1. Study title:
Hospitalization and Mortality due to Infection among Survivors of Childhood Cancer with Asplenia

2. Working group and investigators:

Working groups
Chronic Disease (primary)
Biostatistics/Epidemiology (secondary)

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3. Background and rationale

Children with cancer may require splenectomy during the course of staging or treatment of their disease. Asplenia has long been associated with an increased risk of serious infections including meningitis and sepsis, with high rates of mortality when these occur (1-3). This realization has led to the common, but highly variable practice of providing vaccinations and antibiotic prophylaxis to children who must undergo splenectomy, and a strong desire to prevent total splenectomy and to preserve splenic function whenever possible (4-5).

Historically, the most common indication for splenectomy among children with cancer was as part of the routine staging procedure for Hodgkin lymphoma (HL). Secondary to improved imaging modalities and an appreciation for the negative consequences of splenectomy, the procedure is now rarely performed solely for staging purposes. Indeed, as a result of large numbers of patients having undergone the procedure as part of the routine staging for HL, the implications for future risk of serious infection are now better understood. In 1976, Chilcote and colleagues reported retrospectively that among 200 patients who had undergone splenectomy as part of a staging laparotomy for HL, 20 episodes of septicemia and/or meningitis occurred in 18 patients, only 10 of whom survived their illness (6). In a survey of 325 patients in Norway who had undergone splenectomy for HL staging between 1969-1980, Foss Abrahamsen and colleagues reported a relative risk of pneumococcal septicemia of 20.5 compared to the general Norwegian population (7). In a review of the Swedish Cancer Registry, Andersson and colleagues reported that patients undergoing splenectomy during the course of therapy for HL experienced a nearly 2-fold increase in risk of developing late

serious infections compared to HL survivors who did not undergo splenectomy (8). Still additional reports corroborate the increased risk of serious infections among patients with HL who have undergone splenectomy (9). Conversely, Coker and colleagues retrospectively reviewed 210 patients undergoing splenectomy for HL and found 47 instances of serious infections at a mean of 68 months follow-up, none of which resulted in mortality, and all of which were associated with additional risk factors for infection aside from splenectomy (10). Similarly, Hays and colleagues retrospectively examined a cohort of 234 patients undergoing splenectomy for HL and reported only 5 instances of septicemia and no mortalities during an approximately 5-year follow-up (11). Possible reasons for differences among studies include varied length of follow-up, different historical time periods examined, and variable practices and availability of data regarding use of antibiotic prophylaxis and vaccinations. A larger study with longer follow-up and hard outcomes (ie, infection-specific death and hospitalizations for sepsis) is needed to inform the follow-up care of asplenic childhood cancer survivors.

Despite a relative abundance of literature focused on children undergoing splenectomy as part of a staging laparotomy for HL, studies examining long-term infectious risk in children who have undergone splenectomy in the context of other malignancies are lacking. Splenectomy may also become necessary for primary splenic tumors, for contiguous spread in the context of other abdominal malignancies, as a necessary component of gastrectomy or pancreatectomy for tumors in these organs, or as a complication of bleeding or portal hypertension that may develop during or after operations for intra-abdominal malignancies (12-14). In an analysis of over 12,000 survivors from the CCSS, Perkins and colleagues reported that splenectomy was not independently associated with an increased risk of late infections (15). The analysis, however, focused on all infections and did not stratify based on severity or mortality. Understanding how splenectomy may be related to more serious infections such as sepsis, meningitis, and mortality from these conditions is important.

It has also been recognized that abdominal radiotherapy administered during the course of cancer treatment can lead to reduced splenic volume and impaired splenic function or “hyposplenism” (16-18). It has been suggested that functional hyposplenism secondary to radiotherapy may pose long-term infectious risks similar to that observed post surgical splenectomy (16, 17). Based on these observations, patients treated with high dose radiotherapy ($\geq$ 40 Gy) administered in a field that includes the spleen are considered to be at highest risk for development of functional hyposplenism (16). There is likely a reduced risk associated with lower doses of splenic irradiation, however an exact dose-response relationship between radiation dose and risk for hyposplenism or the time frame for which these patients are at risk, is not entirely understood (19).

