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REAL-TIME MONITORING OF ACUTE LIVER-ALLOGRAFT REJECTION USING THE BANFF SCHEMA[1]

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Background. **The Banff schema is the internationally accepted standard for grading acute liver-allograft rejection, but it has not been prospectively tested.**

Methods. **Complete Banff grading was prospectively applied to 2,038 liver-allograft biopsies from 901 adult tacrolimus-treated primary hepatic allograft recipients between August 1995 and September 2001. Histopathologic data was melded with demographic, clinical, and laboratory data into a database on an ongoing basis using locally developed software.**

Results. **Acute rejection developed in 575 of 901 (64%) patients and the worst grade was mild in 422 of 575 (73%). At least one episode of moderate or severe acute rejection developed in 153 of 901 (17%) patients and most episodes, irrespective of severity, occurred within the first year after transplantation. Patients with moderate or severe acute rejection showed higher alanine aminotransferase ($P=0.007$) and aspartate aminotransferase ($P=0.07$) levels and were more likely to develop perivenular fibrosis on follow-up biopsies ($P=0.001$) and graft failure from acute or chronic rejection ($P=0.004$) than those with mild rejection. Regardless of severity, 80% of patients with acute rejection did not develop significant fibrosis in follow-up biopsies, and graft failure from acute or chronic rejection occurred in only 11 of 901 (1%) allografts.**

Conclusions. **Most acute-rejection episodes are mild and do not lead to clinically significant architectural sequelae. When tested prospectively under real-life and -time conditions, the Banff schema can be used to identify those few patients who are potentially at risk for more significant problems. Creation, capture, and integration of non-free text, or "digital," pathology data can be used to prospectively conduct outcomes-based research in transplantation.**

The Banff schema for grading acute liver-allograft rejection represents the consensus opinion of a group of recognized expert liver transplant pathologists, hepatologists, and surgeons from many of the major hepatic transplant centers in North America, Europe, and Asia (*1*). It incorporates concepts and criteria from several earlier systems that satisfied requirements for simplicity, reproducibility, scientific correctness, and clinical utility (*1–15*). The earliest and one of the most influential systems was derived from fundamental observations by K. A. Porter, who did much of the pioneering work in liver transplantation pathology (*2*). He recognized that the combination of centrilobular inflammation, hepatocyte necrosis, and dropout was a poor prognostic feature, which can be used to identify severe acute rejection (*2*); this constellation of findings was first described in untreated canine liver-allograft recipients by Starzl et al. (*16*) and McBride et al. (*17*). The Banff schema for acute rejection is based on these time-tested systems (*1–15*), but the few publications on its use are limited to comparisons with other grading systems (*18*) or clinical studies focused on other endpoints (*19*,*20*). Recently however, Neil and Hubscher (*21*) more thoroughly examined the centrilobular lesion described and showed that it frequently preceded the development of chronic rejection. No studies have prospectively evaluated the utility of the Banff Schema under real-time and real-life conditions.

At the University of Pittsburgh Medical Center (UPMC), a locally derived grading system for liver-allograft rejection had been used since the inception of the program (*11*,*22*). In 1995 we converted to the Banff schema, which incorporates a descriptive grade virtually identical to our local schema (*11*,*22*), which in turn, provided the basis for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grading system (*12*). The Banff schema also includes a semiquantitative rejection activity index (RAI) (*1*), which is the conceptual equivalent of the hepatitis activity index (*23*) and derived from the European grading system (*13*). At the same time, we instituted the routine scoring of specific histologic features listed on a template (see *http://tpis.upmc.edu/tpis/schema/AlloLiver.html*).

The completed template and diagnosis, or diagnoses, are downloaded from an anatomic pathology software system (CoPath, Dynamic Healthcare Technologies, Inc., Lake Mary, FL) into the Electronic Data Interface for Transplantation (EDIT) software, which melds the pathology data with other demographic, clinical, and laboratory data. The consolidated data are then represented in a convenient fashion to transplant physicians and other healthcare providers for transplant-recipient management. This system of evaluating and scoring biopsies and storing the data provided a unique opportunity to prospectively assess the clinical and biological impact of acute rejection using the Banff schema for data collected under real-life and real-time conditions during the

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past 6 years. A secondary goal was to describe the structure of our data-collection system, which should be of value in conducting outcomes-based research in transplantation.

