

# Effectiveness of Prophylactic Antibiotics in a Population-Based Cohort of Patients Undergoing Planned Cholecystectomy

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## Abstract

**Background** In the absence of randomized controlled trials with sufficient power to assess the effectiveness of prophylactic antibiotics (PA), the best evidence is provided by large population-based register studies.

**Methods** The Swedish Register of Gallstone Surgery and ERCP (GallRiks) started in May 2005 and reached 75% national coverage in 2007. During 2006 and 2007, a total of 16,400 operations were registered in GallRiks. In the present study, all elective procedures performed in 2006–2007 in units performing at least 25 operations annually were included in an analysis of the risk for postoperative infectious complications

**Results** Altogether 10,927 procedures were performed 2006–2007. Univariate logistic regression analysis revealed a paradoxical increase in postoperative infectious complications requiring antibiotic treatment and postoperative abscess if PA were given ( $p < 0.05$ ). This increase disappeared in multivariate analysis with adjustment for age, gender, presence of cholecystitis, accidental gallbladder perforation, and presence of bile duct stones.

**Conclusion** No benefit from PA was seen in this study on elective cholecystectomy. Although a randomized controlled trial could possibly show a reduction in the risk for postoperative infectious complications not detected in this study, such a reduction must be weighed against the risk of promoting drug resistance by the widespread use of PA.

**Keywords** Prophylactic antibiotics · Cholecystectomy · Elective

## Introduction

Despite increasing concern about the risk of promoting the development of resistant bacteria,<sup>1</sup> prophylactic antibiotic treatment is widely used in routine surgery for gallstone disease.<sup>2</sup> The absence of evidence has led to uncertainty regarding the benefit of prophylactic antibiotics. A number of randomized controlled trials of prophylactic antibiotic treatment in laparoscopic cholecystectomy have been reported,<sup>3–8</sup> none of which have shown any reduction in the rate of infectious complications by the administration of prophylactic antibiotics. The inability of these trials to show significant outcome may, however, have been due to insufficient statistical power. In order to achieve a larger patient sample, two meta-analyses of low-risk patients undergoing laparoscopic cholecystectomy have recently been performed.<sup>9,10</sup> These meta-analyses were also not able to show any benefit from prophylactic antibiotics.

The effectiveness of prophylactic antibiotic treatment in cholecystectomy cannot be fully assessed without

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stratification for low-risk and high-risk procedures. Whereas all randomized controlled trials so far published have focused on low-risk procedures, no study on high-risk procedures has been published. As high-risk cholecystectomies are more infrequent, it is difficult to assemble study samples of sufficient size for this group. On the other hand, the low incidence of infectious complications following low-risk procedures makes it impossible to reach sufficient statistical power in a trial on this group without a very large patient sample.<sup>2</sup> An alternative method covering large numbers of patients is through the use of a register study.

The question is not only whether or not prophylactic antibiotics prevent postoperative infectious complications but also whether it is worthwhile risking adverse reactions and the development of resistant bacteria in order to reduce the risk for rather infrequent and often harmless infectious complications after gallstone surgery. The purpose of this study was to explore the effectiveness of prophylactic antibiotics in preventing infectious complications in a population-based setting.

## Materials and Methods

The Swedish Register for Cholecystectomy and ERCP (GallRiks) was started in May 2005 with the aim of registering indications, complications, results, and quality-of-life outcome of gallstone surgery on a national standardized basis. By the end of 2007, 56 hospitals were included in GallRiks. All surgical procedures for gallstone disease are registered online in GallRiks by the surgeon performing the procedure. Registered data include personal registration number, gender, medical history, American Society of Anesthesiologists (ASA) classification, data on indication for surgery, operation method, and perioperative complications. Administration of antibiotics is defined as prophylactic if it does not exceed 24 h. No standardized follow-up visit is performed, but 30 days after surgery, the local coordinator at each unit performs a review of the patient notes in order to detect and record any postoperative adverse event. The register is validated each year by blinded reassessment of a randomly selected sample of patient notes. The prevalence of errors has so far been lower than 2%. This study is based on data assembled in 2006–2007. All units where at least 25 procedures were performed annually were included.

