Determination of Clinical Decision Rules and Risk Stratification of Patients Admitted with Acute Lower Gastrointestinal Hemorrhage

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A. Outcomes in Lower Gastrointestinal Bleeding

Acute lower gastrointestinal bleeding (LGIB) is a significant health problem in the United States with an annual incidence in the adult population of 20-27 cases per 100,000. Mortality related to acute LGIB is low, but the care of these patients requires the use of considerable amount of health care resources. It would be useful to be able to identify which patients are at low risk for negative outcomes (rebleeding, surgery, death.) This would allow appropriate triage of patients, and perhaps the selection of a group who could be discharged from the hospital early and undergo outpatient evaluation. The specific aims of this study are: 1) To develop a clinical prediction rule that could predict which patients with lower GI bleeding might be safely discharged from the hospital and undergo an outpatient evaluation; and 2) To document the costs associated with the care of patients admitted and treated for LGIB and to calculate the potential savings associated with early hospital discharge and outpatient evaluation for low risk patients. In a preliminary study that we recently completed, 89 consecutive patients admitted for LGIB were stratified as high risk or low risk according to a pilot scoring system. There were 19 patients assigned to the high-risk group, of whom 12 rebled, 2 required surgery and 1 died. The 70 patients assigned to the low risk group suffered no adverse outcomes. Interestingly, in this pilot study, the endoscopic diagnosis (i.e. findings on colonoscopy) did not predict 30 day adverse outcomes. The problems with our pilot scoring system at present are two-fold. First, 24 hours of observation are required for the score. In addition, because of the small sample size, we have not been able to attach a specific degree of risk to the components of the score in order to develop a more valuable clinical prediction rule. Our current proposal is designed to address these problems. We plan to enroll consecutive patients with LGIB in an observational study to develop a clinical prediction rule based on day-of- admission criteria.

B. Study Purpose and Rationale

1. To establish clinical prediction rules that can predict which patients with lower gastrointestinal bleeding (LGIB) are at low risk for adverse events and therefore could be safely discharged from the hospital and undergo an outpatient evaluation.

2. To document the hospital costs and length of stay associated with the care of patients admitted and treated for LGIB and to calculate the potential savings associated with early hospital discharge and outpatient evaluation for low risk patients.

Acute lower gastrointestinal bleeding (LGIB) is a significant health problem in the United States with an annual incidence in the adult population of 20 - 27 cases per 100,000.[1,2] Mortality related to acute LGIB is low, <5% in multiple studies.[3] The most common sources of bleeding are diverticula, cancer or polyps, colitis (inflammatory bowel disease, infectious, radiation, ischemic, vasculitis), anorectal sources (hemorrhoids, anal fissures, rectal ulcers), and iatrogenic (e.g. post-polypectomy).[3,4]

The traditional management of patients with LGIB has stressed admission with rapid colonoscopy (within 12 -48 hours). Jensen et al. studied at the role of therapeutic endoscopy in patients with severe diverticular hemorrhage. He found that urgent colonoscopic treatment led to decreased rebleeding, surgery and length of stay.[5] Practice guidelines published by the American College of Gastroenterology in

1998 stress the importance of rapid endoscopic evaluation, but the authors clearly state that the algorhythin they propose is intended for patients with "instability of vital signs, anemia, and/or need for blood transfusion."[6] However, this description applies to a minority of patients admitted with LGIB, as patients with mild to moderate bleeding make up the majority of the patients. Unlike an upper gastrointestinal hemorrhage (UGIH), patients with a LGIB are less likely to present with shock or orthostasis (35% versus 19%, respectively) and are less likely to require blood transfusions (64% versus 36%, respectively; $p < 0.00001$)[7] In fact, a consensus statement issued by the American Society for Gastrointestinal Endoscopy in 1998 states, "Moderate blood loss comprises the majority of acute bleeding instances and is characterized by either spontaneous cessation of rapid bleeding after a brief period or by rectal bleeding of a slower rate but longer duration." They define moderate bleeding loosely as acute blood loss without hemodynamic instability, which is not sufficient to require immediate transfusion, but they still recommend rapid colonoscopic evaluation. [8]

Several studies have stratified patients presenting with UGIH according to risk of rebleeding and mortality.[9,10] The results of these studies have helped clinicians manage patients, enabling them to send low risk home expeditiously. Risk factors that have been found to place patients at high risk of rebleeding, surgery, and death include advanced age, comorbid disease, orthostasis at time of bleed, and stigmata of recent hemorrhage on upper endoscopy (active bleeding or visible vessel). Another recent study, the BLEED study, has risk stratified all patients with GI bleeding based on the presence of certain criteria on admission--ongoing Bleeding, Low blood pressure, Elevated prothrombin time, Erratic mental status, or unstable comorbid Disease." However, little data are available for stratifying patients presenting with LGIB according to risk of short term, i.e. within 30 days, episodes of rebleeding, need for surgery, or mortality.

