Hyperbilirubinemia and Gallbladder Complications in Pediatric Hematopoietic Stem Cell Transplant Patients

A Thesis submitted to The University of Arizona College of Medicine-Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Abstract

**Background:** Hyperbilirubinemia in pediatric hematopoietic stem cell transplant (HSCT) patients presents a diagnostic and therapeutic dilemma. This study was designed to determine the frequency of known causes of hyperbilirubinemia, correlate its effect on survival, review the effects of gallbladder procedural interventions on outcomes, and to define parameters to guide patient care.

**Methods:** 60 Pediatric HSCT patients transplanted between August 2003 and March 2010 were stratified according to bilirubin levels, presence of Veno-occlusive Disease (VOD), also known as Sinusoidal Occlusive Syndrome (SOS), gallbladder involvement, and surgical intervention. Subgroups were analyzed for peak liver enzyme levels, Intensive care unit (PICU)/hospital length of stay (LOS), and mortality.

**Results:** Fifty-five per cent of patients developed hyperbilirubinemia. Survival was 55% in that group versus 85% in the normo-bilirubin patients. 79% of the hyperbilirubinemia patients exhibited gallbladder involvement and 31% of those underwent surgical intervention. Survival was 60% in the patients with gallbladder involvement without SOS who underwent surgery versus 50% in the non-surgical. In patients with both SOS and gallbladder involvement, survival was 33% in the intervention group versus 50% in the non-intervention group. Overall survival in the SOS alone, SOS with gallbladder involvement, and gallbladder involvement only patients was 50%,
44%, and 53% respectively. Hepatic enzymes were increased in patients who received intervention compared to the non-intervention groups, but no individual lab or combination of labs predicted intervention or mortality. Intervention patients spent more days in the hospital post bilirubin peak.

**Conclusions:** Pediatric HSCT patients with elevated bilirubin levels and SOS are at increased risk for gallbladder complications and death. Patients receiving gallbladder procedures are more likely to require longer hospital stays than patients who do not. Surgical intervention may decrease mortality in patients with gallbladder involvement that do not have SOS, but no conclusion regarding a positive impact of gallbladder intervention on patients with coexisting SOS can be made on other patients based on this data set.

**Keywords:** Bilirubin, Hyperbilirubinemia, Hematopoietic stem cell transplant, Cholecystectomy, Cholecystostomy, Veno-occlusive disease, Sinusoidal obstructive syndrome
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Introduction

Hematopoietic stem cell transplant (HSCT) patients are at risk of developing complications involving the liver and gallbladder. Cholecystitis may occur in this population and is potentially treatable through surgical or radiographic-directed intervention. Since cholecystitis is often seen within the context of multi-system organ dysfunction such as graft versus host disease (GVHD) and sinusoidal obstructive syndrome (SOS), [formerly known as veno-occlusive disease], the diagnosis may be under-recognized or obscured by the coexisting diseases. The incidence of SOS has been reported to be between 22% and 28% in patients who receive an allogeneic transplant from an HLA-identical sibling [1-4]. The incidence of clinically significant cholecystitis in this patient population has not been extensively reported in the literature. One study has reported the incidence of acute cholecystitis in BMT patients as less than 1% [5]. Another reported a 20% incidence of biliary complications in their BMT population in addition to a similar incidence of less than 1% of acalculous cholecystitis [6].

Significance

HSCT patients frequently develop elevated total bilirubin levels which then pose difficult diagnostic and therapeutic dilemmas for the clinician. This situation is worsened since cholecystitis may have similar clinical and radiological signs as other associated causes of liver dysfunction. Therapies for patients with hepatobiliary dysfunction are often aimed primarily at
treatment of associated SOS and some patients may who may benefit from
gallbladder intervention may not be promptly obvious.

Goals

Determination of which pediatric HSCT patients were at an increased
risk for gallbladder involvement and which patients benefited from
gallbladder intervention would potentially allow quicker recovery and
improved survival.

