

Surgical interruption of the Enterohepatic Circulation is Associated with an Increased Risk of Liver Transplantation or Death in Children with Alagille Syndrome

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Background: Alagille syndrome (ALGS) is an inherited cholestatic disorder. Previous studies demonstrate variable efficacy of surgical interruption of the enterohepatic circulation in improving pruritus and xanthomas. We sought to evaluate the impact of surgical biliary diversion (SBD) on the natural history of liver disease in ALGS.

Method: GALA is a multicenter retrospective study of children with clinically and/or genetically confirmed ALGS. Clinical and laboratory data were collected pre and post-SBD. Paired sample t-tests were used to compare continuous variables, and McNemar’s test was applied to binominal variables. Native liver survival (NLS) was evaluated with Cox proportional hazards models.

Results: Of 1674 ALGS patients, 3.7% (n=64; 55% male) underwent SBD from 26 centers. The median age of SBD was 2.5 years (IQR 1.8 – 4.4). Most underwent partial external biliary diversion (55%, n=34). All patients reported pruritus prior to SBD, and 51% (n=18/35) reported xanthomas. ALGS-SBD patients had a 2.9-fold greater risk of liver transplantation (LT) or death (95% CI 1.8 – 4.1; $p<0.01$). Post-SBD, there were no significant differences in total bilirubin (8.8 vs. 9.1mg/dL, $p=0.51$), ALT (160 vs. 190 U/L, $p=0.38$), or GGT (495 vs. 460 U/L, $p=0.21$). There were no significant improvements in pruritus (100% vs. 91.7%, $p=0.25$) or xanthomas (51.4% vs. 45.1%, $p=0.67$) post-SBD. In 10 patients with available data, SBD was associated with a significant reduction in serum bile acids (sBA) (257 vs. 98 μmol , $p=0.05$). Among these patients, rates of NLS were 80% at 18-years.

Conclusion: Overall SBD in ALGS was associated with an increased risk of LT or death. In a small subset of patients in whom sBA dropped post-SBA, NLS appeared improved. A propensity score analysis is warranted to determine whether SBD is a marker for a severe hepatic phenotype or if the procedure adversely alters the trajectory of liver disease outcomes in ALGS.

Commented [HV1]: Not clear if this refers to the subgroup of SBA responders or to the total of SBD patients. Also not clear what the median follow up time was here, because from the ASBTi studies it appeared that it lasted at least 3-6 mo before xanthomas started to decrease.

Commented [SV2R1]: Revised!

Commented [HV3]: NLS is unclear if you do not specify for how long, 5 years post-SBD? 10 yrs post SBD? And where do you compare this to? Is 80% high or low? (I know this is supposedly high, but the reader cannot make this from the text, I feel.