results AP was administered to 1,307 patients (81.4%). In this group, 3.4% of the patients had infectious complications compared with 3.7% in the non-AP group. The overall AE rates in the AP and non-AP groups were 14.6% and 15.2%, respectively. The incidence of cholangitis was 3.1% in the AP group and 3.4% in the non-AP group. Using multivariable analysis, both infectious complications (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.54–1.57) and AEs (OR 0.87, 95% CI 0.65–1.16) remained unaffected by AP administration.

Conclusions No reduction in infectious complication rates and AEs was seen with AP administration for SOC. The continued need for AP in SOC remains uncertain.

Introduction

The use of peroral cholangioscopy (POC) when performing endoscopic retrograde cholangiopancreatography (ERCP) has emerged as a state-of-the-art technique for the diagnosis of biliary strictures and treatment of difficult bile duct stones [1, 2]. Evidence on the effects of antibiotic prophylaxis (AP) during this procedure is scarce, but it is recommended in most guidelines [3]. POC allows direct visualization of the bile duct, and its utilization is expanding. The technology of the single-operator cholangioscopy (SOC) system (SpyGlass, Boston Scientific Corporation, Natick, Massachusetts, United States), has further developed throughout the years since its launch in 2005 [1, 2]. Peroral cholangioscopy is associated with a higher risk of adverse events (AEs) than ERCP alone. This is particularly recognized for post-ERCP cholangitis (PEC) [4, 5], with a reported incidence of 1% to 12.2% [4, 5, 6, 7, 8, 9, 10, 11, 12, 13] compared to 0.5% to 3% for regular ERCP [3, 14, 15]. The underlying mechanism for the higher PEC rates in SOC points to the added therapeutic nature of the procedure [9]. Biopsy sampling [10], lithotripsy, older age, and previous stent placement have all been reported to be risk factors [12] for developing PEC. In addition, it has been hypothesized that the active use of water irrigation during SOC is an underlying mechanism [4]. PEC is the principal theoretically preventable outcome through the use of AP, but it has only been studied previously in small series [9, 13].

There is a lack of larger studies examining the effectiveness of AP when performing ERCP with SOC in preventing AEs in general and PEC in particular. As such, current evidence for the use of AP in SOC is limited. This study sought to examine whether AP administration affects post-procedure infectious or overall AEs in patients undergoing ERCP with SOC.

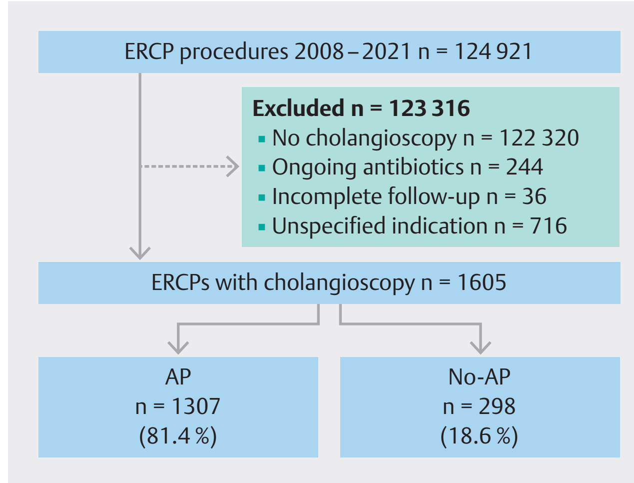
Patients and methods

Study design and population

We conducted a nationwide cohort study using patient data from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks). All ERCPs with SOC procedures performed between January 1, 2008 and December 31, 2021 were evaluated for inclusion in this study (▶ **Fig. 1**). The procedures included were performed at 22 different centers or clinics. Four tertiary referral centers accounted for 68.7% of the procedures performed. The exclusion criteria were incomplete 30-day follow-up and ongoing antibiotic therapy. The primary outcome was post-procedure infectious complications and the secondary outcome was overall AEs. Previous techniques for cholangioscopy using two operators, such as "mother-baby," were not included in the current study. In 2015, a new digital SOC (DSOC) system was introduced (SpyGlass DS, Boston Scientific Corporation, Natick, Massachusetts, United States). Most likely, procedures using this new system were included in the data, but the exact type of system was not recorded in the registry.

