

Endoscopy for Acute Nonvariceal Upper Gastrointestinal Tract Hemorrhage: Is Sooner Better?

A Systematic Review

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Background: While the effectiveness of upper endoscopy has been established for acute nonvariceal upper gastrointestinal tract hemorrhage, its optimal timing has not been clearly defined. Early endoscopy has been advocated for its ability to achieve prompt diagnosis, risk stratification, and therapeutic hemostasis.

Objective: To determine whether early vs delayed endoscopy improves patient and economic outcomes for all risk groups with nonvariceal upper gastrointestinal tract hemorrhage.

Methods: A systematic review of 3 computerized databases (MEDLINE, HEALTHSTAR, and Cochrane Database of Systematic Reviews) was performed along with hand searching of published abstracts to identify English-language citations from 1980 to 2000.

Results: Twenty-three studies met explicit inclusion criteria. The highest-quality study examining outcomes in low-risk patients found no significant complications at 1-month follow-up for any outpatients managed with early

endoscopy. The largest randomized trial of high-risk patients showed no mortality benefit but a significant decrease in transfusion requirements with early endoscopy. Seven of the 8 studies examining the effect of early endoscopy on length of stay as a measure of resource utilization demonstrated a significant reduction compared with that of delayed endoscopy. However, most included studies were found to suffer from 1 or more potentially significant methodologic shortcomings.

Conclusions: The overwhelming majority of existing data suggest that early endoscopy is safe and effective for all risk groups. The clinical and economic outcomes of early endoscopy should be confirmed in additional well-designed randomized controlled trials. Given the strength of the evidence, efforts to develop a more standardized and time-sensitive approach to acute nonvariceal upper gastrointestinal tract hemorrhage should be undertaken.

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UPPER gastrointestinal tract hemorrhage (UGIH) occurs in 150 per 100 000 people annually, results in up to 300 000 hospitalizations, and costs more than \$2.5 billion per year.^{1,2} Despite earlier studies to the contrary,^{3,4} endoscopy has been established as being effective for acute nonvariceal UGIH^{5,6} and is now the standard of care for patients presenting with this frequent and costly condition.^{7,8} Once a medical intervention is deemed effective, its optimal timing of use in clinical practice must be clearly defined. In many instances, effectiveness and timing are inseparable, as timing alone often dictates clinical success. For example, it is not adequate to simply provide coronary angioplasty for patients with myocardial infarction, but to perform it within 1 hour of presentation.⁹ Similarly, while tissue plas-

minogen activator has proved effective in acute ischemic stroke, it must be initiated within 3 hours of onset to maximize outcomes.¹⁰

The optimal timing of endoscopy in UGIH, however, has not been clearly established. Well-designed prospective studies, including a trial demonstrating the safety of early refeeding after therapeutic endoscopy¹¹ and a sequential endoscopic confirmation of the low rebleeding risk of clean-based ulcers,¹² bolster the argument that early endoscopy may provide clinical benefit by promoting safe patient disposition for both high- and low-risk groups. Moreover, it has been suggested that delayed endoscopy provides no additional benefit over standard medical management.^{13,14} Nonetheless, mortality rate has remained unchanged despite therapeutic endoscopy,¹⁵ and an increased rate of compli-

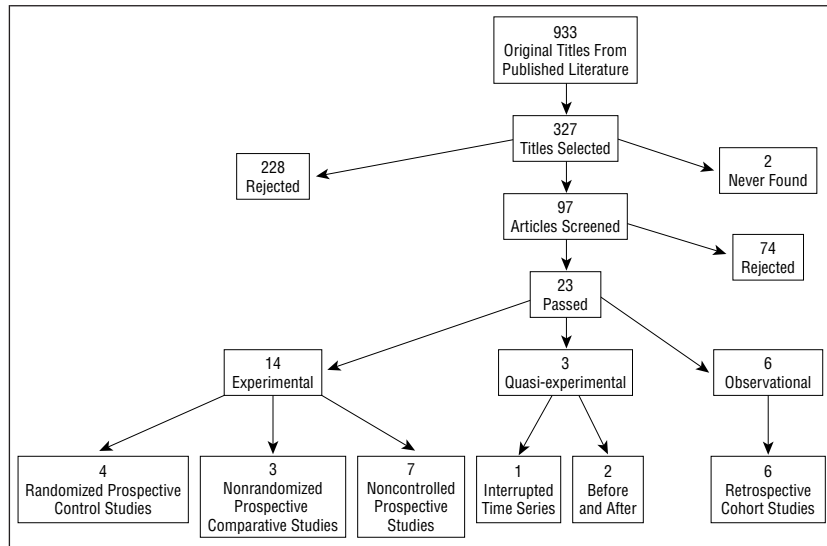


Figure 1. Results of literature search.

cations with early vs delayed endoscopy has been reported.^{16,17} The controversy is further confounded by the paucity of literature specifically addressing the timing of endoscopy and by the lack of clear guidelines on the timing of endoscopy in major consensus statements.^{7,8}

In the absence of clear guidelines, early endoscopy is presently an inconsistent practice. For example, the decision to perform early vs delayed endoscopy has been independently associated with sex,¹⁸ insurance status,¹⁹ and day of the week.¹⁹ The definition of “early” endoscopy varies as well, ranging from 1²⁰ to 24¹⁹ hours after initial presentation. Current evidence suggests that upper gastrointestinal tract endoscopy is performed within 24 hours of admission in 40% to 70% of cases.^{19,21}

How might the effectiveness of early endoscopy be measured? The end point of a successful management strategy may be to ensure patient safety while stemming costs by minimizing unnecessary hospitalizations and reducing length of stay. With the advent of therapeutic potential, the use of early endoscopy may achieve these objectives by allowing prompt diagnosis, risk stratification, and therapeutic hemostasis.²² To prove a benefit from early endoscopy, a link must be established between this practice and significant clinical and economic

outcomes. Our objective was to perform a systematic review of the medical literature^{23,24} to address the following questions: (1) Does early endoscopy allow for safe and prompt discharge of low-risk patients with acute nonvariceal UGIH? (2) Does early endoscopy improve patient outcomes vs delayed endoscopy in high-risk patients with acute nonvariceal UGIH? (3) Does early endoscopy reduce resource utilization vs delayed endoscopy for all comers with acute nonvariceal UGIH?

