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Post-transplant biopsy risk for stable long-term pediatric liver transplant recipients: 451 percutaneous biopsies from two multi-center immunosuppression withdrawal trials

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Abstract

Although liver biopsy is the gold standard for assessing allograft health, its attendant risk has deterred its use in routine monitoring of stable liver transplant recipients during long-term follow-up. We utilized prospectively collected data on adverse events from two clinical trials of immunosuppression withdrawal to quantify the risk of liver biopsy in pediatric liver transplant recipients. The trials included 451 liver biopsies in 179 children. No biopsies led to bleeding requiring transfusion or intervention, suggesting a clinically significant bleeding risk of <0.8%. Complications were reported in 5.5% of biopsies (95%CI 3.6–8.1%): 5.8% (21/363) of protocol biopsies and 4.5% (4/88) of for-cause biopsies (p=0.80). Mild complications occurred in 1.8% of biopsies, moderate in 1.8%, and severe in 2.0%. The majority of complications (89%) resolved within one week. Six of nine (67%) severe complications were related to biliary issues; 5 were episodes of cholangitis. Biopsy-related cholangitis occurred only in children with underlying biliary strictures. Overall, biopsy-related complications were infrequent and resolved quickly. Severe complications were rare, with occult biliary stricture as the dominant driver. Our study provides evidence for clinicians who are considering the risk versus benefit of surveillance liver biopsies in pediatric liver transplant recipients.

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INTRODUCTION

Single center, cross-sectional studies in long-term, stable, adult and pediatric liver transplant recipients have reported a high prevalence of “silent” chronic graft damage in spite of normal liver tests.[1–3] These observations have been strengthened by studies of biopsies performed to determine eligibility for participation in prospective, multi-center clinical trials of immunosuppression withdrawal.[4–6] These data clearly show that liver tests lack both sensitivity and specificity to detect graft injury and as such, may be inadequate as the sole guide for immunosuppression management.[7,8] Although liver biopsy is accepted as the gold standard for assessing allograft health, its invasiveness and the attendant risk of potentially serious complications have deterred its widespread use. Clarifying the equipoise of liver biopsy is particularly critical when considering periodic surveillance biopsies as a tool for optimizing immunosuppression decision-making.

Previous reports of liver biopsy risk in children are predominantly retrospective, small or single-center, and not transplant-specific.[9–13] In contrast, this report is based on prospectively collected data from two multi-center, immunosuppression withdrawal trials [WISPR (NCT00320606) and iWITH (NCT01638559)]. These biopsies, uniformly conducted in stable, long-term pediatric liver transplant recipients with normal liver function offer a unique opportunity to comprehensively and rigorously evaluate liver biopsy risk. Our findings directly inform the risk/benefit considerations for surveillance biopsies in clinical practice.

METHODS

Prospectively collected data on adverse events (AEs) from two clinical trials of immunosuppression withdrawal were retrospectively reviewed. In brief, WISPR (Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients) was a pilot safety study that enrolled recipients of parental living donor grafts at three centers in the United States. iWITH (Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients) was an efficacy study that enrolled recipients of both living and deceased donor grafts at 12 centers in North America. Eligibility for both trials required that patients underwent transplant more than four years earlier, were stable on calcineurin-inhibitor monotherapy without rejection within the preceding year, with ALT and GGT consistently < 50 IU/L, and an eligibility biopsy without significant inflammation or fibrosis.[14,15] In both trials, liver biopsies were performed per-protocol (at screening for trial eligibility and serially to assess for tolerance and overall allograft health; Figure 1) and for-cause (at the discretion of the investigator or mandated for ALT or GGT>100 IU/L without other etiology).

All biopsies were performed percutaneously. Study protocols did not specify a specific biopsy technique but required collection of a core of ≥4 cm in length and therefore frequently required more than a single pass. Biopsies were performed according to each center’s standard-of-care (Table S1). Data on biopsy technique was not collected prospectively for individual biopsies; center practices were reported retrospectively. WISPR biopsies were done with 16 or 18-gauge needles; all iWITH biopsies were performed with

16-gauge biopsy needles. Trial participants were followed in the WISPR and iWITH study for five and four years, respectively. Eleven tolerant WISPR subjects enrolled in a four year extension study such that total study participation was for nine years. (Figure 1).

