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Antibiotic prophylaxis prior to endoscopic retrograde cholangiopancreatography in patients with obstructive jaundice: is it worth the cost?

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SUMMARY

Background: There are few published data concerning the economic impact of antibiotic prophylaxis prior to endoscopic retrograde cholangiopancreatography in the setting of biliary obstruction.
Aim: To perform decision analysis to determine the costs of prophylaxis in patients undergoing endoscopic retrograde cholangiopancreatography for obstructive jaundice.
Methods: A decision analysis model was constructed. The probability of biliary sepsis, death and endoscopic retrograde cholangiopancreatography complications was obtained from the medical literature and from a retrospective analysis of our own experience. Costs were obtained from Medicare reimbursement at our institution. The strategies evaluated were endoscopic retrograde cholangiopancreatography with and without single-dose antibiotic prophylaxis. We compared the total costs, number of episodes of cholangitis and deaths associated with each strategy.
Results: Based on published data and the results of our retrospective analysis, the strategy of administering single-dose prophylactic antibiotics prior to endoscopic retrograde cholangiopancreatography in patients with obstructive jaundice resulted in lower total costs, fewer episodes of cholangitis and fewer deaths compared to a strategy of not administering antibiotics. The results were sensitive to the rates of cholangitis, cost of antibiotics and the cost of treating an episode of cholangitis.
Conclusions: Antibiotic prophylaxis prior to endoscopic retrograde cholangiopancreatography results in fewer cases of cholangitis and is cost saving when compared to a strategy of no prophylaxis in patients with obstructive jaundice.

INTRODUCTION

Cholangitis is a well-recognized complication of endoscopic retrograde cholangiopancreatography (ERCP). The incidence varies greatly depending on the patient population studied and has a reported mortality of 10%.[1] Multivariate analyses in prospective studies have identified jaundice and inadequate drainage of biliary obstruction as risk factors for the development of cholangitis.[2, 3] Therefore, both the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology recommend antibiotic prophylaxis for ERCP in the setting of bile duct obstruction.[4, 5] However, there are few published data concerning the economic impact of this strategy. A recent meta-analysis concluded that single-dose antibiotic prophylaxis has little or no impact on the outcome of cholangitis/sepsis following ERCP.[6] However, this meta-analysis[6] included patients undergoing ERCP for reasons other than obstructive jaundice and also

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included patients undergoing percutaneous transhepatic cholangiography.

Although previous studies have suggested that the routine use of antibiotic prophylaxis cannot be justified, or should be provided in the setting of inadequate biliary drainage,[6, 7] future prospective, randomized, controlled trials evaluating the efficacy of antibiotic prophylaxis are unlikely to be performed given the medico-legal ramifications of not following previously published society guidelines regarding antibiotic prophylaxis.[4, 5] As the clinical efficacy of antibiotic prophylaxis prior to ERCP in patients with obstructive jaundice is not clearly established, and future trials are unlikely to be allowed, cost-effectiveness analysis provides an alternative means of using previous data to determine the utility of antibiotic prophylaxis.

Given the uncertainties regarding the economic impact of single-dose antibiotic prophylaxis in patients undergoing ERCP for suspicion of obstructive jaundice — the subset of patients in whom antibiotic prophylaxis is currently recommended and in whom cholangitis is most likely to develop — we performed decision analyses to evaluate the overall costs associated with a strategy of single-dose antibiotic prophylaxis compared to that of no antibiotic prophylaxis from data in the literature. To compare the effect of antibiotic prophylaxis at our institution with published data, we also performed a retrospective analysis of patients undergoing ERCP for biliary obstruction at our institution and obtained centre-specific probabilistic data. These results were later entered into the model and compared to the model based on the literature review.