METHODS

A structured search of 3 computerized bibliographic databases (MEDLINE, HEALTHSTAR, and the Cochrane Database of Systematic Reviews), along with a CD-ROM-assisted (DDW [Digestive Disease Week] Abstracts-on-Disc; American Gastroenterological Association, Bethesda, Md) review of published abstracts from 3 major subspecialty journals, was performed to identify English-language publications from January 1980 to January 2000. The search strategy, including selection of subject headings and key words, was performed with an expert librarian to maximize search sensitivity for targeted information. Generated titles were assessed for relevancy and were rejected only if they fulfilled explicit exclusion criteria, including (1) not written in English; (2) not con-

cerned with human subjects; (3) not related to UGIH or lesions that can cause UGIH; (4) solely related to variceal bleeding or other complications of portal hypertension; (5) solely related to nonendoscopic interventions or complications thereof; and (6) solely related to occult, subacute, or chronic UGIH. Selected abstracts were reviewed and were rejected if they (1) made no reference to outcome or process measurement, (2) referred only to bleeding severity, but not to the effectiveness of endoscopy, or (3) made no reference to time factors. Disagreements were resolved by consensus. In addition, bibliographies of included studies and key review articles were reviewed for references not captured by the search strategy.

Remaining studies were independently reviewed and included if they had information regarding the effectiveness of early endoscopy, as determined by impact on patient outcomes (mortality, rebleeding, transfusion requirements, need for emergency surgery, endoscopic complications, and readmission) and economic outcomes (length of stay and direct costs). Where methodology was unclear, authors were contacted for additional information. Each included study was independently abstracted for data, and randomized clinical trials were assessed for methodologic quality by means of a standardized instrument focusing on features related to internal validity. Quasi-experimental designs, including interrupted time series and controlled before-and-after trials, were assessed for methodologic quality by means of criteria established by the Cochrane Collaboration on Effective Professional Practice.²⁵

RESULTS

The search strategy identified 933 titles (Figure 1). Of these, 327 were selected for abstract review, of which 97 studies were retained for consideration. Independent review of these remaining studies yielded 23 that met our explicit inclusion criteria. Interrater agreement was high ($\kappa=0.70$).

DOES EARLY ENDOSCOPY ALLOW FOR SAFE AND PROMPT DISCHARGE OF LOW-RISK PATIENTS WITH ACUTE NONVARICEAL UGIH?

Risk stratification of patients with nonvariceal UGIH involves a combination of both clinical and endoscopic criteria. Therefore, early endoscopy may potentially assist in the selection of low-risk patients eligible for prompt discharge by rapidly confirming clinical suspicion. Twenty studies were identified that examined the relationship between the timing of endoscopy and outcomes for low-risk patients with nonvariceal UGIH. These reports may be categorized both by study design and by whether early endoscopy was the principal focus of the study intervention (**Figure 2**).

The most direct evidence comes from experimental studies with discharge protocols that explicitly include early endoscopy. Of these, strategies that compare the protocol with a control population undergoing standard medical management provide the strongest evidence. Other study designs examine discharge protocols that do not explicitly involve early endoscopy, but that nonetheless perform post hoc analysis relating the timing of endoscopy to outcomes for low-risk patients.

Table 1 summarizes the controlled trials that compare early endoscopy with “usual care” for low-risk patients. There were 3 randomized studies. In the largest, Lee et al²⁰ compared a strategy of prompt endoscopy within 2 hours of presentation vs direct hospital admission for clinically “stable” subjects. The study group was retained in the emergency department until endoscopy could be performed, at which point clinically stable patients without stigmas of recent hemorrhage were discharged. The control group was hospitalized and underwent endoscopy within 24 to 48 hours. With this strategy, 46% of the study group avoided hospitalization and had no complications or readmissions at 30 days’ follow-up despite the initial impression by the emergency department staff that these patients would require admission. The study is notable for a careful delin-

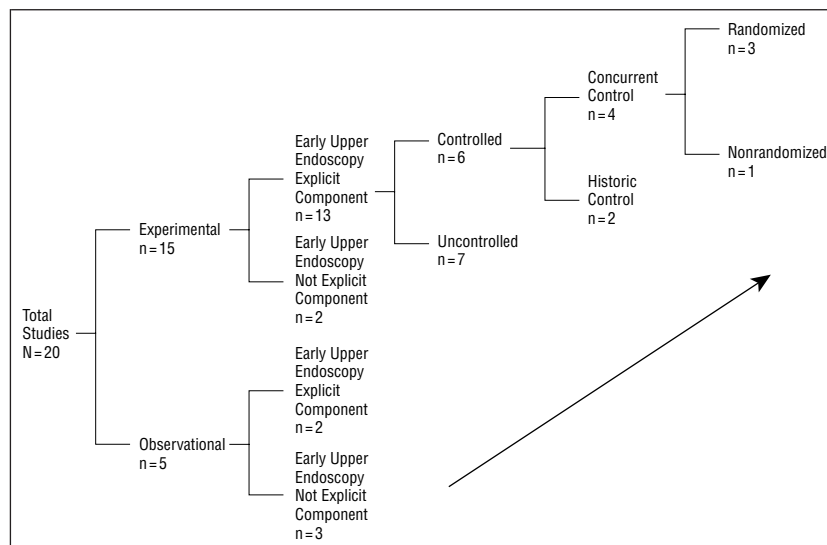


Figure 2. Studies that relate to timing of endoscopy for low-risk patients with nonvariceal upper gastrointestinal tract bleeding. Arrow indicates direction of strongest evidence by study strategy and design. Values indicate number of studies in each subcategory.

eation of inclusion and exclusion criteria, a randomized design with concealed allocation (in the form of opaque envelopes), and thorough patient follow-up with a full description of patient dropouts. A potential shortcoming of this study is that patients with suspected variceal bleeding by clinical criteria were excluded before endoscopy. Because patients with clinical signs of portal hypertension frequently bleed from a nonvariceal source, this study may underestimate the true prevalence of nonvariceal hemorrhage.

Campo et al²⁶ compared a strategy of inpatient vs outpatient care of low-risk subjects undergoing endoscopy within 12 hours of admission. Clinically stable patients without stigmas of recent hemorrhage and with adequate home support were randomly assigned to either discharge on a proton pump inhibitor regimen with daily telephone follow-up for a week or admission for standard inpatient management. In those allocated to outpatient care, there were no deaths and only 1 episode of successfully treated “minor” rebleeding within 1 week. Although the study design was randomized, there was no indication of concealed allocation and no description of withdrawals and dropouts. In addition, the follow-up period of 1 week may have been inadequate to fully account for all post-discharge complications.