The primary outcome for our analysis was AE related to liver biopsy. All AEs reported as definitely or possibly related to a liver biopsy were included. We included all biopsies (n=451) performed in all subjects (n=179) enrolled in both studies. AEs were classified as serious or non-serious using standard National Institute of Allergy and Infectious Diseases (NIAID) and Food and Drug Administration guidelines. Serious AEs required hospitalization >24 hours, prolongation of an existing hospitalization, sequela of persistent or significant incapacity, characterization as life-threatening, or intervention to prevent one of these outcomes. AEs were also graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE, NCI Versions 3.0 for WISPR, 4.03 for iWITH). AEs were graded mild if they required no or minimal intervention (e.g. a single dose of pain medication), moderate if they caused mild or moderate limitation in activity but still required no or minimal intervention, and severe if they markedly limited activity and required intervention. The relationship of AEs to biopsy was determined by site investigators and subsequently reviewed by medical monitors from the study sponsors (Immune Tolerance Network and NIAID) as well as the NIAID Data Safety and Monitoring Board (DSMB).

Statistics were primarily descriptive. Differences between children with any vs. no biopsy-related complications were calculated using Fisher's exact tests or chi-squared tests for categorical variables and Wilcoxon Rank Sum Tests for continuous variables; this data is summarized in the text.

RESULTS

Complications possibly or definitely related to liver biopsies were reported for 12.3% (22 of 179) of subjects and 5.5% (25/451; 95% CI 3.6–8.1%) of biopsies. Complications occurred in 5.8% (21/363) of protocol biopsies and 4.5% (4/88) of for-cause biopsies (p=0.80). There were 8 (1.8%) biopsies with mild complications, 8 (1.8%) with moderate, and 9 (2.0%) with severe complications. (Table 1) No biopsies led to bleeding that required transfusion, intervention, or surgery. No hemothorax, pneumothorax, or arteriovenous fistulas – rare complications after liver biopsy in adults – were reported. Nearly all (26/28 AEs; 93%) biopsy-related complications were detected within one day. Two serious complications presented later: a single episode each of cholangitis and cellulitis were reported on post-biopsy day four and seven, respectively. (Table 1) Resolution of complications occurred in ≤1 day for 39% and in 2–3 days for 25%; 89% of all complications resolved within one week. (Table 1)

Six of the nine (67%) severe biopsy-related complications were related to biliary issues. Cholangitis accounted for five severe and one mild biopsy-related complication. These six episodes occurred in four subjects at three centers; two WISPR subjects had two episodes each. Cholangitis related to liver biopsy only occurred in children with underlying biliary strictures; in the four subjects without known biliary stricture, the biopsy-related cholangitis triggered the diagnostic evaluation and confirmed the diagnosis. Three children with this

complication had received partial grafts from living donors and one had received a whole graft from a deceased donor. Four cholangitis episodes occurred following protocol biopsies; one was a trial eligibility screening biopsy and the other three occurred in children that had preceding for-cause biopsies for fluctuating liver enzymes. One episode of biopsy-related pain was graded as severe; the subject was later diagnosed with a biliary stricture. One additional episode of mild biopsy-related abdominal pain was followed by report of a bile leak associated with a later biopsy in a child with a split liver graft.

For the 25 biopsies with complications, 28 AEs were reported. The most common non-severe biopsy-related complication was pain (11/19; 58%), which occurred in 11 children from six centers. Five pain episodes lasted 0–1 days (45%), five last 2–4 days (45%) including the 1 severe AE, and 1 lasted 7 days. Five of the pain AEs occurred in biopsies of whole liver grafts and six in biopsies of split liver grafts. Two biopsies incurred multiple AEs; all were graded as mild. One subject had a rash at the biopsy site and vomiting; the second subject had biopsy site contact dermatitis, pain, and nausea. Neither subject had complications related to other biopsies.

Children with versus those without biopsy-related complications did not differ significantly with respect to age at transplant or at screening biopsy, transplant indication, donor type (living versus deceased), graft type (whole versus split), or by ALT, GGT, or platelet count at baseline (data not shown). Of the 13 subjects with biopsy complications who had partial livers, 10 were from living and three were from deceased donors, accounting for 14% and 8% of all living and deceased donor recipients.