METHODS

Patient Population

Included in this analysis were 901 adult (>18 years old at the time of transplantation) primary liver-allograft recipients who underwent liver transplantation at the University of Pittsburgh Medical Center (UPMC) and a liver-allograft biopsy between 8/12/1995 and 9/10/2001 with complete Banff grading. Nonprimary liver-allograft recipients, multiorgan allograft recipients, and patients who underwent transplantation elsewhere, but were followed at UPMC, were excluded. Using the aforementioned selection criteria, 2,038 biopsies were included in the analysis.

Most of the patients (>95%) were initially treated with intravenous tacrolimus, administered at a dose of 0.05 mg/kg per day; oral tacrolimus therapy was commenced when bowel function returned, usually between 2 and 5 days after transplantation. Patients were administered intravenously 1 g of methylprednisone at the time of transplantation with or without an additional total dose of 600 mg of methylprednisolone, tapered over the next 5 days. During this time, biopsies were liberally obtained to assess suboptimal liver function but not on a strictly temporal protocol basis. Patients with "indeterminate" grade acute rejection were not treated with increased immunosuppression. Patients with mild acute rejection were generally treated with increased immunosuppression if there were also increased liver-injury tests or a dissatisfaction clinical course that was not explained by other problems.

Pathology Workflow

All liver-allograft biopsies obtained at UPMC were reviewed initially by a general surgical pathologist (1981–1990) or a transplant pathologist (1990–present) and assigned a free-text diagnosis or diagnoses. Before August 1995, the local grading system for acute rejection was applied to 2,353 liver-allograft biopsies from 1,255 primary adult (>18 years old) hepatic allograft recipients. Our local system was based on the fundamental observation of K. A. Porter (*2*) and our own early observations (*22*), both of which were subsequently incorporated into the Banff schema for acute liver-allograft rejection (*1*). On August 12, 1995, we adopted the Banff schema for acute liver-allograft rejection, which includes a descriptive grade: none, indeterminate, mild, moderate, and severe and semiquantitative scoring (on a scale of 0–3) of the three key histopathologic findings: portal inflammation, bile duct damage, and venous subendothelial inflammation, which are used to establish the diagnosis (RAI) (*1*). The RAI is conceptually similar to the hepatitis activity index used to score the necroinflammatory activity in chronic hepatitis (*23*). In addition, the signout pathologist scored a series of 31 histologic findings using a histologic template (see *http://tpis.upmc.edu/tpis/schema/AlloLiver.html*).

One pathologist (A.J.D.) reviewed the biopsies a second time for discussion at a weekly clinicopathologic conference. At this time, the free-text diagnosis assigned by the primary pathologist was converted into "coded" diagnosis or diagnoses. This exercise simultaneously fulfilled quality assurance and creation of additional research data. Significant differences between the primary signout diagnosis and the coded diagnosis (present in <5% of cases) were resolved on an ongoing basis by a consensus review. When more than one diagnosis was entered, the most important was listed first. The majority of biopsies had two or less coded diagnoses, but up to four were allowed.

Electronic Data Interface for Transplantation

The EDIT software was designed and developed specifically for the Thomas E. Starzl Transplantation Institute at UPMC. It is a Windows-based application that functions as an information portal by interfacing with other hospital information systems and databases that store relevant information on donor and recipient demographics, laboratory tests, medications, pathology, tissue typing, and other clinical information (Fig. 1). EDIT also contains manually entered data from external sources generated during inpatient, ambulatory, or outpatient care. Standard computerized transplantation-specific forms in EDIT are based on those developed by the NIDDK-Liver Transplantation Database (*24*). EDIT contains 100 transplant-specific tables with more than 700 variables, tracking patients from initial referral through posttransplant follow-up. The EDIT portal creates a comprehensive view of the patient history and medical status from a transplant perspective, automatically downloads pertinent data to United Network Organ for Sharing for required routine follow-up and provides a reliable source of research data for clinical trials and studies. A working group comprised of surgeons, physicians, coordinators, biostatisticians, and programmers meet weekly for continuous validation, quality control, and improved functionality of EDIT.

