Are prophylactic antibiotics indicated for endoscopic retrograde cholangiopancreatography?

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A research report submitted to the Department of Surgery, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree Master of Medicine in Surgery.

Johannesburg, 2010

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine in Surgery, to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.

Martin Brand

day of 20

PREFACE

My interest in the use of antibiotics in general was sparked during the three years that I worked in the Republic of Ireland, where antibiotic resistance is becoming a significant medical conundrum. I began reading information behind antibiotic protocols and soon realized that the evidence base for many of our so called routines is quite poor. On return to South Africa, during a ward round where we were discussing a patient for endoscopic retrograde cholangiopancreaticogram, the question was raised, does he need prophylactic antibiotics? Recently qualified consultants often related stories of how it was their responsibility that each and every patient going down to the scope room had to have their drip up, connected to that essential vaculitre containing an antibiotic. If not, they were liable to be hung, drawn and quartered at the next available opportunity by their consultant. No one questioned why, it was assumed to be the right thing to do. This led me to ask the question *why?*

I would like to thank, and express my appreciation to:

My supervisor, **Professor Damon Bizos,** for helping in formulating the initial question, and then providing the motivation to pursue the final answer with regular words of encouragement. For making time available to read the various drafts, and offering positive critique.

Our department's statistician and research co-coordinator, **Dr Geoff Candy**, for advice regarding the statistics involved, and for his encouragement in achieving the final product.

A friend, and colleague, **Dr Peter O'Farrell**, for his vital assistance in collecting and analyzing all the trials revealed by our extensive literature search.

The Cochrane collaboration, specifically **Taryn Young** of the South African Cochrane Group, and **Dimitrinka Nikolova** of the Hepatobiliary Group, for their endless time, advice and patience with my efforts in producing the meta-analysis.

Finally, my wife, **Liezl**, for her understanding and patience during this time consuming task.

LIST OF ABBREVIATIONS

ERCP	endoscopic retrograde cholangiopancreatography
>	greater than
CRP	C-reactive protein
IU/l	international units per litre blood
ASGE	American Society of Gastro-Enterology
NHS	National Health Services (United Kingdom)
CI	Confidence Interval
NNT	Number needed to treat

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ABSTRACT

Background

The use of prophylactic antibiotics before endoscopic retrograde cholangiopancreatography (ERCP) is recommended by all major international gastroenterological societies, especially in the presence of an obstructed biliary system. Their use is intended to decrease or eliminate the incidence of complications following the procedure, namely cholangitis, cholecystitis, septicaemia, and pancreatitis.

Objectives

To assess the benefits and harms of antibiotics before elective ERCP in patients without evidence of acute or chronic cholecystitis, or acute or chronic cholangitis, or severe acute pancreatitis.

Data collection and analysis

We audited South African endoscopists who perform ERCPs in the form of a questionnaire.

The review was conducted according to the recommendations of The Cochrane Collaboration as well as the Cochrane Hepato-Biliary Group. Review Manager 5 was used employing fixed-effect and random-effects model meta-analyses. Only randomised clinical trials were included in the analyses, irrespective of blinding, language, or publication status. Participants were patients that underwent elective ERCP that were not on antibiotics, without evidence of acute or chronic cholecystitis, cholangitis, or severe acute pancreatitis before the procedure. We compared patients that received prophylactic antibiotics before the procedure with patients that were given placebo or no intervention before the procedure.

Results

The audit revealed that no specific protocols were being implemented in South Africa, and there was a marked difference in the practice between surgical and medical gastroenterologists, with surgeons using antibiotics more often. There was also a wide spectrum of antibiotic types and combinations being used.

Nine randomised clinical trials (1573 patients) were included into the review analyses. The majority of the trials had risks of bias. When all patients providing data for a certain outcome were included, the fixed-effect meta-analyses significantly favoured the use of prophylactic antibiotics in preventing cholangitis (relative risk (RR) 0.54, 95% CI 0.33 to 0.91), septicaemia (RR 0.35, 95% CI 0.11 to 1.11), bacteriaemia (RR 0.50, 95% CI 0.33 to 0.78), and pancreatitis (RR 0.54, 95% CI 0.29 to 1.00). In random-effects meta- analyses, only the effect on bacteriaemia remained significant. Overall mortality was not reduced (RR 1.33,

95% CI 0.32 to 5.44). If one selects patients in whom the ERCP resolved the biliary obstruction at the first procedure, there seem to be no significant benefit in using prophylactic antibiotics to prevent cholangitis (RR 0.98, 95% CI 0.35 to 2.69, only three trials).

Conclusions

Prophylactic antibiotics reduce bacteriaemia and seem to prevent cholangitis and septicaemia in patients undergoing elective ERCP. In the subgroup of patients with uncomplicated ERCP, the effect of antibiotics may be less evident. Further research is required to determine whether antibiotics can be given during or after an ERCP if it becomes apparent that biliary obstruction cannot be relieved during that procedure.

CHAPTER 1

1. INTRODUCTION

1.1 Literature review

Endoscopic retrograde cholangiopancreatography (ERCP) involves cannulation of the ampulla of Vater. It is a modality that combines endoscopic and fluoroscopic techniques. Through the endoscope, the physician can see the inside of the stomach and duodenum, and can inject dye into the ducts in the biliary tree and pancreas via the ampulla of Vater. Using fluoroscopy the ductal anatomy can be seen on x-rays.

Thus it has diagnostic as well as therapeutic capabilities, although the number of non-therapeutic ERCP's is decreasing [1]. Diagnostically it is used in the investigation of jaundice, assessment of the bile ducts before or after cholecystectomy, in the investigation of abdominal pain thought to be of pancreatic origin, and in diagnosing sphincter of Oddi dysfunction. Therapeutic benefits include evacuation of ductal gallstones and the palliation of biliary and pancreatic strictures [2]. Endoscopic sphincterotomy, stone extraction, and stenting are not without complications. The most widely recognized of these include bleeding (0.7-2%), perforation (0.3-0.6%), pancreatitis (7%), cholangitis (1%) and cholecystitis (0.2-0.5%) of patients. Procedure-related mortality is between 0.3% to 1% of patients [3,4]. In addition ERCP induces a transient bacterobilia and bacteraemia [5].

A review of international guidelines regarding the use of prophylactic antibiotics with ERCP show that the routine use of antimicrobials is recommended for biliary obstruction and pancreatic pseudocysts. Whether antibiotics, such as ciprofloxacin, clindamycine, gentamicin, cefuroxime, and others reduce the incidence of cholangitis could not be proven in several studies [5-7]. It has also been postulated that antibiotics will reduce the incidence of pancreatitis following ERCP [8].

A recent review of the literature highlighted a meta-analysis of seven trials, concluding that there was no benefit in prescribing prophylactic antibiotics before commencing ERCP[9].

