

Endoscopic Screening for Esophageal Varices in Cirrhosis: Is it Ever Cost Effective?

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Current guidelines for the management of patients with compensated cirrhosis recommend universal screening endoscopy followed by prophylactic β -blocker therapy to prevent initial hemorrhage in those found to have esophageal varices. However, the cost-effectiveness of this recommendation has not been established. Our objective was to determine whether screening endoscopy is cost-effective compared with empiric medical management in patients with compensated cirrhosis. Decision analysis with Markov modeling was used to calculate the cost-effectiveness of 6 competing strategies: (1) universal screening endoscopy (EGD) followed by β -blocker (BB) therapy (EGD \rightarrow BB) if varices are present, (2) EGD followed by endoscopic band ligation (EBL) (EGD \rightarrow EBL) if varices are present, (3) selective screening endoscopy (sEGD) in high risk patients followed by BB therapy if varices are present (sEGD \rightarrow BB), (4) selective screening endoscopy followed by EBL (sEGD \rightarrow EBL) if varices are present, (5) empiric β -blocker therapy in all patients, and (6) no prophylactic therapy ("Do Nothing"). Cost estimates were from a third-party payer perspective. The main outcome measure was the cost per initial variceal hemorrhage prevented. The "Do Nothing" strategy was the least expensive yet least effective approach. Compared with the "Do Nothing" strategy, the empiric β -blocker strategy cost an incremental \$12,408 per additional variceal bleed prevented. Compared with the empiric β -blocker strategy, in turn, both the EGD \rightarrow BB and the EGD \rightarrow EBL strategies cost over \$175,000 more per additional bleed prevented. The sEGD \rightarrow BB and sEGD \rightarrow EBL strategies were more expensive and less effective than the empiric β -blocker strategy. In conclusion, empiric β -blocker therapy for the primary prophylaxis of variceal hemorrhage is a cost-effective measure, as the use of screening endoscopy to guide therapy adds significant cost with only marginal increase in effectiveness. (HEPATOLOGY 2003;37:366-377.)

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Chronic liver disease is a prevalent and clinically significant health care problem in the United States today, affecting 360 per 100,000 persons in the general adult population, resulting in 300,000 hos-

pitalizations annually, and costing over \$2 billion per year.¹⁻³ The most advanced stage of chronic liver disease is cirrhosis, and up to half of patients with Child's class A or B cirrhosis have moderate or large underlying esophageal varices.⁴⁻⁷ Once esophageal varices form, the risk of variceal bleeding within 2 years is 20% to 35%,^{8,9} and the risk of dying from an initial variceal bleed is up to 50%.¹⁰ In light of the substantial human and economic costs of variceal hemorrhage, several strategies have been developed for the primary prophylaxis against an initial bleed, including β -blocker (BB) therapy and endoscopic band ligation (EBL).

Previous economic models have evaluated the cost-effectiveness of competing strategies for the primary prophylaxis of variceal bleeding.¹¹⁻¹³ These analyses concern patients in whom esophageal varices have already been detected and focus on the preferred method to minimize a first episode of bleeding. However, the clinician evaluating a compensated cirrhotic patient is often unaware of whether there are underlying varices and is faced with the dilemma of whether or not to perform screening upper endoscopy. Proponents of screening endoscopy contend

Abbreviations: BB, β -blocker; EBL, endoscopic band ligation; EGD, universal screening endoscopy; sEGD, selective screening endoscopy; ICER, incremental cost-effectiveness ratios.

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that the procedure allows for the detection of esophageal varices, targeted endoscopic treatment in patients with esophageal varices, and reduction of unnecessary therapy in patients without esophageal varices.¹⁴ Both American¹⁵ and European¹⁶ consensus guidelines recommend universal screening endoscopy (EGD) in patients with cirrhosis, followed by BB therapy for those patients with esophageal varices. Opponents argue that a strategy of universal screening endoscopy requires an excessive use of resources to identify the subset of at-risk patients¹⁷ and that empiric medical therapy may be a more cost-effective approach that can be carried out in the primary care setting without reliance on specialist care.

In deference to both strategies, a recently proposed alternative approach is to perform *selective* screening endoscopy only in patients at high risk for underlying moderate or large esophageal varices.⁵⁻⁷ Several retrospective case-control studies^{5,7,18} and 1 prospective cohort study⁵ have identified 4 clinical variables that significantly correlate with the presence of varices: platelet count less than 88,000/mL,⁵⁻⁷ prothrombin activity less than 70%,⁶ splenomegaly,⁵ and a portal vein diameter greater than 13 mm on ultrasonography.⁵ These clinical predictors may allow physicians to select the subgroup of cirrhotic patients most likely to have underlying varices and, therefore, most likely to benefit from screening endoscopy. Despite arguments in favor of this approach, its cost-effectiveness has also not been formally compared with competing strategies, including universal screening endoscopy and empiric medical management.

In light of these recent data and the lack of consensus regarding the role of screening endoscopy in patients with cirrhosis, we sought to determine whether screening endoscopy might be a cost-effective strategy. We, therefore, evaluated the cost-effectiveness of 6 competing strategies for the primary prophylaxis of esophageal variceal hemorrhage in patients with compensated cirrhosis in whom the presence of esophageal varices is unknown (Fig. 1).