The observation that moderate bleeding makes up a majority of patients admitted with LGIB has been confirmed at Columbia Presbyterian Medical Center. In a pilot study, conducted on eighty-nine consecutive patients admitted for LGIB between July 1997 and November 1998, a scoring system to stratify patients as low risk or high risk for in hospital adverse events was developed based on data obtained within the first 24 hours of admission. The scoring system was based on the following clinical variables: age>75, I point; prothrombin time >3 seconds over control, I point; 3 or more chronic comorbid diseases, I point; hemodynamic instability, 2 points; and greater than 2 units of blood transfused within 24 hours. Patients with less than or equal to 3 points were stratified as low risk. The results of the study showed that the 19 patients assigned to the high-risk group, of whom 12 rebled, 2 required surgery and I died. This produced a rebleeding rate of 13%. The 70 patients who fell into the low risk group suffered no adverse outcomes. The individual variables associated with rebleeding were transfusion requirements, elevated prothrombin time, and greater than 3 comorbid diseases. *12* The endoscopic diagnosis (i.e. findings on colonoscopy) did not predict 30 day adverse outcomes.

If colonoscopic findings are unlikely to predict negative outcomes, and since a majority of patients admitted with LGIB are at low risk for rcbleeding, surgery and death, some low risk patients who present to the ER might be safely sent home (or admitted for one-day stay) and scheduled for outpatient colonoscopy. For this type of management to be effective and safe, it is important to carefully establish the low risk group by prospectively defining an appropriate scoring system.

C. Study Design and Statistical Analysis

All patients greater than 18 years old admitted to the New York Presbyterian Hospital, at both the New York Weill Cornell and Columbia-Presbyterian sites, with a primary diagnosis of acute lower GI bleed will be screened for entry into the study. Acute LGIB is generally defined as blood loss from the gastrointestinal tract of recent onset which emanates from a location distal to the ligament of Treitz. For this study LGIB is further defined as passage of at least one cup of bright red blood, blood coated stool, or maroon stool or clots per rectum.

Baseline demographic, historical, and clinical data will be collected upon presentation. Historical and demographic data include: age, gender, race, previous history of LGIB, previous colonoscopic or

barium enema data, chronic comorbid diseases, use of NSAIDS, time since onset of symptoms, and type of symptoms on presentation (abdominal pain, fever, diarrhea). Physical examination data include: blood pressure, pulse, orthostasis, temperature, abdominal tenderness, findings on rectal examination and anoscopy. Laboratory data will include: hematocrit, platelet count, leukocyte count, prothrombin time and INR. In addition, we will record any blood transfusions given while in the emergency department.

Data obtained from colonoscopy will include the time from emergency room presentation to the procedure, diagnoses, and the degree of confidence that the bleeding source was found (possible, probably, definite). Any therapeutic procedures done at colonoscopy will be recorded. Total number of units of blood transfused as well as number of units transfused in the first 24 hours. The primary endpoints are: rebleeding or any adverse event (rebleeding, surgery or mortality) within 7 days. Secondary endpoints are surgery, mortality, total transfusion requirements, and hospital length of stay, and resource utilization.

After identifying patients admitted with LGIB and recording their historical data and initial vital signs, the laboratory, colonoscopy report, cost and length of stay information will be directly obtained from the hospital's central database via an automated system. Utilizing the Columbia-Presbyterian Medical Center's Department of Medical Informatics' central repository of clinical information, all hospital events, including timing of blood transfusions are coded and will form the core of data collection for this study. Additionally, this system will be document hospital resource utilization for 30 days after presentation both as an inpatient and an outpatient. The charge to cost ratio method will be used to estimate true costs from the hospital data. A similar arrangement is to be structured with the New York-Weill Cornell center.

Kollef s study reports rebleeding in 32% of high risk patients and a rebleeding rate of 14% in low risk patients. The number of subjects to be enrolled using these outcome percentages could be calculated via the test of proportions of two groups:

$$n \text{ (in each group)} = 8 \frac{P_1 q_1 + P_2 q_2}{(effect)^2} + \frac{2}{effect} + 2$$

P_1, P_2 are the proportions in the two groups;
q= 1-p
effect is the difference in p

As such, the power calculation for 80% power, testing at P = 0.05 results in 97 subjects per group, for a total of 194 patients.[11] This would be sufficient if we were proposing univariate or Chi-squared analyses of the data.

However, multivariable regression analysis will be the primary statistical technique employed for data analysis." These models use a mixture of categorical and continuous variables and are able to process data with partially observed (censored) responses. The simultaneous effects of the uncontrolled variables are controlled using a regression model so that the effect of the factor of interest can be more purely estimated. To calculate the number of patients, we will use the following formula:

$$p > m/10$$

p=total number of parameters (columns of the design matrix) examined during the course of analysis.
m=the number of patients in the less frequent outcome category (i.e. patients who rebleed)

Assuming a rebleeding rate of 13%, as was established in the pilot study and is a more conservative estimate than was seen in the Kollef data, we propose using 6 clinical variables in the multivariate model which would then yield a sample size of 460 patients. The six variables to be included

in the model are age, prothrombin time, number of comorbid diseases, hemodynamic instability, number of units of blood transfused within first 24 hours, history of LGIB.