Data Handling and Statistical Analysis

Pertinent data from EDIT was first rendered anonymous by stripping it of unique patient identifiers, according to the exempt institutional review board-approved protocol (IRB no. 020177). Laboratory values obtained on the day of, or one day before, the date of the biopsy were used to compare liver-injury tests with the primary descriptive grade and RAI component scores. During initial data review, 732 biopsies were found to have an assigned RAI score but no signout or coded diagnosis of acute rejection. The vast majority of these biopsies (>99%) had a total RAI score of less than 3, and most had recurrent viral or autoimmune hepatitis or biliary obstruction as the primary diagnosis. Therefore, according to the original guidelines in the Banff consensus document (*1*), these biopsies were reassigned a total RAI score of 0.

Summary statistics are presented as the number and percentage for categorical data and as the median and range for continuous data. Cox hazard models with time-dependent co-variates were used to examine the relationship between various outcomes and graft failure. Logistic regression was used to model risk factors for early acute cellular rejection (ACR) (<42 days) and for the effect of severe rejection on graft failure. Estimates corresponding to the risk ratios (RR) of each covariate were also obtained. The chi-square and Wilcoxon rank-sum tests were performed for analysis of categorical and lab data, respectively. *P* values of less than 0.05 were considered significant. All analyses were performed using Statistical Analysis System (version 8.0, Statistical Analysis System Institute, Inc., Cary, NC).

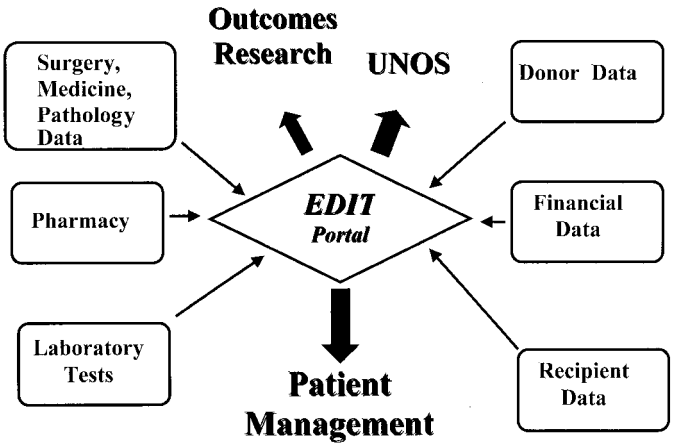

FIGURE 1. Data flow through EDIT.

RESULTS

Distribution of Acute Rejection According to Grade and Time after Transplantation and Correlation Between Descriptive Grade and Total Rejection Activity Index Score

In total, 575 of 901 (64%) patients showed evidence of any severity of acute rejection (indeterminate to severe), in any diagnosis rank, at any time after transplantation. Consequently, this number included "indeterminate" acute-rejection episodes and episodes of mild rejection, occurring in the setting of a primary diagnosis of recurrent hepatitis that is not routinely treated with increased immunosuppression. Of the patients who experienced any rejection at all, the worst grade of acute rejection on any biopsy was mild in 422 of 575 (73%). Conversely, 153 of 575 (27%) patients who developed any acute rejection after transplantation (153 of 901; 17% of all patients) experienced at least one episode of moderate or severe acute rejection. Figure 2 shows the distribution and severity of acute-rejection episodes according to the time after transplantation. Most episodes (72%) occurred within the first year after transplantation; this was especially true for moderate and severe acute-rejection episodes: 82% of these episodes occurred within the first year. Late-onset (>1 year) moderate and severe acute-rejection episodes were often associated with noncompliance with immunosuppressive drugs or inability to treat acute rejection because of a serious infection or posttransplant lymphoproliferative disorder.