Patients and Methods

Decision analysis is a quantitative method for estimating the cost-effectiveness of alternative management strategies under conditions of uncertainty. Using decision analysis software (DATA version 3.5, TreeAge Software, Boston, MA), we evaluated a hypothetical cohort of patients with compensated (Child's Class A or B) cirrhosis in whom the presence of underlying esophageal varices was not known. We, therefore, assumed that the patients had not undergone prior evaluation for varices, such as upper endoscopy, barium swallow, or computerized tomography of the chest or abdomen. Patients with contraindications to BB therapy, including advanced obstructive

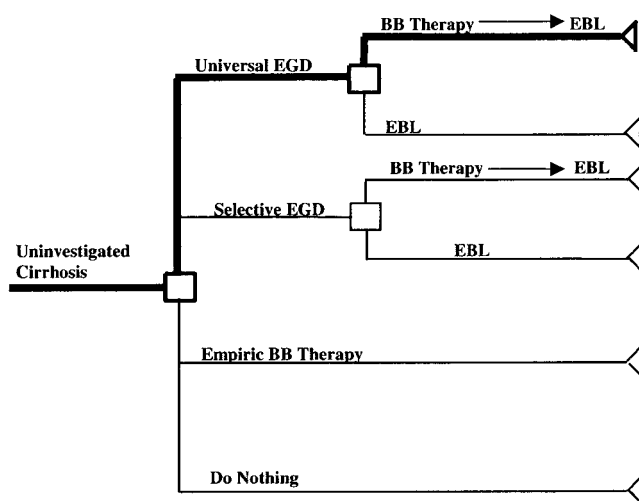


Fig. 1. Truncated diagnostic flow chart of 6 strategies for the management of a base case patient with Child's Class A or B cirrhosis in whom the presence of underlying varices is unknown. **Square nodes** denote decision points when the clinician may choose between alternative paths. The first pair of strategies begins with universal screening endoscopy (EGD) for varices, followed by either β -blocker (BB) therapy or endoscopic band ligation (EBL) if varices are present. The second pair of strategies begins with *selective* screening EGD for high-risk patients, again followed by either BB or EBL if varices are present. The 2 remaining strategies include the use of empiric BB therapy in place of screening endoscopy and the "Do Nothing" strategy. Patients that develop intolerance to β -blocker therapy subsequently progress to EBL, as denoted by **arrows**. The strategy recommended by current guidelines is marked in **bold lines**. See text for details regarding individual strategies.

tive lung disease, baseline hypotension, bradycardia, or heart block, were excluded from this analysis. Patients entered the model after presenting to their primary care provider for initial evaluation and were followed for 3 years. We used Markov modeling with 1-month-transition intervals to simulate the natural history of esophageal varices in each arm over the 36-month time horizon (Fig. 2).

Data Sources

Our model incorporated 18 separate probability estimates derived from a systematic review of the medical literature (Table 1). We performed a structured search of published reports from the MEDLINE and HealthSTAR bibliographic databases to identify relevant English-language publications from January 1985 to January 2002. When there was a range of data, we chose estimates that would tend to favor the current American¹⁵ and European¹⁶ guidelines of universal screening endoscopy and, therefore, biased the model against the competing strategies.

Cost Estimates

Costs were estimated from the perspective of a third-party payer, considering only direct health care costs (Ta-

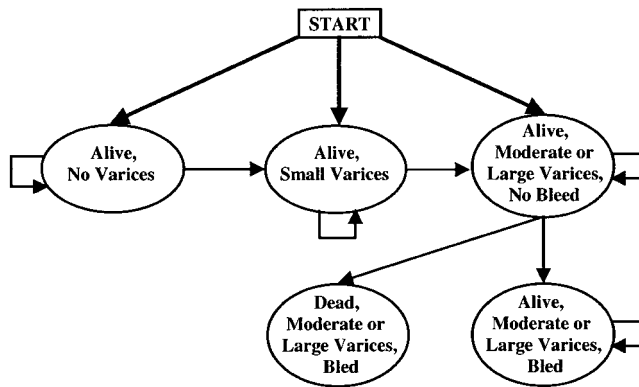


Fig. 2. Markov state diagram of cohort with uninvestigated compensated cirrhosis. Patients enter the model in 1 of 3 initial health states: (1) alive with no underlying varices, (2) alive with small underlying varices, or (3) alive with moderate or large underlying varices. During each 1-month cycle, individual patients either remain in their assigned health state (recursive arrows) or progress to a new health state (straight arrows). Patients without varices may progress to form small varices. Small varices are assumed to not bleed but may progress to form moderate or large varices. Moderate or large varices may bleed, which may or may not lead to death. Transition rates between health states were derived from the literature and were selected to represent the most likely clinical scenarios. Each patient progressed through the health states until either the 36-month time horizon was reached or the patient died from a variceal bleed. We assumed that death from nonvariceal causes was equal between health states and, therefore, did not model it as a separate health state.

ble 2). Cost discounting was not performed because of the relatively short time horizon and the even distribution of costly events (e.g., initial variceal bleeds) over time.

Outcomes

The main outcome measure was the cost per initial variceal bleed prevented by each strategy. We then calculated the incremental cost-effectiveness ratios (ICERs) for each strategy compared with the “Do Nothing” strategy, in which patients received no prophylactic intervention and were followed clinically.

Because mortality has not been shown to be significantly different between interventions for the primary prophylaxis of variceal hemorrhage, we did not model death as a primary outcome. However, because costs cease to accrue when a patient dies, our model did incorporate the risk of dying from a variceal hemorrhage (See “Model Assumptions” below). We assumed that death from nonvariceal etiologies was equal between the competing strategies.