1.2 Hypothesis

There is no difference in the incidence of infective complications following ERCP in patients receiving prophylactic antibiotics compared to those not receiving antibiotics.

1.3 Objectives

To determine South African ERCP endoscopist prophylactic antibiotic practice, followed by an assessment of the level of evidence in the literature through a meta-analysis.

1.4 Aims

To determine whether or not we should be using routine prophylactic antibiotics with every ERCP, or on an individual patient case scenario, or at all.

CHAPTER 2

2. METHODS OF INVESTIGATION

2.1 Assessment of South African practice

Before commencing the study, and in order to ascertain what the current antibiotic practice is amongst South African endoscopists who perform ERCP's, an anonymous questionnaire was handed out during the annual Hepato-Biliary Association of South Africa meeting in 2008. It was also sent via email to all members of the South African Gastro-Enterology Society. A copy of the questionnaire appears in appendix 1.

2.2 Meta-analysis

The meta-analysis was carried out according to the principles of a Cochrane review, using the suggested statistical software (Revman software). The latter requires that two investigators review the literature. Dr Peter O Farrel and I performed the literature review, and acquisition of copies of all applicable studies.

2.2.1 Outcome measures

Primary outcome measures

- All-cause mortality.
- Acute cholangitis (right upper quadrant pain, pyrexia, and elevated inflammatory markers).
- Septicaemia (positive blood cultures with a systemic inflammatory response).
- Adverse drug events: The International Conference on Harmonisation Guidelines [35] defines adverse events as serious and non-serious. A serious fatal or nonfatal adverse event is any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it. All other adverse events will be considered non-serious. This outcome is specific for antibiotic or placebo-related events.
- Quality of life.

Secondary outcome measures

- Mortality directly attributable to ERCP-induced sepsis.
- Bacteraemia (positive blood cultures with no evidence of a systemic inflammatory response).
- Pancreatitis (a three-fold rise of serum amylase accompanied with abdominal pain).

2.2.2 Format of literature search

Electronic searches

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register*[10], the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 4, 2009), *MEDLINE* (1974 to October 2009), *EMBASE* (1980 to October 2009), *LILACS (1982 to October* 2009*)*, and *Science Citation Index Expanded* (1974 to October 2009)[11] .The search strategies with the time span of the searches are given in Appendix 2.

Conference proceedings

- The Society of American Gastrointestinal and Endoscopic Surgeons annual meeting (2000 to 2008).
- American Society for Gastrointestinal Endoscopy annual meeting (1974 to 2008).
- United European Gastroenterology Week (1992 to 2008).
- British Society of Gastroenterology annual scientific meeting (1980 to 2008).
- Canadian Digestive Diseases Week (1974 to 2008).

Reference list

Reference lists of all studies identified by the above methods were also searched.

2.2.3 Criteria for considering studies for this review

Types of studies

We included randomised clinical trials only, irrespective of blinding, language, or publication status. Quasi-randomised clinical trials, cross-over trials, cohort studies, and case control studies were excluded.

Types of participants

Our meta-analysis included patients that underwent elective ERCP that were not on antibiotics, without evidence of acute or chronic cholecystitis, cholangitis, or severe acute pancreatitis before the procedure.

Types of interventions

Patients given prophylactic antibiotics before the procedure were compared to patients that were given a placebo or no intervention before the procedure. Trials were included regardless of the type, dose, or route of administration of the antibiotic.

2.2.4 Selection of studies and data extraction

Martin Brand (MAB) and Peter O'Farrell (PEF) independently identified trials for inclusion using the criteria specified above, as well as searched the references of these studies for further relevant trials. None of the studies matching the above mentioned criteria were

excluded. No language or publication status restrictions were applied. MAB and PEF independently extracted the following data from identified trials:

- Year and language of publication
- Year of study
- Inclusion and exclusion criteria
- Sample size
- Indication of intervention
- Type, dose, and route of prophylactic antibiotic
- Incidence of complications
- Methodological quality.

MAB and PEF recorded whether the authors of the trials used a sample size calculation, and whether or not they made their analyses using an intention-to-treat principle. The bias risk of each trial was independently assessed. Any unclear or missing information was clarified by contacting the authors of the specific trial. Differences in opinion between the authors extracting data were resolved through discussion.

2.2.5 Assessment of the risk of bias of included trials

Generation of the allocation to treatment group sequence

The sequence generation of trial allocation was described as either Yes adequate/ Unclear/ No inadequate as follows:

- Yes adequate: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.

- Unclear: the trial is described as randomised but the method of sequence generation was not specified.

- No inadequate: the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Yes adequate: allocation was controlled by a central and independent randomisation unit, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.

- Unclear: the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.

- No inadequate: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding

- Yes adequate: the trial was described as double blind and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.

- Unclear: the trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.

- No not performed: the trial was not double blind, so that the allocation was known during the trail.

Incomplete outcome data

- Yes adequate: the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.

- Unclear: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

- No inadequate: the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Yes adequate: pre-defined, or clinically relevant and reasonably expected outcomes are reported on.

- Unclear: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.

- No inadequate: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Any other bias

- Yes adequate: the trial appears to be free of other components that could put it at risk of bias.

- Unclear: the trial may or may not be free of other components that could put it at risk of bias.

- No inadequate: there are other factors in the trial that could put it at risk of bias, eg, no sample size calculation made, early stopping, industry involvement, or an extreme baseline imbalance.

Trials with an adequate generation of allocation sequence, allocation concealment, blinding and handling of incomplete outcome data, with no selective outcome reporting, or other bias risks were considered low-bias risk trials. Trials with one or more unclear or inadequate quality components were considered high-bias risk trials. However, in such a large number of reviews optimal division of trials may not be possible.

2.2.6 Measurement of treatment effect

Dichotomous data were analysed for relative risk ratio (RR) and the absolute effects were measured with the risk differences. Calculation of 95% confidence intervals were done for these measures of effect. Treatment effect was also considered by using available case analysis.

The Mantel-Haenszel method was used for the meta-analysis [12,13]. Results are presented on a forest plot graphic.

2.2.7 Heterogeneity and subgroup analysis

Statistical heterogeneity was tested using the I^2 test [14]and chi-squared test, with a P-value of 0.10 representing statistical significance. If heterogeneity was identified, we considered performing subgroup analyses. Subgroups that were considered included diagnostic compared with therapeutic ERCP's, biliary compared with pancreatic indications for ERCP, different antibiotics, and trials with low bias risk compared to trials with high bias risk (one

or more than one of the components inadequate or unclear). When the results in the fixed-effect and random-effects models did not differ, we reported the fixed-effect model.