Table 1 shows the distribution of the primary diagnosis descriptive grade and RAI scores for all biopsies prospectively classified according to the Banff schema. A large majority of the biopsies had a primary diagnosis other than acute or chronic rejection (n=1,458, 71.5%). Acute rejection was the primary diagnosis in 454 of 2,038 (22.3%) biopsies: indeterminate (n=85, 4.2%); mild (n=285, 14.0%); moderate (n=73, 3.6%); and severe (n=11, 0.5%). The remaining biopsies were difficult to grade because treatment was given before the biopsy was obtained (n=55, 2.7%) or there was overlap with chronic rejection (n=71, 3.5%). Another 136 of 2,038 (6.7%) biopsies received a secondary diagnosis of indeterminate (n=51, 2.5%), mild (n=67, 3.3%), moderate (n=12, 0.6%), or severe (n=6, 0.3%) acute rejection.

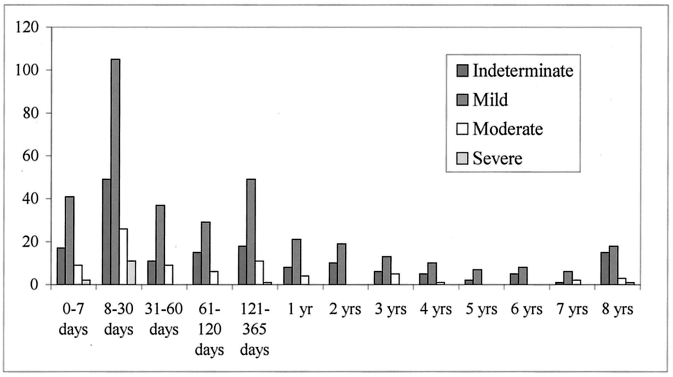

FIGURE 2. Distribution of acute-rejection episodes according to grade and time after transplantation. Most acute-rejection episodes, especially those graded as moderate or severe, occur within the first year after transplantation. Also, the first month after transplantation is a particularly important risk period for acute rejection, which is related to the mass migration of donor hematolymphoid cells into the recipient-lymphoid tissues.

The modal total RAI values progressively increased for indeterminate (2; range from 1–5), mild (3; range 1–6), moderate (5; range 2–8), and severe (6; range 3–8) acute rejection, as expected. No biopsy had a total RAI equal to 9, and RAI component scores of 3 were rare: portal inflammation (0.53%); bile duct damage (0.50%); and venous endothelial inflammation (3.0%). The majority, 363 of 491 (73.6%), of biopsies assigned a total RAI score greater than or equal to 3 had a primary-coded diagnosis of acute rejection. The higher the total RAI score, the more likely a primary diagnosis of acute rejection (Table 1).

Correlation of Banff Grade and RAI with Liver-injury Tests

Correlation of the liver-injury tests with the descriptive grading and RAI component scores showed that patients whose biopsies were graded as moderate or severe demonstrated significantly higher serum alanine aminotransferase (ALT; $P=0.007$) values, aspartate aminotransferase (AST; $P=0.07$) values, and total bilirubin levels ($P=0.05$) than patients with indeterminate or mild acute rejection (Table 2). In addition, patients with a portal inflammation or bile duct damage component score of 3 demonstrated significantly higher total serum bilirubin levels than those with a score of 0 for the same categories (Table 3). As expected, patients whose biopsies scored a 3 for bile duct damage also showed higher alkaline phosphatase (ALP) and γ-glutamyl transpeptidase values than those with lower scores (Table 3). Patients with biopsies assigned a subendothelial score of 3 showed significantly lower total bilirubin values than patients with biopsies showing less subendothelial inflammation; the same was true for alkaline phosphatase.