The incidence of long-term infectious-related mortality among survivors of any childhood cancer who undergo splenectomy is not known. Furthermore, the effect of abdominal radiotherapy or the dosage of such therapy on risk for long-term infectious-related mortality in a large group of survivors of childhood cancer is understudied. The proposed study will determine the incidence of hospitalization due to infection, all-cause mortality, and cause-specific mortality secondary to sepsis or meningitis among childhood cancer survivors. The relationship between increasing dose of abdominal radiotherapy with hospitalization due to infection, all-cause mortality, and cause-specific mortality secondary to sepsis or meningitis among childhood cancer survivors, possibly secondary to altered splenic function, will also be examined.

4. Specific aims/objectives/research hypotheses

Specific Aim 1

Estimate the cumulative incidence of (1) hospitalization due to infection, (2) cause-specific mortality secondary to sepsis or meningitis, and (3) all-cause mortality among childhood cancer survivors who had a (a) splenectomy or (b) splenic irradiation (dose-stratified) in the first five years following the cancer diagnosis.

Specific Aim 2
Determine whether the relative rate of (1) hospitalization due to infection, (2) cause-specific mortality secondary to sepsis or meningitis, and (3) all-cause mortality is greater in:

Aim 2a. Survivors who had a splenectomy in the first five years after their primary cancer diagnosis compared to survivors without splenectomy or splenic irradiation;

Aim 2b. Survivors exposed to splenic irradiation (reported as average dose to left upper quadrant of the abdomen) in the first five years after their primary cancer diagnosis compared to survivors without splenectomy or splenic irradiation.

Hypothesis: Anatomically (post-surgical) and functionally (post radiation) asplenic cancer survivors will have a greater risk of hospitalization due to infection, cause-specific mortality secondary to sepsis or meningitis, and all-cause mortality when compared to cancer survivors who did not undergo a splenectomy or were treated with splenic irradiation.

Specific Aim 3
Determine if a dose-response relationship exists between splenic irradiation and (1) hospitalization due to infection, (2) cause-specific mortality secondary to sepsis or meningitis, and (3) all-cause mortality.
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Hypothesis: Increasing doses of splenic irradiation are associated with an increased risk of cause-specific mortality secondary to sepsis or meningitis.

5. Analysis framework

a. Outcomes of Interest
The primary outcomes will be (1) hospitalization due to infection, (2) cause-specific mortality secondary to sepsis or meningitis, and (3) all-cause mortality

Sepsis related ICD-9 codes (primary cause of death): 995.91, 995.92, 785.52, 998.02, and 790.7
Meningitis-related ICD-9 codes (primary cause of death): 003.21, 013.00, 013.01, 013.02, 013.03, 013.04, 013.05, 013.06, 036.0, 047.0, 047.1, 047.8, 047.9, 049.1, 053.0, 054.72, 072.1, 090.42, 091.81, 094.2, 098.82, 100.81, 112.83, 114.2, 115.01, 115.11, 115.91, 320.0, 320.1, 320.2, 320.3, 320.7, 320.81, 320.82, 320.89, 320.9, 321.0, 321.1, 321.2, 321.3, 321.4, 321.8, 322.0, 322.1, 322.2, 322.9

b. Subject population
Inclusion criteria**:** All survivors who completed baseline survey (original and expansion cohorts). All siblings.
Exclusion criteria**:** None