## Statistics

Two outcome measurements, any postoperative infection requiring antibiotic treatments and a postoperative abscess, were assessed. Postoperative abscess was defined as any localized infection that required percutaneous or surgical

drainage. They were used as dependent variable when univariate logistic analyses were performed, and gender, age, indication for surgery (gallstone disease with secondary complications versus uncomplicated gallstone disease), method of approach, and operative time were used as predictors. In order to assess the effectiveness of prophylactic antibiotics, we also performed multivariate logistic analyses with the same outcome measures and prophylactic antibiotics as covariate and adding potential confounding variables as covariates one by one.

We also did subgroup analyses of patients with accidental preoperative gallbladder perforation, patients undergoing open cholecystectomy, procedures lasting more than 90 min, and patients older than 60 years to see whether there was any group that had more benefit from prophylactic antibiotics than the rest of the group.

## Results

By the end of 2007, 54 units were included in GallRiks. Between 2006 and 2007, altogether 15,652 cholecystectomies were registered comprising 4,725 emergency procedures and 10,927 planned procedures. The latter constitute the study group in this report—7,729 women and 3,198 men. Mean age was 49.9 years and standard deviation was 15.48 years. In 8,555 patients, surgery was performed because of pain attacks without complication secondary to the gallstone disease, and 2,372 underwent surgery because of secondary complications such as cholecystitis, pancreatitis, or cholangitis. Laparoscopic techniques were performed in 9,755 procedures, whereas 1,172 were conducted with an open approach. Prophylactic antibiotics were given to 2,715 patients. The distributions of the covariates included in the multivariate analyses are shown in Table 1. Altogether 377 patients were treated for postoperative infectious complications requiring antibiotics and 93 for postoperative abscess.

Univariate logistic regression analysis of postoperative infection requiring antibiotic treatment revealed a paradoxical increase in the risk for postoperative infection if prophylactic antibiotics were given (Fig. 1). This increase, however, disappeared if potential confounders were added in multivariate analysis. Nevertheless, the odds ratio never declined to a level significantly lower than 1, i.e., a significant reduction in the risk for postoperative infection if prophylactic antibiotics were given was not seen no matter how many covariates were added (Fig. 2). No additional variable had any significant impact on the confidence interval for the odds ratio for prophylactic antibiotics. The same outcome was seen with postoperative abscess as dependent variable (Figs. 3 and 4). No statistically significant reduction in the risk of postoperative

**Table 1** Distributions of the Covariates Included in the Multivariate Analyses

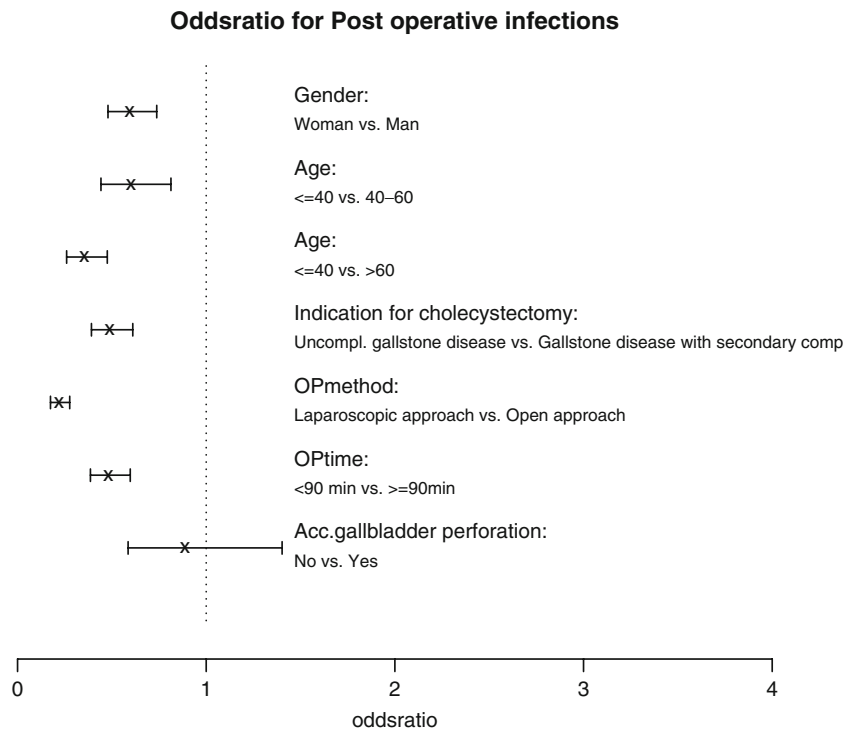
	Prophylactic antibiotics	No prophylactic antibiotics	Total
<b>Gender</b>			
Men	1,004 (31%)	2,194 (69%)	3,198
Women	1,711 (22%)	6,018 (78%)	7,729
<b>Age</b>			
≤40 years	571 (17%)	2,762 (83%)	3,333
40–60 years	1,031 (22%)	3,562 (78%)	4,593
>60 years	1,113 (37%)	1,882 (63%)	2,995
<b>Indication for cholecystectomies</b>			
Uncomplicated gallstone disease	1,663 (19%)	6,892 (81%)	8,555
Gallstone disease with secondary complication	1,052 (44%)	1,320 (56%)	2,372
<b>Operative approach</b>			
Laparoscopic approach	2,091 (21%)	7,664 (79%)	9,755
Open approach	624 (53%)	548 (47%)	1,172
<b>Operative time</b>			
<90 min	961 (16%)	5,023 (84%)	5,984
≥90 min	1,754 (36%)	3,186 (64%)	4,940
<b>Accidental gallbladder perforation</b>			
No	2,461 (24%)	7,811 (76%)	10,272
Yes	241 (41%)	345 (59%)	586

