Endoscopic Screening for Varices in Cirrhosis: Findings, Implications, and Outcomes

DENNIS M. JENSEN
CURE Digestive Diseases Research Center, University of California Los Angeles School of Medicine, and the Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California

At least two thirds of cirrhotic patients develop esophageal varices during their lifetime. Severe upper gastrointestinal (UGI) bleeding as a complication of portal hypertension develops in about 30%–40% of cirrhotics. Despite significant improvements in the early diagnosis and treatment of esophagogastric variceal hemorrhage, the mortality rate of first variceal hemorrhage remains high (20%–35%). Primary prophylaxis, the focus of this article, is treatment of patients who never had previous variceal bleeding to prevent the first variceal hemorrhage. The potential of preventing first variceal hemorrhage offers the promise of reducing mortality, morbidity, and associated health care costs. This article (1) reviews endoscopic grading of size and stigmata for esophageal and gastric varices, (2) describes data on prevalence and incidence of esophageal and gastric varices from prospective studies, (3) discusses independent risk factors from multivariate analyses of prospective studies for development of first esophageal or gastric variceal hemorrhage and possible stratification of patients based on these risk factors, (4) comments on the potential cost effectiveness of screening all newly diagnosed cirrhotic patients and treating high-risk patients with medical or endoscopic therapies, and (5) recommends further studies of endoscopic screening, stratification, and outcomes in prospective studies of endoscopic therapy. The author’s recommendations are to perform endoscopic screening for the following subgroups of cirrhotics: all newly diagnosed cirrhotic patients and all other cirrhotics who are medically stable, willing to be treated prophylactically, and would benefit from medical or endoscopic therapies. Exclude patients who are unlikely to benefit from prophylactic therapies designed to prevent the first variceal hemorrhage, those with short life expectancy, and those with previous UGI hemorrhage (they should have already undergone endoscopy). For low or very low risk cirrhotic patients—those found to have no varices or small varices without stigmata—repeat endoscopy is recommended because screening for progression may be warranted in 2 or more years.

At least two thirds of cirrhotic patients develop esophageal varices during their lifetime, as reported in older studies.1,2 More recently, with endoscopic assessment and follow-up, the prevalence of esophageal varices has been reported to be as high as 80%–90%.3,4 Severe upper gastrointestinal (UGI) bleeding as a complication of portal hypertension develops in about 30%–40% of cirrhotic patients.5,6 Although esophageal varices are the most frequent source of UGI hemorrhage when emergency endoscopy is performed in patients with cirrhosis, gastric varices, Mallory-Weiss tears, peptic ulcers, and portal hypertensive gastropathy are also common causes of acute UGI bleeding in cirrhotic patients, accounting for up to 50% of initial UGI bleeds in some reports.7 Despite significant improvements in the early diagnosis and treatment of esophagogastric variceal hemorrhage, the mortality rate of first variceal hemorrhage remains high (20%–35%), even in recent prospective studies.6–9 In multivariate analyses of randomized studies, mortality from esophageal variceal hemorrhage increases with age10 and Child–Pugh class10–12—particularly related to ascites and encephalopathy.10 Therefore, the potential of preventing first variceal hemorrhage offers the promise of reducing mortality, morbidity, and associated health care costs.

For definitions relative to prophylactic treatment of esophagogastric varices, primary prophylaxis is treatment of patients who have never had previous variceal bleeding to prevent the first variceal hemorrhage. Secondary prophylaxis is treatment to attempt to prevent rebleeding of patients with prior, documented variceal hemorrhage. This article focuses on issues related to primary prophylaxis.

In the past 2 decades, there have been major advances in the knowledge and management of portal hypertension and variceal hemorrhage.7,13–15 For prediction of first variceal hemorrhage in patients who have never bled, different classifications have been developed by using clinical data (such as Child–Pugh class), laboratory results (such as coagulation tests), endoscopic findings

Abbreviations used in this paper: NIEC, Northern Italian Endoscopic Club; UGI, upper gastrointestinal.