The GallRiks registry

The GallRiks registry (https://www.ucr.uu.se/gallriks) was founded by the Swedish Surgical Society in 2005. This registry is supported by the Swedish National Board of Health and Welfare. During the study period, the number of participating hospitals continually increased, and the registry now has national coverage of more than 90% of ERCP procedures performed in Sweden. The GallRiks registry currently contains data on more than 130,000 ERCP procedures and is well validated, with an accuracy of more than 97% compared with medical records [16]. The registry is continually assessed by independent reviewers who control the conformity between the registry and randomly



▶ **Fig. 1** Inclusion/exclusion of procedures. ERCP, endoscopic retrograde cholangiopancreatography; AP, antibiotic prophylaxis.

selected medical records, thereby guaranteeing the accuracy of the data. The variables in the registry are prospectively recorded online by the investigator at the time of the procedure. Thereafter, the questionnaire is closed, which prohibits the investigator from making any future changes. There is the possibility of registering more than 100 variables in each ERCP procedure, where many are mandatory. After 30 days, a follow-up is performed on the patient records by an appointed coordinator at each participating hospital, where AEs are noted and entered into the registry.

Definition of variables

For clarification and use in analysis, variables from the GallRiks registry are defined below.

The administration of antibiotics during the SOC procedure was registered in GallRiks, with options for entering whether it was administered as prophylaxis, whether the patient was on therapy, or whether no antibiotics were administered. However, the type and dose of antibiotics were not recorded in the registry.

Age was dichotomized according to the median age of 65 years. Different models for age were explored using quartiles and optimal binning.

The American Society of Anesthesiologists (ASA) classification was dichotomized into ASA 1–2 or ASA 3–4.

Cannulation of the bile duct or pancreatic duct was recorded based on the intention of cannulation and was presented at baseline. However, the actual cannulation differed from the intention, which means that cannulation of the bile duct could also encompass manipulation of the pancreatic duct and vice versa. Hence, any unintended interference with either duct was classified as the cannulation category of both.

Precut sphincterotomy is a technique for achieving access to the bile duct through an incision made before a guidewire can be inserted into the duct, typically by a needle sphincterotome. Procedures with both a precut and a regular sphincterotomy were allocated as precut performed.

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The duration of the procedure was dichotomized into more or less than 71 minutes using optimal binning methods in relation to AP.

Single-operator peroral cholangioscopy was defined as the introduction of an additional endoscope through the working channel of the duodenoscope, through which direct endoscopic visualization of the bile or pancreatic duct can be achieved. It was not possible to determine from the variable in the registry whether the former SOC or the latter DSOC system was used.

Post-procedure infectious complication was defined by combining PEC and abscess formation at the 30-day follow-up. The basis was that both were theoretically affected by AP.

The overall AEs included any AE registered at the 30-day follow-up, such as abscess, cholangitis, perforation, pancreatitis, bleeding, bile leakage, postoperative antibiotic treatment, readmission, admission to the Intensive Care Unit, blood transfusion, drainage, or any reintervention.

Statistical analysis

Categorical variables are expressed as absolute category frequencies with percentages, and Pearson's chi-squared test was used for the analysis. Continuous variables are presented as mean ± standard deviation (SD), and Student's *t*-test was used for calculations.