Materials and Methods

This study is a retrospective, single-center study to determine the relative
frequency of hyperbilirubinemia among HSCT patients and define the
frequency of known causes in this patient population. The study was
approved by the Institutional Review Board of Phoenix Children’s Hospital.
Study population included all patients undergoing HSCT at Phoenix
Children’s Hospital (Phoenix, Arizona) from August 2003 to March 2010.
Data was extracted through direct review of the physical and computer-based
records and kept in password-protected database. Data points collected
included total and direct bilirubin, alkaline phosphatase, GGT, AST, and
ALT levels, presence of gallbladder wall thickening, common bile duct
dilation, or gallstones, the ICU LOS relative to peak bilirubin levels, and
mortality (general and within 100 days).
The prognosis of patients with various causes of hyperbilirubinemia such as SOS and choleystitis will be determined. Survival of patients with gallbladder involvement with and without surgical interventions will be calculated. Finally, the role of standard laboratory values and radiographic studies in determining which patients benefitted from gallbladder interventions will be examined.

Gallbladder involvement was defined as gallbladder wall thickening, common bile duct dilation, or gallstones. Gallbladder intervention was defined as cholecystostomy or cholecystectomy. Comparisons were made between the groups concerning peak levels of bilirubin, alkaline phosphatase, GGT, AST, ALT, the ICU LOS relative to peak bilirubin levels, and mortality.

Statistical Analysis

Descriptive analysis of the patients in this study was accomplished using summary measures including ranges, means, medians, and standard deviations. Comparisons were made within and between the various groups and subgroups via non-parametric tests (Fisher's exact, Wilcoxon).

Results

Patient Characteristics

The mean age was 8.2 years +/- 5.9 years. The age range was 3 months to 22 years with 47% males. One-third of the patients received allogeneic transplants from related donors, while two-thirds received
transplants from unrelated donors. 18 of the 20 transplants from relatives were complete matches. 17 of the 40 recipients from unrelated donors were incomplete matches. All of the patients underwent complete myoablation. The patients were divided into two groups based on bilirubin levels. Patients with bilirubin levels of 3.0 mg/dL or greater were considered to have hyperbilirubinemia. See figure 1. Of the patients with hyperbilirubinemia, eight received allogeneic transplants from related donors, while 25 received transplants from unrelated donors. All but one of the recipients of transplants from relatives were complete matches. Nine of the 25 recipients from unrelated donors were incomplete matches.

The hyperbilirubinemia patients were then grouped according to whether or not they exhibited gallbladder involvement, SOS, or both. See figure 1.

Overall Survival
Sixty pediatric HSCT patients were identified. Of the 60, 33 had total bilirubin levels greater than 3.0mg/dL with an overall survival of 55%. Survival was 85% among the normobilirubin patients (p=0.13). Of the 33 hyperbilirubinemia patients, 11 (33%) had gallbladder involvement only, 2 (6%) had SOS only, 9 (27%) had SOS and gallbladder involvement, 5 (15%) with hyperbilirubinemia did not have SOS or gallbladder involvement.
Figure 1. Schematic breakdown of patient characteristics and outcomes. Bili>3 resulted in decreased survival. The elevations in bilirubin of the non-SOS/non-gallbladder disease patients were seen concomitantly with receipt of packed red blood cells (PRBC’s) in 2 patients, after receipt of methotrexate in one patient, and after developing multi-organ failure in the final 2 patients. In the SOS+GB+Intervention group, both deaths were within 100 days. In the SOS+GB-No Intervention group, all 3 deaths were within 100 days. In the GB disease only+intervention patients, one of the 2 deaths was within 100 days. In the GB disease only-no intervention patients, 3/6 deaths were within 100 days.
Of the 11 patients with gallbladder involvement alone, 5 underwent surgical intervention (60% survival, of the 2 deaths one was within 100 days) and 12 did not (50% survival, 3 died within 100 days, and 3 passed away post 100 days). See figure 1. Of the 9 patients with both SOS and gallbladder involvement, 3 underwent surgical intervention and 6 did not. Survival in the intervention group was 33% compared to 50% in the intervention group (p=0.52). Of the 3 patients that underwent surgical intervention, 2 died within 100 days of their bone marrow transplant. The first died 60 days post transplant which was also 25 days post cholecystostomy and 14 days post bilirubin max. The cause of death was recurrent AML, multiorgan system failure, and end stage pulmonary disease. The second died 67 days post transplant, which was also 19 days post cholecystectomy, and one day post bilirubin maximum due to multisystem organ failure (cardiac, renal, respiratory, liver), CMV, and HHV viremia. Of the 6 patients who did not undergo surgical intervention, 3 died within 100 days of their BMT. The first died 10 days post BMT (1 day post bilirubin max) due to multisystem organ failure (respiratory, renal, cardiovascular), septic shock, and shock liver. The second died 88 days post BMT (19 days post bilirubin max) due to multisystem organ failure, sepsis, CMV viremia, graft versus host disease, and JMML. The third died 66 days post initial BMT (4 days post 2nd BMT) of unknown causes. This patient’s bilirubin level was peaked at the time of
death. Among patients with SOS, the presence or absence of gallbladder disease was not associated with survival (respectively, 56% vs. 50%, p=1.00).