© 2002 by the American Gastroenterological Association

0016-5085/02/$35.00
prophylaxis particularly related to endoscopy, and the prospective study of 281 men with alcoholic liver disease prophylaxis of first esophageal varix hemorrhage. This therapy compared with sham therapy for primary prophylactic cooperative trial of prophylactic sclerotherapy for large multicenter trials of primary prophylaxis. In the United States, the lag in investigation, screening, and treatment related to primary prophylaxis of variceal hemorrhage probably relates to health care–related issues: the negative results of a large, influential Veterans Administration trial for primary prevention of first variceal hemorrhage reported in 1991, the lack of a CPT (Current Procedural Terminology) code (and routine reimbursement) for endoscopic therapies as primary prophylaxis to prevent first variceal hemorrhage, the limited federal funding (such as from the National Institutes of Health) for large multicenter trials of primary prophylaxis particularly related to endoscopy, and the emphasis of treatment after development of a symptomatic condition rather than primary prevention in most U.S. health care organizations.

One exception for the United States was the report of a study performed more than 15 years ago as a Veterans Administration trial for primary prophylaxis of first esophageal variceal hemorrhage. This prospective study of 281 men with alcoholic liver disease was terminated early because the mortality rate in the sclerotherapy group (32.2%) was significantly higher than in the sham group (17.4%). There was no obvious explanation for the excess mortality in the endoscopic group. Paradoxically, the patients receiving sclerotherapy had fewer episodes of esophageal variceal bleeding than the sham group. This study appeared to have a negative impact on the funding and performance of subsequent, large U.S. primary prophylactic studies for prevention of first variceal hemorrhage.

With the application of medical treatments for chronic management of portal hypertension (e.g., propranolol or nadolol) and the development of rubber band ligation for esophageal variceal obliteration, there is a renewed interest in primary prophylaxis to prevent first variceal hemorrhage. This has particularly stimulated investigators in Europe and Asia to perform and report studies. As a recent example, Sarin et al. reported 2 different randomized prospective studies of patients with large esophageal varices and no history of previous hemorrhage. In both studies, significantly lower rates of first variceal hemorrhage were reported with rubber band ligation than the comparator groups (no therapy or propranolol). In the first trial, banding was superior to no therapy for primary prevention of the first variceal hemorrhage and resulted in lower mortality. In the second study by Sarin et al., rubber band ligation as prophylactic treatment was associated with significantly lower rates of first esophageal varix hemorrhage but not mortality. The cumulative 20-month rate of first esophageal varix hemorrhage in the propranolol group was 43% and the rubber band ligation group was 10% (P < 0.04). These results are very promising, but should be confirmed by larger, multicenter studies, particularly in the United States, where β-blockers are recommended for prophylaxis against first varix hemorrhage and prophylactic endoscopic therapies are infrequently used.

This article (1) reviews endoscopic grading of size and stigmata for esophageal and gastric varices, (2) describes the data on prevalence and incidence of esophageal and gastric varices from prospective studies, (3) discusses independent risk factors from multivariate analyses of prospective studies for development of first esophageal or gastric variceal hemorrhage and possible stratification of patients based on these risk factors, (4) comments on the potential cost effectiveness of screening all newly diagnosed cirrhotic patients and treating high-risk patients with medical or endoscopic therapies, and (5) recommends further studies of endoscopic screening, stratification, and outcomes in prospective studies of endoscopic therapy.

**Endoscopic Grading of Size and Stigmata of Varices and Their Risk for Hemorrhage**

Several endoscopists have described different classifications of esophageal varices by size, form, color, and stigmata. These have been used to stratify patients into low- or high-risk subgroups for prediction and study of first esophageal variceal hemorrhage. In nonbleeding cirrhotic patients who are normovolemic, most endoscopists can agree on the color of the esophageal varices (blue or other color) and the size of esophageal varices (absent, small, medium, or large) in the distal esophagus. Figures 1–4 show esophageal varices of different colors and sizes.