Brullet et al²⁷ randomized clinically stable patients to outpatient vs inpatient management after undergoing emergent epinephrine and polidocanol injection of nonbleeding visible vessels within 12 hours of presentation. There were no deaths or episodes of rebleeding in the outpatient group. However, this study suffers from a small sample of only 8 subjects in the outpatient arm, no description of concealed allocation or patient withdrawals, and a potentially inadequate 1-week follow-up. Moreover, the method used (epinephrine alone) is no longer considered adequate for effective hemostasis. Nonetheless, the study is notable for demonstrating safe outpatient management for a group that might normally be deemed high risk by endoscopic criteria.

Almela et al²⁸ compared outpatient vs inpatient care of all comers with UGIH undergoing immediate endoscopy in the emergency department. Clinically stable patients without stigmas of recent hemorrhage were either admitted for inpatient care or discharged with follow-up at 1 month. Those with active bleeding, stigmas of recent hemorrhage, or hemodynamic instability were admitted for inpatient care. Of 201 outpatients, there were 3 deaths (1.5%) and 1 episode of successfully treated gastrointestinal tract bleeding from an aortoenteric fistula vs 20 deaths (2.6%) and 56 episodes of rebleed-

Table 1. Controlled Trials Relating to Timing of Endoscopy for Low-Risk Patients With Nonvariceal Upper Gastrointestinal Tract Hemorrhage*

Source, y	Patients	Design	Comparison	Exclusion Criteria	Patient Outcome Measure	Conclusion
Lee et al, ²⁰ 1999	110 "Stable" patients with NVUGIH admitted to university ED	Randomized trial	Prompt upper endoscopy in ED vs direct admission with delayed upper endoscopy	History of variceal bleeding, cirrhosis, portal hypertension, hemodynamic instability, coagulopathy, history of UGIH within previous month, unable to consent or refused upper endoscopy	Mortality, rebleeding, need for surgery, readmission	Prompt upper endoscopy allowed immediate discharge of 46% with no complications or readmissions at 30 d
Campo et al, ²⁶ 1998	83 "Low-risk" patients with NVUGIH presenting to community hospital	Randomized trial	Outpatient vs inpatient care of low-risk patients undergoing upper endoscopy within 12 h of presentation	Variceal bleeding, hemodynamic instability, visible vessel or adherent clot on upper endoscopy, poor accessibility to hospital, lack of adequate home support	Mortality, rebleeding	No complications in outpatient group with 7-d follow-up
Brullet et al, ²⁷ 1998	20 Patients with NVUGIH and nonbleeding visible vessel on upper endoscopy presenting to community hospital	Randomized trial	Outpatient vs inpatient care of selected patients with nonbleeding visible vessel treated by endoscopic epinephrine injection within 12 h of presentation	Hemodynamic instability, peptic ulcer >10 mm, poor accessibility to hospital, lack of adequate home support	Mortality, rebleeding	No mortality in either group, and 1 episode of successfully treated rebleeding in outpatient group with 7-d follow-up
Almela et al, ²⁸ 1999	983 Patients with NVUGIH admitted to university ED	Prospective nonrandomized study	Outpatient vs inpatient care of all comers undergoing prompt upper endoscopy in ED	Variceal bleeding, hemodynamic instability, stigmas of recent hemorrhage, unable to have upper endoscopy	Mortality, rebleeding, need for surgery	3 Deaths (1.5%) and 1 successfully treated rebleeding in outpatient group at 30 d
Hussain et al, ²⁹ 1995	92 Patients with peptic ulcer bleeding presenting to health maintenance organization hospital	Before-and-after study	Outcomes of patients treated before and after implementation of early-discharge protocol requiring upper endoscopy within 12 h of presentation	Not stated	Need for surgery, length of stay	"Patients with clear ulcer base may be managed on outpatient basis"
Rockall et al, ³⁰ 1997	3957 Patients with UGIH presenting to 45 hospitals	Before-and-after study	Outcomes of patients treated before and after implementation of national early-discharge protocol encouraging upper endoscopy within 24 h of presentation	Age <16 y	Mortality, length of stay, time to upper endoscopy	Patients underwent upper endoscopy more frequently and earlier after guidelines in place without change in severity-adjusted mortality

*UGIH indicates upper gastrointestinal tract hemorrhage; NVUGIH, nonvariceal UGIH; and ED, emergency department.

ing (7.3%) in 767 inpatients. The authors conclude that outpatient care of selected patients is a safe alternative to admission. This study is limited by a lack of randomization and by an apparent incompatibility between the control and study groups, because low-risk subjects managed as inpatients were grouped with hospitalized high-risk patients.

The methodologic quality of the 4 trials with concurrent control

groups is summarized in **Table 2**. With the use of a validated scoring scale,³¹ only the study by Lee et al²⁰ is considered high quality. All of the trials describe explicit inclusion and exclusion criteria, and 3 of the 4 describe the study design as randomized. However, only the study by Lee et al described a concealed randomization process (this refers to measures taken to prevent investigators from influencing the allocation

process, such as using serially numbered, opaque, sealed envelopes, or central randomization). None of the studies was blinded. However, in settings where blinding is not possible, outcome can be assessed by individuals blinded to the original treatment allocation. This was not described in any of the studies. Concealment of allocation and blinding are study quality indicators and, when not satisfied, may result in an

Table 2. Quality Assessment of Controlled Trials Relating to Endoscopy for Low-Risk Patients With Nonvariceal Upper Gastrointestinal Tract Bleeding

Source, y	Inclusion/Exclusion Criteria	Randomized Design	Concealment of Allocation	Blinding	Dropouts Accounted for	Described Methods of Analysis	Quality Score*
Lee et al, ²⁰ 1999	Yes	Yes	Yes	No	Yes	Yes	3
Campo et al, ²⁶ 1998	Yes	Yes	No	No	No	No	1
Brullet et al, ²⁷ 1998	Yes	Yes	No	No	No	No	1
Almela et al, ²⁸ 1999	Yes	No	No	No	Yes	No	0

*Poor quality is less than 3 on a 5-point scale.³¹

overestimation of the intervention effect.