Laboratory Studies

The average peak level of alkaline phosphate, total bilirubin, direct bilirubin, AST, and ALT were all greater in the intervention group. ALT and alkaline phosphate in the SOS (VOD)+GB-no intervention group were the only scenarios in which the non-intervention group range was greater than the intervention group. See table 1, figures 2-6.
<table>
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<tr>
<th>Group</th>
<th>Alk Phos peak (u/L)</th>
<th>Tbili peak (mg/dL)</th>
<th>Dbili peak (mg/dL)</th>
<th>GGT peak (u/L)</th>
<th>AST peak (u/L)</th>
<th>ALT peak (u/L)</th>
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<td><strong>SOS + GB</strong> (No intervention)</td>
<td>1035 (425 – 3303, +/- 1116)</td>
<td>11.9 (3.5 – 22.7, +/- 8.6)</td>
<td>7.4 (2.7 – 14.6, +/- 5.3)</td>
<td>n/a</td>
<td>747.8 (31 – 4044, +/- 1617)</td>
<td>425.2 (37 – 2305, +/- 921)</td>
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<td><strong>SOS + GB</strong> (Intervention)</td>
<td>478 (405 – 540, +/- 68.2)</td>
<td>24.5 (10.5 – 44.5, +/- 17.8)</td>
<td>18.5 (5.2 – 36.3, +/- 16)</td>
<td>296.7 (145 – 565, +/- 233)</td>
<td>2256 (282 – 5015, +/- 2462.2)</td>
<td>1015 (498 – 1444, +/- 479.1)</td>
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<tr>
<td><strong>GB Only</strong> (No Intervention)</td>
<td>710.3 (278 – 1322, +/- 415.9)</td>
<td>7.3 (3 – 15.1, +/- 4.03)</td>
<td>4.8 (1.3 – 12.3, +/- 3.4)</td>
<td>n/a</td>
<td>131.4 (33 – 644, +/- 185.8)</td>
<td>152 (25 – 783, +/- 233.1)</td>
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<td><strong>GB Only</strong> (Intervention)</td>
<td>825.75 (403 – 1826, +/- 671.9)</td>
<td>13.35 (4.5 – 38.8, +/- 17)</td>
<td>8 (1.9 – 22.5, +/- 9.7)</td>
<td>453.75 (430 – 473, +/- 21.6)</td>
<td>488.75 (168 – 1215, +/- 493.9)</td>
<td>232.5 (147 – 327, +/- 89.4)</td>
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**Table 1.** Peak enzyme level ranges of various groups with gallbladder involvement ± SOS. Bold value = Mean (min – max, SD). The most extreme values are seen in patients with SOS + GB, however within both subsets peak levels were greater in the patients that underwent intervention and there is much overlap between all of the groups.

