Delayed Splenic Rupture After Non-Operative Management of Blunt Splenic Injury
A AAST Multi-Institutional Prospective Trial
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I. Background and Significance

In the United States, over 1.5 million adults are admitted to a hospital after injury. Of those, almost 39,000 will suffer a blunt splenic injury (BSI). Little controversy exists over the optimal management for the hemodynamically unstable patient with evidence of intra-abdominal bleeding. However, if a patient arrives hemodynamically stable and is found to have a BSI, there is much more controversy. Because of a lack of prospective, multi-institutional data, the significance of splenic pseudoaneurysms, the use of imaging to follow the healing process, the use of angioembolization of the spleen and even the appropriate time to return to full activity are unclear.

II. Specific Aims

The *long-term* goal of this project is to advance our understanding of the factors that influence the need for delayed splenectomy after initial non-operative management of BSI so that optimal management guidelines can be established for this common injury. The *objective of this application*, which is the first step in pursuit of this goal, is to pursue the following *specific aims and hypotheses*:

1. **Ascertain the 180-day risk of splenectomy after non-operative management of blunt splenic injury.**

2. **Determine factors related to failure of non-operatively managed blunt splenic injuries.**

This proposal addresses a *fundamental gap* in the literature regarding the management of BSI. Using a multi-institutional team of researchers we will capitalize on the expertise of a distinguished group of experienced trauma surgeons and the patient volume needed to carry out this study of a relatively rare event. A multi-institutional, prospective observational study will be carried out to reach the objectives of this application. Over a 2-year period, 1500 patients with non-operatively managed BSI will be recruited for the study. The patients will be followed for 180-days (6 months) to determine the 180-day risk of splenectomy. Patient demographic, physiologic, and injury related variables will be gathered along with patient management variables will be gathered so that factors associated with failure of non-operatively managed BSI can be determined. By achieving the research objectives of this application the future care of injured patients, particularly those with BSI, will be *positively impacted.* Once we understand the baseline risk of delayed splenectomy after BSI as well as potential factors associated with delayed splenectomy, randomized controlled trials can be developed to better delineate the optimal management of patients with BSI. This significant *innovation* in the care of injured persons would help to reduce the overall societal burden of injury.

DRAFT 10/09

III. Study Sample and Recruitment Plans:

Study Sample: The selection criteria are designed to produce a cohort of patients admitted after injury who have a BSI and who are successfully managed non-operatively for twenty-four hours. All participants, or their surrogates, will be required to give voluntary consent prior to cohort entry by signing an informed consent statement. Adult (age ≥ 18) persons who suffer a BSI and who have been successfully managed non-operatively for 24 hours will be eligible for recruitment. Persons will be excluded from the study if they: 1) are more than twenty-four hours

from the time of injury when they are admitted to the hospital; 2) have a history of a previous splenic injury; 3) have a history of surgery involving the spleen; 4) have a history of a significant bleeding disorder (eg. Factor VII deficiency, Factor VIII deficiency); 5) are pregnant women (assessed by a urine pregnancy test); 6) or who have a history of any of the following:

a. Hereditary elliptocytosis
b. Hereditary spherocytosis
c. sickle cell disease
d. Thallassemia
e. Hodgkins or Non-Hodgkins lymphoma
f. Other lymphomas
g. Leukemia
h. Polycythemia vera
i. Myeolofibrosis
j. Metabolic storage diseases
k. Amyloidosis
l. Splenic vein thrombosis
m. Cirrhoisis
n. Splenic cysts
o. Sarcoidosis
p. Systemic lupus erythematosous

We plan to make recruitment of women and minorities a priority for this project and we will include persons of any race who meet the inclusion and exclusion criteria. Persons under the age of 18 will not be included in this study because the management of children with BSI is much less controversial and because children are much less likely to suffer delayed splenectomy after BSI.

***Recruitment Plans*:** The institutional PI or his or her designee will carry out recruitment for this study. Based on preliminary data, we expect that for every 1000 admissions at a participating center that 26 patients will be admitted with BSI. Of those, nearly 10% will have splenectomy within 24 hours leaving 23 patients eligible for study enrollment per 1000 admissions. We expect that two-thirds of eligible people will consent for the study, meaning 16 people per 1000 admissions would be able to be recruited. We estimate that in order to observe 105 in-hospital ruptures and 50 outpatient ruptures within 6 months, a total of 1500 patients will be needed over the 2-year recruitment period.