Two controlled studies compared early endoscopy for low-risk patients with historical or retrospective controls. Rockall et al³⁰ compared outcomes of all comers with UGIH before and after implementation of a national early discharge protocol that encouraged endoscopy within 24 hours. The authors found that, compared with a preintervention control group, patients underwent endoscopy more frequently and earlier after the guidelines were in place, without any impact on severity-adjusted mortality rates. It is unclear whether the study had sufficient power to detect a mortality reduction, or whether this is the most relevant outcome in low-risk patients. Additional relevant outcomes, including rebleeding and readmission, were not reported, nor was there follow-up of outpatients on discharge. Finally, this study included variceal and nonvariceal causes of UGIH, thereby further confounding conclusions specifically regarding nonvariceal hemorrhage.

Hussain et al²⁹ compared outcomes for patients with peptic ulcer bleeding before and after implementation of an early discharge protocol requiring endoscopy within 12 hours of admission. Clinically stable patients with a clean-based ulcer were discharged from the hospital on a histamine₂-blocker regimen and contacted for follow-up at 5 to 7 days, while those with active bleeding underwent immediate hemostasis and were hospitalized. Compared with a retrospective control group, fewer patients required surgical intervention in the postguideline period. Although the authors conclude that low-risk patients with clean-based ulcers can be safely managed as outpatients, it is unclear whether the study findings substantiate this conclusion. In particular, the authors did not

report any outcomes for the patients discharged, nor did they describe the completeness of outpatient follow-up. While need for emergent surgery is an important patient outcome, it relates more directly to high-risk groups and may not contribute meaningfully to conclusions regarding outpatient management of low-risk subjects.

Six uncontrolled trials examined early endoscopy for low-risk patients (**Table 3**). Cebollero-Santamaria et al³² evaluated a protocol in which clinically low-risk elderly (age ≥ 65 years) patients were discharged after immediate endoscopic confirmation in the emergency department. Those with a low risk for rebleeding, as determined by explicit endoscopic and clinical criteria, were discharged and followed up intermittently for 1 month. The authors reported no deaths, rebleeding, or readmissions among 24 outpatients. Although limited by the lack of a control group, this study is notable for focusing on the elderly population, a group that tends to be at higher risk and is often treated more conservatively.

Of the remaining 6 uncontrolled trials,³³⁻³⁸ all showed low complication rates of outpatients triaged by early endoscopy. In particular, there were no deaths and rebleeding occurred in 0%³³ to 2.9%³⁶ of patients. All incidents of rebleeding were successfully treated with readmission. The follow-up period ranged from 1 week^{33,37} to 16 months.³⁴ Five studies focused exclusively on nonvariceal hemorrhage,³³⁻³⁷ while the study by Chang et al³⁸ included variceal hemorrhage as well. The trial by Hsu et al³³ specifically evaluated peptic ulcer hemorrhage, while Lai et al³⁴ focused only on patients with duodenal ulcer hemorrhage. Patients were selected for outpatient care by a combination of

both clinical and endoscopic criteria in all studies. Two studies^{32,36} excluded potential variceal hemorrhage before endoscopic confirmation by selecting out subjects with evidence of alcoholic liver disease. One study excluded from enrollment patients taking noncorticosteroidal anti-inflammatory drugs.³³

There were 2 experimental studies in which early endoscopy was not the primary focus of the intervention, but the authors nonetheless drew corollary findings relating timing of endoscopy to patient outcomes. Hay et al,²¹ in a prospective controlled time-series study with an alternate-month design, evaluated the safety of a clinical guideline that recommended early discharge for patients with acute UGIH considered to be at low risk for subsequent complications. Recommendations for length of stay were dependent on a combination of validated clinical and endoscopic criteria. The authors found that there were 3 deaths and only 1 episode of rebleeding at 1 month of follow-up among 209 patients deemed low risk by the guideline. The deaths were related to chronic medical conditions and not to complications of UGIH. While early endoscopy was not an explicit component of the intervention guidelines, it was found to be an independent predictor of decreased length of stay for low-risk patients. These data were confirmed by Moreno et al³⁹ in a study using the same discharge guidelines. In contrast to the Hay et al study, this trial covered a continuous period and compared data with retrospective controls. Moreover, during the study period, guidelines were implemented by 1 team in consecutive patients. There were 1 death and 7 episodes of rebleeding among 488 low-risk patients at 1 week of follow-up. The authors conclude that "most" low-risk patients can be safely discharged.

Table 3. Uncontrolled Trials Relating to Timing of Endoscopy for Low-Risk Patients With Nonvariceal Upper Gastrointestinal Tract Hemorrhage*

Source, y	Patients	Study Question	Exclusion Criteria	Patient Outcome Measure	Conclusion
Cebollero-Santamaria et al, ³² 1999	84 Elderly patients with NVUGIH admitted to ED of teaching hospital	Can "low-risk" elderly patients be safely treated as outpatients through use of early discharge protocol encouraging immediate upper endoscopy in ED?	Age <65 y, variceal bleeding, presence of 1 major or 3 minor explicit clinical criteria	Rebleeding	No episodes of rebleeding in 24 outpatients at 4-wk follow-up
Chang et al, ³⁸ 1992	381 Patients with UGIH presenting to ED-based GI unit of teaching hospital	Can "stable" patients be safely treated as outpatients through use of early discharge protocol encouraging upper endoscopy within 6 h of presentation?	Unstable vital signs, SRH	Mortality, rebleeding	No mortality and 3 episodes of rebleeding in 131 outpatients (follow-up time not stated)
Hsu et al, ³³ 1996	404 Patients with peptic ulcer bleeding admitted to ED of university hospital	Can "stable" patients be safely treated as outpatients through use of early discharge protocol requiring upper endoscopy within 24 h of presentation?	Lesion other than peptic ulcer, any SRH, hemodynamic instability, alcoholism, bleeding disorder, NSAID use, coexisting acute illness	Mortality, rebleeding	No mortality and 2 episodes of rebleeding in 139 outpatients at 1-wk follow-up
Koch et al, ³⁷ 1996	27 Patients With NVUGIH presenting to university hospital	Can "stable" patients be safely treated as outpatients through use of early discharge protocol requiring "emergent" outpatient upper endoscopy?	Evidence of alcoholic liver disease, inadequate social support, SRH	Mortality, rebleeding, readmission	No mortality and 1 episode of rebleeding in 14 outpatients at 1-wk follow-up
Lai et al, ³⁴ 1997	76 "Stable" patients with duodenal ulcer bleeding presenting to university hospital	Can "stable" patients be safely treated as outpatients through use of early discharge protocol requiring upper endoscopy within 24 h of presentation?	Lesion other than duodenal ulcer, Hb <100 g/L, SBP <100 mm Hg, HR <100/min, orthostatic vital signs, presence of CHF, COPD, cirrhosis, renal failure, stroke, coagulopathy, hematologic malignancy, SRH on upper endoscopy, age <60 y	Rebleeding	No rebleeding in any patients at 6-wk follow-up
Longstreth and Feitelberg, ³⁶ 1995	145 Patients with NVUGIH presenting to health maintenance organization hospital	Can "selected" patients be safely treated as outpatients through use of early discharge protocol requiring "urgent" upper endoscopy?	Absolute criteria: variceal bleeding, portal hypertensive gastropathy, SRH; nonabsolute criteria: debilitation, orthostatic vital signs, severe liver disease, serious concomitant disease, coagulopathy, hematemesis or multiple melena on day of admission, Hb <80 g/L, inadequate home support	Rebleeding, transfusion requirement after discharge, readmission, presyncope, syncope	No transfusion requirement and 1 episode of rebleeding successfully treated with readmission in 34 outpatients at 1-mo follow-up
Longstreth and Feitelberg, ³⁵ 1998	176 Low-risk patients with NVUGIH presenting to HMO hospital	Can low-risk patients be safely treated as outpatients through use of early discharge protocol encouraging prompt upper endoscopy?	Same exclusion criteria as for Longstreth and Feitelberg, ³⁶ 1995	Mortality, rebleeding, readmission	No mortality and 2 episodes of rebleeding successfully treated with readmission at average follow-up of 16 mo