**Figures 4, 5, 6.** Direct bilirubin, ALT, AST means and ranges within various groups. Dbili in mg/dL, AST/ALT in u/L. Means and ranges are greater in the intervention groups when compared to non-intervention groups of similar disease category with the exception of ALT (where the mean is lower, but range is higher).
Intervention vs. Non-Intervention

Of the eight patients that underwent gallbladder intervention, bilirubin 7 days after intervention decreased in five patients. The average decrease in those patients was 30.5% (median = 32.9%, +/- 13.0 %). In one of the eight there was no change in bilirubin level. The remaining two patients saw an increase in bilirubin of 42% (died within 100 days) and 111% (survived 100 days) respectively. The average bilirubin decrease in the patients that lived was 23.5%, +/- 19.9% while the decrease was 35.2%, +/- 7.5% in the patients that died. In patients that did not receive intervention, and survived 100 days, the average bilirubin level 7 days after peak was decreased by 62.6% (median = 67%, +/- 25.6%). In the non-intervention patients who did not survive 100 days, average bilirubin level 7 days after peak was decreased by 35% (median = 22.5%, +/- 31.2%). Overall, in the non-intervention group, average bilirubin level 7 days after peak decreased by 48% (median = 56.7%, +/- 31.2%).

**Figure 7.** On average, intervention did not decrease hospital length of stay in patients that survived. Patients that underwent intervention passed away on average before patients that did not have intervention.

**Figure 8.** Intervention did not decrease length of PICU stay in survivors. Among all patients, Intervention patients died sooner, which led to a shorter PICU stay.
Of the patients that survived, those that underwent surgical intervention spent an average of 39 days in the PICU after their bilirubin levels reached a peak. Those that did not undergo surgical intervention spent on average 16 days in the PICU after reaching peak bilirubin levels. The surgical intervention patients who survived were discharged after a mean of 130 days (median = 90, +/- 77) and the non-intervention patients were discharged after a mean of 32 days (median = 20, +/- 35). Surgical intervention had a significant impact on LOS within this group (122 vs. 32 days, p=0.02).

Of the patients that died, those that underwent surgical intervention lived for a mean of 10 days (median = 14, +/- 7) after they reached peak bilirubin levels. Those that did not undergo surgical intervention lived for a mean of 15 days (median = 12, +/- 19) after their peak bilirubin level. See figure 7, 8. As stated previously, surgical intervention was undertaken in 31% (8 of 26) of patients with suspected gallbladder disease. Survival in those patients was 50% (4/8) while non-intervention survival was 50% (9/18), (p=1.00). Among patients with GB disease without SOS (n=17), surgical intervention did not correlate with survival (60%; 3/5) compared to those without intervention (50%; 6/12), (p=1.00).

Discussion

Damage to the biliary system is a common occurrence during bone marrow transplantation and this damage can present in various forms. Elevated
bilirubin, LFT's, thickened gall bladder walls, sludge, and gallstones have all been documented and routinely seen in this patient population [7]. This study presents a broad view on clinical and lab data which may guide a physician in determining which HSCT patients will benefit from procedural intervention. In our patient population, a bilirubin level of 3.0 mg/dL or greater was associated with a significant increase in mortality. Within this group, transaminases and alkaline phosphatase, were not helpful in distinguishing which patients would eventually develop gallbladder complications. In our patient population there was much overlap between the various groups in terms of transaminases and alkaline phosphatase regardless of eventual clinical outcome. There was a small subset of patients that developed hyperbilirubinemia without clinical evidence of hepatobiliary disease. Of these five, two of the patient's levels rose after receiving packed red blood cells, one rose concomitantly with respiratory and cardiovascular failure, the fourth rose after being administered methotrexate, and the fifth rose after developing multi-organ failure.

Based solely on transaminase, bilirubin, and alkaline phosphate levels, the patients that underwent surgical intervention experienced more severe clinical courses than the patients that did not undergo surgery. This suggests that those undergoing surgery were already at an increased mortality risk. While not statistically significant, the decreased mortality in the gallbladder involvement only intervention group compared to the non-
intervention group, suggests there might be an improvement in outcomes for HSCT patients whose morbidity is limited to gallbladder involvement only. Patients with clinical signs of both gallbladder disease and SOS, may not benefit from surgical intervention in terms of long term mortality. However, selection of patients undergoing intervention may have been biased towards the more clinically ill patients. It may be that earlier intervention is warranted in patients that display signs of both SOS and gallbladder disease.

Limitations of this study include lack of control over which patients received intervention, the timing of intervention, and the relatively small number of patients included.