2.2.8 Sensitivity analysis

MAB and PEF independently performed sensitivity analyses at the end of the review by examining the trial inclusion criteria, reassessing excluded trials, re-analysing data imputed, and re-analysing data using the Der Simonian and Laird method [15].

2.2.9 Funnel plot

We used a funnel plot to explore bias [16,17]. A linear regression approach described by Egger et al [16] was used to determine the funnel plot asymmetry.

CHAPTER 3

3. RESULTS

3.1 Standard practice of South African endoscopists

Thirty nine endoscopists (22 surgeons, 16 physicians and 1 radiologist) responded to our questionnaire. The majority of these endoscopists had more than six years of experience (30/39) and performed more than 10 ERCP's per month (22/39). Approximately half (19/39) were aware of ERCP antibiotic protocols, either the ASGE or NHS recommendations. Comparisons between surgeons verse other endoscopists in using antibiotics during the various procedures were conducted and the results are shown in table 1 below. 'Always' implied that the endoscopist used antibiotic prophylaxis with each patient, 'selected' with specific indications and 'never' implied no usage of antibiotic prophylaxis.

	SURGEONS (n=22)			PHYSICIANS & RADIOLOGIST (n=16+1)			p-values
ERCP	**Always**	**Selected**	**Never**	**Always**	**Selected**	**Never**	
Diagnostic biliary	14	5	3	2	8	5	0.01
Diagnositic pancreatic	13	6	3	2	4	11	0.0018
Therapeutic biliary	19	2	1	5	10	2	0.012
Therapeutic pancreatic	19	2	1	5	9	3	0.0014

Table1: Audit results

It is clear from the audit results that surgeons are more likely to use antibiotics for any indication of ERCP, compared to other endoscopists. There were no endoscopists that performed sphincter of Oddi pressure studies. The preferred prophylaxis was piperacillin-tazobactam (14/39), followed by gentamicin (8/39), cephalosporins (6/39), ciprofloxacin (4/39) and co-amoxiclavulanic acid (3/39). Thirty endoscopists administered their antibiotic as a single dose before the procedure, 5 preferred a 24 hour course, 3 for 48 hours and 1 gave antibiotics for 5 days. All except three administered the antibiotics intravenously.

3.2 Meta-analysis

3.2.1. Description of Included Studies

Our search strategy identified forty-nine references, nine of which were potentially eligible trials, and all of these trials have been included in this review. Of the forty studies that were not included in our review, thirty three were not placebo controlled trials and compared antibiotic regimes with one another. Five were not randomised control trials and two included patient's that were already on antibiotic treatment for their disease. All the exclusions were based on the title or abstract.

Brandes et al [18] performed their trial in Braunschweig, Germany. One-hundred and eighteen patients were randomised into three groups. One group received no prophylaxis (n = 39), the second received 200 mg oral minocycline (n = 39), the third group received no antibiotics but were kept fasting and had a nasogastric tube placed for 36 hours after the ERCP (n = 40). For the purposes of this review, the two groups that did not receive any antibiotics were combined and assessed as one group.

Byl et al [19] performed their trial in the Erasme Hospital, Brussels, Belgium. Initially 82 patients were randomised, of which 14 were excluded. Grounds for exclusion included two with positive blood cultures before ERCP, three failed cannulations, two were discovered to have cholangitis during the ERCP, two had previous antimicrobial therapy, and five had incorrect drug administration. After the procedure, the patients were divided into two groups. Those that had complete biliary drainage had their treatment discontinued, while those who did not have complete drainage had their antibiotic or placebo administered until the obstruction was relieved by successive ERCP procedures for a maximum of seven days.

Llach et al [5] carried out their trial in Barcelona, Spain. The aim of the trial was to analyse the efficacy of intramuscular clindamycin and gentamicin before ERCP. It was not clear from the publication whether or not the patients that developed cholangitis had undergone a diagnostic or therapeutic ERCP. It was also not clear if biliary obstruction was diagnosed at ERCP, if it was completely relieved.

Lorenz et al [6] performed their trial in Munich, Germany. Patients were included if they had either a biliary or pancreatic obstruction, and were to undergo either an ERCP or percutaneous transhepatic cholangiography (PTC) with drainage. Initially 110 patients were randomised; however, 11 were excluded. Of these, only six had a diagnostic procedure, three failed CBD cannulations, one patient was already on antibiotics, and another patient had clinical evidence of cholangitis before the procedure. There were 86 patients that underwent ERCP alone, 40 in the prophylaxis group, and 46 in the control group. These were the patients that we considered for our review. We excluded the PTC patients.

Niederau et al [20] included patients who were likely to undergo a therapeutic or complicated diagnostic ERCP. The trial took place in Dusseldorf, Germany. Initially 124 patients were recruited, but following randomisation, 24 were excluded. These included 16 patients that only had diagnostic ERCP's, and eight failed procedures. During the follow-up period antibiotics were only given if there was clinical and bacteriological evidence of septic cholangitis. No antibiotic prophylaxis was given to the 33 patients in the control group in whom the biliary obstruction could not be relieved. It was not stated if the complications that occurred in the control group were amongst those patients in whom the biliary obstruction was or was not relieved.

Räty et al [21] aimed at evaluating whether or not antibiotic prophylaxis had any effect on post ERCP pancreatitis versus post ERCP cholangitis. The trial was performed in Tampere,

Finland. A total of 321 patients were randomised; however, six were excluded due to failure in relieving the biliary obstruction, leaving 155 patients in the prophylaxis group and 160 in the control group.

Sauter et al [7] performed their trial in Munich, Germany. A total of 96 patients were recruited, with 100 ERCP's being performed; fifty in the prophylaxis as well as the control groups. It was not stipulated why four patients had to undergo a second ERCP, and if they were in the control or study groups.

Spicak et al [22] undertook a multicentre trial performed in the Czech Republic. Patients were randomised before the ERCP to receive either antibiotic or no treatment, and included into the trial analysis if the obstruction was relieved at the first ERCP.

Van den Hazel et al [8] performed their trial in Amsterdam, Holland. They randomised 562 patients, but 11 were excluded as they met major exclusion criteria. No antibiotic was to be administered as prophylaxis after the procedure. Patients that had been referred to their centre were transferred back to their local hospital for observation and further management after the ERCP. Patients were discharged on the day of the procedure if no abnormality had been found, and no interventions had taken place. After the ERCP the physicians responsible for the patient were asked to record the patient's body temperature until their discharge or for the first 48 hours after the ERCP. Follow-up information was obtained through a telephone interview with the attending physician for the first 2 days after the ERCP. After seven days the patient was contacted telephonically in a structured interview. It was not mentioned how many patients eventually underwent only a diagnostic ERCP without any interventions. Forty-four patients were inadvertently given antibiotics at their local hospitals (16 in the prophylaxis group, and 28 in the placebo group), while 53 patients underwent a second ERCP. All these patients were included in the final analyses, and it is not mentioned how

many of these patients had complications. Nineteen patients had a significant complication during their initial ERCP and were still included in the final statistics. These complications included: seven haemorrhages, six perforations of the common bile ducts, four gastro-intestinal tract perforations, one stent release mechanism failure, and one bradycardia.