None of the subjects were on anti-coagulation medications, including aspirin, at study entry or at the time of any liver biopsy. The biopsy of splenic tissue occurred in a child with a split liver graft, at a center that utilizes interventional radiologists and real-time ultrasound guidance The five complications related to procedural sedation occurred at five different centers, three with interventional radiologists and two with hepatologists performing the biopsies; we did not collect data on sedation or anesthetic medications utilized.

DISCUSSION

In stable pediatric liver transplant recipients with normal liver function, biopsy-related complications are infrequent (5.5% of all biopsies), generally mild, and resolve quickly without sequelae. Serious or severe complications are rare, occurring in less than 2% of all liver biopsies. The dominant driver of serious or severe complications was occult biliary stricture. Importantly, there were no episodes of bleeding that required blood transfusion or invasive intervention. Considering that our study included 451 liver biopsies, we estimate that the risk of clinically significant bleeding in this population is less than 0.8%.

Our study is unique for the following reasons. First, it is the largest study to date of biopsy-related complications in pediatric liver transplant recipients. Second, it is exclusively focused on stable recipients with normal liver tests and liver function, exactly reflective of the population who might undergo periodic surveillance biopsies to guide long-term immunosuppression management. Finally, and of critical importance, it is the only pediatric

study of liver biopsy complications that reports prospectively collected data.[16] All biopsies were performed within the rigorous clinical trial context. Liver biopsy was explicitly identified as a "study procedure" and, as such, the protocol stipulated that any complication that was even possibly related must be reported. Moreover, the multiple layers of oversight, beginning with the site principal investigators, the study team, the independent on-site and remote clinical monitors, the medical monitors, and finally, the NIAID DSMB provides robust reassurance that all biopsy-related complications were indeed captured.

Pain, which undoubtedly occurred to some extent in many biopsies, was reported as an AE in only 2.4% of biopsies. The low prevalence may reflect several considerations. Biopsies were typically conducted with sedation or general anesthesia which, in addition to preventing awareness, may decrease peri-procedural anxiety and memory of pain. The reporting of the subjective symptom of pain may not have been uniform over time or across centers, although AEs of pain were reported by six of the 12 centers. It is also possible that pain that did not require any concomitant medications or other treatment was not reported. Overall, our data provides some reassurance that biopsy-related pain is unlikely to be severe.

One critical relationship that emerged from our study is that biopsy-related cholangitis signaled undiagnosed biliary stricture. This has not been previously reported in pediatric liver transplant recipients. Studies in adults have reported biliary stricture as a risk factor for sepsis following liver biopsy.[17] Earlier studies implicated choledochojejunostomy as a risk factor for post-biopsy sepsis in adults,[18] but subsequent studies clarified that the risk factor is underlying biliary abnormalities like stricture, not the type of surgical anastomosis.[17,19]

The episodes of biopsy-related cholangitis lead to two recommendations. First, we suggest that liver transplant recipients with a recently diagnosed or untreated biliary stricture, or with a history of biopsy-related cholangitis, receive antibiotic prophylaxis at the time of biopsy. Second, an episode of biopsy-related cholangitis should trigger definitive evaluation for occult biliary stricture, either with endoscopic retrograde cholangiography or percutaneous transhepatic cholangiogram and biliary drainage. This recommendation is supported both by our data and by previous studies that describe the low sensitivity and specificity of liver tests, ultrasound examination, magnetic cholangiopancreatography (MRCP), and even liver biopsy to diagnose biliary stricture.[20–22] These studies reveal a much lower sensitivity and specificity of both ultrasound and MRCP in detecting biliary strictures in patients with bilio-enteric anastomoses instead of duct-to-duct, which is very commonly the case in children.[20, 22]

Previous reports of liver biopsy complications in children report a rate of serious complications comparable to our findings, and a broad range of minor complication rates. (Table 3) These studies were all retrospective, single-center studies; the broad range of minor complication rates likely reflects heterogeneity in screening for and recording of complications. Similarly, reports of adult liver biopsy complications reported a 0.4–18% incidence of minor complications (pain, bleeding without need for transfusion) and a 0–1.7% incidence of major complications.[21,23]

The implications of our study are limited by the characteristics of the study cohort in several respects. Our cohort included stable pediatric liver transplant recipients at least four years after liver transplant with normal liver tests and function. Therefore, our data may not accurately reflect biopsy complication rates if performed in children early after liver transplant or late after liver transplant but with abnormal allograft function, portal hypertension, ascites, and/or coagulopathy. Of note, more than half of our cohort did have a split graft, and children with split grafts were not more likely to have biopsy-related complications. Long-term survival after pediatric liver transplant is excellent, with rates more than 80% at 10 years.[24] But our cohort was selected for their normal liver enzymes and very stable courses, which is not achievable by all transplant recipients. The majority of children underwent transplant for biliary atresia or acute liver failure. When considering liver biopsy for any transplant recipient, unique factors that increase bleeding risk such as a particular transplant indication, personal and/or family bleeding history, must be weighed.