Correlation of Banff Grade and RAI with Architectural Changes in Subsequent Biopsies

We determined whether the subcomponent scoring of portal inflammation, bile duct damage, and venous endothelial inflammation predicted the development of portal fibrosis, bile duct loss, or central vein fibrosis, respectively, in subsequent biopsies. Patients without follow-up biopsies were excluded from this analysis. After removing from the analysis those patients who showed co-existing conditions such as hepatitis, infection, or biliary obstruction on previous biopsies, it was found that patients showing a portal inflammation score of greater than or equal to 2 were more likely to develop portal fibrosis in subsequent biopsies than patients showing none or mild portal inflammation. However, the difference in fibrosis between the two groups was mild versus none, respectively. The RAI score for bile duct damage did not correlate with subsequent bile duct loss. Patients with a venous endothelial inflammation score of greater than or equal to 2 were significantly more likely to develop central vein or perivenular fibrosis in follow-up biopsies than those with a score of 0 or 1 ($P<0.003$).

The same analysis was conducted on the grading of acute rejection. The severity of acute rejection did not correlate with subsequent bile duct loss or portal fibrosis. However, patients with moderate or severe acute rejection were significantly more likely ($P=0.005$) to develop perivenular fibrosis in follow-up biopsies than those with a grade of indetermi-

TABLE 1. Distribution of primary descriptive diagnosis (columns) and correlation with the total RAI score (rows) for all biopsies assigned complete Banff grading and scoring (Aug. 12, 1995–Sept. 10, 2001)

Total RAI score	Indeterminate N (%)	Mild N (%)	Moderate N (%)	Severe N (%)	Partially treated N (%)	Early chronic N (%)	Chronic rejection, NOS N (%)	Other, nonrejection diagnosis N (%)	Totals
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.3)	7 (24.1)	7 (16.7)	1239 (85.0)	1257 (61.7)
1	12 (14.1)	3 (1.1)	0 (0.0)	0 (0.0)	5 (9.1)	8 (26.7)	9 (21.4)	42 (2.9)	79 (3.9)
2	35 (41.2)	31 (10.9)	2 (2.8)	0 (0.0)	14 (25.5)	12 (41.4)	20 (47.6)	82 (5.6)	196 (9.6)
3	32 (37.6)	138 (48.4)	1 (1.4)	1 (9.1)	17 (30.9)	2 (6.7)	5 (11.9)	65 (4.4)	261 (12.8)
4	5 (5.9)	75 (26.3)	15 (20.5)	0 (0.0)	8 (14.6)	0 (0.0)	1 (2.4)	20 (1.3)	124 (6.1)
5	1 (1.2)	33 (11.6)	26 (35.6)	2 (11.1)	5 (9.1)	0 (0.0)	0 (0.0)	6 (0.4)	73 (3.6)
6	0 (0.0)	5 (1.8)	19 (26.0)	3 (27.3)	1 (1.8)	0 (0.0)	0 (0.0)	3 (0.2)	31 (1.5)
7	0 (0.0)	0 (0.0)	8 (11.0)	4 (36.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	13 (0.6)
8	0 (0.0)	0 (0.0)	2 (2.7)	1 (9.1)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Totals	85 (4.2)	285 (14.0)	73 (3.6)	11 (0.5)	55 (2.7)	29 (1.4)	42 (2.1)	1458 (71.5)	2038

TABLE 2. Correlation between descriptive grade of acute-cellular rejection and liver-injury tests

Liver injury test	Severity of Rejection		*P* value[a]
	Indeterminate/mild	Moderate/severe	
ALT (IU/L)			0.007
Mean (SD)	236.2 (274.2)	350.8 (364.8)	
Median (range)	162.0 (13–2,959)	203.0 (20–2,230)	
AST (IU/L)			0.07
Mean (SD)	161.5 (310.0)	230.9 (316.4)	
Median (range)	98 (7–5,706)	110 (17–2,311)	
Total bilirubin (mg/dL)			0.05
Mean (SD)	5.5 (7.5)	7.4 (5.4)	
Median (range)	2.1 (0.3–46.5)	6.4 (1.1–17.8)	