Table 2 and Table 3 tabulate the characteristics of included studies.

Study	Cholangitis	Hyperamylasaemia	Pancreatitis
Brandes [18]	Clinical signs not specified	Not applicable	Clinical signs not specified
Byl [19]	Right upper quadrant pain and fever (axillary temp. >38.5 °C)	Not applicable	Not applicable
Llach [5]	Fever (temp. >38°C), increasing jaundice or rising bilirubin level and a positive blood culture	Not applicable	Not applicable
Lorenz [6]	Positive blood culture and two of four criteria: fever, rigor, systemic response (tachycardia), leokocytosis or leukopenia	Not applicable	Not applicable
Niederau [20]	Clinical signs not specified	Not applicable	Not mentioned
Räty [21]	Rising fever over 2 days, increased CRP, leukocyte count and liver function values	Serum amylase > 900IU/L	Clinical findings, serum amylase >900IU/L, increased CRP level and leukocyte count with no signs of cholangitis

Sauter[7]	Clinical signs, fever >38°C and leukocytosis of >10000/mm^3.	Serum amylase >120 IU/L or doubling of pre-ERCP level	Not specified
Spicak [22]	Pyrexia > 38.5°C, with the exclusion of other causes of infection	Protracted pain with a three fold rise in serum amylase	Not applicable
Van den Hazel [8]	Temperature >38°C, if clinical symptoms (right upper quadrant pain or jaundice) were severe enough to commence antibiotics, and no cause of fever outside of the biliary tract was identified	Not applicable	Not applicable

Table 2: Study definitions of cholangitis, hyperamylasaemia, and acute pancreatitis

Study	Male		Female		Age	
	Controls	AB group	Controls	AB	Controls	AB
Brandes [18]	No information supplied					
Byl [19]	21	20	13	14	66.5± 16.3	67.1± 11.6
Llach [5]	28		33		69± 7.6	
Lorenz [6]	51		48		60.6± 19.2	61± 17
Niederau[20]	No information supplied					
Räty [21]	71	61	89	94	63 (60-65)	59 (57-62)
Sauter [7]	43%	53%	57%	47%	57.2± 16	59.3± 14
Spicak [22]	No information supplied					
Van den Hazel [8]	125	122	156	148	66.2± 15.1	67.5± 14.3

Table 3: Study demographics

3.2.2 Risk of Bias of Included Studies

All included trials were randomised controlled trials. Five had adequate generation of allocation sequence [7,8,19,21,22], and four trials had adequate allocation concealment [7,8,19,21].

Only two trials [8,19] were double blind, having both the attending physicians and patients were blinded, and thus the two trials had adequate blinding.

Incomplete outcome data and selective outcomes were reported in all trials but two, where there was not enough information in the text [8,18]. Consequently, it was also not possible to report whether or not there were other sources of bias in these two trials. The remaining seven trials had a low risk of bias in regard to their incomplete outcome data, and all seven trials were free of selective outcome reporting. After considering the risk of bias of all nine trials, we concluded that only Byl et al [19]was a low risk of bias trial. Although Van den Hazel et al [8] had adequate generation of allocation sequence and allocation concealment with blinding, the trial is at high risk of bias due to transgressions in its antibiotic protocol. The

remaining trials also high bias risk due to the fact that they were unblinded. The risk of bias in all trials is illustrated in figure 1 and figure 2.

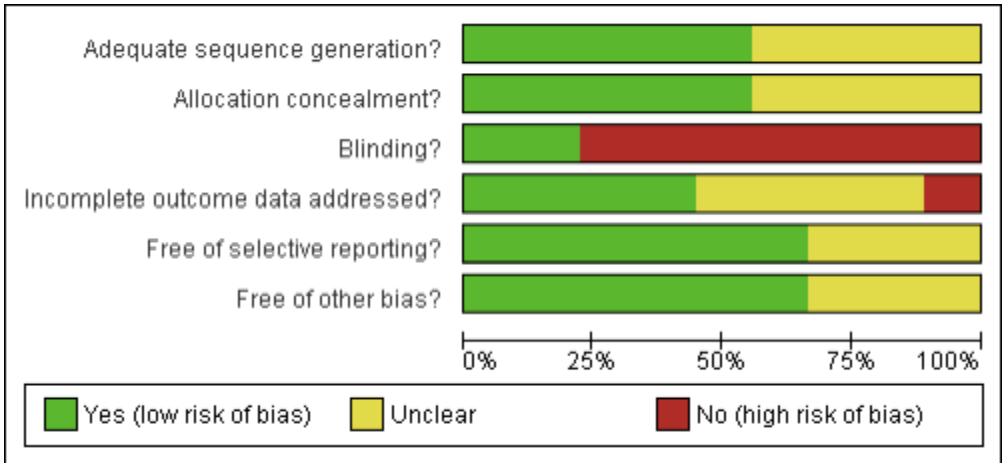

Figure 1: Methodological quality graph: each methodological quality item is presented as a percentage across all included studies.

