

JOURNAL CLUB SUMMARY
5/19/05 – BILIARY ATRESIA

(attendees: Breuer, McKee, Moss, Seashore, Touloukian, Tashjian, Silverman, Jose, Chang, Reddy, Mahoney, Anthony, Goyal, Henry)

- I. Altman RP, Lilly JR, Greenfeld J et al. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. *Annals of Surgery* 226(3): 348-55.

Presented by Marion Henry, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
Yes		A clear description of study design	Retrospective review of outcomes on 266 patients
Yes		The number and practice type of institutions where cases were performed	All operations were performed in either Washington DC or Denver
Yes		Number of surgeons who actually operated in study	Two surgeons performed all operations
	X	A statement as to whether the same surgeon operated on pts from different treatment groups or just one group	
Yes		The precise timeline during which patients were treated	1972 - 1996
Yes		A clear description of how patients were selected into study	295 pts operated on during that time period, 266 available for long-term follow-up
Yes		The number of eligible patients at the study sites excluded during the study	Those not available for long-term follow-up
Yes		A clear description of the study population	All comers who had surgery for BA
No		A clear description of the relevant diagnostic criteria used to identify cases	Not given
No		A clear description of critical aspects of operative technique and peri-operative care	Though did say that 206 cases had modifications of the intestinal conduit
No		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	Not reported
		RESULTS	
No		Appropriate measures of central tendency of all relevant demographic and baseline variables	Not reported
No		Range and median for length of follow-up reporting	Not reported
Yes		Relevant outcome variables are presented with appropriate measures of range and variability	Survival curves for different outcomes presented with confidence intervals
Yes		Methods for measuring outcomes of interest are clearly described	
Yes		Statement is made whether any data is missing (and how missing data is addressed)	Data on missing pts excluded
No		Number and appropriate details regarding all complications	No details of complications
		IF MORE THAN ONE TREATMENT GROUP	
No		Appropriate measures of central tendency for all relevant demographic and baseline variables for all treatment groups	
No		The range and median for length of follow-up reporting for each treatment group	
	X	A precise timeline during which all patients were treated for each group	
Yes		Outcome variables being compared between groups are presented with appropriate measures of variability (eg standard deviation)	Survival curves presented
Yes		Measure of type I error: (p-values) for comparison statistics are presented with actual values if p=0.01 or larger (eg. P=NS and p<0.05	

		are not acceptable).	
Yes		Type I error cont: Confidence interval presented	
No		Measures of type II error should not be >0.2 (study should have at least 80% power)	
No		A description of how patients were selected into each treatment group	
No		A statement is made as to whether the same surgeons operated on patients from different treatment groups	

Summary: A retrospective review of 266 out of 295 patients operated on for biliary atresia by the two authors between 1972 and 1996. Failure defined as transplant or death. Overall freedom from failure was 86% at 6 months falling to 21% at 20 years. Among the variables they investigated, age at surgery, surgical decade and atretic bile duct anatomy were independent risk factors for failure. It is unclear from the review why the other 30 patients were not included other than that they were loss to follow-up. No summary demographics were reported so it is not possible to determine who this population of patients is other than pts who had an operation for biliary atresia. Of definite significance is the fact that 206 of the 266 had modifications to the intestinal conduit either through external venting, incorporation of an intussuscepted valve or both. No differences were explored between these 206 pts and the 60 pts who did not have any modification.

Result summary:

Demographics: None reported

Figure 1: Overall survival (without transplantation) curve - 86% at 6 months, 67% at 1 yr falling to 21% at 20 yrs

Table 1: Independent risk factors for failure post Kasai determined by Cox model - age >70 days 1.69 (1.15-2.48), 1970s 1.916 (1.42-2.59), type a anatomy 1.791 (1.21-2.65), type c anatomy 2.175 (1.07-4.41) were the significant independent risk factors

Figure 2: Definition of bile duct anatomy: type A - fibrotic extrahepatic bile ducts in continuity, type B - fibrotic proximal ducts, distal ductal patency, type C - fibrotic gallbladder with absent or scanty remnants of remaining ductal structures

Figure 3: Survival stratified by ductal histology - type I (ductules >150 micrometers in diameter) had greater survival than types 2 and 3 which are smaller structures. This was a highly significant independent risk factor.

Figure 4: Survival stratified by liver histology - no difference in survival based on hepatic histology

Figure 5: Survival based on post-Kasai drainage (no definition for how this was determined is given) - without drainage there were no survivors past 5 years. With drainage, 49% survival at 15 years

Figure 6: Survival post-liver transplant - no follow-up beyond 2 years at which time survival is 71%. This is then extrapolated as 71% survival for all future time periods up to 25 years.

Figure 7: Survival stratified by age at time of Kasai - those greater than 70 days had decreased survival.