Decision Model

We evaluated 6 strategies for the primary prophylaxis of variceal hemorrhage in a hypothetical 50-year-old base case patient with newly diagnosed Child’s class A or B

Table 1. Base Case Clinical Probability Estimates

Variable	Base Case Estimate	Range in Literature	Range Tested	References
Probability of underlying varices in cirrhotic patients unstratified by risk with Child’s Class A or B cirrhosis	40%	9%-50%	0%-100%	4-7,18
Odds ratio of underlying varices in high-risk patients with Child’s Class A or B cirrhosis vs. low-risk patients	2.9	1.7-5.8	1.0-10.0	5-7,18
Proportion of cohort with 1 or more risk factors for underlying varices (high-risk proportion)	70%	60%-80%	0%-100%	5,6
Three-year rate of variceal hemorrhage once varices have formed in patients on no prophylactic therapy	33%	20%-35%	0%-80%	22-44
Odds ratio of variceal hemorrhage once varices have formed in patients on β -blocker therapy vs. no prophylactic therapy	0.5	0.47-0.54	0-1.0	45-49
Odds ratio of variceal hemorrhage once varices have formed in patients receiving prophylactic EBL vs. no prophylactic therapy	0.36	0.36	0-1.0	21
Probability of noncompliance with medical therapy in patients receiving empiric β -blockers				
Drop-out probability	10%	0%-15%	0%-33%	22-32
Reported noncompliance probability	15%	4%-20%	0%-33%	22-32
Unreported noncompliance probability	10%	No Range	0%-33%	Assumption
Total	35%			
Probability of noncompliance with medical therapy in patients receiving β -blockers after confirming varices by screening endoscopy	30%	No Range	0%-100%	Assumption
Proportion of patients receiving prophylactic EBL who do not complete full course of therapy	20%	3%-20%	0%-100%	33,34
Average number of sessions required to obliterate varices with prophylactic EBL	3.3	3-4	0-6	21
Probability of severe complications requiring hospitalization and surgery from screening endoscopy	0.02%	0.02%	0%-3%	51-53
Probability of severe endoscopic complications requiring hospitalization and surgery from prophylactic band ligation	0.02%	No Range	0%-5%	Assumption
Annual rate of developing new esophageal varices	7%	10%	0%-50%	4,19,20
Annual rate of small esophageal varices progressing to moderate or large varices	10%	10%	0%-50%	4
Probability of dying from an initial variceal hemorrhage	33%	20%-50%	20%-80%	10
Average length of hospital stay for an initial variceal hemorrhage	4	No Range	1-20	54

Table 2. Current Procedural Terminology and Costs to Medicare

Variable	Base Case Cost Estimate (\$)	Range Tested (\$)
Cost of screening upper endoscopy:		
Endoscopist's consultation fee:	160	
Endoscopist's procedure fee:	231	
Facility Fee:	433	0-2,000
Total cost	824	
Cost of 1 session of endoscopic band ligation		
Endoscopist's consultation fee	160	
Endoscopist's procedure fee	299	
Facility fee	433	0-2,000
Total cost	892	
Cost of 1 month of β -blocker therapy (propranolol 10 mg 3 times daily)	10	0-100
Cost of inpatient admission for variceal hemorrhage		
Medicare DRG for complicated ulcer hemorrhage	10,124	
Cost of emergency room fee	168	
Cost of gastroenterologist consult	160	
Cost of endoscopist's fee for endoscopic band ligation	299	
Cost of follow-up visit by gastroenterologist	53/d \times 3	
Total cost	10,910	0-20,000
Cost of inpatient admission of severe endoscopic complication:		
Medicare DRG for bowel perforation	13,531	
Initial surgical consultation	97	
Surgeon's fee	710	
Anesthesiologist's fee	299	
Surgeon's follow-up visit	53 \times 5	
Total cost	14,902	0-20,000

NOTE. Costs for endoscopic and surgical procedures and physician services were obtained from the 2001 American Medical Association Current Procedural Terminology codebook and the 2001 Medicare Fee Schedule. Drug costs were obtained from the 2001 Red Book of average wholesale prices for pharmaceuticals.

cirrhosis in whom the presence of underlying varices is not known (Fig. 1).

Current Guidelines (EGD \rightarrow BB). This strategy is based on the current American College of Gastroenterology (ACG) guidelines for the primary prophylaxis of esophageal variceal hemorrhage¹⁵ and is similar to the European guidelines established by the Baveno III Consensus Workshop.¹⁶ Specifically, *all* patients with compensated cirrhosis receive screening upper endoscopy to evaluate for underlying varices. Patients with small or no varices at the time of endoscopy do not receive prophylactic therapy and subsequently undergo repeat screening endoscopy every other year. Patients with moderate or large varices found on initial *or* repeat screening endoscopy receive propranolol, with doses titrated to reduce the

systolic blood pressure by 25% or to reduce the resting heart rate to 55 beats per minute. Patients who develop intolerance to BB therapy are offered prophylactic EBL. Patients are followed clinically during the 3-year period and either bleed or do not bleed. Patients with a variceal bleed are admitted to the hospital and receive urgent EBL for hemostasis.

Universal Screening Endoscopy With EBL (EGD \rightarrow EBL). Patients in this strategy are initially managed with universal screening endoscopy, as described in the current guidelines. However, unlike the current guidelines, patients found to have moderate or large varices on initial or repeat endoscopy are treated with prophylactic EBL, rather than BB therapy. Management then proceeds as described in the current guidelines.

Selective Screening Endoscopy With BB Therapy (sEGD \rightarrow BB). Patients in this strategy are initially stratified into high- and low-risk groups for underlying varices as based on laboratory and ultrasonographic criteria. Specifically, patients with either a platelet count less than 88,000/mL, a prothrombin time activity less than 70%, a portal vein diameter greater than 13 mm, or splenomegaly are considered to be at high risk for varices.⁵⁻⁷ High-risk patients receive screening endoscopy and are placed on BB therapy if moderate or large varices are found, whereas low-risk patients are followed clinically without prophylactic therapy. High-risk patients found to have small or no varices on screening endoscopy also do not receive prophylactic therapy but subsequently undergo repeat screening endoscopy every other year. Patients who develop intolerance to BB therapy are offered prophylactic EBL. Management then proceeds as described in the current guidelines.

Selective Screening Endoscopy With EBL (sEGD \rightarrow EBL). In this strategy, patients are also initially stratified into high- and low-risk groups based on laboratory and ultrasonographic criteria and are then managed as described in the sEGD \rightarrow BB strategy. However, unlike the sEGD \rightarrow BB strategy, patients in this strategy receive prophylactic EBL rather than BB therapy.