**Future Directions**

One of the limitations of this study is the number of patients analyzed. Expanding the data set looked at overtime would allow for clearer trends in outcomes to be identified. Ultimately the most powerful study would be a randomized control trial in which similar patients were randomized to the gallbladder procedure group or no intervention group.
References


Hyperbilirubinemia and Gallbladder Disease in Pediatric Hematopoietic Stem Cell Transplant Patients

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Background
Pediatric patients undergoing hematopoietic stem cell transplant (HSCT) receive significant toxic and immunosuppressive medications during the course of their treatment.

Hyperbilirubinemia (HH) defined as total bilirubin >10 mg/dL, is a frequently occurring complication in pediatric HSCT patients, arising from multiple etiologies including Sinusoidal Obstruction Syndrome (SOS), biliary atresia (BA), and potentially other etiologies.

HSCT patients with HH tend to be systematically ill and elevated bilirubin presents a diagnostic and therapeutic dilemma in these often critically ill patients.

Objectives
1. Identify relative frequency of known causes of HH in patients undergoing HSCT
2. To correlate the effect of HH on survival
3. To review the effects of choledochal cyst or choledochoenterostomy on outcomes
4. To be able to predict survival outcomes and make treatment recommendations to guide patient care.

Methods
- Study design: Retrospective chart review
- Sample: 50 pediatric patients undergoing HSCT patients (transplanted between August 2003 and March 2010)
- Data collection:
  - Bilirubin and liver enzyme levels
  - Clinical characteristics of Sinusoidal Obstruction Syndrome
  - Bilirubin levels by pathology or radiology
  - Surgical or interventional radiology/endoscopy results
  - Length of stay (LOS) and ICU LOS
  - Mortality rates
- Analysis: Descriptive statistics
- Schematic representation of patient characteristics and outcomes

Results
- Patients with GB disease:
  - 35% (17 of 50) of patients with GB disease also had a clinical diagnosis of SOS
  - In patients with both SOS and gallbladder involvement, overall survival was 46% (4/9)
  - Gallbladder drainage or removal: Survival was 73% (5/7)
  - Post-infection: Patients were 55% (5/9) vs 53% (3/6)
  - Alkaline phosphatase and transaminase values in patients with GB due to SOS, GB, and both diagnoses overlapped considerably. See Figures 2-5
  - GB drainage or removal was undertaken in 25% (10 of 40) of patients with suspected GB disease.
  - Gallbladder drainage or removal: Survival was 54% (4/7)
  - Post-infection: Patients were 55% (5/9) vs 53% (3/6)
  - Among patients with GB disease without SOS (n=17), surgical intervention did not correlate with survival (50% 95% confidence interval: 39-69)

Effect of Gallbladder drainage:
- Among patients with SOS, the presence or absence of gallbladder disease was associated with survival (respectively, 100% in 5/5 patients vs 44% in 28/62 patients, p<0.001)

- A gallbladder procedure was more common among patients with increased hepatitis.

- No increased failure rate of patients who received preparation for gallbladder procedure or mortality in SOS.
- Among survivors, patients with a choledochal cyst or choledochoenterostomy had a significantly shorter LOS than those that died (72 vs 32 days, p<0.001)

Conclusions
- Hyperbilirubinemia in pediatric HSCT patients is associated with a significant increase in mortality in pediatric HSCT.
- Within the subset of patients with HH, transaminases and alkaline phosphatase were found to be predictive, yet gallbladder disease did not have an impact on survival.
- Surgical intervention may potentially decrease mortality in HSCT patients that have gallbladder disease without SOS (SOS).
- Patients with clinical signs of both gallbladder disease and SOS may not benefit from surgical intervention.
- The overall survival in the study population was not improved by surgical intervention in patients with HH.
- Limitations of this study include:
  - Small sample size
  - Limited data on fetal alcohol syndrome
  - Further studies would include a prospective approach with defined endpoints using standard parameters and guidelines for timing and indications for intervention.

Overall outcomes
- Patients with GB disease:
  - Survival: 54% (4/7)
  - Post-infection: Patients were 55% (5/9) vs 53% (3/6)

Surgical intervention did not improve mortality/morbidity when compared with no intervention.

Figure 1. Schematic breakdown of patient characteristics and outcomes.

Table: Sample Characteristics (n=50)