*All trials cited were designed as uncontrolled prospective studies. UGIH indicates upper gastrointestinal tract hemorrhage; NVUGIH, nonvariceal UGIH; ED, emergency department; GI, gastrointestinal; HMO, health maintenance organization; SRH, stigmas of recent hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; Hb, hemoglobin; SBP, systolic blood pressure; HR, heart rate; CHF, congestive heart failure; and COPD, chronic obstructive pulmonary disease.

Our review identified 5 observational studies,^{19,40-43} of which 2^{42,43} directly examined the effect of early endoscopy on patient outcomes. In a large retrospective cohort study, Lindenauer et al⁴² failed to detect a mortality benefit for all comers un-

dergoing early (<24 hours) vs delayed (≥24 hours) endoscopy and extended these conclusions to low-risk patients through multivariate analysis stratifying patients by clinical severity. However, mortality was the only outcome assessed. In a ret-

rospective application of a discharge protocol encouraging early endoscopy, Rockall et al⁴³ projected that 25% of all comers with UGIH could have been safely discharged immediately after prompt endoscopy.

Hay et al,⁴¹ in a retrospective validation of the previously described discharge protocol by the same authors, found a 0.6% complication rate for patients deemed low risk. Conversely, in a large retrospective cohort study of consecutive patients with UGIH, Cooper et al¹⁹ established through multivariate analysis that early endoscopy was associated with a slightly higher but not statistically significant risk of in-hospital death for patients in the lowest risk group. In a second retrospective study by the same authors,⁴⁰ early endoscopy was found to be equivocal as a risk factor for poor patient outcomes in low-risk subjects. Because of limitations of study design, it is difficult to draw firm conclusions for low-risk patients from these observational studies, as there was no postdischarge follow-up, no description of additional important patient outcomes beyond mortality and need for surgery, and no distinction between variceal and nonvariceal causes of bleeding.

It appears that the weight of the evidence supports early vs delayed endoscopy for low-risk patients with acute nonvariceal UGIH (**Figure 3**). If only the highest-quality controlled study is considered, Lee et al²⁰ showed that early endoscopy and prompt discharge of low-risk patients was safe and effective. Of the remaining controlled trials, all showed low complication rates for low-risk subjects managed as outpatients. Furthermore, there were no deaths and only 9 instances of rebleeding of a combined 594 low-risk outpatients in 7 uncontrolled prospective trials.³³⁻³⁸ Of the 20 described studies, 16 suggested that early endoscopy for low-risk patients is safe and effective, 3 were equivocal, and only 1 detected a statistically insignificant trend toward increased mortality.

DOES EARLY ENDOSCOPY IMPROVE PATIENT OUTCOMES VS DELAYED ENDOSCOPY FOR HIGH-RISK PATIENTS WITH ACUTE NONVARICEAL UGIH?

Although many prospective studies have carefully documented the timing of emergent endoscopy for high-risk patients with nonvariceal UGIH,⁴⁴⁻⁴⁷ few have used a control group of patients undergoing delayed endoscopy to compare pa-

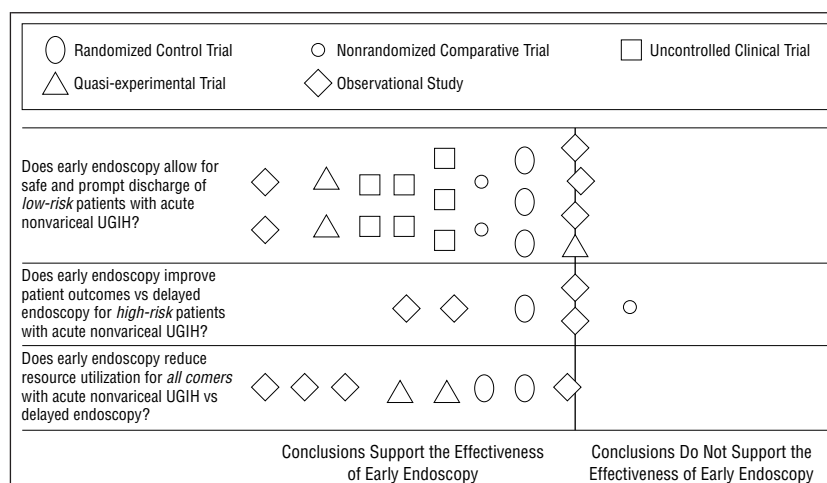


Figure 3. Literature synthesis. For each clinical question, the conclusions either support or do not support the effectiveness of early vs delayed endoscopy in the management of acute nonvariceal upper gastrointestinal tract hemorrhage (UGIH).

tient outcomes on the basis of timing alone. Moreover, of the studies that have made this comparison, few have examined the role of early endoscopy as both a diagnostic and a therapeutic tool. These trials are summarized in **Table 4**.