Empiric BB Therapy. Patients in this strategy are uniformly offered empiric propranolol regardless of the clinical suspicion for underlying varices. Patients who develop intolerance to BBs are referred for upper endoscopy and then receive prophylactic EBL if moderate or large esophageal varices are identified. Management then proceeds as described in the current guidelines.

Do Nothing. Patients in this strategy are followed clinically and neither receive screening endoscopy nor empiric medical therapy. Therapeutic interventions are only offered if a variceal bleed occurs.

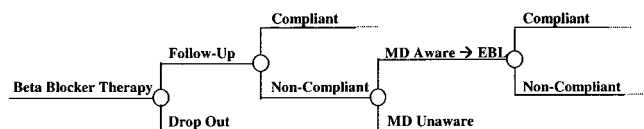


Fig. 3. Compliance scheme for decision model. Patients on β -blocker therapy either follow-up with their physician or drop out. Patients that drop out are assumed to be noncompliant and have a risk of bleeding equal to untreated controls. Patients that follow-up are either compliant with the prescribed course of therapy or are not. Noncompliant patients either inform their physician of their noncompliance (*i.e.*, admit to limiting side effects) or do not. If the physician is aware of noncompliance, the patient is referred for prophylactic endoscopic band ligation (EBL). If the physician is unaware of noncompliance, the patient's risk of bleeding is equal to untreated controls. Patients receiving EBL are either compliant with the full course of EBL (*i.e.*, attend all follow-up sessions until varices obliterated) or are not. Patients noncompliant with EBL have a bleeding risk equal to untreated controls.

Model Assumptions

(1) The decision model was based upon intention-to-treat analysis. Figure 3 portrays the compliance scheme incorporated into the model, which accounts for the rate of patient dropout, the rate of noncompliance with therapy, and the likelihood of reporting noncompliance to the physician.

(2) Patients without esophageal varices at the start of the time horizon developed new small varices at a rate of 7% per year.^{4,19,20} This estimate was varied from 0% to 50% in our sensitivity analysis.

(3) Patients with small varices did not develop variceal hemorrhage. However, we assumed that small varices progressed to moderate or to large varices at a rate of 10% per year.⁴ This estimate was varied from 0% to 50% in our sensitivity analysis.

(4) Patients with variceal hemorrhage were admitted to the hospital and received EBL for hemostasis. We assumed that one third of patients with a variceal bleed died¹⁰ and varied this estimate between 20% and 80% in our sensitivity analysis.

(5) Patients surviving an initial variceal bleed received an average of 3.3 additional sessions of EBL as an outpatient (based upon mean from 9 randomized controlled

EBL studies)²¹ and were all placed on BB therapy and followed monthly thereafter by their physician.

Clinical Inputs and Probability Estimates Derived from Systematic Review

Probability of Underlying Varices. *In compensated cirrhotic patients unstratified by risk.* The prevalence of moderate or large varices among unstratified cirrhotic patients without a history of variceal hemorrhage has been reported in several trials and ranges from 9% to 50%.^{4-7,17} The mean prevalence of moderate-to-large varices in the subgroup of patients with Child's class A or B cirrhosis is 40%,^{4-7,17} and we adopted this as our base case estimate. Because the precision of this estimate is unlikely to be reproduced between different populations, we varied it from 0% to 100% in our sensitivity analysis.

In patients stratified by risk. Several reports have identified clinical risk factors that may predict the presence of underlying moderate or large esophageal varices, (Table 3).^{5-7,17} Based on these reports, we assumed that 49% of high-risk patients (patients with thrombocytopenia, splenomegaly, elevated prothrombin time, or enlarged portal vein on ultrasonography) had underlying moderate or large varices, and only 17% of low-risk patients had underlying varices. Furthermore, we assumed that 70% of the hypothetical cohort was at high risk for varices (*i.e.*, had 1 or more risk factors), whereas the remaining 30% was at low risk for varices. See Appendix A for the extended rationale supporting these base case estimates. Because the precision of these estimates is unlikely to be reproduced in different populations, we varied each over a wide range in sensitivity analysis.

Bleeding Rates. *In patients on no prophylactic therapy.* Once moderate or large esophageal varices have formed, the risk of bleeding without prophylactic therapy ranges from 20% to 35% over the subsequent 3 years.^{8,9} The mean probability of bleeding in the placebo arms of 23 published randomized controlled primary prophylaxis studies of varying design, patient population, and follow-up is 33%.²²⁻⁴⁴ We varied the 3-year estimate be-

Table 3. Clinical Predictors of Esophageal Varices With Corresponding Odds Ratios From Published Reports

Authors	Study Design	Child's Class	No.	Clinical Risk Factor	Odds Ratio* (CI)
Chalasanani et al. ⁵	Retrospective cohort	A, B, C	346	Platelet < 88 K	1.7 (1.0-3.0)
				Splenomegaly on exam	2.0 (1.1-3.8)
Schepis et al. ⁶	Prospective cohort	A or B	143	Platelet < 100 K	2.8 (1.3-6.3)
				PT activity < 70%	5.8 (2.6-12.8)
				Portal vein > 13 mm	2.9 (1.3-6.3)
Zaman et al. ⁷	Unmatched Case-control	A	66	Platelet < 90 K	2.3 (1.4-3.9)
		B or C	234	Platelet < 90 K	2.8 (1.3-5.8)

Abbreviations: K, 1,000.

*Odds of esophageal varices in patients with presence of risk factor vs. odds of esophageal varices in patients with absence of risk factor.

tween 0% and 80% in sensitivity analysis.

In patients on BB therapy. We identified 11 randomized controlled trials comparing BB therapy with placebo in the primary prophylaxis of variceal bleeding,²¹⁻³¹ and these have been summarized in 5 metaanalyses.⁴⁵⁻⁴⁹ The pooled odds ratio for variceal bleeding on BB therapy versus placebo ranges from 0.47 to 0.54, with a mean of 0.50. We therefore assumed that the risk of bleeding for patients with moderate or large varices who were compliant with their medication was 50% lower than the risk of those patients on no therapy. The risk of bleeding over the 3-year time horizon was therefore set at 16.5% (33% placebo rate \times 0.5).