METHODS

Retrospective analysis

Following Institutional Review Board approval, all patients who had undergone ERCP at the University of Alabama at Birmingham between August 1998 and July 2000 were identified, and the endoscopic reports and clinical data of each of these patients were reviewed. A total of 243 patients underwent ERCP for obstructive jaundice, defined as a total bilirubin of ≥ 2.5 mg/dL or, in the absence of a documented bilirubin, having frank jaundice documented by physical examination at the time of ERCP. Patients were excluded if they were younger than 18 years of age, had received antibiotics other than single-dose prophylaxis during the 7 days prior to ERCP or had received antimicrobial drugs during or following ERCP based on ERCP findings or for a febrile illness other than biliary sepsis or cholangitis. Patients were also excluded if they had been transferred from another institution and if insufficient records existed to determine whether they had received antibiotics prior to ERCP or within 7 days following ERCP. Patients were considered to have cholangitis secondary to ERCP if they developed a temperature of > 38 °C as an in-patient or reported a febrile illness as an out-patient within 7 days following ERCP, had abdominal pain and had no other identifiable causes of fever, and antimicrobial therapy was instituted. During this time, all patients were prospectively followed by telephone to monitor for any procedure-related complications including cholangitis.

The model

A decision tree was constructed using DATA 3.5 (TreeAge Inc., Williamstown, MA, USA). The costs and outcomes of a strategy of pre-ERCP antibiotic prophylaxis were compared to a strategy of no antibiotic prophylaxis prior to ERCP in patients with presumed biliary obstruction without evidence of infection.

A hypothetical cohort of 100 patients entered the model with obstructive jaundice and either received or did not receive antibiotic prophylaxis prior to ERCP (Figure 1). The movement of the cohort through the tree to terminal branches was determined by transition probabilities (Table 1), which were obtained from our retrospective analysis and a search of Medline using the terms 'ERCP', 'biliary obstruction', 'cholangitis', 'antibiotic', 'prophylaxis' and 'antibiotic prophylaxis'. The references of articles located via Medline were also used to identify additional sources. After ERCP, patients may recover uneventfully or develop cholangitis or other complications from the procedure (pancreatitis, bleeding, perforation), with death resulting from any of these complications. In addition, our model incorporated the possibility of an unsuccessful ERCP and assumed that these patients would undergo percutaneous transhepatic cholangiography, which also carries a risk of procedure-related morbidity and mortality. For model completeness, we also included the probability of severe adverse reaction to prophylactic antibiotics. The costs and outcomes associated with each strategy were accrued and computed.

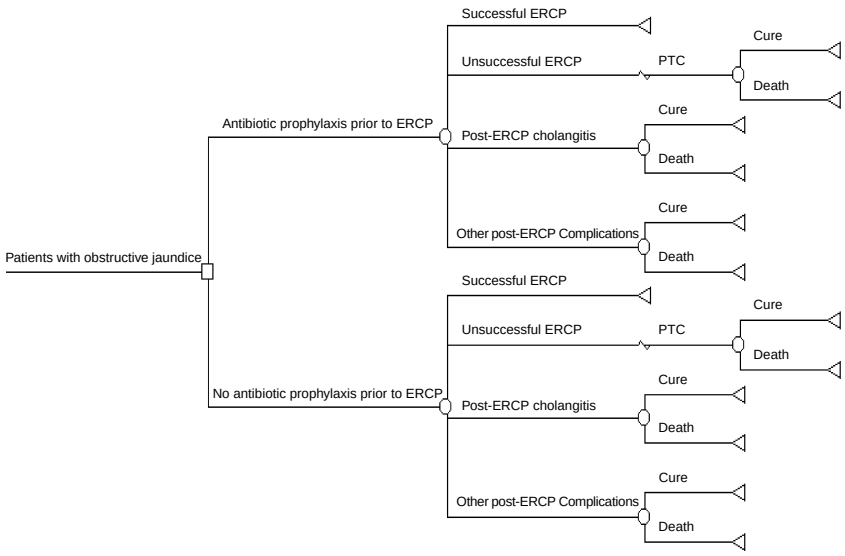

Figure 1. Schematic outline of the decision model. The tree demonstrates the decision of antibiotic prophylaxis vs. no prophylaxis in patients with obstructive jaundice prior to endoscopic retrograde cholangiopancreatography (ERCP). ERCP may be successful or unsuccessful. Cholangitis and other complications (bleeding, perforation) from the procedure may occur. If unsuccessful, patients undergo percutaneous transhepatic cholangiography (PTC). Death may occur due to complications of ERCP or PTC. *The probabilities emanating from each decision node do not all add up to zero for simplification purposes.