infections from prophylactic antibiotics was seen in any of the subgroups (accidental preoperative gallbladder perforation, patients undergoing open cholecystectomy, procedures lasting more than 90 min, and patients older than 60 years).

**Discussion**

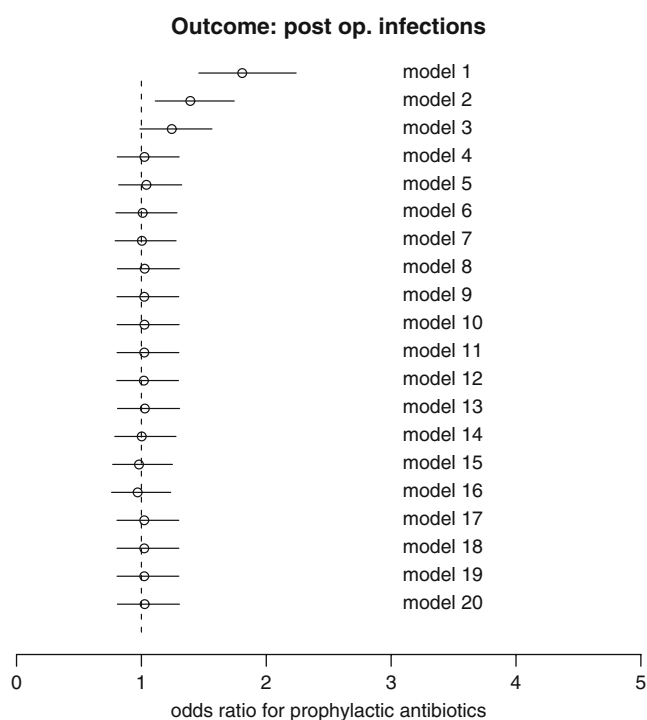
No benefit from prophylactic antibiotics was seen in the present study. Univariate analysis revealed a paradoxical

**Figure 1** Odds ratios for the risk for developing postoperative infectious complications requiring antibiotic treatment determined from univariate logistic regression analyses.



increase in infectious complication rate. This increase is probably an effect of confounding factors that also increase the risk for postoperative infectious complications influencing the decision to give antibiotics. This increase did not remain significant if adjustment was made for the most important confounding factors. Indeed, we did not see any significant reduction in the incidence of infectious complications, no matter how many variables were considered.