In patients receiving prophylactic EBL. Nine randomized controlled trials have evaluated the effect of EBL for primary prophylaxis, and these were recently summarized in a comprehensive metaanalysis.²¹ The pooled relative risk of variceal bleeding versus untreated controls is 0.36. The risk of bleeding over the 3-year time horizon was therefore set at 11.9% (33% placebo rate \times 0.36) for patients completing the full course of EBL. This estimate was varied from 0% to 50% in sensitivity analysis.

Probability of Compliance. *In patients on BB therapy.* Nonselective BBs have several undesirable side effects, including fatigue, lightheadedness, symptomatic bradycardia, hypotension, and impotence. Therefore, many patients cannot tolerate BBs and require alternative methods for primary prophylaxis. Based on our review of the literature, we assumed that 35% of patients receiving empiric BBs were noncompliant with therapy. Because patients receiving empiric BBs may be less likely to comply with therapy compared with patients known to have varices by screening endoscopy, we assumed that only 30% of patients in the screening endoscopy strategies were noncompliant (compared with 35%). This conservative assumption biases the model in favor of the screening endoscopy strategies by penalizing the empiric BB strategy with a higher rate of noncompliance. Because this assumption is conjectural, we also performed a separate analysis assuming equal compliance. See Appendix B for the extended rationale supporting these estimates.

In patients receiving prophylactic EBL. For EBL to be successful in the primary prophylaxis of variceal hemorrhage, the esophageal varices should optimally be obliterated, which requires an average of 3.3 endoscopic sessions to accomplish.²¹ Based on our review of the literature, we assumed that 20% of patients receiving prophylactic EBL did not complete the full course of endoscopic therapy. See Appendix B for the extended rationale supporting this estimate.

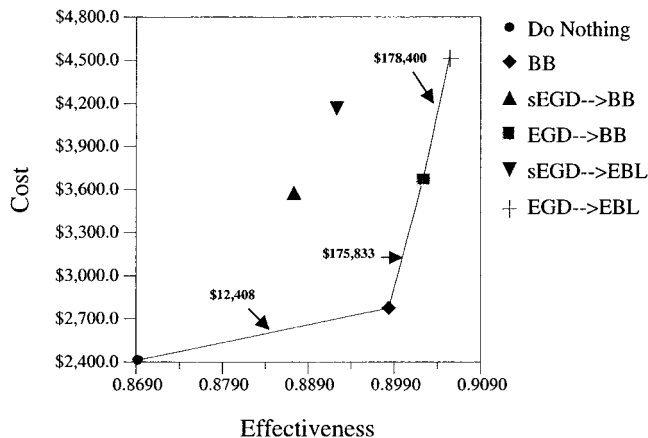


Fig. 4. Results of base case cost-effectiveness analysis. The **vertical axis** displays the 3-year cumulative cost, and the **horizontal axis** displays the proportion of patients avoiding a variceal hemorrhage. The “Do Nothing” strategy is located at the origin and is the least expensive and least effective of the 6 competing strategies. Each **line** represents the incremental cost-effectiveness ratio (ICER) between the connected strategies. The ICER between strategies represents the additional cost that must be expended to prevent 1 additional variceal bleed when adopting the more expensive of the 2 compared strategies. The dominated strategies (sEGD→BB and sEGD→EBL) fall above and to the left of the concave border that outlines the 4 strategies that compose the “cost-effectiveness frontier.”

Probability of Complications with Upper Endoscopy and EBL. See Appendix C for the extended rationale supporting these base case complication estimates.

Sensitivity Analysis

We performed sensitivity analyses to evaluate the effect of varying the cost and probability estimates over ranges exceeding the degree of uncertainty expected based on the medical literature. We evaluated the impact of sensitivity analysis on the ICER between the competing strategies and report the threshold at which the ICER is \$50,000, a value commonly cited as the acceptable “cut-off” for the cost-effectiveness of medical interventions.⁵⁰ However, because this value is arbitrary and different third-party payers have different willingness-to-pay thresholds, we also report key analyses graphically to demonstrate the full range of generated ICERs.

Results

The results of our base case analysis are displayed in Fig. 4, which depicts the cumulative 3-year cost versus the proportion of patients avoiding a variceal hemorrhage among the 6 competing strategies. The “Do Nothing” strategy cost \$2,401 per average patient treated and prevented a variceal hemorrhage in 87% of the cohort and was therefore the least expensive but also the least effective of the 6 competing approaches. Compared with the “Do

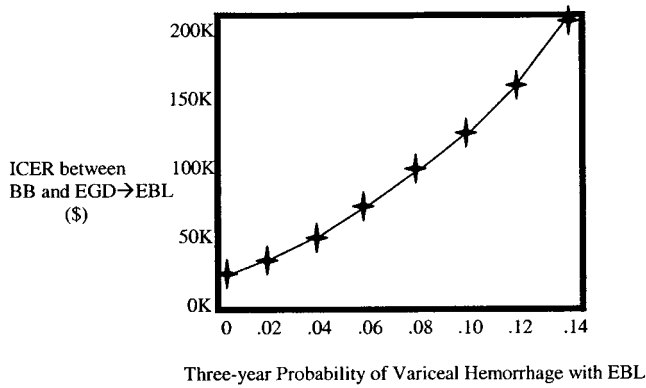


Fig. 5. One-way sensitivity analysis comparing the incremental cost-effectiveness ratio (ICER) between the empiric β -blocker strategy (BB) and the EGD→EBL strategy as the probability of variceal hemorrhage in patients receiving EBL is varied. Under base case conditions (11.9% probability), the EGD→EBL strategy costs an additional \$167,805 per additional variceal bleed prevented compared with the empiric BB strategy. However, the ICER falls to less than \$50,000 when the 3-year bleeding rate falls to less than 4%.