Logistic regression analysis was used to compute odds ratios (ORs) expressed together with 95% confidence intervals (CIs) to assess the association between AP and main outcomes. Directed acyclic graphs (DAGs) were created to explore possible cause-effect relationships among the variables in the model and to avoid adjustment of collider variables [17]. All variables were tested using univariable and multivariable approach. Logistic model assumptions and any interfering correlations were checked using Spearman's correlation to avoid multicollinearity. Outliers were monitored using linear regression and Mahalanobis distance. As the use of DAGs were used for model exploration, we implemented backward stepwise regression according to Hosmer's purposeful selection model, with the elimination of variables with an alpha >0.1. Model characteristics were overseen at each step. Age and sex were predetermined to be included in all models. A two-sided P <0.05 was considered statistically significant.

JMP version 15.2.0 (64-bit, SAS Institute, Cary, North Carolina, United States) and IBM SPSS Statistics version 29.0.0.0(241) (IBM Corp, Armonk, New York, United States) were used for statistical analysis.

Ethics

This study was approved by the Swedish Ethical Review Authority (DNR: 2021–05952–02).

Results

Between 2008 and 2021, 124,921 ERCP procedures were entered into the GallRiks registry. After exclusion, 1,605 procedures remained in which SOC was performed. AP was used in 81.4% of procedures (▶ **Fig. 1**). Patients receiving AP were

▶ **Table 1** Baseline characteristics.

Total n = 1,605	AP n = 1,307 (81.4%)	No AP n = 298 (18.6%)
Sex, n (%)		
▪ female	557 (42.6)	133 (44.6)
▪ male	750 (57.4)	165 (55.4)
Age, mean (SD), years	57.9 (17.4)	60.1 (17.2)
ASA, n (%)		
▪ 1–2	1,008 (77.1)	226 (75.8)
▪ 3–4	299 (22.9)	72 (24.2)
Indication, n (%)		
▪ PSC	478 (36.5)	89 (29.9)
▪ Malignancy	309 (23.6)	81 (27.2)
▪ CBD stone	296 (22.6)	80 (26.8)
▪ Chronic pancreatitis	112 (8.6)	28 (9.4)
▪ Jaundice/cholangitis	96 (7.3)	18 (6.0)
▪ Benign stenosis	16 (1.2)	2 (0.7)
Cannulation intention, n (%)		
▪ Bile duct	1,217 (93.2)	267 (89.6)
▪ Pancreatic duct	71 (5.4)	27 (9.1)
▪ Both	18 (1.4)	4 (1.3)
High center, n (%)	957 (73.2)	146 (49.0)
Low center, n (%)	350 (26.8)	152 (51.0)

AP, antibiotic prophylaxis; SD, standard deviation; ASA, American Society of Anesthesiologists classification; PSC, primary sclerosing cholangitis; CBD, common bile duct.

▶ **Table 2** Adverse events at 30-day follow-up.

Total n = 1,605	AP n = 1,307 (81.4%)	No AP n = 298 (18.6%)
Overall, n (%)		
▪ Infectious complications	44 (3.4)	11 (3.7)
▪ Overall adverse events	186 (14.6)	45 (15.2)
Specific, n (%)		
▪ Cholangitis (PEC)	39 (3.1)	10 (3.4)
▪ Infection with abscess	5 (0.4)	1 (0.3)
▪ Pancreatitis	84 (6.6)	15 (5.1)
▪ Perforation	10 (0.8)	3 (1.0)
▪ Bleeding	14 (1.0)	3 (1.0)
▪ Antibiotic treatment	95 (7.4)	21 (7.1)

AP, antibiotic prophylaxis; PEC, post-ERCP cholangitis.

▶ **Table 3** Associations between patient-, indication-, and procedure-related risk variables and post-procedure infectious complications.

