

**The role of prophylactic antibiotics in
Endoscopic Retrograde Cholangio-
Pancreatography (ERCP) when
cannulation fails**

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Abstract

Introduction: Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is the endoscopic modality with the highest complication-rate, occurring in 5-15% of the procedures regarding overall perioperative complications. Some of the adverse events are related to infections, like cholangitis or abscesses, and could theoretically be avoided through prophylactic antibiotics administered adjacent to the ERCP-procedure. The challenge consists of identifying the patients gaining the most positive effects from antibiotic prophylaxis. It has been postulated that ERCPs where cannulation fails should benefit more from antibiotic prophylaxis, hereby diminishing complication rates without accordingly increasing negative side effects from antibiotics.

The aim of this study is to evaluate the effects on the adverse event rate after an ERCP in a subset of patients where cannulation fails in relation to administration of prophylactic antibiotics

Methods: Data were extracted from the nationwide web-based Gallriks (The Swedish National Quality Register for Gallstone Surgery and ERCP) which is a Swedish nationwide web-based quality registry where both cholecystectomies and ERCP procedures are registered and complications reported. Data on several parameters regarding the ERCP, like antibiotic administration and perioperative complications are entered into the registry.

All ERCP procedures from patients registered in GallRiks from 2006 to 2018 were included in the study (n=96 818) but patients with missing data (n=2 017) were excluded. The subset of procedures where cannulation failed consisted of all in all of 6 058 ERCP procedures (6.4%). Other procedures that were excluded from the subset consisted of entries where the patient had ongoing antibiotic therapy (n=1 062). The data were then analyzed using multivariate analysis to determine the relationship between antibiotic prophylaxis and perioperative complications in patients where cannulation failed.

Results: Antibiotic prophylaxis versus no prophylaxis, in ERCPs where cannulation failed, showed a statistically significant difference in postoperative complications, 289 of 2 124 (13.6%) when prophylactic antibiotics were given, compared to 490 out of 2 872 (17.1%) (p=0.0008) if not given. This was also the case in postoperative abscess formation where 17 out of 2 124 (0.8%) in the prophylaxis group developed an abscess and 41 out of 2 872 (1.4%) in the non-prophylaxis group (p=0.04).

However, there was no statistically significant difference when comparing cholangitis, intraoperative complications or total perioperative complication rate. In cholangitis the frequency was 1.3 % (27 out of 2 124) in the prophylaxis group and 1.7 % (50 out of 2 872) in the non-prophylaxis group with a nonsignificant result ($p= 0.18$). In the intraoperative complications group the complication rate was 7.7% (163 out of 2 124) in the group receiving antibiotic prophylaxis and 6.3% (181 out of 2 872) when no antibiotic prophylaxis was given ($p=0.0591$). Finally, regarding the total perioperative complication rate the frequency was 19.3% (411 out of 2 124) in the group who received prophylaxis compared to the non-treated group which had a complication rate of 21.4 % (616 out of 2 872; $p=0.068$). *e*

The Odds Ratio (OR) for postoperative complications within 30 days of the procedure in the group that received prophylaxis was 0.76 (95 % CI 0.68-0.93) when corrected for age, sex, precut sphincterotomy, pancreatic cannulation, procedure time and indication (Table 2). Even though it was a secondary outcome, correcting for different indications during the multivariate analysis showed that ERCP with failed cannulation with the indication of jaundice and malignancy had significantly lower risk as compared to common bile duct stones. When ERCP procedures with the indication of jaundice was compared to CBDS the OR was 0.55 (95% CI; 0.45-0.68) and for malignancy the OR was 0.58 (95% CI; 0.47-0.73).

Conclusion: The main results of this study indicate that antibiotic prophylaxis may be beneficial in diminishing overall postoperative complication rates after ERCP in cases of failed cannulation as well as in decreasing the risk of postoperative abscess formation. However, comparing our results to other studies on antibiotic prophylaxis in unselected ERCP-procedures where cannulation was successful, the effect of antibiotic prophylaxis in patients where cannulation fails does not seem to add any significantly benefit. Therefore, even though antibiotic prophylaxis seems to decrease the rate of postoperative complications in patients with failed cannulation, the strategy of antibiotic prophylaxis should not differ from the standard strategy when cannulation is successful. Further research is needed to find out if antibiotic prophylaxis could be beneficial in ERCP-procedures where cannulation is difficult depending on the indication of the procedure, especially in cases where the indication for the procedure is CBDS since our results indicate the greatest risk for adverse events in this group.