Nothing” strategy, the empiric BB strategy cost an incremental \$12,408 per additional variceal bleed prevented (represented by the line connecting the 2 strategies in Fig. 4). The introduction of screening endoscopy increased the relative cost significantly, with only a small relative increase in effectiveness as demonstrated by the sharp incline of the successive ICERs in Fig. 4. Specifically, the strategy supported by the current ACG guidelines (EGD→BB) cost an incremental \$175,833 per additional variceal bleed prevented compared with the empiric BB strategy. In turn, the EGD→EBL strategy cost an incremental \$178,400 compared with the current guidelines. The selective screening endoscopy strategies (sEGD→BB and sEGD→EBL) were both more expensive and concurrently less effective than the empiric BB strategy and were therefore dominated.

We performed sensitivity analysis to determine whether our findings were robust to changes in the base case probability estimates. Although sensitivity analysis did not alter the relative order of the 6 strategies, variation of several key estimates did impact the ICERs among the strategies. For example, the effectiveness of EBL impacted the model results when varied over a wide range. Figure 5 demonstrates the impact of varying the effectiveness of prophylactic EBL on the ICER between the EGD→EBL strategy and the empiric BB strategy. As the effectiveness of EBL increased, the ICER between the strategies fell rapidly. For example, the ICER fell to \$50,000 when the 3-year rate of variceal hemorrhage with EBL fell from the base case estimate of 11.9% to 4% (a 66% reduction).

Compliance with BB therapy plays a pivotal role in determining the cost-effectiveness of competing strategies

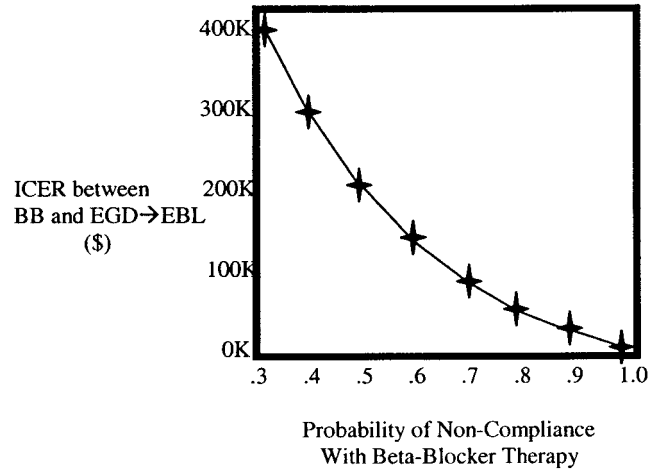


Fig. 6. One-way sensitivity analysis comparing the incremental cost-effectiveness ratio (ICER) between the empiric β -blocker strategy (BB) and the EGD→EBL strategy as probability of noncompliance with β -blocker therapy is varied. Under base case conditions (35% noncompliance rate), the EGD→EBL strategy costs an additional \$167,805 per additional variceal bleed prevented compared with the empiric BB strategy. However, the ICER falls to less than \$50,000 when more than 80% of the cohort receiving β -blocker therapy is noncompliant.

and therefore also impacted the model results. Figure 6 demonstrates the impact of varying the probability of noncompliance on the ICER between the EGD→EBL strategy and the empiric BB strategy. As the probability of noncompliance increased from the 35% base case estimate, the ICER again fell rapidly. For example, the ICER between strategies was \$50,000 when 80% of the cohort was noncompliant and only \$4,000 when the entire cohort was noncompliant.

Our base case analysis assumed that patients with known varices from endoscopic screening were more likely to remain compliant with BB therapy, whereas those receiving empiric BBs were less likely to comply. Because this assumption is conjectural, we performed a separate analysis in which compliance was equal between groups. Table 4 displays the results of this analysis for the “Do Nothing” and empiric BB strategies, respectively. Specifically, both strategies became equally effective assuming equal compliance. Therefore, because screening endoscopy was more expensive than empiric BB therapy,

Table 4. Results of Cost-Effectiveness Analysis Assuming Equal Compliance With β -Blockers Between Patients Receiving Empiric Therapy and Patients With Known Varices From Screening Endoscopy

Strategy	Cost	Effectiveness	ICER
Empiric BB	\$2,772	89%	–
EGD→BB	\$3,737	89%	Infinity

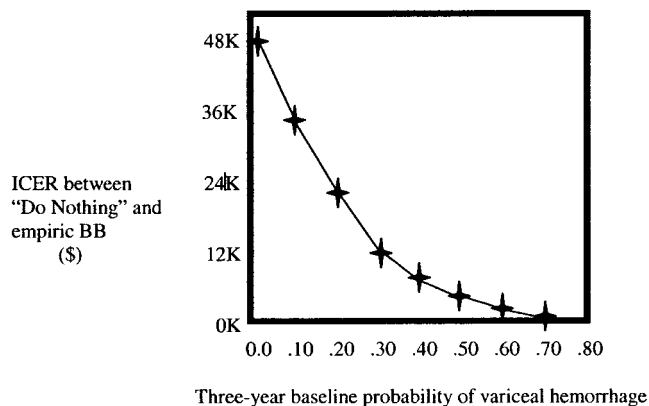


Fig. 7. One-way sensitivity analysis comparing the incremental cost-effectiveness ratio (ICER) between the "Do Nothing" strategy and the empiric β -blocker strategy (BB) as the baseline probability of variceal hemorrhage is varied. Under base case conditions (33% probability), the BB strategy costs an additional \$12,408 per additional variceal bleed prevented compared with the "Do Nothing" strategy. However, the ICER falls rapidly as the baseline risk of bleeding increases and reaches \$0.00 when the probability is 73%. Conversely, the ICER increases to \$48,000 when the probability of bleeding falls to 5% and reaches infinity when the probability is 0%.

the ICER between strategies became infinity (additional cost with no additional benefit).