All biopsies were performed in large-volume, well-established pediatric transplant centers, albeit by both hepatologists and interventional radiologists using a variety of localization techniques and needles. (Table S1) As such, our findings may not translate to small volume and/or nascent transplant centers. We did not prospectively collect data on technical details of biopsy procedures performed at each center. However, the low rate of complications severely limits our ability to identify safety differences associated with specific techniques. We did not employ a standardized pain scale during the trial; however, standardized definitions of AE severity were used by study investigators for grading. Finally, data on the number of biopsy passes made and the post-biopsy hematocrit was not recorded in the trial. Of note, surveillance biopsies may not all require 4cm of liver tissue; this was required in the trial because tissue was also evaluated for mechanistic studies.

In conclusion, liver biopsy is an invasive but low-risk procedure for pediatric liver transplant recipients. This data suggests that surveillance liver biopsies can be utilized to proactively manage immunosuppression without incurring excessive risk in the long-term management of stable pediatric liver transplant recipients. Particularly in light of the ever-widening swathe of data attesting to the high prevalence of silent chronic graft injury, our study provides solid evidence that clinicians can use when considering the risk versus the benefit of periodic surveillance liver biopsies to guide immunosuppression management and monitor allograft health, with the aim of maximizing both graft and patient longevity. This risk profile supports the feasibility of future liver biopsy-based studies aimed at finetuning immunosuppression in these children—to provide adequate graft protection while minimizing adverse effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AE	Adverse event
ALT	Alanine aminotransferase
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety and Monitoring Board
GGT	Gamma glutamyl transpeptidase
IQR	Interquartile range
iWITH	Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients
NIAID	National Institute of Allergy and Infectious Diseases
SAE	Serious adverse event
WISPR	Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients

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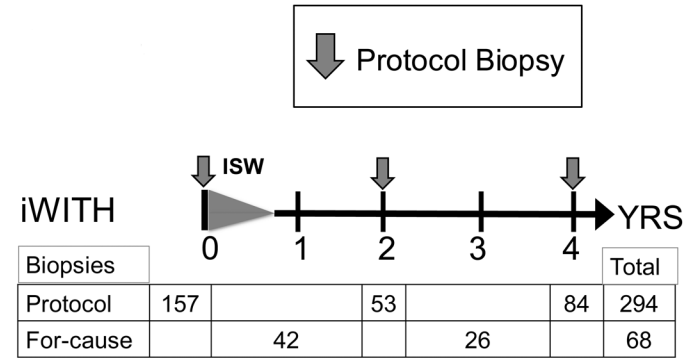
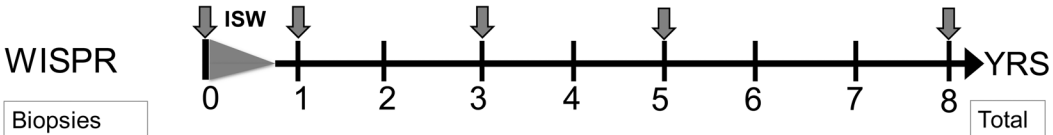


Biopsies						Total
Protocol	157		53		84	294
For-cause		42		26		68

All biopsies	
Protocol	363
For-cause	88
Total	451



Biopsies										Total
Protocol	22		15		10		11		11	69
For-cause		8		7		3		2		20

Figure 1:

Timeline of biopsies in the WISPR and iWITH trials. In both trials, protocol biopsies at time 0 were done to assess trial eligibility. WISPR included protocol biopsies in 22 children (20 eligible, 2 ineligible) and for-cause biopsies in 12 trial participants. iWITH included protocol biopsies in 157 children (88 eligible, 69 ineligible) and for-cause biopsies in 53 trial participants. ISW = Immunosuppression withdrawal

TABLE 1:

Complications of percutaneous liver biopsy in stable pediatric liver transplant recipients