Discussion: This paper is a retrospective review of a large continuous cohort of patients. To better be able to determine applicability and external validity, more information on the patient demographics would be useful. An explanation of what happened to the 30 patients not included would also be useful - did they all die or just immediately lost to follow-up? Even still, they could have been included and counted as censored events. There is no explanation or comparison of the group of patients who did not receive modification of their intestinal conduit which would be extremely useful since many patients do not undergo this procedure currently. Unfortunately, there was also no discussion of post-operative cholangitis and its influence on outcome. No other complications were mentioned either. The survival graph post-transplant does not support the conclusion that there is a 71% post-transplant survival since there is only follow-up for these patients (at least as presented in the graph) for 2 years. Overall, however, this is a very large series which gives some insight into possible risk factors for failure post-Kasai procedure in patients with biliary atresia.

II. Davenport M, Puricelli V, Farrant P et al. The outcome of the older (>100 days) infant with biliary atresia. J Ped Surg 39(4):575-581, 2004.

Presented by Dave Tashjian, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
Yes		A clear description of study design	Retrospective review
Yes		The number and practice type of institutions where cases were performed	Tertiary center, largest biliary/hepatic ctr in UK
Yes		Number of surgeons who actually operated in study	2
Yes		A statement as to whether the same surgeon operated on pts from	All operated on by these two

		different treatment groups or just one group	surgeons
Yes		The precise timeline during which patients were treated	1980 - 2000
Yes		A clear description of how patients were selected into study	Had surgery at >100 d
Yes		The number of eligible patients at the study sites excluded during the study	422 infants had Kasai, 35 at 100 days or later
Yes		A clear description of the study population	Only those undergoing Kasai after 100 days
Yes		A clear description of the relevant diagnostic criteria used to identify cases	
Yes		A clear description of critical aspects of operative technique and peri-operative care	
Yes		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	Only 2 surgeons did cases, waited until after learning curve
		RESULTS	
Yes		Appropriate measures of central tendency of all relevant demographic and baseline variables	Median age 133 (range 100-301)
Yes		Range and median for length of follow-up reporting	Broken down by outcome groups
Yes		Relevant outcome variables are presented with appropriate measures of range and variability	
Yes		Methods for measuring outcomes of interest are clearly described	
Yes		Statement is made whether any data is missing (and how missing data is addressed)	
No		Number and appropriate details regarding all complications	

Summary: A retrospective review of 35 patients who underwent Kasai operation at 100 days or older between 1980 and 2000 in the United Kingdom. This is the largest single center series of “older” patients to undergo Kasai operation. The outcomes reported are very good and much better than other reports. Some of this discrepancy may be due to the fact that this is clearly a referral center that does high numbers of these operations. Unfortunately, the authors do not present the survival data on their other patients for complete comparison.

Result summary:

Demographics: 35 patients (21 female, 14 male) who underwent surgery at 100 days or later. Median age at surgery was 133 days (100-301).

Figure 1: Actuarial survival on infants undergoing surgery at 100 days or later - 10 yr survival was 40%.

Figure 2: Survival according to type of atresia - no survival advantage for correctable (types 1 & 2) versus uncorrectable (type 3)

Figure 3: Effect of cirrhosis on survival - no significant survival disadvantage

Table 1: Relationship of histologic criteria to survival outcome - no significant relationship of fibrosis, duct destruction, parenchymal cholestasis or giant cell transformation on survival

Discussion: In contrast to other reports, they conclude that there is reasonable survival in pts undergoing Kasai after 100 days. Unfortunately, their patients who underwent surgery earlier were not presented as a comparison group as this would be an interesting and relevant comparison to make. One third of the patients in this series died early, and information is not presented on this high mortality. Additional information contrasting the late patients to the early patients may also contribute to outcomes and information regarding differences in socioeconomic levels, access to care, primary care information would have been useful. Given the large volume at this center and the fact that it is a large referral center, these results may be more representative as a sample of patients with biliary atresia than similar reports from smaller, single institutions that do not have similar volume. Finally, changes in medical care over the two decade period of the study may have influenced the outcome in this study.

III. Dillon PW, Owings E, Cilley R et al. Immunosuppression as adjuvant therapy for biliary atresia. J Ped Surg 36(1): 80-85, 2001.

Presented by Robert Chang, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
Yes		A clear description of study design	A retrospective review
Yes		The number and practice type of institutions where cases were performed	3 institutions, all university children's hospitals
No		Number of surgeons who actually operated in study	
No		A statement as to whether the same surgeon operated on pts from different treatment groups or just one group	
Yes		The precise timeline during which patients were treated	1991-1999
No		A clear description of how patients were selected into study	Those in the study received Kasai and post-operative steroids, but how these pts were selected was not described
No		The number of eligible patients at the study sites excluded during the study	Inclusion and exclusion criteria not mentioned
No		A clear description of the study population	Only described in terms of their treatment, not their presentation or diagnostic features
No		A clear description of the relevant diagnostic criteria used to identify cases	
No		A clear description of critical aspects of operative technique and peri-operative care	
No		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	
		RESULTS	
No		Appropriate measures of central tendency of all relevant demographic and baseline variables	
Yes		Range and median for length of follow-up reporting	Mean follow-up was 50 months (range 18-119 months)
	X	Relevant outcome variables are presented with appropriate measures of range and variability	
Yes		Methods for measuring outcomes of interest are clearly described	Survival is outcome of interest
Yes		Statement is made whether any data is missing (and how missing data is addressed)	
Yes		Number and appropriate details regarding all complications	32% developed cholangitis

Summary: A retrospective case series with few patients. Methodologically, there was a small number of patients, variables were inadequately defined, and it is not clear how this group of patients was selected for this study.