The baseline probability of variceal hemorrhage varies widely between studies. We therefore performed a sensitivity analysis on this variable (Fig. 7). As the 3-year rate of hemorrhage fell from the baseline estimate of 33%, the ICER between the "Do Nothing" and BB strategies increased dramatically (Fig. 7). Conversely, as the 3-year rate increased to 73%, the ICER fell to \$0.00.

We used 1-way sensitivity analysis to examine whether altering the cost estimates affected our results. The cost of screening endoscopy impacted the model results when varied over a wide range. For example, the ICER between the current guidelines (EGD \rightarrow BB) and the empiric BB strategy fell from \$175,873 to \$50,000 when the cost of screening endoscopy fell by two thirds (from \$824 to \$281). The cost of generic propranolol also impacted the model results in sensitivity analysis. For example, the ICER between the EGD \rightarrow EBL strategy and the empiric BB strategy fell from \$177,142 to \$50,000 when the cost of generic propranolol increased 7-fold (from \$10/month to \$70/month).

Discussion

The current guidelines for the primary prophylaxis of esophageal varices recommend universal screening endoscopy for patients with Child's class A or B cirrhosis, followed by BB therapy for those found to have moderate or large varices.^{15,16} Our analysis of alternative management strategies for uninvestigated cirrhotic patients suggests

that this practice may not be a cost-effective approach. Compared with the use of empiric BB therapy alone, the use of screening endoscopy to guide therapy may cost over \$175,000 more per additional variceal bleed prevented. This finding persists even when accounting patient dropouts, reported noncompliance, and unreported noncompliance with medical therapy. Our model suggests that the use of screening endoscopy may only become cost-effective compared with empiric medical therapy when noncompliance with BBs exceeds 80% or when the rate of hemorrhage with EBL falls by 66% of its current rate.

Our analysis further suggests that the use of selective screening endoscopy in patients at high risk for underlying varices, although conceptually attractive, is unlikely to be cost-effective under typical clinical circumstances. Based on our calculations (see Appendix A), the use of clinical prediction rules to direct screening endoscopy under base case conditions will still miss varices in 17% of the low-risk patients and will find varices in only 49% of high-risk patients. Therefore, selective screening endoscopy is only likely to be cost-effective when the proportion of high-risk patients is minimized and the probability of underlying varices in the high-risk proportion is maximized. Until prediction rules with high positive and negative predictive values are developed and prospectively validated, selective screening endoscopy will likely remain less cost-effective than empiric medical management.

Although metaanalysis of the available data reveals that EBL is more effective than BB therapy for the primary prophylaxis of variceal hemorrhage,²¹ our analysis produces nearly equivalent effectiveness among all therapeutic arms, regardless of the therapy employed (Table 4). This seeming inconsistency is clarified by a consideration of the base case population. Although EBL is more effective²¹ and, under certain circumstances, more cost-effective¹³ than BB therapy for the subgroup of patients with *established* varices, our analysis concerns the broader population of compensated cirrhotic patients in whom the presence of varices is unknown. Under base case conditions, only 40% of this uninvestigated population has underlying varices,^{4-7,17} of which 33% will bleed without any intervention.²²⁻⁴⁴ Therefore, even while accounting for the 5% to 10% rate of new variceal formation per year,^{4,19,20} only 16% of the initial uninvestigated cohort will develop variceal bleeding over a 3-year period *without* any prophylactic intervention. Although EBL may reduce this rate by nearly two thirds,²¹ its *net* effect on the entire cohort when accounting for noncompliance with follow-up endoscopy sessions is to reduce the probability of hemorrhage from 16% to 10%. Likewise, although BB therapy may reduce the rate by half,⁴⁶⁻⁵⁰ its net effect on the entire cohort when accounting for significant non-

compliance is to reduce the probability from 16% to 12%. Therefore, the *absolute* risk reduction for variceal hemorrhage between the empiric BB and EGD→EBL strategies is only 2% (12% vs. 10%, respectively). This marginal difference in effectiveness appears inadequate to offset the significant difference in cost between the empiric BB strategy and the sEGD→EBL and EGD→EBL strategies. In this context, offering no prophylactic therapy at all and accepting a 16% probability of hemorrhage (*i.e.*, the “Do Nothing” strategy) has the lowest average cost-effectiveness ratio, even when accounting for the substantial economic penalty of variceal hemorrhage. Although withholding prophylactic therapy may not be ethically justifiable given the availability of inexpensive alternatives, its potential cost-effectiveness highlights the fact that prophylactic interventions only marginally impact uninvestigated cirrhotic patients as a whole, in contrast to their significant impact on the select subgroup of compensated cirrhotic patients with known varices.

There are several limitations to this study. As with any decision analysis, the results depend upon the validity of the base case estimates. Because our base case point estimates are unlikely to reflect all populations, our results are unlikely to be precisely reproduced in all populations. Moreover, several of our estimates are based on studies of varying design, patient population, follow-up, and quality. We have attempted to guard against inaccurate base case results by systematically reviewing the literature, relying upon preexisting metaanalyses when available, and selecting conservative estimates that tend to bias the model in favor of the current guidelines of universal screening endoscopy. Despite this conservative approach, our model indicates that the current guidelines may not be cost-effective compared with empiric medical management.

In conclusion, this analysis suggests that the current guidelines recommending universal endoscopic screening for varices in cirrhosis may cost over \$170,000 per variceal bleed prevented when compared with empiric BB therapy alone. Additionally, the practice of selective screening endoscopy using clinical predictors of underlying varices is unlikely to be cost-effective until prediction rules with higher positive and negative predictive values are developed and prospectively validated. Until such time, empiric medical therapy of patients with Child’s class A or B cirrhosis appears to be the most cost-effective approach, with EBL reserved for patients with contraindications to or intolerance of medical management. In light of this analysis, using the best data available at this time, we suggest that the endorsement of the current guidelines be reappraised with a prospective trial comparing the ac-

rued cost and effectiveness of these competing management strategies.