The CURE Hemostasis Research Group screened 251 stable cirrhotic patients for potential entry into a randomized study of primary prophylaxis. Figure 5 details the screening results. In all, 57 patients (23%) with large esophageal varices were randomized and 194 others (77%) were excluded based on clinical, laboratory, and...
endoscopic criteria. For all 251 patients, the prevalences of different sizes of esophageal varices were: giant 2.3%, large 33.5%, medium 20.8%, small 25.3%, and absent 18.1%.

In some prospective or multicenter trials, esophageal varix diameter (in mm) has been estimated by comparison with biopsy forceps or other accessories of known dimensions. In an early prospective study of alcohol-induced cirrhotic patients, Dagendi reported that patients with large varices and red spots had a high risk for esophageal varix hemorrhage. In a retrospective study, Beppu et al. reported that various endoscopic stigmata on esophageal varices (e.g., red wale markings, cherry-red spots, and hematocystic spots) were significantly associated with the risk for esophageal variceal hemorrhage. Figures 6 and 7 are examples of different red markings, as is Table 1. Beppu et al. developed an endoscopic scoring system to estimate the probability of esophageal varix hemorrhage. However, in a subsequent prospective study, the Beppu score significantly overestimated the probability of first esophageal varix hemorrhage in a multicenter Italian study.

Whether different endoscopists can reproducibly agree about the endoscopic size and characteristics of esophageal varices is debatable, particularly outside study centers and groups such as the Northern Italian Endoscopic Club (NIEC). Nevertheless, the NIEC reported fair to excellent agreement in their study of Beppu features with \( \kappa \) values between 0.52 and 0.95. In another Italian study, reliability of endoscopy in assessment of variceal features was also reported. Fair to good agreement (based on \( \kappa \) scores) was found among 6 skilled endoscopists on esophageal variceal location, size, lumen occupancy, presence of blue color, and presence and extent of red color signs or hematocystic spots on esophageal varices.

Other classifications and indices by Snady and Feinman and the NIEC were developed and prospectively validated for estimating the probability of developing a first esophageal varix hemorrhage in cirrhotic patients with varices. The latter group reported that only 3 factors were independent risk factors for development of first esophageal varix hemorrhage: Child-Pugh class, size of the varices, and presence of red wale markings. Table 2 is a guide to calculating the NIEC index. The actual cumulative percentage of patients with different NIEC indices (scores) who bled during the prospective study were stratified by risk class and these results are shown in Table 3. The actual cumulative percentage of patients with different NIEC indices (scores) who bled during the prospective study were stratified by risk class and these results are shown in Table 3.
In the NIEC prospective study of 321 cirrhotic patients, 26.5% developed UGI hemorrhage during a median follow-up of 23 months. The cumulative risk in the first year was 0.16 (e.g., 16% bled) and during the second year was 0.11 (e.g., 11% bled). However, the cumulative hazard for high-risk classes 4–6 was 32%–63.6% as shown in Table 2.

These NIEC indices were used to select high-risk patients for prospective studies of different prophylactic treatments. However, De Franchis et al. estimated that use of the NIEC index to select patients with more than a 50% risk for first variceal hemorrhage would include less than 20% of all cirrhotic patients with varices who were screened.

In contrast to these combination scoring systems, other investigators such as Paquet et al. have been successful in using variceal size (large), with red signs (veins-on-veins or cherry-red spots, see Figures 4, 6, and 7) or coagulopathies in selecting high-risk patients for prophylactic sclerotherapy trials. His selections were not based on Child–Pugh class, though his treatment groups were similar at baseline in this parameter. As an example of the use of endoscopic stratification in the first Paquet trial, which had 24 months of follow-up in 65 cirrhotic patients, significantly more patients in the control group developed variceal hemorrhage than in the sclerotherapy group (66% vs. 2%) and significantly more died (42% vs. 6%). Paquet et al. reported similar results in the second trial. Few other investigators have been as successful in identifying such high-risk groups to study for primary prophylaxis of first variceal hemorrhage, though Sarin et al. in recent studies of prophylactic banding have found similar very high-risk patients.