Result summary:

Demographics: 25 infants with an overall survival rate of 88% with a mean follow-up time of 50 months.

Table 1: 25 pts followed for a mean of 50 months. Overall survival is 88%. 76% of patients remain jaundice free without a new liver. 4 patients subsequently

Table 2: Stratified by age at time of Kasai - only 3 pts of age > 12 weeks at time of surgery and all failed

Table 3: Bilirubin levels in treatment responders and failures - not surprisingly, the levels are lower in those who responded to a drainage procedure

Discussion: In addition to the small size of the study and the fact that there is no indication as to how/why these patients were selected and others were excluded, this study also has some methodological or reporting problems in that the prednisone treatment is not adequately described, particularly concerning the tapering schedule. Furthermore, data on the doses of antibiotics and ursodeoxycholic acid are not described. Without data on their other patients, it is not possible to form a comparison. They report

cholangitis incidence of 32% which is somewhat elevated, thus begging the question of what their rates are in the non-steroid treatment group.

This is a phase I or II drug trial, showing that this is safe treatment in these patients. It in no way proves that such therapy positively impacts the outcome of this disease after a Kasai.

IV. Meyers RL, Book LS, O’Gorman MA et al. High-dose steroids, ursodeoxycholic acid, and chronic intravenous antibiotics improve bile flow after Kasai procedure in infants with biliary atresia. J Ped Surg 38(3):406-411, 2003.

Presented by Vic Reddy, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
Yes		A clear description of study design	Retrospective review
Yes		The number and practice type of institutions where cases were performed	One institution, university children’s hospital
No		Number of surgeons who actually operated in study	
No		A statement as to whether the same surgeon operated on pts from different treatment groups or just one group	
No		The precise timeline during which patients were treated	“past 8 years”
Yes		A clear description of how patients were selected into study	28 consecutively treated pts, treated per surgeon preference
No		The number of eligible patients at the study sites excluded during the study	
No		A clear description of the study population	
No		A clear description of the relevant diagnostic criteria used to identify cases	
No		A clear description of critical aspects of operative technique and peri-operative care	
No		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	
		RESULTS	
No		Appropriate measures of central tendency of all relevant demographic and baseline variables	
No		Range and median for length of follow-up reporting	Mean follow up reported but not ranges
Yes		Relevant outcome variables are presented with appropriate measures of range and variability	
Yes		Methods for measuring outcomes of interest are clearly described	
No		Statement is made whether any data is missing (and how missing data is addressed)	
No		Number and appropriate details regarding all complications	
		IF MORE THAN ONE TREATMENT GROUP	
No		Appropriate measures of central tendency for all relevant demographic and baseline variables for all treatment groups	
No		The range and median for length of follow-up reporting for each treatment group	Mean but no range reported
No		A precise timeline during which all patients were treated for each group	
No		Outcome variables being compared between groups are presented with appropriate measures of variability (eg standard deviation)	
No		Measure of type I error: (p-values) for comparison statistics are presented with actual values if p=0.01 or larger (eg. P=NS and p<0.05 are not acceptable).	
No		Type I error cont: Confidence interval presented	
No		Measures of type II error should not be >0.2 (study should have at least	

		80% power)	
Yes		A description of how patients were selected into each treatment group	Surgeon preference
No		A statement is made as to whether the same surgeons operated on patients from different treatment groups	

Summary: A retrospective review of 28 patients treated with Kasai and regular steroid therapy or high-dose protocol post-operatively. There is no description of the two groups provided so that they can be appropriately compared. Patients were divided into each treatment group based on surgeon preference leaving room for significant selection bias.

Result summary:

Demographics: not provided

Figure 1: Pre and post op bilirubin levels in the two treatment groups - Statistically significant decrease in steroid group

Table 1: Outcome of infants in the two different groups - Steroid group had a significantly lower incidence at transplant <1 yr of age, significantly better overall survival and survival to 1 yr of age.

Figure 2: Age at time of Kasai - no differences between the two treatment groups in age range at time of operation

Table 2: Histology of liver and biliary plate - neither was an independent predictor of success or failure

Discussion: This study is a retrospective review of 28 pts treated during 8 yr time period at U. Utah. Decisions for group assignment were based on surgeon preference which could result in significant bias. There were no comparisons made on demographics or other characteristics between the two groups. We cannot tell causality of this treatment leading to better outcomes from this study. The group undergoing standard therapy has an extremely HIGH mortality at one year (85%) which may suggest that there is a bias in the selection of these two groups. In order to adequately compare two groups with different steroid protocols, a better designed comparative study, such as a randomized trial, is necessary.