Table 1. Transition probabilities and costs

Variable	Value	Source
Probability of cholangitis with prophylaxis	0.0549	7–9
Probability of cholangitis without prophylaxis	0.0661	7–9
Probability of complications from ERCP	0.05	10
Probability of complications from PTC	0.18	11
Probability of death from cholangitis	0.1	1
Probability of death from complications from ERCP	0.025	10
Probability of death from complications from PTC	0.051	11
Probability of serious drug reaction	0.01	Assumed
Cost of antibiotics	$26.00	12
Cost of cholangitis	$10 000	*
Cost of complications of ERCP	$10 000	*
Cost of ERCP	$750	*
Cost of PTC	$1000	*
Cost of antibiotic side-effect	$1000	Assumed

ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography.

Costs

All medical and procedural costs were assigned a current procedural terminology or diagnosis-related group code to identify the average 2000 Medicare reimbursement rate at our institution. Drug costs utilized in our analysis represent the average wholesale price.[12] The costs are shown in Table 1.

Sensitivity analysis

Sensitivity analyses were performed to explore the degree to which our results were influenced by uncertainty regarding the parameter values used in the model. In one-way sensitivity analyses, results were recalculated as the values of model parameters were varied one at a time. In addition, two-way sensitivity analyses were performed to examine the results of simultaneously varying select pairs of variables that were found to be influential in one-way sensitivity analyses.

RESULTS

Retrospective analysis

Of the 243 patients who underwent ERCP for presumed biliary obstruction at the University of Alabama at Birmingham between August 1998 and July 2000, 148

Table 2. Patient characteristics and endoscopic results

Variable	No prophylaxis (91), *n* (%)	Prophylaxis (5), *n* (%)
Age (years)*	61.2 ± 18.3	39.2 ± 18.1
Male	49 (54%)	3 (60%)
Bilirubin (mg/dL)*	11.8 ± 9.1	9.4 ± 7.4
In-patient	17 (19%)	3 (60%)
Endoscopic findings		
Biliary stricture	56 (62%)	1 (20%)
Choledocholithiasis	15 (16%)	3 (60%)
Primary sclerosing cholangitis	6 (7%)	1 (20%)
Other	3 (3%)	0
No obstruction	6 (7%)	0
Unsuccessful cannulation of CBD	5 (5%)	0
Endoscopic intervention†		
Successful drainage	82 (90%)	5 (100%)
Stone extraction	12 (13%)	3 (60%)
Sphincterotomy	24 (26%)	2 (40%)
Placement of endoprosthesis	56 (62%)	2 (40%)

CBD, common bile duct.
*Values expressed as mean ± s.d.
†Percentage of interventions does not add up to 100% as some patients had multiple interventions.

were excluded from our analysis. One hundred and eight patients were excluded for receiving antibiotics other than single-dose antibiotic prophylaxis, 34 patients were excluded for receiving antibiotics following ERCP for reasons other than cholangitis, five patients were excluded for insufficient data and one patient was excluded for an age less than 18 years. After exclusion of these patients, a total of 95 patients remained and their characteristics are listed in Table 2. Ninety patients had not received antibiotic prophylaxis and five patients had received single-dose antibiotic prophylaxis. Of the five patients receiving prophylaxis, two patients received ciprofloxacin and one patient each received gentamicin, ceftriaxone and piperacillin with tazobactam. None of the patients in the prophylaxis group developed cholangitis, while three patients in the group that did not receive prophylaxis developed cholangitis. All of the patients who developed cholangitis had strictures noted on ERCP (one patient each with pancreatic carcinoma, cholangiocarcinoma and

Table 3. Results of the cost analysis of pre-endoscopic retrograde cholangiopancreatography (ERCP) antibiotic prophylaxis vs. no prophylaxis using data from the literature

Strategy	Cost*	Episodes of cholangitis expected (*n*) (per 100 patients)	Deaths due to cholangitis expected (*n*) (per 100 patients)
Antibiotic prophylaxis	1925	5	0.5
No prophylaxis	2005	6	0.6

*Costs in 2000: US$ per patient.