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Introduction

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is the endoscopic modality with the highest complication-rates, occurring in 5-15% of the procedures regarding overall adverse events(1, 2). Some of the adverse events are related to infections, like cholangitis or abscesses, and could theoretically be avoided through prophylactic antibiotics administered adjacent to the ERCP-procedure. However, the risk of postoperative infectious complications is low and a high number of patients needs to be given prophylaxis to avoid one complication, but it also increases the risk of inducing negative side-effects for the individual patient. The challenge consists of indentifying the patients gaining the most benefit from antibiotic prophylaxis, where failed cannulation represents such a group (3-6).

It has been postulated that ERCPs where cannulation fails should benefit more from antibiotic prophylaxis, hereby diminishing complication rates without accordingly increasing the risk of negative side effects from antibiotics (7). This thesis has been confirmed in a Cochrane review on the issue of antibiotic prophylaxis in ERCP (5) advocating this policy in cases of unrevealed biliary stasis, however the effect was not convincing in uncomplicated ERCP procedures and the rationale for using antibiotic prophylaxis in routine ERCP procedures could not be replicated in another meta-analysis on the subject (6) which concludes that further studies are needed on the subject of prophylactic antibiotics in ERCPs where cannulation fails.

In one study it was shown that the incidence of post-ERCP pancreatitis was higher in cases of difficult cannulations (8) and in selected cases where patients undergoing ERCP were classified as high risk, having conditions such as sclerosing cholangitis and malignant stenosis, intraductal antibiotic prophylaxis seemed to decrease the rate of postoperative infectious complications(9). Failed cannulation has even been shown through multivariate analysis to be an independent risk factor for increased overall complication rate during ERCP (10).

Aim

The aim of this study is to evaluate the effects on adverse events after ERCP with failed cannulation in relation to administration of prophylactic antibiotics assessed from a nationwide registry (GallRiks) with data on several parameters regarding the ERCP, like failed cannulation, antibiotic administration and postoperative complications. The main outcome is to evaluate whether antibiotic prophylaxis affects overall postoperative morbidity and mortality and especially make a subgroup analysis on infectious complications.

Material and methods

Study population

The study population in our report is composed of all patients registered in GallRiks from 2006 to 2018 undergoing ERCP where cannulation was unsuccessful which occurred in approximately 8% of the procedures according to previous data (11) and has been shown to significantly increase the rate of postoperative complications (8).

In this study we have focused on a sub-group of patients where a failed attempt at cannulation has been registered in GallRiks, to evaluate the effect of antibiotic prophylaxis with the main outcome of intra- and postoperative complications in general and specifically infectious complications like cholangitis and abscess formation.

Methods

This is a population-based registry study classified as a retrospective nested cohort study. We have used the Swedish Registry for Gallstone Surgery and ERCP, GallRiks, as a source of data. GallRiks is a nationwide registry that has previously been described by Enochsson et al (11). It is a Swedish web-based quality registry where both cholecystectomies and ERCP procedures are registered and complications are reported (11). The database is continuously validated and post-ERCP complications are registered for up to thirty days by a local coordinator at each participating hospital. Nationwide coverage of ERCP procedures has been reported to be greater than 90%. (11)

The main quality measures in the registry in regard to ERCP are deep cannulation of the bile duct, frequency of pancreatitis and other intra- and postoperative complications (11). Antibiotic prophylaxis is also registered as a separate entry, however neither type nor dosage is reported.

Data were extracted to determine the relationship between antibiotic prophylaxis and the outcome of intra- and postoperative complications. Entries with a successful cannulation, missing data or ongoing antibiotic therapy were excluded.

Validation of the registry is performed on a regular basis, where medical records of 25 randomly selected patients from each unit are scrutinized externally, by independent observers and compared to entries in the registry and has been found accurate in more than 95% (11) The registry is supported by the Swedish National Board of Health and Welfare.