At each study site, similar recruitment procedures will be followed. The site PI or his or her designee will screen all trauma admissions for study eligibility on for at least 5 out of 7 days every week. If the patient meets inclusion criteria and does not meet the exclusion criteria the study will be explained to him or her, and he or she will be invited to participate and study consent will be obtained.

Because injured patients can have altered mental status due to sedation, pain medication, or from injury, the PI or RA will assess the ability of the patient to provide consent. If an eligible person is deemed cognitively impaired at the initial screen, a surrogate decision maker will be approached for study consent. Once the patient is no longer cognitively impaired, the patient will have the opportunity to consent to the study. If the patient decides not to participate, the patient's data will be excluded from the study dataset and the patient will no longer be included in the study. At the time of consent, the site PI or designee will verify inclusion and exclusion criteria obtained from the chart with the patient and a final determination of whether the person is eligible for inclusion in the cohort will be made. Participants will also be informed of their rights to determine who has access to their personal health information in compliance with

DRAFT 10/09

HIPAA regulations. If it is determined that the study participant has difficulty reading the informed consent or other study collection forms, study personnel will assist the participant in reading these forms

IV. Study Plan:

***Screening and Baseline Data*:** At the time of obtaining consent, detailed contact information will be obtained and the baseline data will be gathered. The baseline data will include patient demographics, past medical history and physiologic and radiologic details up to the time of study enrollment.

***Follow-up*:** Participants will be followed for 180-days after study enrollment. During the in-patient hospital stay, the patient will be followed at least 5 out of 7 days by study personnel at each site to determine if the patient has had a spleen related intervention. If the patient underwent a spleen related intervention since the time of the previous review, information regarding the intervention will be obtained.

Once a subject is discharged, the subject will be contacted on a monthly basis either in person or by telephone to determine if he or she has had a spleen related intervention since the last follow-up. If the subject has had a spleen related intervention, then data will be gathered regarding the intervention. At each monthly follow-up the subjects will complete, either in person or via telephone, a Stanford Brief Activity Survey (SBAS) so that activity level can be determined.

***Maintaining the Cohort*:** Because follow-up can be variable for studies of injured patients we will use several strategies to maintain the cohort. The first strategy will be to maintain up to date contact information on each participant. At the time of the baseline survey and at each follow-up contact, the participant's contact information will be verified. At the same time, the participant will be asked to provide the names and contact information of two people who always know where the participant is located.

Injured persons commonly have medical appointments as a result of their injury. As much as possible we will attempt to schedule study related follow-up at the same time as medical appointments. If a face-to-face visit cannot be scheduled, we will attempt a telephone interview. To determine if the patient is truly lost to follow-up we will cross reference all participants lost to follow-up with the Social Security Death Master File to make sure the participant did not die since the last study related follow-up. Also, we will use available "address finding" services to verify our contact information. If we find that our contact information is out of date, then we will use the new contact information to attempt to contact the participant for follow-up. At the time informed consent is obtained we will notify the participants of the efforts that will be made to maintain follow-up including getting permission to search "address finding" databases in order to verify contact information.

V. Study Measurements and Definitions:

Study Measurements:

A. At study enrollment

1. Demographic data and past medical history
2. Admission physiologic characteristics
3. Injury characteristics
4. Spleen injury characteristics

B. At the time of any spleen related intervention (in-patient or out-patient)

1. Splenic angiography and/or embolization
2. Splenorrahphy
3. Splenectomy

DRAFT 10/09

C. At Hospital Discharge

1. Discharge related information

D. Out-patient monthly follow-up out to 180-days after injury

1. Screen for spleen related intervention or complication
2. Stanford Brief Activity Survey

Please see attached data collection tool for details of data to be gathered.

Details about the Charlson Comorbidity Index and the Stanford Brief Activity Survey:

Charlson Comorbidity Index (CCI): Since injured persons may present to the trauma center with pre-existing medical conditions that could impact quality of life and functional capacity as well as survival, we will adjust for pre-existing medical disease using the CCI. The CCI contains 19 categories of comorbidity, which are primarily defined using ICD-9 diagnoses codes. Each category has an associated weight, taken from the original Charlson paper (8), which is based on the adjusted risk of one-year mortality. The overall comorbidity score reflects the cumulative increased likelihood of one-year mortality. The CCI has been utilized to adjust for comorbidities in studies of injured persons and can be given in a self report form (9,77). The CCI will be calculated at the time of study enrollment.

Stanford Brief Activity Survey (SBAS): The SBAS provides a quick assessment of the usual amount and intensity of physical activity that a person performs throughout the day. The SBAS has been validated in a large study and is intended for use in large-scale epidemiologic studies. Based on answers the answers to the SBAS, respondents are placed into one of 5 activity levels. The SBAS will be administered at the time of discharge and at each monthly out-patient follow-up.