	Number cases (%)/controls	Univariable OR (95% CI)	Multivariable OR (95% CI)
Antibiotic prophylaxis			
▪ Yes	44 (3.6)/1,232	0.93 (0.47–1.82)	0.94 (0.48–1.85)
▪ No	11 (3.7)/286	1.00 (Ref)	1.00 (Ref)
Sex			
▪ Female	26 (3.8)/651	1.19 (0.70–2.05)	1.17 (0.68–2.01)
▪ Male	29 (3.2)/867	1.00 (Ref)	1.00 (Ref)
Age, years			
▪ >64	28 (4.0)/671	1.31 (0.76–2.24)	1.32 (0.76–2.27)
▪ ≤64	27 (3.1)/846	1.00 (Ref)	1.00 (Ref)
ASA			
▪ 3–4	18 (5.0)/342	1.67 (0.94–2.98)	–
▪ 1–2	37 (3.1)/1,176	1.00 (Ref)	1.00 (Ref)
Cannulation			
▪ PD only	1 (0.8)/131	0.22 (0.03–1.58)	0.19 (0.03–1.14)
▪ Both	14 (5.1)/261	1.51 (0.81–2.81)	–
▪ BD only	40 (3.4)/1,126	1.00 (Ref)	1.00 (Ref)
Precut sphincterotomy			
▪ Yes	1 (3.6)/27	1.02 (0.14–7.67)	–
▪ No	54 (3.5)/1,491	1.00 (Ref)	1.00 (Ref)
Procedure time, minutes			
▪ >71	36 (3.4)/1,014	0.94 (0.54–1.66)	–
▪ ≤71	19 (3.6)/504	1.00 (Ref)	1.00 (Ref)
Indication PSC			
▪ Yes	20 (3.6)/536	1.05 (0.60–1.83)	–
▪ No	35 (3.4)/982	1.00 (Ref)	1.00 (Ref)
Low center			
▪ Yes	22 (4.4)/477	1.46 (0.84–2.52)	–
▪ No	33 (3.1)/1,041	1.00 (Ref)	1.00 (Ref)

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists classification; PD, pancreatic duct; BD, bile duct; PSC, primary sclerosing cholangitis.

slightly younger (57.9 vs. 60.1 years) and more likely to be treated at a tertiary referral center (73.2% vs. 26.8%). In addition, primary sclerosing cholangitis was more common in the AP group (36.5% vs. 29.9%). Baseline characteristics are shown in ▶ **Table 1**.

When AP was administered during SOC, infectious complications occurred in 3.4% of cases compared with 3.7% when AP was not administered. The incidence rate of cholangitis was 3.1% in the AP group compared with 3.4% in the non-AP group (▶ **Table 2**). AEs were observed in 14.6% of patients in the AP group compared with 15.2% in the non-AP group (▶ **Table 2**). For comparison, using the full cohort of ERCP procedures excluding ongoing antibiotics and primary sclerosing cholangitis indication, an average of 2.9% of cases had post-procedure infectious complications and 2.1% had PEC.

In the analysis of possible associative risk factors, a borderline lower OR (OR 0.19, 95% CI 0.03–1.14) for post-procedure infectious complications was observed when only the pancreatic duct was cannulated during SOC (▶ **Table 3**). On the other hand, the OR for AE increased when both ducts were cannulated (OR 1.49, 95% CI 1.06–2.10) (▶ **Table 4**). When SOC was performed in female patients, there was a 44% increase in the

▶ **Table 4** Associations between patient-, indication-, and procedure-related risk variables and overall adverse events.