Values are given as mean \pm standard deviation (SD), or median with interquartile range (IQR). For categorical values absolute numbers and the distribution in percentages on available data are given. The factors affecting the postoperative adverse events were analyzed through multivariable logistic regression modelling and all variables were tested uni- and multivariably according to the model of Hosmer's purposeful selection (18). These models were tested for effect modification, multicollinearity and then assessed using the Hosmer-Lemeshow goodness of fit test. The effect of the variables is presented as odds ratios (OR) and 95% confidence intervals (CI).

Age was dichotomized to over or under 70 years and the indications of the ERCP procedures were divided into four categories (common bile duct stone, obstructive jaundice, malignancy or others). Gender was dichotomized between men and women. The procedure time was dichotomized to over and under forty minutes, the amount of time representing the median operation time in the study population. We also compensated in the model for the factors if a precut sphincterotomy was performed or not and if a pancreatic cannulation occurred or not during the ERCP procedure. The outcome was presented as percentage of overall postoperative complications, but a subgroup analysis of the septic complications was also performed (i.e. cholangitis or abscesses).

The JMP version 14.2.0 (SAS Institute, Cary, NC, USA) was used for the statistical analysis.

The population consisted of all ERCP procedures from patients registered from 2006 to 2018 (n=96 818). 2 017 procedures were excluded based on missing data. Of the entries left (n=94 801) our selected subgroup, where there was a registered failed cannulation, contained all in all 6 058 entries. Finally, 1 062 ERCPs were excluded, since they had an on-going therapy with antibiotics at the time of the ERCP, as the study aimed to investigate prophylaxis only. For a detailed flow chart of how exclusion was done see Figure 1.

Ethics

The study protocol was submitted to the regional ethics board and approved before the initiation of data collection from GallRiks and the study was approved by the Swedish Research Ethics Committee, Sweden (EPN). Diary number 2019-03717.

Time table

The data was extracted from GallRiks during autumn 2019 and analysed by an external statistician. During the first half of 2020 we wrote this paper on the subject at hand.

Financial disclosures

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- Lars Enochsson, MD, Professor, Department of Surgical and Perioperative Sciences, University of Umeå
- Greger Olsson, MD, PhD, Department of Research and development, Region Kronoberg.

Results

After exclusion for successful cannulation, on-going antibiotic therapy or missing data a study population of 4 996 patients remained. Out of these procedures 2 124 (42.5%) obtained antibiotic prophylaxis whereas the rest had none (n=2 872 (57.5%)). For an overview of patient inclusion and exclusion see figure 1.

The overall intraoperative complication rate was 7.7% (163 out of 2 124) in the group receiving antibiotic prophylaxis and 6.3% (181 out of 2 872) when no antibiotic prophylaxis was given ($p=0.0591$).

Postoperative complications within 30 days after the procedure occurred in 289 of 2 124 (13.6%) when prophylactic antibiotics were given and in 490 out of 2 872 (17.1%) where the patient did not receive prophylaxis ($p=0.0008$). The Odds Ratio (OR) for postoperative complications in the group that received prophylaxis was 0.76 (95% CI 0.65-0.89) when corrected for age, gender and the indication of ERCP, procedure time, pancreatic cannulation, precut sphincterotomy and dichotomized based on age. (Table 2).

When comparing the perioperative complication rates (intra- and postoperative complication rate pooled together) of 19.3% (411 out of 2 124) in the group who received prophylaxis to the non-prophylaxis group which had a complication rate of 21.4 % (616 out of 2 872; $p=0.068$).

Cholangitis was a relatively rare complication, with a rate of 1.3 % (27 out of 2 124) in the prophylaxis group and 1.7 % (50 out of 2 872) in the non-prophylaxis group ($p= 0.18$) (Table 3).

However, in the group of patients who postoperatively developed an abscess, 17 out of 2 124 (0.8%) in the prophylaxis group and 41 out of 2 872 (1.4%) in the non-prophylaxis group, antibiotic prophylaxis did seem to make a difference ($p=0.04$). (Table 3).