**Prevalence and Incidence of Esophageal or Gastric Varices**

**Prevalence of Esophageal Varices**

Numerous, randomized, prospective, or controlled studies of β-blockers, sclerotherapy, or rubber band ligation have been reported as prophylactic treatments and describe the safety and efficacy of medical or endoscopic treatments for patients with portal hypertension and esophageal varices. Most patients have cirrhosis in reports from the United States or Europe, but other etiologies of portal hypertension and...
varices are included, particularly in trials from India.\textsuperscript{8,18} Most reports do not include details about all patients who are screened but excluded from the trials. Details such as the prevalence and size of esophageal and gastric varices in the population from which the study patients came are often left out of reports. A few trials include such details and are discussed. In addition, results of screening for a CURE study of prophylactic therapies to prevent first esophageal varix hemorrhage are discussed.\textsuperscript{15}

In an autopsy study from Sweden of cirrhotic patients, Olsson\textsuperscript{44} reported that 61% (150 of 244) had esophageal varices. Two thirds of the patients with varices had experienced variceal hemorrhage and this represented 41% of all cirrhotic patients studied.\textsuperscript{44} More that half the patients had alcohol-induced liver disease. These are prevalence data in end-stage liver disease and have the disadvantage of not including data on size, stigmata, and presence or absence of gastric varices.

There are more detailed data from a recent prospective trial that included information on all cirrhotic patients screened by endoscopy (Figure 8).\textsuperscript{3} These were cirrhotic patients from Taiwan with a high prevalence of viral hepatitis. The investigators stratified patients for risk for developing the first esophageal varix hemorrhage based on the Japanese classification of esophageal varices\textsuperscript{19} and

Table 1. Endoscopic Appearance and Correlation With Esophageal Varix Hemorrhage

<table>
<thead>
<tr>
<th>Positive correlation</th>
<th>Negative correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red color sign (wale of red spot)</td>
<td>Location</td>
</tr>
<tr>
<td>Blue color of varix</td>
<td>White color of varix</td>
</tr>
<tr>
<td>Large size</td>
<td>Esophagitis</td>
</tr>
</tbody>
</table>

Adapted and reprinted with permission from Beppu et al.\textsuperscript{19}

performed a randomized, controlled trial of the 24% in the high-risk group.

In another large study for prediction of first variceal hemorrhage in cirrhotic patients, the NIEC screened 383 cirrhotic patients.\textsuperscript{12} Their data on prevalence and size of esophageal varices from the screening endoscopy are shown in Figure 9.

Based on these studies, large esophageal varices or high-risk varices can be expected in only 15%-25% of cirrhotic patients (who are screened endoscopically) from unselected populations of newly diagnosed cirrhotic patients. Approximately 18% will not have esophageal varices and the rest will have small-, medium-, or low-risk varices.\textsuperscript{3A2}

Recently, Merkel et al.\textsuperscript{45} revised the NIEC index after performance of a prospective study to predict first esophageal variceal hemorrhage. By regression analysis and modeling, they reported that the size of esophageal varices and the presence of red wale markings were much more important than the Child-Pugh class for prediction of first esophageal variceal hemorrhage. These are represented by different regression coefficients (which are used to calculate indexes) for the original and revised NIEC indices, as compared in Table 4. The weighting of the revised NIEC index, with a very low coefficient for Child-Pugh class, makes this index resemble the Paige\textsuperscript{21,26} and Sarin\textsuperscript{8A8} grading systems. Whether the

Table 2. Guide to Bedside Calculation of the NIEC Index

<table>
<thead>
<tr>
<th>Child-Pugh Class</th>
<th>Points to add</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.5</td>
</tr>
<tr>
<td>B</td>
<td>13.0</td>
</tr>
<tr>
<td>C</td>
<td>19.5</td>
</tr>
<tr>
<td>Size of varices</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>8.7</td>
</tr>
<tr>
<td>Medium</td>
<td>13.0</td>
</tr>
<tr>
<td>Large</td>
<td>17.4</td>
</tr>
<tr>
<td>Red wale markings</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>3.2</td>
</tr>
<tr>
<td>Mild</td>
<td>6.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>9.6</td>
</tr>
<tr>
<td>Severe</td>
<td>12.8</td>
</tr>
</tbody>
</table>