Description	Total	Serious AEs*	AE* grade			AE* duration (days)
			Severe	Moderate	Mild	
Hepatobiliary						
Cholangitis	6	5	5		1	5, 5, 6, 18†, 35†, 94
Bile leak	1	1	1			4
Biopsy of splenic tissue	1			1		0
Related to biopsy site, cutaneous						
Pain	11	1	1	5	5	0–7
Rash at biopsy site	3				3	2–3
Cellulitis, biopsy site	1	1	1			7
Related to procedural sedation						
Nausea/vomiting	2				2	0
Hypotensive episode	1		1†			0
Sedation reaction	1			1		0
Fever	1			1†		1

*AE = adverse event. All AEs were classified as serious or non-serious, and were graded by severity (mild, moderate, severe, life-threatening, death).

†Occurred following for-cause biopsies. All other complications occurred following protocol biopsies.

TABLE 2:

Characteristics of the pediatric liver transplant recipients with biopsy-related complications

	N (%) or median (IQR)
Female	14 (64)
Race	
White	20 (91)
Black	0
Other	1 (4.5)
Unknown	1 (4.5)
Transplant indication	
Biliary atresia	14 (64)
Acute liver failure	3 (14)
Metabolic liver disease	2 (9)
Other	3 (14)
Graft type	
Whole	9 (41)
Split	13 (59)
Age at transplant (years)	0.7 (0.5 −1.8)
At screening for study entry:	
Age, years	10.1 (6.7–11.9)
ALT (IU/L)	27 (17–33)
GGT (IU/L)	16 (11–21)
Platelets (x 10^9/L)	234 (192–291)
Years followed in trial	4.1 (4.1–4.2)

TABLE 3:

Published reports of percutaneous liver biopsy complications in children that include pediatric liver transplant recipients, 2000–2018

Author, year	Number of biopsies	Biopsy method	Prevalence of complications[16]		Types of complication
			Minor	Major	
Post-transplant liver biopsies, all for-cause					
Mandal 2014[9]	219	IR, US-guided Cutting needle	N/A	0.91%	**Major**: 2 bleeds requiring transfusion
Sornsakrin 2010[10]	120	IR,US-marked Suction needle	3.3%	1.7%	**Minor**: sedation-related, self-limited bleed **Major**: 1 bile leak/peritonitis, 1 abscess
All percutaneous liver biopsies					
Bolia 2017[11]	626 163 post-LT	IR: US-guided GI:US-marked	2.7%	2.1%	**Minor**: self-limited bleed **Major**: fever (5), hemobilia (2), bleeding (3; 2 transfused), gelfoam anaphylaxis (2), sepsis (1)
Bilreiro 2017[12]	228 127 post-LT	US-guided Needle N/A	11.8% 0.8% post-LT	0%	**Minor**: self-limited bleed
Almeida 2017[25]	163	N/A	66%	0%	**Minor**: pain, self-limited bleeds
Govender 2013[13]	597 111 post-LT	IR US-guided Cutting needle	8.2%	1.7%	**Minor**: self-limited bleed, pain, sedation-related **Major**: bleeding (9; 5 transfused), pneumothorax (1), fever requiring antibiotics (1)
Short 2013[26]	328 31 post-LT	IR US-guided Cutting needle	8.2%	2.4%	**Minor**: pain, self-limited bleed, sedation-related, 1 ascites leak **Major**: bleed requiring transfusion (6), hemorrhagic shock/death (1), infection (1)
Westheim 2012, 2013[27, 28]	311 114 post-LT	IR US-guided Cutting needle	25% 18% post-LT	1.3% 0.9% post-LT	**Minor**: self-limited bleed, pain, sedation-related, 2 asymptomatic AV fistulas **Major**: 3 bleeds (1 in post-LT on LMWH, 2 surgeries, 1 transfused)
Potter 2011[29]	294 28 post-LT	IR US-guided Cutting needle	0.34%	1.0%	**Minor**: 1 self-resolving pneumothorax **Major**: 2 bleeds (2 transfused, both with bone marrow failure), 1 sepsis in post-LT
Schiemann 2000[30]	249 140 post-LT	+/− US-guided Needle varied	4.4%	2.4% 3.6% post-LT	**Minor**: pain, fever, sedation-related, rash **Major**: hemothorax (3), bleed requiring surgery (3) with 1 death (child with HUS)