When correcting for different indications of ERCP with failed cannulation during the multivariate analysis two indications for the ERCP procedure, jaundice and malignancy, seemed to correspond to a significantly lower risk of postoperative complications when compared to common bile duct

stone as the reference (CBDS) (Table 2). When ERCP procedures with the indication of jaundice was compared to CBDS the OR was 0.55 (95% CI; 0.45-0.68) and 0.58 (95% CI; 0.47-0.73) for malignancy respectively.

Discussion

The main results of this study indicate that antibiotic prophylaxis may be beneficial in diminishing overall postoperative complication rates after ERCP in cases of failed cannulation as well as in decreasing the risk of postoperative abscess formation. The overall postoperative complication rate was 13.6% in the prophylaxis group versus 17.1% in the non-prophylaxis group, this represents an OR of 0.76 (95%CI 0.65-0.89) when corrected for age, gender, the indication of ERCP, procedure time, pancreatic cannulation and precut sphincterotomy (Table 2) in the multivariate analysis. This corresponds to a number needed to treat (NNT) of 29 patients that requires to be treated to avoid one postoperative complication. When comparing the rate of postoperatively abscess formation in the prophylaxis group (0.8%) with the non-prophylaxis group (1.4%), we also achieved a significant difference, however these numerical figures are small, and the NNT 159 which makes it questionable to use antibiotics prophylactically, for this as the only reason.

There are some weaknesses in our study. Firstly, this is neither a prospective study nor is it a randomized controlled trial. Hereby, the results may be harbouring confounding factors, although we tried to compensate for this in the multivariate analysis. But there may still exist factors not compensated for in the analysis, which can lead to confounding by indication through the case mix within the registry data. The operator can simply be more prone to administer antibiotics when the ERCP was difficult, which may skew the results. This could possibly contribute to diluting the potential beneficial effect of antibiotic prophylaxis since an unknown number of patients were probably treated with antibiotics without a proper indication.

Through the selection process patients were excluded in three steps. The first step of exclusion consisted of entries with missing data and corresponded to 2.0% of the initial patient population. In the second step of exclusion all the cases with successful cannulation were excluded, all in all they made up 91.7% of patients of the original population. This was done on purpose, as the aim of this study was to study the effect of antibiotic prophylaxis in cases with failed cannulation only. In the last step of exclusion all the patients with ongoing antibiotic therapy were excluded, these are usually the most complicated ERCP-cases. They made up a share of our selected subgroup of patients with failed cannulation corresponding to 17.5% (n=1 062). This last exclusion might have an effect on the results which would favor the non-prophylaxis group. Therefore, one might

speculate that these cases with ongoing antibiotic therapy would show a potential greater advantage of antibiotic prophylaxis in complicated cases with failed cannulation if they had not already been started on antibiotic treatment and therefore had to be excluded. Excluding these patients may have undermined the interpretation of the results on the potential advantage of antibiotic prophylaxis in cases with failed cannulation.

Also, the type or dosage of antibiotic prophylaxis is not entered into the registry, since this is the way GallRiks is constructed. This makes the registry to quite a blunt instrument and also the data are put into the registry retrospectively, sometimes after a longer time period increasing the risk of recall bias.

One strength of the study is the size of the study population which is huge, almost five thousand patients, which diminishes the risk of random errors. The fact that almost all ERCPs performed in Sweden are registered in GallRiks (>90%) almost abolishes the risk of selection bias as only a few percent of all ERCP procedures are missed in the registry. The accuracy of the data in the registry entries is also high with a correctness of more than 95% (Enochsson et al. 2013). The study population also represents a cross sectional population of ERCPs performed in Sweden in every clinical practice, making it more representative than ERCPs performed at highly specialized endoscopic centra, where more complex procedures are performed. This makes the result more applicable in general clinical practice.

The reason why intraoperative complication rate is not affected by antibiotic prophylaxis is probably that the intraoperative complications are not usually related to infectious complications. Intraoperative complications usually consist of bleeding, perforation or extravasation of contrast media.