NOTE. The NIEC index is calculated by adding the scores for the 3 different variables shown. (Adapted from NIEC.\textsuperscript{12})

Table 3. Cumulative Percentages of Patients Bleeding According to the NIEC Index at Entry

<table>
<thead>
<tr>
<th>Risk class</th>
<th>NIEC index*</th>
<th>Patients</th>
<th>% With esophageal varices hemorrhage\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;20</td>
<td>63</td>
<td>9.5%</td>
</tr>
<tr>
<td>2</td>
<td>20-25</td>
<td>76</td>
<td>15.8%</td>
</tr>
<tr>
<td>3</td>
<td>25.1-30</td>
<td>63</td>
<td>22%</td>
</tr>
<tr>
<td>4</td>
<td>30.1-35</td>
<td>56</td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td>35.1-40</td>
<td>48</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>&gt;40</td>
<td>11</td>
<td>63.6%</td>
</tr>
</tbody>
</table>

*For the NIEC Index (score) refer to Table 1.
\textsuperscript{b}The median follow-up was 23 months. (Adapted from NIEC.\textsuperscript{12})

Figure 8. Prevalence and risk for esophageal varices in cirrhotic patients without prior UGI hemorrhage—Taiwan study. Adapted and reprinted with permission from Lay et al.\textsuperscript{3}
383 Cirrhotics Assessed
9.4%-36 patients excluded
7.5%-26 patients lost
83.8%-321 patients included

Refusal 63.9%
49.8%*(160) 34.9"(112) 15.3%(49)
Small size Medaum SEe Large Size

Figure 9. Prevalence and size of esophageal varices without prior UGI hemorrhage–Northern Italian Study. Adapted and reprinted with permission from NIEC.12

Revised NIEC index will be validated and useful in other prospective observational and therapeutic trials remains to be ascertained.

Incidence and Change in Size of Esophageal Varices

Esophageal varices have been reported to increase, decrease or disappear, or not change in size with serial follow-up and endoscopic grading.4,20,22,46,47 Changes in size have especially been noted in alcoholic patients during abstinence or progression of their cirrhosis in 1 prospective study.20

In 2 other studies, the natural history of esophageal varices was reported.46,47 Gores et al.46 reported on the incidence of esophageal varices in primary biliary cirrhosis in 265 patients with no varices at baseline. During a median follow-up of 5.6 years, esophageal varices developed in 31% of patients and the highest incidence was with severe primary biliary cirrhosis (stage IV in biopsy). The incidence of esophageal varices was about 12% per year in severe primary biliary cirrhosis and about 4% per year for all primary biliary cirrhosis patients. In another study of 84 cirrhotic patients by Cales et al.4°, the change in variceal size was reported during 16 months of follow-up. For the 41 patients without baseline esophageal varices, 56% did not develop them, whereas 44% did—24% small and 20% medium size. Of the 43 patients with small baseline esophageal varices, 58% either regressed (15%) or remained small (42%), whereas 42% became medium size. In none of the 84 cirrhotic patients did large esophageal varices develop.

D’Amico et al.48 recently reported on the incidence of esophageal varices in cirrhosis. For 494 consecutive, newly diagnosed cirrhotic patients in 1981–1984, 225 (45.5%) with no esophageal varices on baseline endoscopy were followed-up prospectively for a mean of 131 months. Panendoscopies were performed every 1–3 years for surveillance and whenever an UGI bleed occurred. Esophageal varices developed in 41% of patients by 10 years, whereas no varices developed in 55% of patients, and the rest of the patients were lost to follow-up. Progression of small to large varices occurred in 5% of patients per year. The rate of UGI hemorrhage was 7% per year after progression in esophageal variceal size. The cumulative rate of UGI hemorrhage in 10 years was about 66% in those with progression in varix size.48 UGI bleeding without progression was rare, about 15% over 10 years. The cumulative proportion of patients surviving was reported to be 70%, but survival was shorter after progression of esophageal varices.48

Although the risk for first esophageal varix hemorrhage is low in cirrhotic patients with absent or small varices, the size of the varices may change as the liver disease progresses. Periodically, endoscopic screening should be repeated to determine whether esophageal varices are larger. This can be recommended if the endoscopic findings would trigger a change in medical or endoscopic management of the patient for prevention of first esophageal varix hemorrhage. The optimum interval for endoscopic surveillance of patients with absent, small-, or medium-sized varices has not been determined, nor have cost analyses been reported for surveillance.