c. Exploratory variables

- Demographic and social variables
  - Age (continuous and categorical; Baseline #A1; ExpBaseline #A1)
  - Sex (categorical; Baseline #A2; ExpBaseline #A2)
  - Race and ethnicity (categorical: non-Hispanic white, non-Hispanic black, Hispanic, other; Baseline #A4, ExpBaseline #A5)
- Chronic conditions
  - Common Terminology Criteria for Adverse Events (CTCAE) (20)
    - No condition
    - Grade 1 condition (mild)
    - Grade 2 condition (moderate)
    - Grade 3 condition (severe)
    - Grade 4 condition (life-threatening or disabling)
    - Grade 5 condition (fatal)
- Hospitalization rates (binary and ordinal: 0, 1, 2, >2 times; LTFU 2000 #21A-C, LTFU 2005 #A1-2)
- Tobacco use (categorical: never smoker, former smoker, current smoker; Baseline #N1-2, ExpBaseline #O1-8, LTFU 2003 #L1-8, LTFU 2007 #N7-14)
- Medication variables
  - Steroids (categorical; Baseline #B8, ExpBaseline #B8, LTFU 2000 #6, LTFU 2007 #C8)
  - Antibiotics (categorical; Baseline #B8, ExpBaseline #B8, LTFU 2000 #6, LTFU 2007 #C8)
- Cancer variables
  - Initial cancer diagnosis
  - Second malignant neoplasm (binary; ExpBaseline #L1, LTFU 2003 #R1, LTFU 2005 #B1, LTFU 2007 #P1)
- Treatment variables
  - Any chemotherapy (binary)
    - Alkylating agent (binary)
      - Cyclophosphamide equivalent dose (CED) score (categorical: 0, 1-3999, 4000-7999, ≥8000mg/m^2) (21)
    - Anthracycline (binary)
      - Anthracycline score (categorical: 0, <250, ≥250 mg/m^2) (22)
    - Platinum agent (binary)
      - Platinum agent score (categorical: 0, 1, 2, 3) (23)
  - Any radiotherapy (binary)
  - Splenic radiotherapy (using average left upper quadrant abdominal XRT dose as surrogate)
    - Total dose (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy)
  - Stem cell transplant
  - Splenectomy (ExpBaseline #I18, LTFU 2007 #J18)

d. Statistical Methods

We will first compare demographic and clinical variables among participants who

have undergone splenectomy and those who have not (Table 1). In doing so, we will tabulate the prevalence of splenectomy (occurring within 5 years of cancer diagnosis. To compare categorical data, we will use the chi-square test (or Fisher's exact test when necessary). To compare continuous data, we will use the two-sample t-test (or Mann-Whitney *U* test when necessary).

We will perform a multivariable analysis using piecewise exponential models to carefully delineate the relationship between asplenia and mortality rates (i.e. all-cause mortality [Table 2a] and mortality due to sepsis or meningitis [Table 2b]) among childhood cancer survivors. If necessary, the analysis will be stratified by cancer diagnosis, radiotherapy status, or other factors. The multivariable models will incorporate time since cohort entry as well as age, as time-dependent variables.

We will also employ standardized mortality ratios to evaluate the impact of asplenia on mortality, relative to the age-, calendar year-, sex-, and race-matched United States' general population. Cause of death will be determined from the National Death Index (1979-2012) or death certificates prior to 1979. Cause-specific death due to sepsis or meningitis will be determined by ICD-9 codes (Table 3).

Additionally, we will graphically represent cumulative incidence of all-cause mortality and mortality due to sepsis or meningitis in childhood cancer survivors undergoing splenectomy, those not undergoing splenectomy, and their siblings (Figure 1). This graph will also be stratified by antibiotic use and include hospitalizations due to infections (Figure 2). Finally, we will graphically represent the cumulative incidence of mortality due to sepsis or meningitis and hospitalization rates due to infections in childhood cancer survivors stratified by dose of abdominal radiation received (Figure 3).

If a participant becomes asplenic, but the age at time of asplenia is missing, we will employ multiple imputation to estimate the missing value.

Sample Tables/Figures:

Table 1. Characteristics of **childhood cancer survivors** who have undergone splenectomy versus those who have not.

Variable	*Splenectomy*	*No Splenectomy*	P
Female			
Race/ethnicity			
Non-Hispanic white			
Non-Hispanic black			
Hispanic			
Other			
Year of diagnosis			
1970 – 1974			
1975 – 1979			
1980 – 1984			
1985 – 1989			
1990 – 1994			
1995 – 1999			
Age at latest questionnaire			
< 20			

- 20-29
- 30-40
- > 40

Cancer Diagnosis
- All cancers
- ALL
- HL
- NHL
- Kidney tumor
- Neuroblastoma
- Osteosarcoma
- Ewing sarcoma
- Soft tissue sarcoma
- CNS Tumor
- Other leukemia
- Other bone tumor
- Other abdominal tumor