	Number cases (%)/controls	**Univariable OR (95% CI)**	**Multivariable OR (95% CI)**
Antibiotic prophylaxis			
▪ Yes	186 (14.6)/1,090	0.96 (0.67–1.36)	0.96 (0.67–1.36)
▪ No	45 (15.2)/252	1.00 (Ref)	1.00 (Ref)
Sex			
▪ Female	117 (17.3)/560	1.43 (1.08–1.90)	1.44 (1.08–1.90)
▪ Male	114 (12.7)/782	1.00 (Ref)	1.00 (Ref)
Age, years			
▪ >64	99 (14.2)/600	0.93 (0.70–1.23)	0.89 (0.67–1.18)
▪ ≤64	132 (15.1)/741	1.00 (Ref)	1.00 (Ref)
ASA			
▪ 3–4	57 (15.8)/303	1.12 (0.81–1.56)	–
▪ 1–2	174 (14.3)/1,039	1.00 (Ref)	1.00 (Ref)
Cannulation			
▪ PD only	22 (16.7)/110	1.30 (0.80–2.11)	–
▪ Both	53 (19.3)/222	**1.55 (1.10–2.18)**	**1.49 (1.06–2.10)**
▪ BD only	156 (13.4)/1,010	1.00 (Ref)	1.00 (Ref)
Precut sphincterotomy			
▪ Yes	3 (10.7)/25	0.69 (0.21–2.32)	–
▪ No	228 (14.8)/1,317	1.00 (Ref)	1.00 (Ref)
Procedure time, minutes			
▪ >71	164 (15.6)/886	1.26 (0.93–1.71)	–
▪ ≤71	67 (12.8)/456	1.00 (Ref)	1.00 (Ref)
Indication PSC			
▪ Yes	81 (14.6)/475	0.99 (0.74–1.32)	–
▪ No	150 (14.7)/867	1.00 (Ref)	1.00 (Ref)
Low center			
▪ Yes	80 (16.0)/419	1.17 (0.87–1.57)	–
▪ No	151 (14.1)/923	1.00 (Ref)	1.00 (Ref)

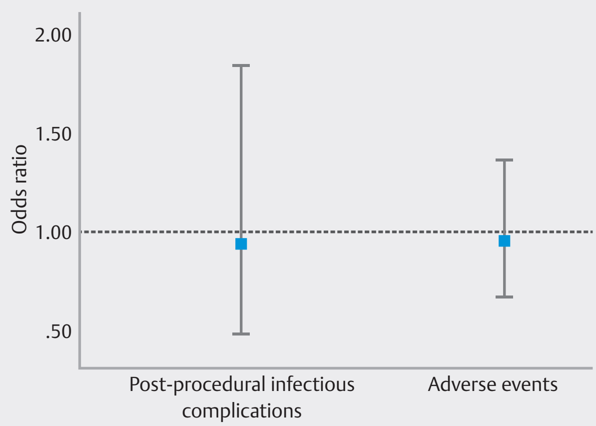
OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists classification; PD, pancreatic duct; BD, bile duct; PSC, primary sclerosing cholangitis

odds of AE compared with males (OR 1.44, 95% CI 1.08–1.90) (▶ **Table 4**).

Both the primary outcome of infectious complications (OR 0.94, 95% CI 0.48–1.85) and the outcome of AEs (OR 0.96, 95% CI 0.67–1.36) (▶ **Table 3** and ▶ **Table 4**) remained had no association with AP after adjustment. The results are shown in ▶ **Fig. 2**.

Discussion

We found no evidence that the use of AP for ERCP performed with SOC reduced the incidence of infectious or overall AEs. To our knowledge, no previous study has directly compared AP and SOC, and a cohort of this magnitude has not been previously reported. Although the majority of procedures included were from tertiary referral centers, the cohort still represents a true national coverage of SOC procedures conducted. Our results call into question the routine use of AP, but the issue may still be unclear.



▶ **Fig. 2** Adjusted odds ratios with 95% confidence intervals for the antibiotic prophylaxis group compared with the non-antibiotic prophylaxis group.