Our results imply that there is some benefit to antibiotic prophylaxis in procedures where cannulation failed in overall postoperative complication frequency and abscess formation. However, if you take into consideration the NNT, one could argue that only the NNT in overall postoperative complication rate seems to motivate antibiotic prophylaxis in a societal and economic perspective. Though if you compare our results in an unselected patient population undergoing uncomplicated ERCP-procedures (Olsson et al. 2015) it does not seem like there is an additional benefit in our study subgroup (procedures with failed cannulation). Therefore, these results could also be interpreted as, that no difference should be made in the strategy of how

prophylactic antibiotics are administered, depending on if cannulation fails or not, as no better effect in diminishing complication rates was seen in this subgroup of failed cannulations, compared to overall ERCP (failed and successful cannulation) (3). In the paper by Olsson et al antibiotic prophylaxis was compared against a non-prophylaxis group in all ERCP cases in a nationwide population-based study and the effect of antibiotic prophylaxis does not seem to be significantly different from our results (OR = 0.74; 95% CI: 0.69-0.79). The OR in this study is even lower when compared to our results which would at least indicate that antibiotic prophylaxis in our subgroup of patients adds no additional benefit in reducing postoperative complications compared to all ERCPS where cannulation is successful.

Other papers have studied the role of antibiotic prophylaxis in reducing post-ERCP complications. In one recent meta-analysis on the effect of antibiotic prophylaxis in reducing post-ERCP cholangitis, they found no significant benefit of antibiotic prophylaxis (6). However, they concluded that more studies on the effect of prophylaxis antibiotics are needed in cases with predicted incomplete biliary drainage, where our study indicates that there is no difference between ERCPS where cannulation is successful and those where it fails.

Conflicting results were reported in another systematic analysis (5), where the authors found that antibiotic prophylaxis seemed to reduce bacteremia and cholangitis in elective ERCP-procedures. They also acknowledged that in uncomplicated cases the effect of antibiotic prophylaxis seemed less evident. Their conclusion was in line with that of Bai (6) that further studies are needed to determine the role of antibiotic prophylaxis in patients with expected biliary obstruction, where our study results contributes by showing no difference in the reduction of complications between ERCPS with or without successful cannulation, when antibiotics are given.

There are several original articles with a randomized controlled design on the effect of antibiotics to reduce postoperative complications in ERCP (12-17), however, most of them are old, many containing only a few cases and with conflicting results. Although not randomized, this makes our findings very relevant representing the only recent study results on this subject.

In the multivariate analysis the data indicate that there is significantly less risk associated with ERCP where cannulation fails if the indication is either malignancy or jaundice as compared to CBDS. This contradicts the general opinion in ERCP, where jaundice usually is considered to strengthen the indication for using prophylactic antibiotic (7).

Our data and results would motivate a conclusion that antibiotic prophylaxis regimens in ERCP procedures overall should not be altered in ERCP-procedures with difficulties of cannulation even though the results indicate a significant difference in overall postoperative complication frequency and rate. However, surprisingly during multivariate analysis it seems that the risk of complications is significantly less in ERCP where cannulation fails if the indication is jaundice or malignancy compared to CBDS. This warrants further research on ERCP with failed cannulation where the indication for the procedure is CBDS.

Figures and tables

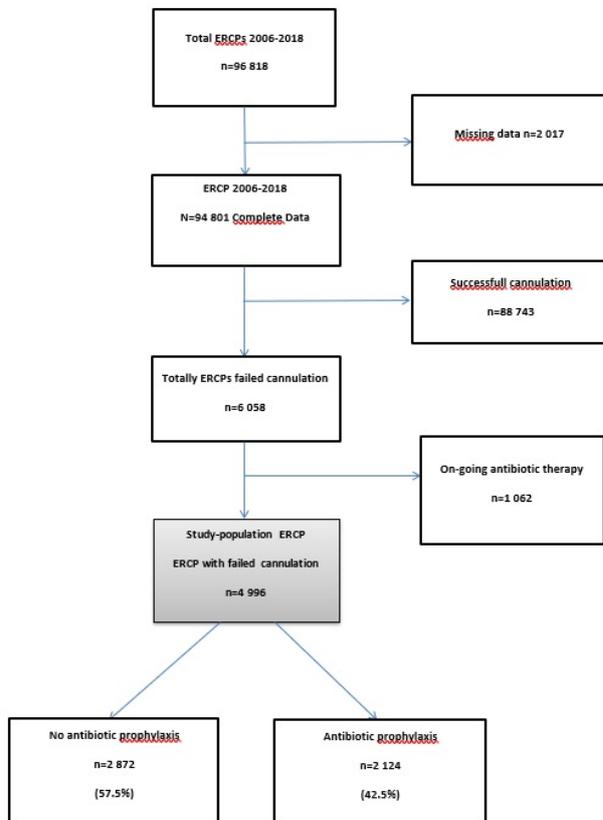


Figure 1. Flow chart of procedures excluded and selection of the study population. The three boxes to the right represent excluded patients.