Age at Diagnosis
- <1
- 1-3
- 4-7
- 8-10
- 11-14
- 14-20

Age at Splenectomy
- <1
- 1-3
- 4-7
- 8-10
- 11-14
- 14-20

Chemotherapy

Alkylating agent CED, mg/m^2
- 0
- 1-3999
- 4000-7999
- >7999

Platinum agent score
- 1
- 2
- 3

Any XRT
- No
- Yes

LUQ abdominal XRT
- None
- <10
- 10-19
- 20-29

30-39	
40-49	
>49	
Chronic conditions*	
CTCAE Grade 1-2	
CTCAE Grad 3-5	
Tobacco use*	
Never user	
Former user	
Current user	
Medication use*	
Corticosteroids	
Antibiotics	
Stem Cell Transplant	
Autotransplant	
Allotransplant	
Secondary malignancy*	
Hospitalizations due to infection*	
0	
1	
2	
>2	
Mortality due to sepsis or meningitis*	
0-5 yrs after diagnosis	
5-10 yrs after diagnosis	
10-20 yrs after diagnosis	
> 20 yrs after diagnosis	
All-cause mortality*	

ALL, acute lymphoblastic leukemia*; HL,* Hodgkin lymphoma*; NHL,* non-Hodgkin lymphoma*; CNS*, central nervous system*; CED*, cyclophosphamide equivalent dose; LUQ, left upper quadrant; XRT, radiotherapy; *data reported as rates

Table 2a. Multivariable analysis of factors associated with all-cause mortality among childhood cancer survivors.

Variable	*Hazard ratio*	*95% CI*	P
Female			
Race/ethnicity			
Non-Hispanic white			
Non-Hispanic black			
Hispanic			
Other			
Year of diagnosis			
1970 – 1974			
1975 – 1979			
1980 – 1984			
1985 – 1989			

1990 – 1994
1995 – 1999
Age at latest questionnaire
< 20
20-29
30-40
> 40
Cancer Diagnosis
All cancers
ALL
HL
NHL
Kidney tumor
Neuroblastoma
Osteosarcoma
Ewing sarcoma
Soft tissue sarcoma
CNS Tumor
Other leukemia
Other bone tumor
Other abdominal tumor
Age at Diagnosis
<1
1-3
4-7
8-10
11-14
14-20
Age at Splenectomy
<1
1-3
4-7
8-10
11-14
14-20
Chemotherapy
Alkylating agent CED, mg/m^2
0
1-3999
4000-7999
>7999
Platinum agent score
1
2
3
Any XRT
No
Yes
LUQ abdominal XRT
None

<10			
10-19			
20-29			
30-39			
40-49			
>49			
Chronic conditions*			
CTCAE Grade 1-2			
CTCAE Grade 3-5			
Tobacco use*			
Never user			
Former user			
Current user			
Medication use*			
Corticosteroids			
Antibiotics			
Splenectomy			
Stem Cell Transplant			
Autotransplant			
Allotransplant			
Secondary malignancy*			

ALL, acute lymphoblastic leukemia*; HL,* Hodgkin lymphoma*; NHL,* non-Hodgkin lymphoma*; CNS*, central nervous system*; CED*, cyclophosphamide equivalent dose; LUQ, left upper quadrant; XRT, radiotherapy; *data reported as rates

Table 2b. Multivariable analysis of factors associated with mortality due to sepsis or meningitis among childhood cancer survivors.

Variable	*Hazard ratio*	*95% CI*	P
Female			
Race/ethnicity			
Non-Hispanic white			
Non-Hispanic black			
Hispanic			
Other			
Year of diagnosis			
1970 – 1974			
1975 – 1979			
1980 – 1984			
1985 – 1989			
1990 – 1994			
1995 – 1999			
Age at latest questionnaire			
< 20			
20-29			
30-40			
> 40			
Cancer Diagnosis			

All cancers
ALL
HL
NHL
Kidney tumor
Neuroblastoma
Osteosarcoma
Ewing sarcoma
Soft tissue sarcoma
CNS Tumor
Other leukemia
Other bone tumor
Other abdominal tumor
Age at Diagnosis
<1
1-3
4-7
8-10
11-14
14-20
Age at Splenectomy
<1
1-3
4-7
8-10
11-14
14-20
Chemotherapy
Alkylating agent CED, mg/m^2
0
1-3999
4000-7999
>7999
Platinum agent score
1
2
3
Any XRT
No
Yes
LUQ abdominal XRT
None
<10
10-19
20-29
30-39
40-49
>49
Chronic conditions*
CTCAE Grade 1-2