In the only randomized trial, Lin et al⁴⁸ compared early vs delayed endoscopy for diagnostic and therapeutic efficacy in patients with bleeding peptic ulcer presenting with clear, "coffee ground," or bloody nasogastric aspirates. Patient were first randomized to either early (<12 hours) or late (12-24 hours) endoscopy on the basis of the time of arrival at the emergency department. Early endoscopy resulted in a reduction in transfusion requirements in those with bloody aspirates but had no improvement in outcomes measured in those with coffee ground aspirates. Of note, it is unclear whether an intention-to-treat analysis was performed, since patients who were unable to cooperate with endoscopy or who had "massive bleeding" but refused endoscopy were excluded from the trial after randomization. This could overestimate the usefulness of the intervention by excluding a potentially confounding group from one arm of the study but not the other. While the authors note that the randomization envelopes of excluded patients were sealed and returned to the pool, this does not negate the potential effect of narrowing the study arm to a select group at the expense of the comparison group. Nonetheless, this

study is notable for its strict delineation of exclusion criteria and for its use of concealed allocation in the form of opaque sealed envelopes.

Yen et al¹⁶ examined the effects of emergent (<2 hours) vs delayed (2-24 hours) endoscopy on oxygen saturation for patients presenting to the emergency department with UGIH. The authors found both a significantly higher rate of oxygen desaturation and a decreased recovery of preendoscopic saturation with early endoscopy, and therefore concluded that early endoscopy is associated with more complications than delayed endoscopy. However, the increased complications associated with early endoscopy were more likely a function of increased patient risk in the study arm, as patients with active hematemesis received early endoscopy, while those without it received delayed endoscopy.

There were 4 observational studies that evaluated the role of early vs delayed endoscopy for high-risk patients.^{19,40,42,49} Cooper et al, in a pair of retrospective multicenter cohort studies,^{19,40} examined the impact of early (≤ 24 hours of admission) vs delayed (>24 hours after admission) endoscopy on in-hospital mortality, surgical intervention, and rebleeding for all comers with UGIH. The authors found that early therapeutic endoscopy for high-risk patients resulted in a significant reduction in rebleeding and surgery and a statistically insignificant trend toward reduced mortality. Lindenauer et al,⁴²

Table 4. Controlled Trials Comparing Early vs Delayed Endoscopy for High-Risk Patients With Nonvariceal Upper Gastrointestinal Tract Hemorrhage*

Source, y	Patients	Design	Comparison	Exclusion Criteria	Patient Outcome Measures	Conclusion
Lin et al, ⁴⁸ 1996	124 Patients with peptic ulcer bleeding presenting to university ED	Randomized trial	Early (<12 h) vs delayed (12-24 h) upper endoscopy for patients with clear, "coffee ground," and bloody nasogastric aspirates	Variceal bleeding, bleeding from malignancy, unknown bleeding source, platelet count <50 × 10 ⁹ /L, anticoagulation, unable to cooperate	Mortality, transfusion requirements, need for surgery	Early upper endoscopy resulted in decreased transfusion requirement only for patients with bloody nasogastric aspirate and had no effect on other outcomes in all groups
Yen et al, ¹⁶ 1997	100 Patients with UGIH who underwent endoscopy in university ED	Prospective nonrandomized study	Early (<2 h) vs delayed (2-24 h) upper endoscopy	Altered mental status, COPD, heart failure, MI within 3 mo, need for continuous oxygen supplementation	Oxygen saturation during and after upper endoscopy	Early upper endoscopy resulted in more frequent and significant oxygen desaturation during procedure and decreased recovery of pre-upper endoscopy saturation after procedure
Cooper et al, ⁴⁰ 1999	909 Patients with UGIH presenting to 13 hospitals	Retrospective cohort study	Early (≤24 h) vs delayed (>24 h) upper endoscopy	None	Mortality, rebleeding, need for surgery	Early therapeutic upper endoscopy resulted in significant reduction in rebleeding and surgery, and a trend toward reduced mortality for high-risk patients
Lindenauer et al, ⁴² 1999	1039 Medicare beneficiaries presenting to California hospitals with UGIH	Retrospective cohort study	Early (≤24 h) vs delayed (>24 h) upper endoscopy	Not a Medicare beneficiary	Mortality	Early upper endoscopy resulted in no effect on mortality for high-risk patients
Cooper et al, ¹⁹ 1998	3801 Patients with UGIH presenting to 30 hospitals	Retrospective cohort study	Early (≤24 h) vs delayed (>24 h) upper endoscopy	Age <18 y, transfer patient from nonstudy hospital	Mortality, need for surgery	Early upper endoscopy resulted in decreased need for surgery but had no effect on mortality for high-risk patients
Choudari and Palmer, ⁴⁹ 1993	114 Patients with "severe" peptic ulcer bleeding presenting to community general hospital	Retrospective cohort study	Early (<6 h) vs intermediate (6-12 h) vs delayed (>12-24 h) upper endoscopy	None	Mortality, rebleeding, transfusion requirements, need for surgery	Early upper endoscopy resulted in no effect on any outcomes

*UGIH indicates upper gastrointestinal tract hemorrhage; ED, emergency department; COPD, chronic obstructive pulmonary disease; and MI, myocardial infarction.

in a large retrospective study of Medicare beneficiaries, detected no mortality advantage of early (≤24 hours) vs delayed (>24 hours) endoscopy for high-risk elderly patients. Finally, in a retrospective evaluation of high-risk subjects with peptic ulcer bleeding, Choudari and Palmer⁴⁹ found no difference in patient outcomes for groups undergoing early (<6 hours), intermediate (>6-12 hours), and delayed (>12-24 hours) endoscopy. However, these were all uncontrolled retrospective studies, had no description of postdischarge complications, and, with the exception of the Choudari and Palmer

study, included variceal and nonvariceal causes of hemorrhage.

In summary, the weight of the evidence supports early vs delayed endoscopy for high-risk patients with acute nonvariceal UGIH (Figure 3). If only the highest-quality clinical trial is considered, the study by Lin et al⁴⁸ showed no mortality benefit but a significant decrease in transfusion requirements for high-risk patients. Of the remaining studies, 2 showed a significant improvement of patient outcomes with early vs delayed endoscopy for high-risk patients, and 2 were equivocal. One study suggested the potential for more com-

plications with emergent nonsedated endoscopy, and no studies detected any significant impact on mortality for high-risk patients.

DOES EARLY ENDOSCOPY IMPROVE UTILIZATION OUTCOMES VS DELAYED ENDOSCOPY FOR ALL COMERS WITH ACUTE NONVARICEAL UGIH?