[a] Wilcoxon rank-sum test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

nate or mild (indeterminate or mild, 197 patients same or better, 47 worse; moderate or severe, 59 same or better, 31 worse). In addition, there was an increased risk of perivenular fibrosis in subsequent biopsies from the 244 patients whose worst acute rejection was mild (197 same or better, 47 worse) compared with patients without any evidence of rejection (129 same or better, 16 worse, $P=0.05$). However, the change was from none to mild in the majority (33 of 47, 70%) of patients who did develop fibrosis. Patients who developed moderate or severe perivenular fibrosis, despite the worst acute rejection being only mild, almost invariably showed co-existing conditions such as recurrent viral or autoimmune hepatitis, or steatohepatitis, which likely contributed to the fibrosis.

Correlation of Banff Grade and RAI Score with Graft Failure from Acute or Chronic Rejection

Eleven of 901 (1%) primary allografts with at least one biopsy-assigned complete Banff grading and RAI scoring failed primarily from acute or chronic rejection at a median of 434 (range 9–5802) days. Patients whose first episode of acute rejection was moderate or severe were at increased risk of graft failure from acute or chronic rejection ($P=0.004$). Cox regression analysis using time-dependent covariates showed that the venous endothelial inflammation is the RAI component most predictive ($P=0.09$) of graft failure because of acute or chronic rejection. Also, the higher the total RAI scores ($P=0.001$), the more likely the graft will fail from rejection, which is expected given the correlation between total RAI and rejection grade.

Analysis of Risk Factors

Logistic regression analysis showed that none of the following factors increased the risk of any acute rejection within 42 days after transplantation: donor race (white, black, other) or sex, recipient race or sex, preoperative diagnosis, or age; histocompatibility matching at the A, B, or DR locus or crossmatch; cold ischemic time or preoperative blood urea nitrogen (BUN), creatinine, total bilirubin, γ-glutamyl transpeptidase, ALP, ALT, or AST. However, the absence of a correlation with BUN and creatinine could be misleading because dialysis was not considered. The following factors significantly increased the risk of any acute rejection within 42 days after transplantation: donor age of greater than 30 years ($P=0.007$, no rejection mean 34.1 SD=16.7, median 29.7, range 7.8–74.7 vs. rejection within 42 days, mean=38.0±17.2, median=37.1, range=2–82.5); and preoperative prothrombin time ($P=0.08$, no rejection=15.8±3.9, median=14.7, range=11.6–45.9 sec vs. rejection, mean=16.3±4.4, median=15.5, range=9.3–64.2 sec). Modeling prothrombin time and donor age, only donor age remained significant ($P=0.006$).

Analyses were also performed to investigate the impact of the timing of the first acute-rejection episode on patient and graft survival. Using proportional hazards regression with time-dependent co-variates, both early and late (>42 days) acute rejection were significantly associated with patient and

TABLE 3. Correlation between RAI component scores and liver-injury tests

Liver injury test	RAI score=0	RAI score=3	*P* value[a]
Portal inflammation			
Total bilirubin (mg/dL)			0.05
Mean (SD)	4.9 (7.7)	8.7 (8.0)	
Median (range)	1.3 (0.5–33.8)	7.3 (1.1–28.9)	
Bile duct damage			
Total bilirubin (mg/dL)			0.02
Mean (SD)	5.3 (7.6)	8.0 (5.1)	
Median (range)	1.8 (0.3–39.9)	10.2 (1.0–13.3)	
ALP (IU/L)			0.02
Mean (SD)	196.0 (124.3)	959.5 (1,132.1)	
Median (range)	145.5 (35.0–512.0)	959.5 (159.0–1,760.0)	
GGTP (IU/L)			0.04
Mean (SD)	442.9 (623.7)	495.8 (249.1)	
Median (range)	253.5 (22–3,170)	567.0 (152–697)	
Subendothelial inflammation			
Total bilirubin (mg/dL)			0.001
Mean (SD)	8.2 (9.5)	2.6 (3.4)	
Median (range)	4.5 (0.4–36.9)	1.1 (0.3–14.7)	
ALP (IU/L)			0.04
Mean (SD)	646.8 (588.4)	392.1 (380.5)	
Median (range)	409.0 (77–1,980)	176.0 (78–1,191)	

[a] Wilcoxon rank-sum test.