Table 4. Results of the cost analysis of pre-endoscopic retrograde cholangiopancreatography (ERCP) antibiotic prophylaxis vs. no prophylaxis using data from a retrospective analysis at our institution

Strategy	Cost*	Episodes of cholangitis expected (*n*) (per 100 patients)	Deaths due to cholangitis expected (*n*) (per 100 patients)
Antibiotic prophylaxis	1419	0	0
No prophylaxis	1694	3	0.3

*Costs in 2000: US$ per patient.

Table 5. Results of one-way sensitivity analyses

Variable	Baseline value*	Total costs† Values*	Prophylaxis	No prophylaxis
Probabilistic variables				
Probability of cholangitis with prophylaxis	0.0549	0.00	1409	2005
		0.025	1620	2005
		0.075	2115	2005
Probability of cholangitis without prophylaxis	0.0661	0.00	1926	1383
		0.025	1926	1595
		0.075	1926	2089
Probability of severe antibiotic reaction	0.01	0.00	1926	2005
		0.025	1950	2005
		0.075	1999	2005
		0.1	2023	2005
Economic variables				
Cost of antibiotic	26	2	1902	2005
		10	1911	2005
		50	1951	2005
		125	2024	2005
Cost of cholangitis	10 011	1000	1465	1450
		5000	1670	1697
		15 000	2184	2316

*Values are expressed as proportions.
†Costs in 2000: US$ per patient.

sclerosing cholangitis after liver transplantation), and all but the patient with sclerosing cholangitis had adequate biliary drainage, defined as complete drainage of contrast material at the completion of the procedure. None of the patients excluded for receiving antibiotics developed cholangitis following ERCP.

Baseline analysis

The results of the analysis utilizing data from the literature are depicted in Table 3. The strategy of administering prophylactic antibiotics prior to ERCP in patients with obstructive jaundice was associated with a total cost of $1925, whereas a strategy of not administering antibiotics cost $2005.

The expected numbers of biliary tract infections and deaths due to biliary sepsis that occurred in the strategy of antibiotic prophylaxis were 5 and 0.5, respectively, compared with 6 and 0.6, respectively, in the 'no antibiotic' strategy.

When the data obtained from our retrospective analysis were entered into the model, the results were similar (Table 4). Antibiotic prophylaxis was a cost-saving strategy compared to a strategy of not administering antibiotic prophylaxis. Prophylaxis was associated with a total cost of $1409 per patient with no cases of biliary tract infection, whereas no prophylaxis cost $1649 per patient and resulted in 3.3 cases of biliary tract infection.

Sensitivity analysis

In most sensitivity analyses, antibiotic prophylaxis remained a cost-saving strategy. One-way sensitivity analyses demonstrated that the overall costs of a strategy of antibiotic prophylaxis exceeded the costs of not administering prophylaxis only when the cost of the prophylactic antibiotic was higher than $105 and the cost of treating an episode of cholangitis was less than $2466. The results of several other one-way sensitivity analyses are shown in Table 5. Figure 2, based on a literature-derived rate of cholangitis following ERCP without antibiotic prophylaxis of 6.6%, identifies the threshold probability of developing cholangitis with the use of antibiotics for prophylaxis to remain cost saving. At a probability of cholangitis with the use of antibiotics

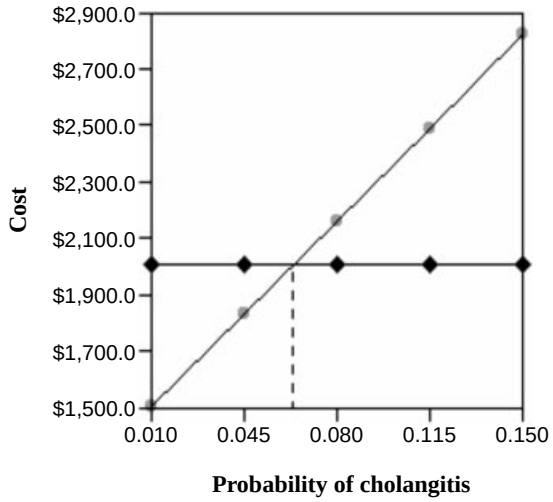

Figure 2. Threshold analysis on the probability of cholangitis with the use of antibiotic prophylaxis. Total costs associated with the strategy of 'antibiotic prophylaxis' increase at an increasing probability of developing cholangitis in this strategy. At a probability of developing cholangitis of 0.063 (relative risk reduction of 4.5%), the cost of the strategy of 'antibiotic prophylaxis' exceeds that of the strategy of 'no prophylaxis'. (●), Antibiotics; (◆) no antibiotics. Threshold values (●, ◆): probability of cholangitis + antibiotics = 0.063.