***Data Analysis, Power Calculations, and Missing Data*:**

***Data Analysis*:**

Descriptive and Preliminary Analyses: Means, standard deviations and frequencies (where appropriate) will be calculated for the entire cohort for demographic data, the CCI, as well as admission ISS, and baseline injury characteristics.

Specific Aim #1: Ascertain the 180-day risk of splenectomy after non-operative management of blunt splenic injury.

Main Outcome: Splenectomy at anytime after study enrollment up to 180-days after injury.

Method of Analysis: Splenectomy rates will be calculated at 5, 10, 30, 60, 90, and 180 days after injury. The numerator for each calculation will be the person time contributed by the patients who have had a splenectomy by the time point. The denominator will be person-time at risk for the cohort up to that time point. The risk of splenectomy at each time-point will also be calculated. For these calculations the numerator will be the number of patients who have had a splenectomy up to the time point of interest. The denominator will be the total number of persons at risk for the outcome.

Secondary Outcome: Any spleen related intervention from time of study enrollment up to 180-days after injury.

Method Analysis: Spleen related intervention rates will be calculated at 5, 10, 30, 60, 90, and 180 days after injury. The numerator for each calculation

DRAFT 10/09

will be the person time contributed by the patients who have had a spleen related intervention by the time point. The denominator will be person-time at risk for the cohort up to that time point. The risk of a spleen related intervention at each time-point will also be calculated. For these calculations the numerator will be the number of patients who have had a spleen related intervention up to the time point of interest. The denominator will be the total number of persons at risk for the outcome.

Specific Aim #2: Determine factors related to failure of non-operatively managed blunt splenic injuries.

Main Outcome: Splenectomy at anytime after study enrollment up to 180-days after injury.

Method of Analysis: Variables that may influence the 180-day risk of splenectomy will be tested using univariable and multivariable regression using hierarchical modeling techniques. Because individual patients are clustered within hospitals, we will hierarchical regression analysis is appropriate to account for patient clustering. Hierarchical regression analysis is a statistical methodology that provides information on variables that are distributed between the individual and the hospital levels, quantifies the clustering of individual factors within hospitals, and permits the examination of cross level interactions between the effects of hospitals and individual level factors. Models will be built utilizing standard model building strategies. Factors that are associated with delayed splenectomy on univariate analysis ($p<0.20$) will be eligible for entry into the multivariable model. Factors with a $p<0.05$ on multivariable analysis will be considered independent predictors of delayed splenectomy after non-operative management of BSI.

Secondary Outcomes: Early splenectomy (≤ 10 days after injury) and Late splenectomy (≥10 days after injury).

Method of Analysis: Factors associated with risk of early splenectomy will be determined using similar techniques as described for the main outcome. A similar analysis will be performed for the late splenectomy outcome.

Power Calculation: We expect to be able to recruit at least 1500 subjects from the participating sites. Of the recruited subjects we expect that 105 will have in-hospital delayed rupture and 50 will have outpatient rupture within 6 months. To estimate our ability to detect relationships between multiple variables and our outcomes, we used power analysis methods suggested by Cohen for multiple correlations (13). We set the alpha level at 0.05 and power at 0.80. The following table indicates the sample sizes for moderate (r^2=0.09) and large (r^2=0.25) proportions of explained variance that we could detect for varying numbers of predictors in the models. As Table 1 indicates, with 1200 subjects with complete data we expect to be able to detect moderate and large proportions of explained variance in our models even if we use up to 15 predictors.

Table 1. Sample Sizes for multiple correlations.

	Number of Predictors		
	5	10	15
Moderate Proportion of explained Variance	136	174	204

DRAFT 10/09

r^2=0.09			
Large proportion of explained variance r^2=0.25	45	59	70

Missing Data:

Every effort will be made to avoid problems with missing data, especially those due to loss to follow-up. We will minimize incomplete data by using a robust online datamangement system. Validation of data will be carried out at the time of data entry so that all entered data will be consistent. If a datapoint Is left blank, the reason will be required. questionnaires by ensuring that participants do not leave any questions blank. This should minimize missing or out of range responses.

Data Archive:

After collection and analysis of the data, and the removal of all personal identifiers, we will make the data set, codebook, and analyses/publications available from the American Association for the Surgery of Trauma.

***Timetable*:**

This research project is expected to require 24 months for enrollment and another 6 months to complete follow-up for a total of 30 months.

10/09

Study Timeline