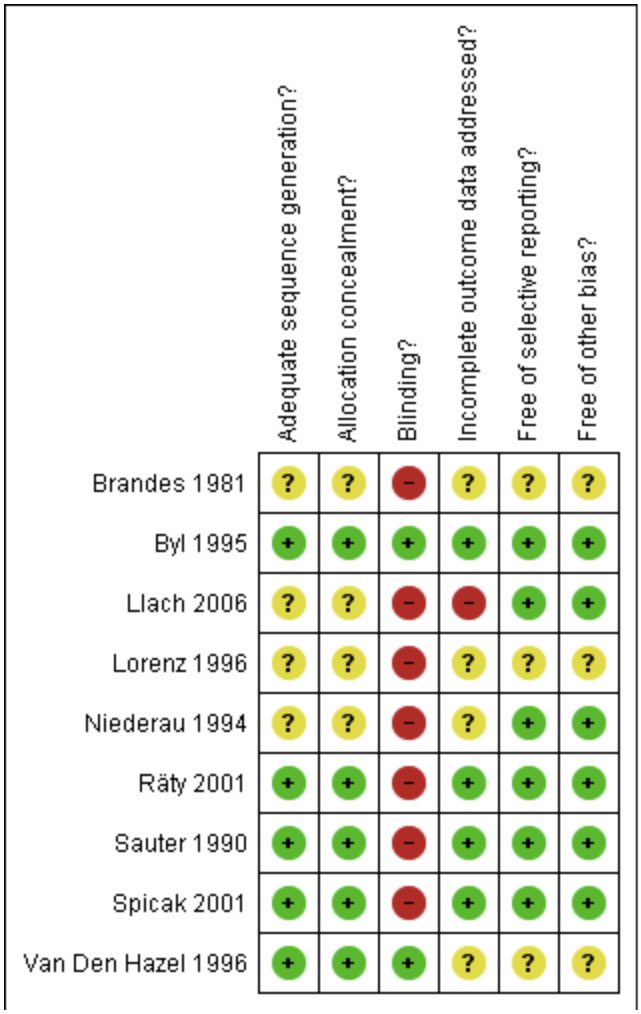

Figure 2: Methodological quality summary

3.2.3 Effects of Interventions

Primary outcome measures

All cause mortality

Nine randomised clinical trials that compared antibiotic prophylaxis to no antibiotic prophylaxis before ERCP were included in the analyses. Total mortality was 7 out of 1294 patients, with four in the antibiotic group, and three in the control group. This gives a relative risk ratio (RR) of 1.29 CI (0.35 to 4.74) P = 0.71, I^2 0% (Figure 3).

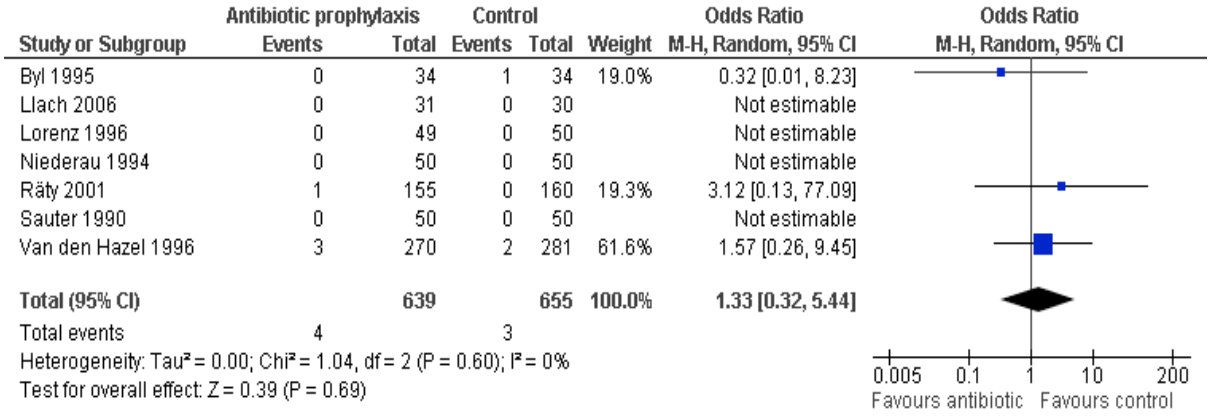

Figure 3

Acute cholangitis (right upper quadrant pain, pyrexia, and elevated inflammatory markers)

Eight trials were included to assess the incidence of cholangitis. This occurred in 61 out of 1474 patients; 21 out of 706 received antibiotics and 40 out of 768 received no antibiotics, with a relative risk ratio of 0.57 CI (0.34 to 0.94) P = 0.02, I^2 0% (Figure 4). When we considered the sub group of patients that underwent a successful first ERCP to relieve a biliary obstruction, we were only able to include information from three studies. There were 20 cases of cholangitis out of 624 patients; 6 out of 302 in the prophylaxis group and 14 out of 322 patients in the control group. This gave a relative risk ratio of 0.98 CI (0.35 to 2.69) P = 0.96, I^2 0% (Figure 5).

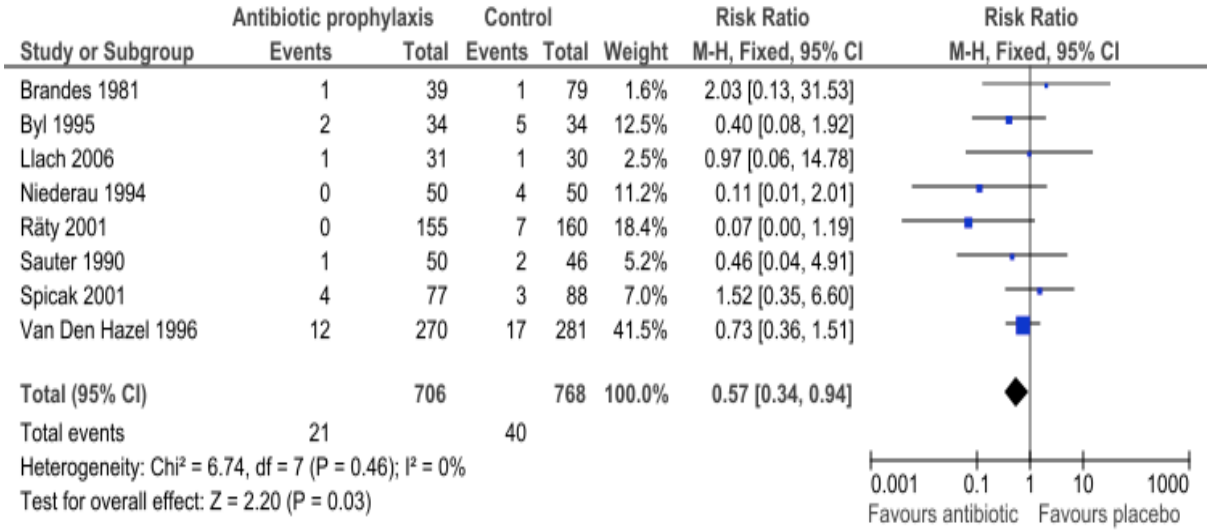

Figure 4

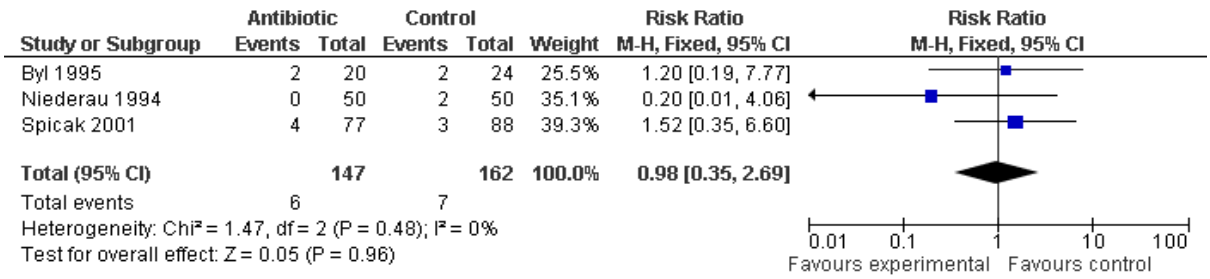

Figure 5

Septicaemia (positive blood cultures with a systemic inflammatory response)

We analysed six trials for the incidence of septicaemia and bacteraemia following ERCP. Septicaemia occurred in 27 of 973 patients, 5 out of 480 in the antibiotic group and 21 out of 493 in the control group. RR is 0.35 CI (0.11 to 1.11) P = 0.07, I^2 24% (Figure 6).