Table 1. Demography

	Antibiotic prophylaxis	No antibiotic prophylaxis	
	n (%)	n (%)	p
Female	1 092 (51.4)	1 494 (52.0)	0.671
Male	1 032 (48.6)	1 378 (48.0)	
ASA 1-2	1 326 (62.4)	1 766 (61.5)	0.499
ASA 3-5	798 (37.6)	1106 (38.5)	
Urgent	1 428 (67.2)	1 937 (67.4)	0.874
Scheduled	696 (32.8)	935 (32.6)	
	Mean	Mean	p
Age	70.1	70.3	0.574

Demography of our study population.

Table 2.

	Numbers			Univariate Analysis		Multivariate analysis	
	Cases	Controls	%	OR	95% CI	OR	95% CI
Age							
>70 years	369	2399	13.3	1	Reference	1	Reference
<70 years	407	1817	18.3	1.46	(1.25-1.70)	1.41	(1.21-1.65)
Sex							
Female	417	2169	16.1	1	Reference	1	Reference
Male	362	2048	15.0	0.92	(0.79-1.07)	0.91	(0.78-1.07)
Antibiotics							
No	490	2382	17.1	1	Reference	1	Reference
Yes	289	1835	13.6	0.77	(0.65-0.90)	0.76	(0.65-0.89)
Comorbidity							
ASA 1-2	518	2574	16.8	1	Reference	1	Reference
ASA 3-5	261	1643	13.7	0.79	(0.67-0.93)	0.97	(0.81-1.15)
Indications							
CBDS	237	906	20.7	1	Reference	1	Reference
Jaundice	212	1 458	12.7	0,56	(0,45-0,68)	0.55	(0.45-0,68)
Malignancy	152	1 025	12.9	0.57	(0.45-0.71)	0.58	(0.47-0.73)
Other	178	828	17.7	0.82	(0.66-1.02)	0.80	(0.64-1.00)
Pancreatic cannulation							
No	444	2 864	13.4	1	Reference	1	Reference
Yes	335	1 353	19.8	1.60	(1.37-1.87)	1.40	(1.19-1.65)
Procedure time							
<40 min	259	1 940	11.8	1	Reference	1	Reference
≥40 min	520	2 276	18.6	1.71	(1.46-2.01)	1.58	(1.34-1.87)
Precut							
No	502	3 008	14.3	1	Reference	1	Reference
Yes	277	1 209	18.6	1.37	(1.17-1.61)	1.23	(1.04-1.46)

The parameters corrected for in multivariate analysis.

Table 3.

	Numbers			p	Univariate Analysis		Multivariate analysis	
	Cases	Controls	%		OR	95% CI	OR	95% CI
Cholangitis								
No antibiotics	50	2 872	1.7	p=0.18	1	Reference	1	Reference
Antibiotics	27	2 124	1.3		0.73	(0.45-1.16)	0.74	(0.46-1.18)
Abscess								
No antibiotics	41	2 872	1.4	p=0.04	1	Reference	1	Reference
Antibiotics	17	2 872	0.8		0.56	(0.32-0.98)	0.54	(0.31-0.96)

Characteristics of cases with cholangitis and postoperative abscess formation in patients comparing prophylaxis with non-prophylaxis groups.

Table 4.

Complications	Antibiotic prophylaxis		No Antibiotic prophylaxis		p
	n=2 124	%	n=2 872	%	
Overall compl.	289	13.6	490	17.1	p<0.001
Bleeding	34	1.6	41	1.4	0,618
Pancreatitis	101	4.8	131	4.6	0,748
Cholangitis	27	1.3	50	1.7	0,183
Abscess	17	0.8	41	1.4	0,041
Perforation	31	1.5	34	1.2	0,395

Complication frequencies in prophylactic group and the non-prophylactic group respectively.

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