

Hyperbilirubinemia and Gallbladder Disease in Pediatric Hematopoietic Stem Cell Transplant Patients

Abimbolu S Makinde¹, David M Notrica^{2,3}, Paul Bakerman², Pamela Garcia-Filion², Roberta Adams^{2,4}

¹University of Arizona College of Medicine - Phoenix, ²Phoenix Children's Hospital, ³University of Arizona College of Medicine, ⁴Mayo Clinic Arizona

Background

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

Hyperbilirubinemia (HB) defined as a total bilirubin >3mg/dL in pediatric HSCT patients may result from many different etiologies including Sinusoidal Occlusive Syndrome (SOS), acalculous cholecystitis (GB) and potentially other etiologies.

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

Study Objectives

1. To identify relative frequency of known causes of HB in patients undergoing HSCT
2. To correlate the effect of HB on survival
3. To review the effects cholecystectomy or cholecystostomy 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: 60 pediatric allogeneic HSCT patients transplanted between August 2003 and March 2010
- Data collection:
 - Bilirubin and liver enzyme levels
 - Clinical documentation of Sinusoidal Occlusive Syndrome (SOS)
 - Gallbladder disease by pathology or radiology
 - Surgical or interventional radiology gallbladder intervention
 - Length of stay (LOS) and PICU LOS
 - Survival status
- Analysis: Descriptive statistics
 - Subgroup comparison of peak liver enzyme levels, intensive care unit (PICU) length of stay (LOS), total LOS, and mortality
 - Comparisons by non-parametric tests (Fisher's exact, Wilcoxon)

Results

	n	%
Hyperbilirubinemia	33	55
Sinusoidal Occlusive Syndrome	11	33
Gallbladder disease	26	79
Surgical intervention	6	24
Overall survival (hyperbilirubinemia)(n=33)	15	55

Table: Sample Characteristics (n= 60)

Results

Patients with GB disease

- 35% (9 of 26) of patients with GB disease also had a clinical diagnosis of SOS.
- In patients with both SOS and gallbladder involvement, overall survival was 44% (4/9).
 - Gallbladder drainage or removal: Survival was 33% (1/3)
 - Non-intervention group: Survival was 50% (3/6) (p=0.52)
- Alkaline phosphatase and transaminase values in patients with HB due to SOS, GBD, and both diagnoses overlapped considerably. See Figures 2-6.
- GB drainage or removal was undertaken in 31% (8 of 26) of patients with suspected GB disease.
 - Gallbladder drainage or removal: Survival was 50% (4/8)
 - 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).

Effect of Sinusoidal Occlusive disease

- Among patients with SOS, the presence or absence of gallbladder disease was not associated with survival (respectively, 56% vs 50%) (p=1.00)
- A gallbladder procedure was more common among patients with increased hepatic enzymes.
- No individual lab or combination of labs predicted need for gallbladder procedure or mortality in SOS.
- Among survivors, patients with a cholecystectomy or cholecystostomy had a significantly longer LOS than those that did not (122 vs 32 days, p=0.02).

Overall outcomes

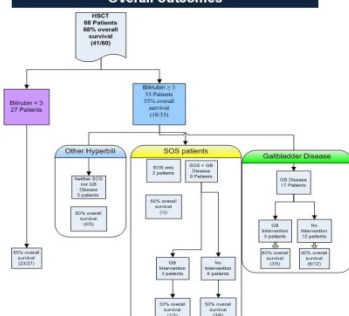


Figure 1. Schematic breakdown of patient characteristics and outcomes.

Other causes of HB

- Transfusion-associated
 - packed red blood cells (2 patients)
- Methotrexate (1 patient)
- Multi-organ failure (2 patients)

Average alk-phos levels greater in pts with both SOS(VOD) & GB disease without intervention

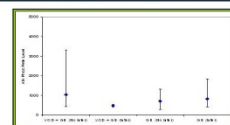


Figure 2. Values in u/L. Means and ranges of alkaline phosphatase within groups were compared in order to further delineate distinctions between groups of patients and generally quantify severity of sickness.

Average Tbili/Dbili levels greater in pts with both SOS(VOD) & GB disease with intervention

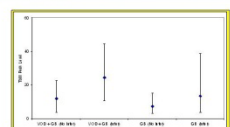


Figure 3. Values in mg/dL. Mean and ranges of total bilirubin within groups. Levels were greater in intervention groups compared to non-intervention.

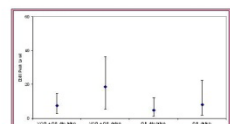


Figure 4. Values in mg/dL. Direct bilirubin means and ranges within various groups. Means and ranges are greater in the intervention groups when compared to non-intervention groups.

Average ALT/AST levels greater in pts with both SOS(VOD) & GB disease with intervention

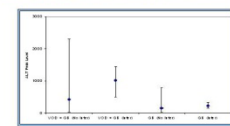


Figure 5. Values in u/L. AST means and ranges are greater in the intervention groups when compared to non-intervention group.

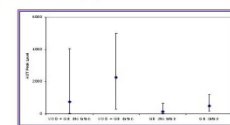


Figure 6. Values in u/L. AST means and ranges are greater in the intervention groups when compared to non-intervention group.

Average ALT/AST levels greater in pts with both SOS(VOD) & GB disease with intervention

Group	Alk Phos peak (mg/dL)	Total peak (mg/dL)	DBili peak (mg/dL)	AST peak (u/L)	ALT peak (u/L)
SOS + GB (n=9)	1550 (425 - 3300)	11.5 (3.5 - 22.7)	7.4 (2.7 - 14.6)	747.8 (31 - 4584)	438.2 (37 - 2305)
SOS + GB (n=17)	479 (405 - 545)	24.0 (10.5 - 44.6)	18.5 (5.2 - 38.5)	2256 (280 - 5515)	1019 (489 - 1444)
GB Only (n=17)	710.3 (379 - 1322)	7.3 (3.5 - 15.1)	4.8 (1.3 - 12.3)	131.4 (50 - 344.4)	182 (58 - 475.1)
GB Only (n=17)	435.19 (405 - 475)	13.35 (4.5 - 26.8)	9 (1.8 - 22.5)	488.19 (188 - 1215)	332.9 (147 - 527)

Table 1. Avg. Peak enzyme level and ranges of various groups with gallbladder involvement ± SOS. 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.

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

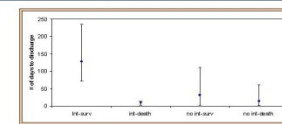


Figure 7. Intervention did not decrease hospital length of stay in patients that survived. Also, patients that underwent intervention died earlier than patients that did not have intervention.

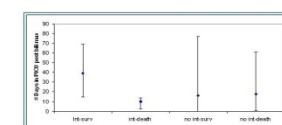


Figure 8. Intervention did not decrease length of PICU stay in survivors. Among all patients, intervention patients died sooner, which led to a shorter PICU stay.

Conclusions

- A bilirubin level of ≥ 3.0 mg/dL appears to be associated with a significant increase in mortality in pediatric HSCT.
- Within the subset of patients with HB, transaminases and alkaline phosphatase, do not reliably distinguish which patients will have radiologic or histologic evidence of gallbladder disease.
- Surgical intervention may potentially decrease mortality in HSCT patients that have gallbladder disease without SOS (VOD).
- Patients with clinical signs of both gallbladder disease and SOS may not benefit from surgical intervention in terms of mortality.
 - However, selection of patients undergoing intervention may have been biased towards the sicker 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
 - Timing of intervention
 - Relatively small number of patients
- Future study designs would include a prospective approach with desired goals of determining parameters and guidelines for timing and indications for intervention