Prevalence of Gastric Varices and Risk for First Hemorrhage

Few studies report the prevalence of gastric varices in cirrhotic patients without previous bleeding. Figure 10 is an example of gastric fundal varices found on a screening endoscopy of a cirrhotic patient. Sarin et al.49 reported that gastric varices (of any type) were present on initial endoscopy in only 4% of patients with portal hypertension of various etiologies and no history of prior UGI hemorrhage. Most investigators screen these patients with gastric varices out of prospective prophylactic trials because they increase the risk for first variceal hemorrhage in some reports.10,49

More recently, Kim et al.50 reported a retrospective and prospective study of risk factors for hemorrhage from gastric fundal varices. They screened 1392 cirrhotic patients with panendoscopy, some of whom had prior UGI hemorrhage. Figure 11 shows a summary of their screening and the prevalence data. The prevalence of fundal

Table 4. North Italian Endoscopic Club Indices

<table>
<thead>
<tr>
<th></th>
<th>Regression NIEC(^a) (N = 321)</th>
<th>Coefficients Revised(^b) (N = 627)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of varices</td>
<td>0.4385</td>
<td>1.12</td>
</tr>
<tr>
<td>Red wale markings</td>
<td>0.3193</td>
<td>0.36</td>
</tr>
<tr>
<td>Child-Pugh class</td>
<td>0.645</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\(^a\)Data from NIEC.12

\(^b\)Data from Merkel et al.45
Figure 11. Prevalence of esophageal and gastric varices—Japanese study. Adapted and reprinted with permission from Kim et al. 50

Risk Stratification Based on Independent Determinants of First Esophageal Variceal Hemorrhage From Multivariate Analyses: Relevance to Screening and Results

There are several strategies that have been reported for risk stratification and selection of patients for randomized prospective trials. To date, these have been exclusively used to enhance the chance of first esophageal varices in the study by enrolling high-risk patients. 5,12,27,51 Another use may be for reassurance and triage of low-risk patients for first variceal hemorrhage to less intense medical follow-up, therapy, or surveillance.

One-time screening endoscopy allowed a significant number of cirrhotic patients to be excluded from a randomized study: patients with no varices (18.1% in the study by Lay et al., 3 Figure 8) or low-risk varices (57.7% of patients). However, in follow-up of the latter subgroup of 300 patients considered low risk by Lay et al., 3 19% developed a first variceal bleed on no therapy in 1 year and 50% in 2 years. Also, the cumulative percentage who died during 24 months was 34.6%. 3 Clearly, 1-time endoscopic screening with the Beppu et al. 19 scoring system used in the study by Lay et al. 3 was not reliable in identifying low-risk patients for potential first variceal hemorrhage. Liver disease severity, degree of portal hypertension, and esophageal varix size all can change with time. 4,46,47 Perhaps other scoring systems such as the revised NIEC index along with other clinical parameters will be needed to follow-up and reserve patients who are willing to be followed-up prospectively. 12,45

Nevertheless, even with older scoring scales, very high-risk patients were identified in the Lay et al. 3 study, which reported a 2-year cumulative bleeding rate of 19% in the rubber band ligation treatment group and 60% in the no treatment group. The cumulative mortalities were 28% and 58%, respectively. For high-risk patients the results according to Child–Pugh class are shown in Table 5.