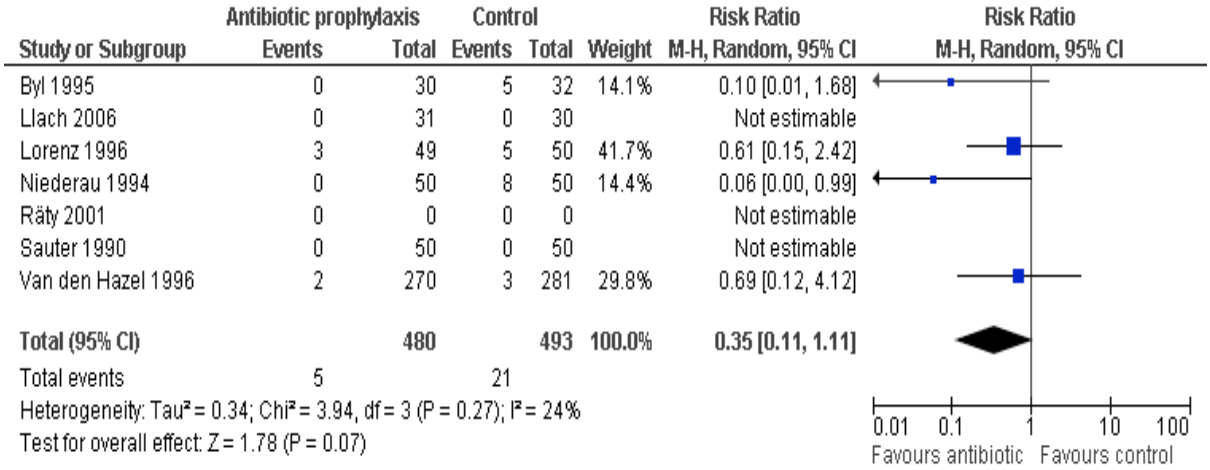

Figure 6

Adverse events

Only one trial documented adverse drug events. The trial by Van Den Hazel [8] reported one non-serious adverse event in the placebo group.

Quality of life

None of the trials used quality of life as an outcome measure.

Secondary outcome measures

Mortality directly attributable to ERCP-induced sepsis

We were unable to determine the number of deaths directly attributable to ERCP-induced sepsis as this was not mentioned in most studies.

Bacteraemia (positive blood cultures with no evidence of a systemic inflammatory response)

Bacteraemia occurred in 77 of 579 patients, 24 out of 283 in the antibiotic group, and 53 out of 296 in the control group. This gave a RR of 0.50 CI (0.33 to 0.78) P = 0.002, I^2 47% (Figure 7).

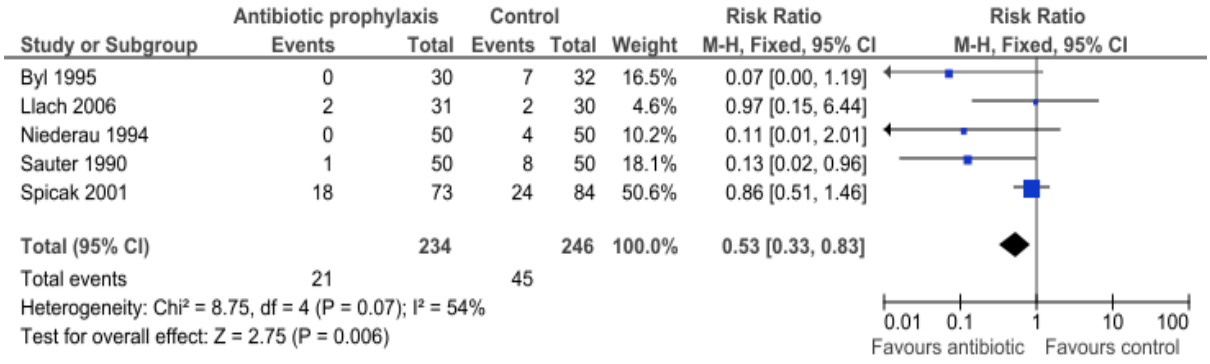

Figure 7

Pancreatitis (a three-fold rise of serum amylase accompanied with abdominal pain)

Only four trials considered pancreatitis as an outcome. The overall incidence was 43 patients out of 698; 14 out of 321 in the antibiotic group and 29 out of 377 in the control group. RR is 0.54 CI (0.29 to1.0) P = 0.05, I^2 10% (Figure 8).

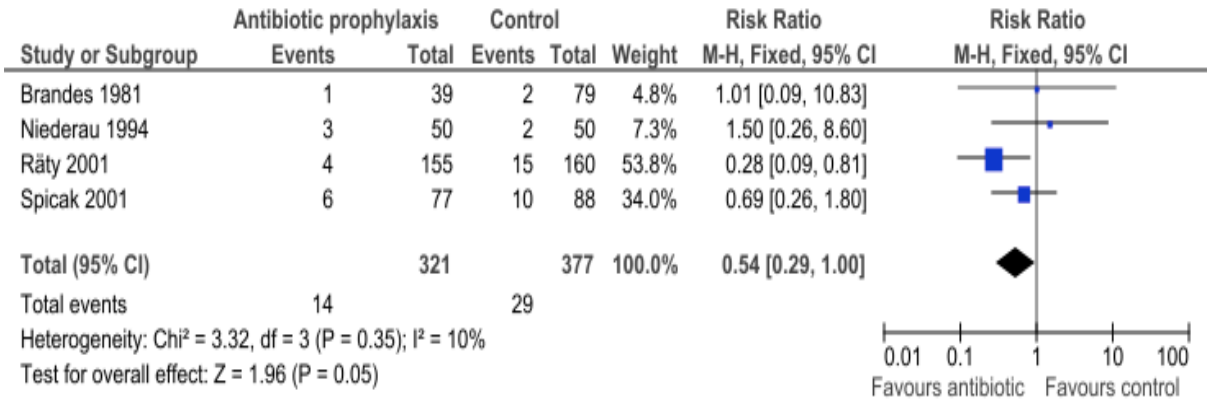

Figure 8

CHAPTER 4

4. DISCUSSION

4.1 South African endoscopy practice

Currently there are 101 gastroenterologists registered with the Health Professions Council of South Africa, consisting of 26 surgeons and 76 physicians, many of whom do not perform ERCP's. The 39 doctors who responded to our questionnaire probably represent the majority (at least 80%)of those practitioners who regularly perform ERCP's. The results of our questionnaire demonstrate that there is no consistent antibiotic protocol followed by South African endoscopists, and that that there is also a significant difference in antibiotic usage between surgeons and non-surgeons. It is postulated that surgeons used antibiotics more often as they are more likely to deal with cases of severe pancreatic sepsis and this may influence their prescribing habit. There appears to be no adherence to evidence based medicine or guidelines in South Africa in this regard.