SD, standard deviation; ALP, alkaline phosphatase; GGTP, γ-glutamyl transpeptidase; RAI, rejection activity index.

graft survival ($P<0.001$). Experiencing late rejection was worse than early rejection for graft ($P=0.003$, HR=1.7) and patient ($P=0.002$, HR=1.8) survival. Even after adjusting for baseline donor and recipient characteristics, such as age, sex, race, and preoperative diagnosis, similar results were obtained.

Because the earlier analyses showed that moderate and severe acute rejection are the most clinically relevant form of acute rejection, we also undertook an analysis of risk factors for this complication. Univariate risk factors for those whose first rejection episode was moderate or severe were younger recipient age ($P=0.01$) and female donors ($P=0.06$). None of the other risk factors listed earlier placed the patient at increased risk of moderate or severe acute rejection. Multivariate regression showed that for those people whose first acute-rejection episode was moderate or severe, recipient age ($P=0.04$) and female donor ($P=0.05$) remained significant.

DISCUSSION

This study illustrated the feasibility of applying systematic data entry to prospectively evaluate the utility of a histopathologic grading system for allograft rejection, in contrast to most retrospective studies (*2–4*,*6–11*,*13–15*,*22*, *25*,*26*). It is our opinion that the method described in this article offers a more robust test of a histopathologic grading scheme, because the data were collected on an ongoing basis and none of the outcome measures were known at the time of biopsy review.

Successful application of systematic workflow approach for prospectively evaluating the utility of a pathology grading schema requires: (1) capture key histopathology findings and diagnosis in a digital format; (2) software that collects and melds the pathology, demographic, clinical, and laboratory data; (3) ongoing quality control efforts; and (4) biostatistical expertise to analyze the data. The first of these requirements is most efficiently achieved by instituting a histopathologic template into the workflow (see *Methods*) and coding or categorization of diagnoses into a predetermined list of possibilities. The pathologist also may enter free text in the surgical pathology report diagnosis and in an uncensored comment field.

Creating and capturing digital pathology data during routine patient care offers several distinct advantages. It enables busy service physicians to simultaneously perform patient care and service work and prospective outcomes-based research, which obviates the need for, but does not preclude, retrospective "re-review" of slides. The digital pathology database also can be used to correlate biopsy findings and diagnoses with assessment of tissue samples by gene arrays or proteomics.

The software used for this study, EDIT, is the result of more than a decade of interdisciplinary collaboration between transplant surgery, medicine, pathology, and biostatisticians within the Starzl Transplant Institute, combined with considerable resource allocations for development of the program. Most of the EDIT data is electronically retrieved, although some hand-entry is required. Stripping the entire population or subpopulations of unique patient identifiers can be used to create a research database. Data managers who generate these research databases serve as "honest brokers" to satisfy Institutional Review Board requirements for patient confidentiality. Most important is not the particular software but the creation of digital patient data (instead of analog free-text information), which can be melded into a single resource for patient management and outcomes-based research (*24*,*27*).

Prospective data entry using a standard template for histologic findings and routine application of the Banff schema enabled us to prospectively examine the utility of the system and the impact of acute cellular rejection on graft function, structure, and survival during the last 6 years at UPMC. The results showed that most episodes of acute liver-allograft rejec-

tion are mild and do not result in clinically significant structural sequelae. Similar to other recent large studies, rejection rarely caused liver-allograft failure (*27–30*), as originally noted after careful review of the first large clinical series by Starzl et al. (*31*). Young recipients of female donors are at increased risk of moderate or severe acute rejection, which are uncommon but associated with higher liver-injury tests, and increased risk of developing perivenular fibrosis in subsequent biopsies and allograft failure (*12,13,27*). We also found that late onset was more deleterious than early-onset acute rejection (*32*), which is at least partially attributable to the inability to treat some late acute-rejection episodes because of potentially fatal immunosuppression-related complications.