Although theoretically there may be minor effects of prophylactic antibiotic treatment that remain obscured by confounding factors, any potential positive effect must be considered in the context of the risks of widespread use of

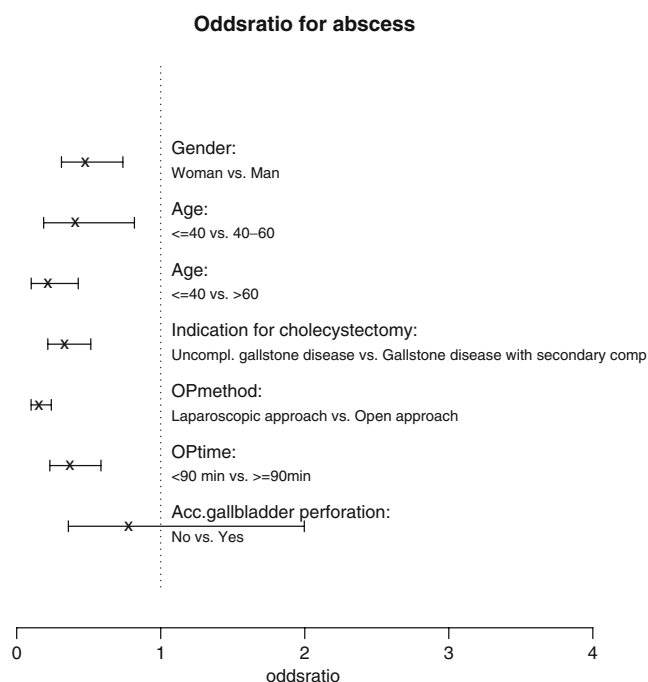


**Figure 2** Odds ratios for the risk for developing postoperative complications requiring antibiotic treatment if prophylactic antibiotics are given preoperatively. *Model 1* is derived from univariate analysis. In the subsequent models, the odds ratios for postoperative complication if prophylactic antibiotics are given preoperatively are determined in multivariate analysis with adjustment for gender, age, and indication for surgery (*model 2*), gender, age, and operative time (*model 3*), gender, age, operative time, and surgical approach (*model 4*), as model 4 + mode of admission (*model 5*), as model 4 + ASA (*model 6*), as model 4 + presence of common bile duct stones (*model 7*), as model 4 + presence of cholecystitis (*model 8*), as model 4 + presence of pancreatitis (*model 9*), as model 4 + elevated bilirubin (*model 10*), as model 4 + previous history of cholecystitis (*model 11*), as model 4 + previous history of pancreatitis (*model 12*), as model 4 + previous history of elevated bilirubin (*model 13*), as model 4 + pathological preoperative cholangiography (*model 14*), as model 4 + preoperative drainage applied (*model 15*), as model 4 + diagnosis at histopathological examination (*model 16*), as model 4 + accidental gallbladder perforation (*model 17*), as model 4 + accidental bowel perforation (*model 18*), as model 4 + preoperative necessitating intervention (*model 19*), and as model 4 + bile duct injury detected intraoperatively (*model 20*).

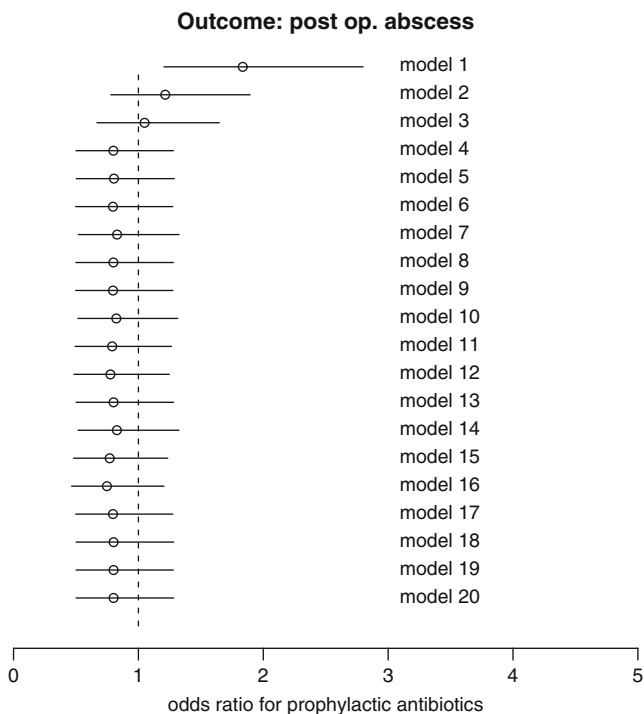
antibiotics, in particular the development of antibiotic resistance. The only definite way of confirming a decrease in infectious complications would be a randomized controlled trial with sufficient statistical power. Assuming a reduction from 4% to 3%, for example, a randomized controlled trial would require a sample of more than 10,000 patients in order to achieve an 80% chance of detecting a significant reduction at the  $p < 0.05$  level. Considering the fact that 4.8% of patients receiving prophylaxis and 3.3% of those who did not receive prophylaxis developed postoperative infectious complications that warranted antibiotic treatment, this seems a reasonable assumption. Although such a study may provide a better evidence base than a cohort study, it would have to be performed not only with the aim of revealing the potential effectiveness of prophylactic antibiotics but also taking the beneficence of the hypothesis of the study into consideration. Infectious complications that are avoided by prophylactic antibiotics are very few and seldom severe, whereas the use of prophylactic antibiotics on a wide scale carries the risk of increasing antibiotic resistance.