Early endoscopy may potentially reduce costs both by reducing hospital length of stay⁵⁰ and by avoiding admission when compared with delayed endoscopy. **Table 5** summa-

Table 5. Studies Comparing Resource Utilization for Patients Undergoing Early vs Delayed Endoscopy*

Source, y	Patient Risk Stratification	Design	Utilization Outcome Measures	Main Finding
Lee et al, ²⁰ 1999	Low-risk	Randomized	LOS, cost savings, postdischarge physician visits	Early upper endoscopy saved \$1594/patient, shortened LOS by 1 d/patient, and resulted in fewer postdischarge physician visits vs delayed upper endoscopy
Lin et al, ⁴⁸ 1996	High-risk	Randomized	LOS	Early upper endoscopy saved 10.5 d/patient for subjects with bloody nasogastric aspirates but had no effect on LOS for patients with "coffee ground" aspirates vs delayed upper endoscopy
Hay et al, ²¹ 1997	All risk groups combined	Quasi-experimental; interrupted time series	LOS, cost savings, postdischarge physician visits	Early upper endoscopy was an independent predictor of shorter LOS when used as part of a discharge guideline and contributed to a 63% decrease in in-hospital costs without an increase in postdischarge physician visits vs usual care
Hussain et al, ²⁹ 1995	Low-risk and high-risk	Quasi-experimental; before and after	LOS	Early upper endoscopy EGD saved 1.24 d/patient for low-risk and 1.01 d/patient for high-risk patients vs delayed upper endoscopy
Cooper et al, ⁴⁰ 1999	Low-risk and high-risk	Retrospective cohort	LOS	Early upper endoscopy saved 1 d/patient for low-risk and 2 d/patient for high-risk patients vs delayed upper endoscopy
Lindenauer et al, ⁴² 1999	All risk groups combined	Retrospective cohort	LOS	Early upper endoscopy reduced LOS by 26% vs delayed upper endoscopy
Cooper et al, ¹⁹ 1998	All risk groups combined	Retrospective cohort	LOS	Early upper endoscopy reduced LOS by 2 d/patient vs delayed upper endoscopy
Rockall et al, ⁴³ 1996	All risk groups graded by severity	Retrospective cohort	LOS	Early upper endoscopy significantly reduced LOS for lowest risk group but insignificantly increased LOS in highest risk group

*LOS indicates length of stay.

rizes the studies investigating the impact of early vs delayed endoscopy on costs and utilization.

Two randomized trials met our inclusion criteria. Lee et al²⁰ evaluated the effect of early endoscopy on length of stay and total costs for low-risk patients with nonvariceal UGIH. The authors found a decrease in mean hospital stay of 1 day (1 vs 2 days) with the use of early endoscopy. Moreover, they calculated a cost reduction of \$1594 per patient (\$2068 vs \$3662) associated with the use of early endoscopy. This savings reflected both a decreased length of stay and a difference in admission location, as significantly fewer patients in the study group were managed in the intensive care unit but were instead admitted to the less costly medical ward. To investigate the potential of cost shifting to the outpatient arena, the authors monitored postdischarge unplanned physician visits. They found significantly fewer visits in the early endoscopy group, thereby contributing to the overall cost

reduction associated with early endoscopy.

Lin et al⁴⁸ investigated the effect of early endoscopy on length of stay for high-risk patients with nonvariceal UGIH. For the subgroup of patients with a bloody nasogastric aspirate, early endoscopy saved 10.5 days per patient compared with delayed endoscopy (4.0 ± 3.5 vs 14.5 ± 10.8 days). While this represents a dramatic reduction, the small sample size and potential outlier effect may have skewed the results.

There were 2 studies with quasi-experimental designs that addressed costs and utilization. Hay et al,²¹ in an interrupted time series with alternate-month design, investigated the impact of a management guideline on length of stay for all comers with nonvariceal UGIH. Although the authors did not perform analysis for individual risk groups, they demonstrated an independent association between early endoscopy and shorter length of stay for all patients, and projected a 63% decrease in total inpatient costs with the early discharge guidelines vs

usual care. There was no evidence of cost shifting, as an equal number of patients in both groups sought postdischarge physician visits. Hussain et al²⁹ compared length of stay for both low- and high-risk patients before and after instituting a management protocol for peptic ulcer bleeding. They found a reduction of 1.24 days per patient for low-risk and 1.01 days per patient for high-risk patients with the use of early endoscopy.

There were 4 observational studies,^{19,40,42,43} all of which demonstrated a significant reduction in length of stay with early endoscopy for low-risk patients (range of 1-2 days per patient). Of the 2 studies that specifically examined high-risk patient subgroups, 1 showed a decreased length of stay (2 days saved per patient)⁴⁰ while 1 demonstrated an insignificant increase in length of stay with early endoscopy.⁴³

Figure 4 displays the composite data on length of stay for the 8 studies as a function of risk group. Of the 4 studies that exam-

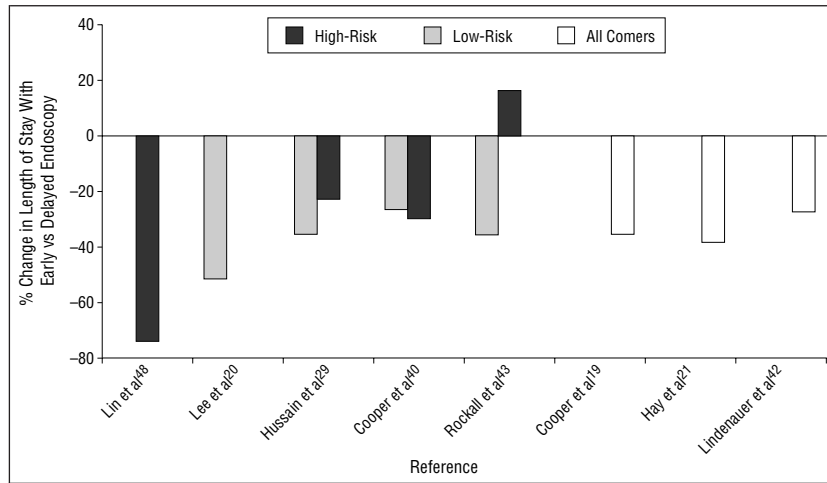


Figure 4. Studies comparing length of stay for early vs delayed endoscopy by risk group. For studies with more than 2 risk groups, data are presented for highest and lowest risk group. Studies without subgroup data are presented as "all comers."

ined low-risk patients, all demonstrated a decrease in length of stay associated with early vs delayed endoscopy. Of the 4 studies that examined high-risk subgroups, all but 1 detected a shorter length of stay. Finally, each of the 3 studies that performed no risk stratification portrayed an advantage for all comers undergoing early endoscopy. All data in support of early vs delayed endoscopy were statistically significant, although the one instance of increased length of stay failed to achieve statistical significance.