CTCAE Grade 3-5			
Tobacco use*			
Never user			
Former user			
Current user			
Medication use*			
Corticosteroids			
Antibiotics			
Splenectomy			
Stem Cell Transplant			
Autotransplant			
Allotransplant			
Secondary malignancy*			

ALL, acute lymphoblastic leukemia*; HL,* Hodgkin lymphoma*; NHL,* non-Hodgkin lymphoma*; CNS*, central nervous system*; CED*, cyclophosphamide equivalent dose; LUQ, left upper quadrant; XRT, radiotherapy; *data reported as rates

Table 2c. Multivariable analysis of factors associated with rates of hospitalization due to infection among childhood cancer survivors.

Variable	*Hazard ratio*	*95% CI*	P
Female			
Race/ethnicity			
Non-Hispanic white			
Non-Hispanic black			
Hispanic			
Other			
Year of diagnosis			
1970 – 1974			
1975 – 1979			
1980 – 1984			
1985 – 1989			
1990 – 1994			
1995 – 1999			
Age at latest questionnaire			
< 20			
20-29			
30-40			
> 40			
Cancer Diagnosis			
All cancers			
ALL			
HL			
NHL			
Kidney tumor			
Neuroblastoma			
Osteosarcoma			
Ewing sarcoma			
Soft tissue sarcoma			

CNS Tumor
Other leukemia
Other bone tumor
Other abdominal tumor
Age at Diagnosis
<1
1-3
4-7
8-10
11-14
14-20
Age at Splenectomy
<1
1-3
4-7
8-10
11-14
14-20
Chemotherapy
Alkylating agent CED, mg/m^2
0
1-3999
4000-7999
>7999
Platinum agent score
1
2
3
Any XRT
No
Yes
LUQ abdominal XRT
None
<10
10-19
20-29
30-39
40-49
>49
Chronic conditions*
CTCAE Grade 1-2
CTCAE Grade 3-5
Tobacco use*
Never user
Former user
Current user
Medication use*
Corticosteroids
Antibiotics
Splenectomy

Stem Cell Transplant	
Autotransplant	
Allotransplant	
Secondary malignancy*	

ALL, acute lymphoblastic leukemia*; HL,* Hodgkin lymphoma*; NHL,* non-Hodgkin lymphoma*; CNS*, central nervous system*; CED*, cyclophosphamide equivalent dose; LUQ, left upper quadrant; XRT, radiotherapy; *data reported as rates

Table 3. Standardized mortality rates (SMR) and 95% confidence intervals (CI)

	All cause mortality			*Sepsis or meningitis*		
Variable	*SMR*	*No. of Deaths*	*95% CI*	*SMR*	*No. of Deaths*	*95% CI*
Splenectomy						
LUQ abdominal XRT						
None						
<10						
10-19						
20-29						
30-39						
40-49						
>49						

LUQ, left upper quadrant; XRT, radiotherapy

Figure 1a. Survival curves for childhood cancer survivors undergoing splenectomy, those not undergoing splenectomy, and their siblings.

Figure 1b. Cumulative incidence of mortality due to sepsis or meningitis in childhood cancer survivors undergoing splenectomy, those not undergoing splenectomy, and their siblings.

Figure 1c. Hospitalization rates due to infection among childhood cancer survivors undergoing splenectomy, those not undergoing splenectomy, and their siblings.

Figure 2a. Cumulative incidence of mortality due to sepsis or meningitis in childhood cancer survivors undergoing splenectomy who regularly take antibiotics compared with those who do not take antibiotics.

Figure 2b. Relative risk of hospitalization due to infection in childhood cancer survivors undergoing splenectomy who regularly take antibiotics compared with those who do not take antibiotics.

Figure 3a. Cumulative incidence of mortality due to sepsis or meningitis in childhood cancer survivors stratified by dose of abdominal radiation received (patients having undergone surgical splenectomy excluded).

Figure 3b. Relative risk of hospitalization due to infection in childhood cancer survivors

stratified by dose of abdominal radiation received (patients having undergone surgical splenectomy excluded).

6. Special consideration

None

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