Another possible source of bias is patients with ongoing infection not related to the surgical procedure, such as pneumonia or urinary tract infection. Although this group is very small, the presence of infections of other locations may have affected the decision to give antibiotics as well as the postoperative course.

No matter how many potential confounding factors the outcome is adjusted for, the results of a nonrandomized



**Figure 3** Odds ratios for the risk for developing postoperative abscess determined from univariate logistic regression analysis.



**Figure 4** Odds ratios for the risk for developing postoperative abscess. *Model 1* is derived from univariate analysis. In the subsequent models, the odds ratios for postoperative abscess if prophylactic antibiotics are given preoperatively are determined in multivariate analysis with adjustment for gender, age, and indication for surgery (*model 2*), gender, age, and operative time (*model 3*), gender, age, operative time, and surgical approach (*model 4*), as model 4 + mode of admission (*model 5*), as model 4 + ASA (*model 6*), as model 4 + presence of common bile duct stones (*model 7*), as model 4 + presence of cholecystitis (*model 8*), as model 4 + presence of pancreatitis (*model 9*), as model 4 + elevated bilirubin (*model 10*), as model 4 + previous history of cholecystitis (*model 11*), as model 4 + previous history of pancreatitis (*model 12*), as model 4 + previous history of elevated bilirubin (*model 13*), as model 4 + pathological preoperative cholangiography (*model 14*), as model 4 + preoperative drainage applied (*model 15*), as model 4 + diagnosis at histopathological examination (*model 16*), as model 4 + accidental gallbladder perforation (*model 17*), as model 4 + accidental bowel perforation (*model 18*), as model 4 + preoperative necessitating intervention (*model 19*), and as model 4 + bile duct injury detected intraoperatively (*model 20*).

study has to be interpreted with great caution when considering the effect of a treatment or intervention. Although multivariate analysis in this study included many of the most important confounding factors, there are some factors that are not covered by the register. Macroscopic contamination in the wound may have a strong impact on the decision to give prophylactic antibiotics as well as the risk for developing infectious complications. Prophylactic antibiotics may also have been given on indications related to concurrent conditions such as cardiac valve disease, immunosuppression, or presence of prosthetic devices. These confounding factors

may to some extent explain the paradoxical increase in infection rate with prophylactic antibiotics, although hardly to the extent that they would obscure a strong relationship between antibiotic prophylaxis and infectious complications.

The outcome of our study is in line with previous randomized controlled trials<sup>3–8</sup> and meta-analyses<sup>9,10</sup> that also failed to show that prophylactic antibiotics reduce the risk for postoperative infectious complications. Although neither the present nor previous studies can rule out the possibility that there may be some benefit from antibiotics in the case of massive bacterial contamination, immunosuppression, or high comorbidity, there is no room for routine administration of antibiotics in uncomplicated cholecystectomy. In our multivariate analysis, we adjusted for several of the factors that are often suggested as risk factors for infectious complications, i.e., open approach,<sup>11</sup> gallbladder perforation,<sup>12</sup> and high age.<sup>13</sup> Not even with these adjustments, however, could a favorable impact of antibiotics be seen.

In conclusion, no benefit from prophylactic antibiotics was seen in elective cholecystectomy. Even though a minor benefit in terms of reduced risk for postoperative infection may theoretically have been obscured by confounding factors in the absence of randomization, the low incidence of postoperative infections raises the issue not only of the effectiveness of prophylactic antibiotics but also whether a potential reduction in incidence is worthwhile when the negative effects of the widespread use of antibiotics are taken into consideration.

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