COMMENT

Since no consensus exists regarding the costs and benefits of early endoscopy in UGIH, we sought to identify and critically appraise the evidence in the medical literature regarding the effectiveness of early vs delayed endoscopy on patient and economic outcomes. For all 3 clinical questions, the weight of the evidence favors early endoscopy (Figure 3). For low-risk patients, the evidence clearly supports the claim that early endoscopy promotes safe patient disposition. However, of the studies that directly investigated early vs delayed endoscopy, only the trial by Lee et al²⁰ was deemed high quality by means of a validated scoring scale. While the study by Hay et al²¹ was also of high quality, it only indirectly examined the association of early vs delayed endoscopy for low-risk patients. The remain-

ing studies were found to suffer from 1 or more potentially significant methodologic shortcomings, including lack of an appropriate comparison group, inadequate patient follow-up, lack of sufficient statistical power, or lack of prospective experimental design.

For high-risk patients, our review suggests that there is a benefit from early vs delayed endoscopy in many patient outcomes, including transfusion requirements, rebleeding, and need for emergency surgery. Furthermore, while there was no evidence that early endoscopy decreases mortality, there was also no evidence that the practice results in patient harm. The data were limited by several methodologic shortcomings, and the only identified randomized control trial did not perform an intention-to-treat analysis.

Regarding resource utilization, the evidence suggests that early endoscopy significantly reduces length of stay compared with delayed endoscopy for all risk groups with nonvariceal UGIH without evidence of cost shifting to the outpatient setting. Of the 2 studies that conducted an absolute cost analysis,^{20,21} both found a significant savings from early endoscopy. There were no formal cost-effectiveness analyses reporting incremental cost-effectiveness ratios.

There is controversy regarding the ideal time to perform endoscopy in patients presenting with UGIH. Early endoscopy may pro-

vide prompt diagnosis, rapidly confirm clinical suspicion, and serve as an aid to decision making regarding triage and subsequent management. For high-risk patients, early endoscopy may result in rapid hemostasis, while low-risk patients may benefit by safely avoiding hospitalization. A policy of early endoscopy may reduce resource use by minimizing potentially unnecessary admissions, by reducing the length of stay for those who are admitted, and by downgrading the admission location to less costly venues. Moreover, data suggest that delaying endoscopy is of little benefit to patients with nonvariceal UGIH.^{13,14}

Conversely, opponents of early endoscopy contend that there is scant evidence to support the claim that endoscopy provides a mortality benefit, regardless of timing.^{3,4,15} Moreover, some indirect evidence suggests that early endoscopy may be associated with more complications than delayed endoscopy.^{16,17} Only 1 study¹⁶ directly assessed the safety of early endoscopy, suggesting that it may result in an increased risk of oxygen desaturation. However, this study used early endoscopy disproportionately in a high-risk group, and all other studies identified suggest that early endoscopy is safe. Therefore, while some argue that emergently subjecting low-risk patients to a potentially unhelpful and invasive procedure is not worth the risk of subsequent or preventable complications, supportive evidence is lacking.

Moreover, a policy of early endoscopy may be difficult and expensive to implement in the real world. The associated costs of operating a 24-hour endoscopy service may be substantial, as this not only requires support of additional physicians, nurses, and equipment technicians, but also requires extensive facility investments, particularly for those institutions not well equipped to perform endoscopy in the emergency department. Early endoscopy could further escalate costs by detecting stigmas of recent hemorrhage that might otherwise have resolved by the time of delayed endoscopy, thereby leading to potentially unnecessary interventions.

There are some limitations to this analysis. As with any system-

atic review, there is a potential for publication bias, which refers to the common practice of publishing only trials with positive outcomes. However, we believe there may be incentive to publish studies that demonstrate negative outcomes for an otherwise time-consuming and potentially costly intervention if it existed. Additionally, there is a paucity of randomized trials, and many of our conclusions are based on uncontrolled and observational studies. The heterogeneity of the study designs, inclusion criteria, timing of endoscopy, and reported end points precluded formal meta-analysis. Nonetheless, where possible, we attempted to weigh the evidence by methodologic rigor and to base our conclusions on the findings from prospective randomized controlled clinical trials.

Although our review identified a substantial number of studies examining the impact of early vs delayed endoscopy, there were few experimental trials and even fewer of high methodologic quality. Additional well-designed, randomized clinical trials comparing early vs delayed endoscopy for all risk groups must be performed before firm conclusions can be reached regarding the impact on long-term patient outcomes. To clarify issues of utilization, there is a need for studies comparing the costs of 24-hour endoscopy services with "usual care." In addition, the definition of *early* must be elucidated and confirmed in comparative trials. For example, is 4 hours better than 12 hours?

These findings suggest that a more streamlined and standardized approach to acute nonvariceal UGIH—akin to the time-sensitive paradigm of acute myocardial infarction management—may improve patient outcomes. A 24-hour gastrointestinal rapid response team, similar to the "code blue" revascularization service omnipresent in major medical centers, would ensure that patients with UGIH receive prompt and high-quality care. For low-risk patients, an emergency department UGIH observation unit,^{38,51} similar to recently proposed "chest pain observation units,"⁵² could serve as a way station for patient triage decisions.

The evidence suggests that hesitancy to discharge low-risk patients may be unfounded, and that it should no longer be obligatory to admit all patients with acute nonvariceal UGIH to the hospital. Likewise, high-risk patients may benefit from a more coordinated and timely delivery of endoscopic hemostasis than the often inconsistent and time-insensitive approach currently practiced. Until additional well-designed trials are conducted, it is difficult to draw definitive conclusions. Until then, existing data suggest that early endoscopy may be safe and effective for all risk groups.

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Correction

Error in Abstract. In the Original Investigation by Ramirez and Bordon titled "Early Switch From Intravenous to Oral Antibiotics in Hospitalized Patients With Bacteremic Community-Acquired *Streptococcus pneumoniae* Pneumonia," published in the March 26 issue of the ARCHIVES (2001;161:848-850), an error occurred in the "Objective" statement of the abstract on page 848. This sentence should have read as follows: "To determine whether the switch from intravenous to oral therapy in such patients, once the patient reaches clinical stability, is associated with poor clinical outcome." The journal regrets the error.