Endoscopic scoring alone has been successful in some recent studies to stratify very high-risk patients for prophylaxis. In a recent study of prophylactic rubber band ligation compared with propranolol to prevent first esophageal variceal hemorrhage, Sarin et al. 8 used a combined grading scale of large variceal size and red color signs (at least 1 present) to identify high-risk patients with portal hypertension. The rate of agreement between 2 observers for the presence of red signs was 94%. The investigators were successful in selection of high-risk patients, as evidenced by the high rates of first esophageal variceal hemorrhage during the prospective follow-up of 18 months: 43% in the propranolol group and 15% in the banding group. These investigators did not exclude patients with gastric varices (19%) or portal gastropathy (21%) and 18% of patients were Child–Pugh class A. 8 The success of enriching the risk for first variceal hemorrhage is reminiscent of the earlier trials of Paquet et al., 21,26 who used an endoscopic scoring system in 2 different prophylactic sclerotherapy studies, irrespective of the Child–Pugh class of patients.

| Table 5. Relationship Between Child-Pugh Class and Rate of First Bleeding Episode |
|-----------------|-----------------------------|
| Controls | Rubber band ligation |
| Child’s A | 12% (2/17) | 0% (0/16) |
| Child’s B | 27% (6/22) | 9% (2/23) |
| Child’s C | 52% (12/23) | 12% (3/25) |

Control is no β-blockers. (Adapted from Lay et al. 3)
Potential Cost Effectiveness of Screening and Medical or Endoscopic Therapies in High-Risk Patients

No prospective studies have assessed the cost effectiveness of screening endoscopy alone in cirrhotic patients. However, 1 cost-effectiveness analysis used Markov modeling to simulate the natural history of esophageal varices. From the literature of endoscopic screening, size of varices and presence of red color signs were incorporated into this model. For the treatments evaluated in this model, prophylactic propranolol resulted in the most cost savings over 5 years and increased quality-adjusted life expectancy by 0.1–0.4 years. sclerotherapy was less cost effective than propranolol. Rubber band ligation was not included as a treatment option. The results of this modeling study have not been verified by any prospective studies with actual cost analyses as one of the outcomes.

In a randomized prospective study of primary prophylaxis of first variceal hemorrhage, the CURE Hemostasis Research Group compared propranolol with rubber band ligation. Routine outcomes and direct costs of health care were quantitated in this study. To date, 57 stable cirrhotic patients with large esophageal varices and no previous esophageal variceal hemorrhage have been randomized into the 2 treatment groups and followed-up for a mean of 8 months. During the prospective follow-up, the mean total direct costs of health care were arithmetically higher in the propranolol than the rubber band ligation group: mean of $3242 vs. $2050, respectively. The higher direct health care costs were directly related to the higher rates of variceal hemorrhage or serious complications of therapy for the propranolol group compared with the rubber band ligation group. No other prospective studies of primary prophylaxis have included an assessment of cost, though this outcome has been reported for studies of secondary prophylaxis.

Future Recommendations About Screening Endoscopy and Stratification of Patients to Different Treatments

The effectiveness of endoscopic screening has not been compared with no screening for different unselected populations of cirrhotic patients who have not had prior UGI hemorrhage. It is doubtful that endoscopic screening alone (without triaging patients to different treatments and careful follow-up) will lead to a significant change in the overall rate of first esophageal hemorrhage or in mortality. However, motivated patients, such as the high-risk subgroup for developing esophageal variceal hemorrhage, will benefit. Whether screening out low-risk patients will benefit them has not been reported. To optimize limited health care resources and better target different treatment strategies, further health services studies are recommended. Now that β-blockers have been shown to reduce the incidence of first variceal hemorrhage compared with placebo and also reduce mortality in 1 report, these treatments ought to be offered to more cirrhotic patients (with moderate to high risk for variceal hemorrhage) outside academic medical centers and randomized studies. Furthermore, if rubber band ligation is confirmed in larger trials to be more effective than propranolol for high-risk patients as in the Sarin et al. study, more cirrhotic patients should be screened for large varices with red color signs and this treatment used in reliable patients to prevent first variceal hemorrhage.