4.2 Meta-analysis

We observed a significant difference in the incidence of bacteriaemia, cholangitis, septicaemia, and pancreatitis favouring the antibiotic prophylaxis group in fixed-effect model meta-analyses. In random-effects model meta-analyses, we were only able to confirm these effects regarding bacteraemia. We were unable to show a statistically significant difference in all-cause mortality after the administration of prophylactic antibiotics to all patients undergoing an ERCP, neither with a fixed-effect nor a random-effects model meta-analysis. We were unable to conduct meta-analyses of adverse events and quality of life.

The patient number needed to treat (NNT) to prevent one episode of cholangitis seems to be 38 patients. Bacteraemia occurred significantly less in the antibiotic groups, as did ensuing septicaemia; however, there was a significant heterogeneity in these two outcomes, possibly attributed to incomplete ERCP procedures. Unfortunately, we were not able to elucidate this from most trials, as not enough details were supplied in the text. The NNT to prevent one episode of septicaemia seems to be 31 patients, and NNT to prevent one episode of bacteraemia seems to be 11 patients. The incidence of pancreatitis was lower in the antibiotic prophylaxis group, with minimal heterogeneity amongst the included trials.

There are a number of weaknesses with the present evidence on which this systematic review rests. First, the majority of the included trials had high risk of bias. This raises the risk of observing beneficial intervention effects that may not be real [26-29]. Second, the number of patients randomised and the number of patients with outcomes were small for all outcome measures. This increases the risk of random errors due to sparse data as well as multiplicity from repeated testing on accumulating evidence [30-34]. Third, a variable number of antibiotics have been used so it is not possible to determine which may and may not provide prophylactic effects. Fourth, we could not assess adverse events like allergy, development of antibiotic resistance, quality of life, etc. This was due to insufficient reporting in the primary

trials. Fifth, the assessment of the effect of antibiotics on most of our outcome measures seems to be influenced by choice of statistical method. This questions the robustness of our present evidence.

Our sub-group analysis showed that the likely benefit observed in all patients could not be demonstrated in the subgroup of patients with a successful first ERCP procedure relieving the biliary obstruction. This can be due to lack of statistical power in this subgroup or due to lack of effect. Based on the latter possibility, we question whether or not antibiotics should be routinely administered before the ERCP procedure. One could argue that up to a few hours delay of antibiotic administration would not harm the patient, as it has been well documented that patients with obstructive jaundice achieve an antibiotic concentration in bile that is below the minimum inhibitory concentration of bacteria [23-25]. Hepatic dysfunction only improves once the cause of jaundice is reversed, ie, obstruction relieved [23].

Our results differ from a recent meta-analysis [9] assessing the incidence of cholangitis and septicaemia in unselected ERCP patients. In this meta-analysis the patients did not seem to benefit from antibiotic prophylaxis. The meta-analysis only conducted random-effects model meta-analyses in case of heterogeneity.
The incidence of pancreatitis was lower in the antibiotic prophylaxis group, with minimal heterogeneity amongst the included trials. NNT is 44.

CHAPTER 5

5. CONCLUSIONS

5.1 Implications for practice

- Routine antibiotic prophylaxis before elective ERCP seems to reduce bacteraemia and may reduce cholangitis, septicaemia, and pancreatitis. We could not demonstrate a significant effect on all-cause mortality. We lack data on the effect of antibiotics on adverse effects and quality of life.
- The potential effect of antibiotics on cholangitis seems largest in patients with a difficult ERCP procedure.

5.2 Implications for research

- We need more randomised clinical trials comparing antibiotics versus placebo for patients undergoing therapeutic biliary ERCP. These trials need to be with low risk of bias (systematic errors) and low risk of play of chance (random errors).
- We need randomised clinical trials on patients undergoing therapeutic biliary ERCP assessing antibiotic usage before the procedure versus antibiotic administration during or after the procedure. A clinical score should be developed to predict the probability of ERCP procedural failure.
- We need a systematic review of the randomised trials that have compared antibiotics head-to-head in patients undergoing therapeutic biliary ERCP.

REFERENCES

1. Romagnuolo J, Cotton PB, Mauldin P, Hawes RH, Lawrence C, Payne KM. Changing Trends in ERCP Practice Over a Decade. *Gastrointestl Endosc* 2005; 61: AB155.

2. ASGE. Guidelines for antibiotic prophylaxis for GI endoscopy. *Gastrointestinal Endoscopy* 2003; **58**: 475-82.

3. Mallery JS et al. Complications of ERCP. *Gastrointest Endosc* 2003; 57: 633-8.

4. Harris A, Chan AC, Torres-Vierra C, Hammett R, Carr-Locke D. Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). *Endoscopy* 1999; 31: 718-24

5. Llach J et al. Prospective assessment of the role of antibiotic prophylaxis in ERCP. *Hepatogastroenterol* 2006; 53: 540-2

6. Lorenz R, Lehn N, Born P, Herrmann M, Neuhaus H. [Antibiotic prophylaxis using cefuroxime in bile duct endoscopy]. *Dtsch Med Wochenschr.* 1996; 121: 223-30

7. Sauter G, Grabein B, Huber G, Mannes GA, Ruckdeschel G, Sauerbruch T. Antibiotic prophylaxis of infectious complications with endoscopic retrograde cholangiopancreatography. A randomized controlled study. *Endoscopy* 1990; 22: 164-7

8. van den Hazel SJ et al. Piperacillin to prevent cholangitis after endoscopic retrograde cholangiopancreatography. A randomized, controlled trial. *Ann Intern*

Med 1996; 125: 442-7

9. Bai Y, Gao F, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot prevent endoscopic retrograde cholangiopancreatography-induced cholangitis: a meta-analysis. *Pancreas* 2009;38(2):126-30

10. Gluud C, Nikolova D, Klingenberg SL, Whitfield K, Alexakis N, Als-Nielsen B, et al. Cochrane Hepato-Biliary Group. *About The Cochrane Collaboration* (Cochrane Review Groups (CRGs)). 2009, Issue 4. Art. No.: LIVER

11. Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *Int. Jour. of Techn. Assess. in Health Care* 2003;19(4):591-603

12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Jour. of the Nat. Cancer Inst.* 1959;22:719-48

13. Greenland S, Robins J. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;41:55-68

14. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;21(11):1539-58

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;7:177-88

16. Egger M, Davey SA, Schneider M, Minder C. Bias in a meta-analysis detected by a simple, graphical test. *BMJ* (Clinincal Research Edition) 1997;315(7109): 629-34

17. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stats in Med.* 2001;20(4):641-54.