greater than 6.3%, the cost of prophylaxis would exceed the cost of no prophylaxis. Therefore, prophylaxis remains cost saving compared to no prophylaxis as long as the relative risk reduction is greater than 4.5%

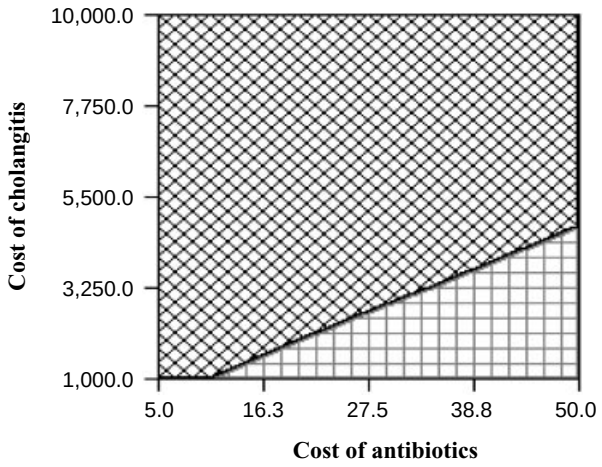

Figure 3. Two-way sensitivity analysis of the cost of cholangitis and cost of antibiotics. As demonstrated by the figure, the strategy of 'antibiotic prophylaxis' is preferable at a lower cost of antibiotic and increasing costs associated with cholangitis. (◇), Antibiotics; (□), no antibiotics.

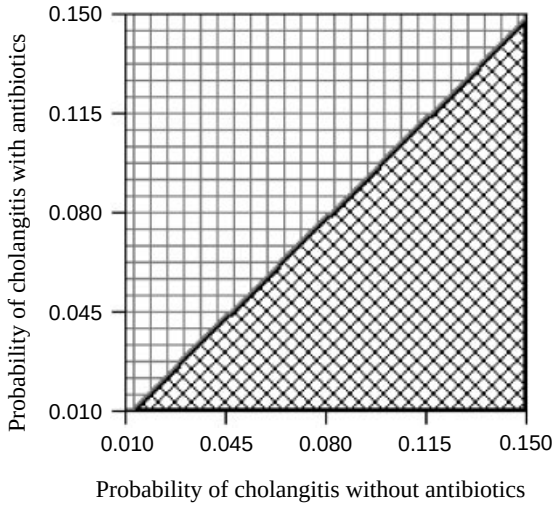

Figure 4. Two-way sensitivity analysis showing the preferred strategy according to the specific risk of cholangitis associated with a strategy of 'antibiotic prophylaxis' and 'no prophylaxis'. (◇), Antibiotics; (□), no antibiotics.

[(6.6 – 6.3)/6.6]. According to the literature, the incidence of cholangitis following ERCP is 6.6% without prophylaxis vs. 5.5% with prophylaxis (relative risk reduction of 16.6%). Figure 3 demonstrates the results of a two-way sensitivity analysis where the cost of antibiotic and cost of cholangitis are varied simultaneously. As shown by the figure, the costs associated with prophylaxis are lower compared to no prophylaxis at lower drug costs and higher costs of treating cholangitis. The least costly strategies at given levels of probabilities of developing cholangitis are represented in Figure 4. As Figure 4 demonstrates, antibiotic prophylaxis is the least costly strategy at higher probabilities of developing cholangitis without prophylaxis and becomes more expensive as the probability of cholangitis after prophylaxis increases.