The theoretically possible positive beneficial outcome of AP administration would be a reduction in the number of infectious complications such as PEC or abscess formation. Our results, with infectious complication rates of 3.4% for AP and 3.7% for non-AP and, more comparatively, a PEC rate of 3.1% and 3.4%, are lower than previously reported. Studies by Thosani et al. [12] and Othman et al. [10], which lay the basis for the guidelines for the routine administration of AP in SOC, have reported PEC rates of 9.7% and 7%, respectively. However, in these two series, all the patients received AP. Another study by Lenze et al. [8] also reported a high PEC rate of 7.5% despite AP use. In contrast, Sethi et al. [4] and Almadi et al. [6] reported PEC rates of 1%. Laleman et al. [7] found a PEC incidence rate of 5.9% in their series, despite antibiotics. They also conducted an aggregated review of the reported literature with a PEC rate of 4.4% for 843 patients. Clearly, the reported rate of PEC is dispersed, and possible explanations include the heterogeneity of different study settings, patient cohorts, and possibly the way the outcome was defined and reported. One possible explanation for the varied incidence rate of PEC for SOC could be that SOC procedures have been more or less therapeutic. Several reports indicate a higher risk of PEC with additional invasive or therapeutic actions, such as biopsies or lithotripsy [9, 10, 12].

Although the concept that ERCP with SOC has a higher incidence rate of PEC than ERCP alone has been widely reported. However, only the studies by Sethi et al. and Lübbe et al. made explicit comparisons [4, 5]. Similarly, the incidence rate of PEC in series with regular ERCP varies considerably, making direct comparison difficult [3, 14, 15]. However, the incidence of PEC for SOC has been consistently reported to be higher than that for ERCP alone [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. Our results of 3.1% and 3.4% are slightly higher than the variable reported PEC rate of 0.5% to 3% for regular ERCP [3], which may call into question the extent to which ERCP with SOC increases the risk of PEC. However, using our entire cohort with some exclusions, we found an average PEC rate of 2.1% with ERCP. Also, Sethi et al. [4] also found a much higher PEC rate for ERCP with SOC of 1% compared with 0.2% with regular ERCP. Furthermore, Lübbe et al. had a large control group of 35,944 regular ERCPs; the PEC rate in this group was 2.7% compared with 4.4% for procedures with cholangioscopy [5], and a large series of regular ERCPs by Andriulli et al. showed a PEC rate of 1.4% [14].

In most previous studies involving SOC, prophylactic antibiotics were administered to all patients or were not reported. Only two previous studies have compared AP administration. First, in contrast to our results, Turowski et al. [13] found a considerably different PEC rate of 1% with AP compared with 12.8% without AP administration. However, in their retrospective cohort, this result was not adjusted for risk factors. In contrast, and partially in agreement with our results, Minami et al. [9] found no beneficial effect of AP administration on the outcome of PEC in a cohort of 183 patients. However, they concluded that AP administration is beneficial in reducing fever, with the explanation that SOC may cause transient bacteremia due to the water irrigation required during the procedure.

We identified a significant association between AE and female sex. This is most likely due to the well-known higher risk of post-ERCP pancreatitis in female patients [3]. Higher odds of AEs also were found for cannulation of both ducts, possibly indicating a more difficult procedure.

Our study has several limitations that could hamper the results. First, due to its retrospective design, selection bias was unavoidable. Patients who received AP may indeed have been administered AP for certain reasons that could not be addressed by statistical adjustment. In the GallRiks registry, there are no defined criteria for the administration of AP, nor are the type or dose registered. AP could have been administered when a particularly difficult SOC procedure was performed, or it could simply be hospital policy that all patients at that particular center receive AP regardless of the complexity of the ERCP procedure. In addition, we were unable to adjust our multivariable model for previously shown risk factors for PEC, including biopsy, dilatation, stent placement, and lithotripsy. We were also unable to adjust for the type of cholangioscope used. Although our results found no evidence that AP reduces post-procedure infectious complications or AEs, this does not mean that there is evidence against its use. Due to the higher risk of PEC in these patients, with some series reporting a significantly higher incidence of this outcome, it is sufficient to say that AP may still play a role.

Conclusions

In patients undergoing ERCP with SOC, we found no evidence that AP reduced post-procedure infectious complications or overall AEs. However, whether AP is required as a routine practice for SOC remains unclear.

Conflict of Interest

The authors declare that they have no conflict of interest.

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