18. Brandes JW, Scheffer B, Lorenz-Meyer H, Korst HA, Littmann KP. ERCP: Complications and Prophylaxis. A controlled study. *Endoscopy* 1981;13:27-30

19. Byl B, Deviere J, Struelens MJ, Roucloux I, De Coninck A, Thys JP, et al. Antibiotic prophylaxis for infectious complications after therapeutic endoscopic retrograde cholangiopancreatography: A randomized, double-blind, placebo-controlled study. *Clinical Infectious Diseases* 1995;20:1236-40

20. Niederau C, Pohlmann U, Lűbke H, Lutz T. Prophylactic antibiotic treatment in therapeutic or complicated diagnostic ERCP: results of a randomized controlled clinical study. *Gastrointestinal Endoscopy* 1994;40(5):533-7

21. Räty S, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post- ERCP pancreatitis: reduction by routine antibiotics. *Jour. of Gastrointest. Surg.* 2001;5 (4):339-45

22. Spicak J, Stirand P, Zavoral M, Keil R, Zavada F, Drabek J. Antibiotic prophylaxis of cholangitis complicating endoscopic treatment of biliary obstruction [Antibioticka profylaxe cholangitidy komplikujici endoskopickou lecbu biliarni obstrukce]. *Ceska a Slovenska Gastroenterologie a Hepatologie* 2001;55(6):211-5

23. Blenkharn JI, Habib IN, Mok D, John L, McPherson GAD, Gibson RN, et al. Decreased biliary excretion of piperacillin after percutaneous relief of extrahepatic obstructive jaundice. *Antimicrobial Agents and Chemotherapy* 1985;28(6):778-80

24. Nagar H, Berger SA. The excretion of antibiotics by the biliary tract. *Surgery Gynaecology and Obstetrics* 1984;158:601-7

25. Quintiliani R, French M, Nightingale C. First and second generation cephalosporins. *Med. Clin. of North America* 1982;66:183-97

26. Schulz KF, Chalmers I, Hayers RJ, Altman DG. Emprirical evidence of bias.

27. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12

28. Moher D, Jadad AR, Moher M. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609-13

29. Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomised trials in meta-analyses. *Ann. of Int. Med.* 2001;135:982-9

30. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* (Clinical Research Ed) 2008;336(7644):601-5

31. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Jour. of Clin. Epidemiology* 2008;61(1):64-75

32. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Jour. of Clin Epidem.* 2008;61(8):763-9

33. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - Trial sequential analysis adjustment for random error risk in conclusive neonatal meta-analyses. *Int. Jour. of Epidem.* 2009;38:287-98

34. Thorlund K, Devereaux PJ, Wetterslev J, Gyuatt G, Ioannidis JPA, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int. Jour. of Epid.* 2009;38:276-86.

35. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;9:86.

36. International Conference on Harmonisation Expert Working Group. Guideline for good clinical practice1997 *CFR & ICH Guidelines*. Vol. 1. PA 19063-2043, USA: Barnett International/PAREXEL. 1997.

APPENDIX 1

ERCP and prophylactic antibiotics: a questionnaire

Thank you for taking the time to fill in our voluntary, anonymous questionnaire regarding endoscopic retrograde cholangiopancreatography and the use of prophylactic antibiotics.

Demographics:

What is your speciality?

Surgeon ☐ Medical gastroenterologist ☐ Radiologist ☐

Where do you practice?

Public sector ☐ Private sector ☐ Both ☐

How many ERCP's do you perform in a month?

0-4 ☐ 5-9 ☐ more than 10 ☐

For how many years have you performed ERCP's?

Less than 1year ☐ 1 to 5years ☐ 5-10years ☐ More than 10years ☐

Do you perform out of hours ERCP?

No ☐ Yes ☐

Prophylactic antibiotics:

(If a patient is not already on antibiotics eg for cholangitis, pancreatitis)

Do you use prophylactic antibiotics for the following:

For purely diagnostic biliary ERCP? Always ☐ Selected cases ☐ Never ☐

For purely diagnostic pancreatic ERCP? Always ☐ Selected cases ☐ Never ☐

For therapeutic biliary ERCP? Always ☐ Selected cases ☐ Never ☐

For therapeutic pancreatic ERCP? Always ☐ Selected cases ☐ Never ☐

If so, which antibiotic is your antibiotic of choice? (please mark only one)

Augmentin ☐ Ciprobay ☐ Tazocin ☐ Any Cephalosporin ☐ Gentamicin ☐

Other_____

For how long do you give prophylactic antibiotics?

Single dose ☐ 24hours ☐ 48hours ☐ Longer, how long _____

Which route of administration do you prefer?

Intravenous ☐ Oral ☐

Are you aware of any antibiotic protocols for ERCP?

No ☐ Yes ☐

If so, which ones?

British ☐ American ☐ Other, please name_____

Do you perform manometry for assessment of the Sphincter of Oddi

No ☐ Yes ☐

If you do perform manometry, do you use prophylactic antibiotics?

No ☐ Yes ☐

Thank you again for your time.

Please drop your completed questionnaire into the marked box at the exit, and enter your name into the register so that we don't contact you after the congress in this regard again.

APPENDIX 2

DATABASE	PERIOD OF SEARCH	SEARCH STRATEGY
The Cochrane Hepato-Biliary Group Controlled Trials Register	October 2009	(antibiotic AND prophylaxis) AND ('endoscopic retrograde cholangiopancreatography')
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 4, 2009	#1 MeSH descriptor Antibiotic Prophylaxis explode all trees #2 MeSH descriptor Cholangiopancreatography, Endoscopic Retrograde explode all trees #3 (#1 AND #2)
Medline	1950-October 2009	#1 explode "Antibiotic-Prophylaxis"/ all subheadings #2 explode "Cholangiopancreatography-Endoscopic-Retrograde"/ all subheadings #3 #1 and #2 #4 random* or control* or blind* or meta-analys*s #5 #3 and #4
Embase	1980-October 2009	#1 explode "antibiotic-prophylaxis"/ all subheadings #2 explode "endoscopic-retrograde-cholangiopancreatography"/ all subheadings #3 #1 and #2 #4 random* or blind* or meta-analys*s or control* #5 #3 and #4
Science Citation Index Expanded (http://pcs.isiknowledge.com)	1945-October 2009	#1 TS=antibiotic prophylaxis #2 TS=endoscopic retrograde cholangiopancreatography #3 #1 AND #2