Standardization of screening practices to assure agreement among endoscopists will be necessary in the community as it has been in prospective studies. This will be a challenge for endoscopy societies and regulators. Further refining of clinical and endoscopic scoring systems is needed to reliably identify low-risk patients for variceal hemorrhage. Stratifying very low-risk cirrhotic patients to less intense follow-up, surveillance, and medical therapies should be cost effective, but has not been reported. Further study of different strategies for periodic repeat screening endoscopy and reassessment of cirrhotic patients at lower risk for development of first variceal hemorrhage is warranted. All of these studies should include routine outcomes, cost assessments, and quality-of-life analyses.

Summary Statement About Which Cirrhotic Patients Should Undergo Endoscopic Screening for Esophageal Varices

The author’s current recommendations are to perform endoscopic screening for the following subgroups of cirrhotic patients: all newly diagnosed cirrhotic patients and all other cirrhotic patients who are medically stable, willing to be treated prophylactically, and would benefit from medical or endoscopic therapies. The author would exclude patients who are unlikely to benefit from prophylactic therapies designed to prevent the first variceal hemorrhage, those with a short life expectancy, and those with previous UGI hemorrhage (they should have already undergone endoscopy). For low or very low-risk cirrhotic patients—those found to have no varices or small varices
without stigmata—a repeat endoscopy as screening for progression may be warranted in 2 or more years, based on a recently reported study.\footnote{10}

Conclusions

1. Stratification of cirrhotic patients into high- and low-risk groups for prediction of first variceal hemorrhage is feasible with clinical and endoscopic parameters.

2. Multivariate analyses of prospective studies indicate that high-risk patients for first variceal hemorrhage have advanced Child–Pugh class, large esophageal varices, and red wale markings. Advanced age, gastric varices, and alcohol-induced cirrhosis increased the risk for variceal hemorrhage and mortality in other studies. It is logical to screen for and offer such patients safe and effective endoscopic or medical therapies to prevent first esophageal hemorrhage. Approximately 25%–33% of cirrhotic patients screened will be in this high-risk category.

3. In contrast, similar analyses of cirrhotic patients have reported that low-risk patients for variceal bleeding have Child–Pugh class A cirrhosis, no or small varices at endoscopy, and/or esophageal varices without red color signs. These patients may benefit from medical therapies that control portal pressure or other factors that cause varices to increase in size or form red color signs. This subgroup represents approximately 66%–75% of cirrhotic patients screened by endoscopy in some reports. No studies have been reported to show the effectiveness of screening for this large group of patients or the efficacy of medical therapy in reducing the size of varices or the likelihood of increasing in size or bleeding.

4. For high-risk cirrhotic patients with esophageal varices, routine outcomes (such as the incidence of first esophageal variceal bleed), and in some trials, mortality, were significantly improved in patients treated endoscopically (with rubber band ligation) compared with no medical therapy, or in some other trials propranolol compared with placebo (or no medical therapy). Screening and endoscopic treatment with rubber band ligation for reliable, motivated, high-risk cirrhotic patients may be worthwhile, if recent promising results of single-center prospective trials are confirmed.

5. The effectiveness of screening vs. no screening for unselected populations of cirrhotic patients has not been reported. Such trials can now be designed and treatment strategies applied because different medical and endoscopic treatments have been reported to be safe and effective in randomized controlled trials. Quantitating routine outcomes (such as the incidence of first variceal hemorrhage, complications, and deaths), cost of care, and quality-of-life changes are recommended in these studies.

References

18. Sann SK, Guptan RK, Jain AK, Sundaram KR. A randomized


Received December 6, 2001. Accepted March 7, 2002.
Address requests for reprints to: Dennis M. Jensen, M.D., CURE Digestive Disease Research Center, Veterans Administration Greater Los Angeles Healthcare System, Building 115, Room 318, 11301 Wilshire Boulevard, Los Angeles, California 90073-1003. e-mail: djensen@mednet.ucla.edu; fax: (310) 794-2908.

Supported in part by National Institutes of Health grants R01 K24 DK02650, R01 DK49527, the CURE Human Studies CORE DK41301, and CRC grant M01-RR00865.

The author is grateful to Julie Pham for word processing this manuscript, Ken Hirabayashi for preparation of the figures, and Rome Jutabha, M.D., and Thomas O. G. Kovacs, M.D., for providing some of the endoscopic photographs.