Appendix A: Rationale for Probability Estimates of Underlying Varices in Patients Stratified by Risk

Table 3 summarizes the findings from 3 identified peer-reviewed studies that identify risk factors for underlying esophageal varices in cirrhosis.⁵⁻⁷ All 3 studies identify thrombocytopenia as a significant risk factor for underlying varices, with an odds ratio ranging from 1.7 to 2.8 versus patients with normal platelet counts. The presence of splenomegaly detected on physical examination has an odds ratio of 2.0,⁵ and the presence of a portal vein size greater than 13 mm on ultrasonography has an odds ratio of 2.9.⁵ The strongest predictive risk factor is a prothrombin activity less than 70%, which carries an odds ratio of 5.8 versus patients with a normal prothrombin activity.⁶ Our analysis did not divide subjects into specific risk groups based on the number of individual risk factors present but, instead, considered the presence of any one risk factor sufficient to deem a patient at high risk for underlying varices. Because there are no data regarding the incremental odds of underlying varices with *combinations* of risk factors, we could not reliably model the potential effect of having more than one risk factor. The mean odds ratio of all the risk factors is 2.9 versus the absence of any risk factors; therefore, we adopted this as our base case estimate. To account for variation in clinical practice, we varied this estimate from 1.0 to 10 in sensitivity analysis. To convert the mean odds ratio into a percentage for use in the decision model, the following relationship was used based on the previous assumption that 40% of the cohort had underlying varices:

$$.40 = (\text{proportion with risk factor})(2.9x) + (\text{proportion without risk factor})(x)$$

Accordingly, “x” is the proportion of patients without any risk factors that has esophageal varices, and 2.9x is the proportion of patients with one or more risk factors that has esophageal varices. Therefore, the total proportion of varices in the cohort is equal to the sum of the proportion of varices in the subgroup with a risk factor and the proportion of varices in the subgroup without any risk factors. The mean proportion of high-risk patients reported in the 3 studies is .70,⁵⁻⁷ and we adopted this as our base case estimate. In other words, we assumed that 70% of our hypothetical cohort had at least 1 of the identified risk factors, including thrombocytopenia, splenomegaly, depressed prothrombin activity, or an enlarged portal vein on ultrasonography. Therefore, the proportion of patients

with esophageal varices in each risk group was the following:

$$.40 = (.70) (2.9x) + (.30) (x)$$

In the equation, $x = .17$ (proportion of varices in patients without risk factor) and $2.9x = .49$ (proportion of varices in patients with risk factor).

Appendix B: Rationale for Probability Estimates of Compliance Rates

Compliance With BB Therapy

To accurately model the effect of noncompliance on outcomes, we used intention-to-treat analysis and attempted to account for patient dropouts and failure to report noncompliance (Fig. 2). The average probability of patient dropout in the BB arms of 11 primary prophylaxis studies is 10%, and we adopted this as our base case estimate.²³⁻³³ We assumed that these patients had a risk of bleeding equal to untreated controls. The average probability of *reported* noncompliance because of intolerable side effects is 15%.²²⁻³² We assumed that these patients were referred for EBL, because the clinician was aware of the noncompliance. The probability of *unreported* noncompliance is difficult to discern, although it may play an important role in determining the effectiveness of BB therapy because unreported noncompliance will not prompt referral for alternative treatment. Few studies have attempted to capture this subgroup by measuring serum drug levels, tabulating pill counts, or measuring heart rate. In light of minimal data, we conservatively assumed that 10% of patients receiving BB therapy were noncompliant without informing their physician, in addition to the 15% probability of reported noncompliance. We assumed that these patients had a risk of bleeding equal to untreated controls. Therefore, the combined probability of noncompliance in patients receiving BBs was 35%, representing the sum of patient dropouts, reported noncompliance, and unreported noncompliance. This estimate was varied between 0% and 100% in sensitivity analysis.

Compliance With Prophylactic EBL

EBL requires, on average, a total of 3.3 endoscopic sessions to successfully obliterate moderate-to-large varices.²¹ Because of the significant time and inconvenience associated with serial endoscopy and conscious sedation, many patients do not comply with the full course of therapy. Only 2 primary prophylaxis studies have reported the probability of noncompliance with EBL, and the average rate is 10%.^{33,34} Because the probability of noncompliance is likely to be higher in uncontrolled clinical settings, we doubled the reported probability and assumed that

20% of the patients receiving prophylactic EBL did not complete a full course of endoscopic therapy. This estimate was varied between 0% and 100% in sensitivity analysis.

Appendix C: Rationale for Probability Estimates of Complication Rates

Complication Rates With Screening Endoscopy and Conscious Sedation

The most common complications of endoscopy are cardiorespiratory and generally require additional observation only. Severe complications of upper endoscopy include bowel perforation and induction of uncontrollable bleeding. Our model assumed a 0.02% probability of severe endoscopic complications requiring hospitalization and surgery.⁵¹⁻⁵³ This estimate was varied between 0% and 3% in our sensitivity analysis. The costs of severe endoscopic complications were modeled after the surgical repair of a bowel perforation (Table 2).

Complication Rates With Prophylactic EBL

The most common complications of EBL are transient and include dysphagia, chest tightness, and low-grade fevers. There are limited data regarding the rates of significant complications from EBL for the primary prophylaxis of variceal hemorrhage. Reported significant complications include stricture formation, perforation, and induction of hemorrhage requiring hospitalization.²¹ In the face of limited data, we assumed a 0% probability of severe complications with EBL. Although significant complications will invariably occur in clinical practice, we adopted this value to bias the model in favor of the EBL strategies and against the empiric medical management strategies.

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