There is no randomization or cross-over in this type of cohort study.

D. Study Procedure

Patients will be managed according to the standards at the New York Presbyterian Hospital as directed by the attending physician caring for the patient. Generally, this will entail colonoscopy within 12 to 48 depending on the acuity of their presentation. Upper endoscopy will be performed if deemed appropriate by the attending physician. Endoscopy will be performed either in the intensive care unit at the bedside or in the endoscopy suite.

All patients screened for the study will be managed in the same fashion. Blood transfusion and discharge decisions will generally be determined by the primary medical team and not by the investigators. Standard clinical care will be applied equally to all patients with LGIB.

The study will likely take 2 - 3 years to enroll a sufficient number of patients given that 89 patients were studied during a 15 month period at the single institution.

E. Study Drugs

No investigational drugs are used in this study.

F. Medical Devices

Colonoscopy will be performed in patients using standard techniques.

G. Study Questionnaires

Patients will not be asked to complete a questionnaire. The gastroenterologist will obtain a medical history which includes the patients chronic co-morbid diseases, use of non-steroidal anti-inflammatory medicines, presenting symptoms, history of previous LGIB, results of previous colonoscopic or barium enema examinations.

H. Study Subjects

All patients greater than 18 years old admitted to the New York Presbyterian Hospital, at both the New York Weill Cornell and Columbia-Presbyterian sites, with a primary diagnosis of acute lower GI bleed will be screened for entry into the study.

The exclusion criteria used are: 1) Hematemesis or melena alone without red or maroon stool; 2) Acute unstable comorbid disease (unstable coronary syndrome, pulmonary edema of any etiology, septic shock, pulmonary embolism, acute renal failure, decompensated cirrhosis); 3) Altered mental status, or otherwise unable to give consent for colonoscopy; 4) Immunosuppression (HIV, neutropenic, post transplant); 5) Gravid women. These patients would be admitted to the hospital regardless of risk stratification score.

There will be no restriction of subjects by gender or race, nor will there be encouragement of women or minorities in this study.

I. Recruitment of Subjects

Subjects are drawn from the patients who present to the Emergency Departments at the New York Presbyterian Hospital: Columbia-Presbyterian Center and New York Weill Cornel Center. There

will be no advertisements or other vehicles of recruitment. Therefore subjects will likely primarily reside in the 10032 and 10021 ZIP-code areas given the location of the two medical centers. Given the potentially acute nature of the presentation of LGIB, there will be no attempt to discuss the study with the patient's primary care physician. Additionally, as this study is purely observational, with no therapeutic intervention, a discussion with the patient's primary physician is unwarranted.

J. Confidentiality of Study Data

All patients screened for the study will be assigned a unique numerical code in sequential order. ldentif~g characteristics (such as name, medical record number, social security number, etc.) will be documented with the numerical code and kept in the locked office file of the principal investigator,

K. Potential Conflict of Interest

There are no conflicts of interests with this investigation for the principal investigators, support staff, College of Physicians and Surgeons of Columbia University, nor Weill Medical College of Cornell University. There are also no parties who have a proprietary interest and stand to benefit financially from the outcome of this study.

L. Location of the Study

The study will begin with the identification and enrollment of patients in the Emergency Departments at the New York Presbyterian Hospital. Patients will then either be admitted to the medical wards or the intensive care unit, and endoscopy will be performed either in the intensive care unit at the bedside or in the endoscopy suite. Given that the New York Presbyterian Hospital: New York Weill Cornell Center has a separate Institutional Review Board, that body will approve a separate IRB proposal.

M. Potential Risks

The risks for the study participants are exactly the same as non-participants as there is no therapeutic intervention being made in this study. Risks of colonoscopy will be explained to patients as part of a separate standard informed consent before that procedure.

N. Potential Benefits

There are no potential benefits for the study participants. They will be part of an observational cohort. Their assignment to high risk or low risk groups does not confer any benefits. The benefits to society, should the study succeed in validating the clinical decision rules, would include timely but not emergent endoscopy for low risk patients. These patients would be able to be sent home safely and then have a colonoscopy as an outpatient. This would decrease utilization of scarce medical resources and allow for health care dollars to be expended on more emergent procedures

O. Alternative Therapies

No alternative therapies are being offered in this study.

P. Compensation to Subjects

There is no patient compensation.

Q. Costs to Subjects

The subjects will incur no additional costs as a result of enrollment in this study.

R. Minors as Research Subjects

No patients under the age of 18 will be enrolled in this study.

S. Radiation or Radioactive Substances

No radioactive substances are used in this study.

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