DISCUSSION

Our model suggests that single-dose antibiotic prophylaxis in patients undergoing ERCP for presumed biliary obstruction results in fewer cases of cholangitis and is a cost-saving intervention, with average savings of $79 per patient.

This model was constructed for a number of reasons: (i) the controversial nature of antibiotic prophylaxis resulting from conflicting outcomes of previous randomized controlled trials; (ii) the possible medico-legal consequences of performing future trials; (iii) the low

probability that a trial of sufficient size to statistically determine the clinical efficacy of antibiotic prophylaxis will ever be performed as it has been estimated that between 6000 and 21 836 patients would need to be enrolled to accomplish this objective;[6, 7] and (iv) the paucity of published data addressing the economic impact of antibiotic prophylaxis. To our knowledge, this is the first study to examine the economic impact of antibiotic prophylaxis prior to ERCP in patients with obstructive jaundice, not only from data available in the literature, but also incorporating data derived from our centre.

The issue of which antibiotic to use for prophylaxis was not addressed in our study. The reported cost savings are based on the use of cephalosporins and piperacillin, as these were the antibiotics utilized in the randomized controlled trials from which we obtained the probability of developing cholangitis. Additional trials comparing multiple dose regimens of oral ciprofloxacin with multiple dose regimens of cefuroxime and cefazolin have yielded similar rates of cholangitis in each group.[13, 14] Based on these findings, it could be hypothesized that single-dose oral ciprofloxacin would be as effective in preventing ERCP-related cholangitis as the previously studied cephalosporins. The use of single-dose oral ciprofloxacin for prophylaxis would result in an even greater cost reduction. The use of oral ciprofloxacin would also be ideal in patients allergic to penicillin. Ultimately, antibiotic choice may be best guided by considering local bacterial pathogens and their susceptibilities.

Limitations of our model and retrospective analysis must be considered. The data upon which our model was constructed were obtained from a total of three randomized controlled trials with 694 patients undergoing ERCP for presumed biliary obstruction;[7–9] the data may be skewed by the fact that 551 of these patients were enrolled in one of these trials.[7] The possibility of bacterial resistance resulting from antibiotic prophylaxis was not considered, as it was beyond the scope of our model and there are few data in the literature addressing the development of resistance after a single dose of antibiotics. Our retrospective analysis is also limited by the fact that the majority of patients in whom biliary drainage was unsuccessful then underwent percutaneous transhepatic cholangiography, for which antibiotic prophylaxis is routinely given at our institution, and were thus excluded from our analysis. Also, the prophylaxis group had a lower incidence of stenting of malignant strictures, which has been identified as a risk factor for cholangitis by univariate analysis.[15] Additional limitations of our retrospective analysis include the small number of patients who received prophylaxis, the fact that the prophylaxis group as a whole was younger and the higher rate of successful drainage in the prophylaxis group. In spite of these limitations, we performed rigorous patient follow-up and adhered to a strict definition of ERCP-related cholangitis.

The two-way sensitivity analysis of the probability of cholangitis with and without prophylaxis, depicted in Figure 4, can be used by individual institutions to determine whether a strategy of antibiotic prophylaxis would be cost saving based on their own rates of cholangitis.

Although a number of studies have failed to reveal statistical significance regarding the use of single-dose antibiotic prophylaxis to prevent ERCP-related cholangitis, data from our institution suggest that prophylaxis reduces the incidence and mortality of ERCP-related cholangitis in the setting of presumed biliary obstruction. In addition to these clinical implications, our study adds an economic dimension that supports the recommendations from the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology. Failure to administer antibiotics prior to ERCP in the setting of suspected biliary obstruction may be viewed as a breach in standard of care; in addition, possible legal costs resulting from the development of cholangitis in patients not receiving antibiotics would only increase the cost savings attributed to antibiotic prophylaxis.

Therefore, we conclude that single-dose antibiotic prophylaxis in the setting of presumed biliary obstruction to prevent ERCP-related cholangitis is a cost-saving strategy, as the additional drug-related expense of prophylaxis is outweighed by the cost of ERCP-related cholangitis. Based on these findings, we recommend adherence to guidelines regarding antibiotic prophylaxis in the setting of presumed biliary obstruction previously published by the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology.

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