An unexpected finding in this study is that severe bile-duct damage (score of 3) correlated with higher ALP and γ-glutamyl transpeptidase levels but did not predict bile-duct loss in subsequent biopsies. This observation is probably attributable to the low incidence of bile-duct loss and rarity of chronic rejection in tacrolimus-treated cohorts (*33,34*) and the relative "duct sparing" properties of tacrolimus immunosuppression (*34,35*). In this study, perivenular fibrosis (a consequence of acute rejection first recognized by Starzl et al. (*36*) in long-surviving canine liver-allograft recipients) replaced bile-duct loss as the most common, but still relatively infrequent, architectural complication of acute rejection. Although the clinical significance and natural history of perivenular fibrosis has yet to be rigorously examined, ascites attributable to this lesion was not a common complication in this cohort. Regardless, this study clearly shows that acute rejection has a much less significant impact on liver-allograft structure and function compared with kidney and heart allografts, and the Banff schema is able to identify those few liver-allograft recipients who are potentially at risk for developing clinically significant rejection-related complications.

Similar to native livers suffering from a variety of insults (*37,38*) once the immunological damage of acute rejection is controlled or removed, the majority of liver allografts recover and heal without significant fibrosis (*35,39–41*). Even if the acute-rejection episode is moderate or severe, only one of three of these patients will develop perivenular fibrosis in subsequent biopsies. Continued follow-up will show improvement or resolution of the fibrosis in some of these patients, although sampling errors cannot be excluded as a possible explanation for the improvement. In contrast, the regenerative capacity of renal or heart allografts is more limited than liver allografts; even mild acute-rejection episodes often heal by fibrosis, leading to a linear decline of structure and function that eventually evolves into chronic rejection (*42–44*). Thus, the regenerative and healing characteristics of liver allografts nicely complement the tolerogenic properties of liver allografts (*45*), which together account for the rarity of transition from acute to chronic rejection compared with nonhepatic allografts. Previous studies have shown that acute rejection-associated fibrogenesis also is significantly influenced by baseline immunosuppression (*34,35,40*). Perhaps perioperative administration of growth factors could be used to make kidneys react more like liver allografts during the critical early time after transplantation (*46*).

CONCLUSION

Although the findings and conclusions that this article reports are remarkably similar to the early clinical experience reported by Starzl et al. in 1976 (*31*), it is useful to interpret them in the context of current initiatives to induce clinical tolerance (*47,48*). We speculate that liver-allograft recipients may be the ideal population to safely test protocols geared toward preoperative T-cell depletion and minimal-use immunosuppression after transplantation for the following reasons (*49–53*). First, clinically significant acute rejection is an uncommon but manageable problem; it can be safely monitored by liver biopsies and reversed pharmaceutically. Studies of conventionally treated liver-allograft recipients showed that a small percentage of mild acute-rejection episodes will resolve spontaneously (*27,54*), similar to observations in experimental animal models (*36,55,56*). Second, if pretransplant T-cell depletion strategies are incomplete, the graft itself can further contribute to T-cell depletion (*55*). Third, an objective endpoint of complete withdrawal of immunosuppression without undue risks could be reasonably expected (*36,57–59*). Fourth, the "robustness" of the tolerance would be challenged by the high rate of original disease recurrence in liver allografts. It will be interesting to determine whether tolerance-inducing strategies that rely on "hiding" the graft from the immune system will be conceptually at odds with the hypothesis that ongoing communication between the graft and immune system is necessary for true tolerance or chronic rejection-free allograft acceptance in an antigenically challenging environment (*60*).

One shortcoming of the Banff schema is the lack of an algorithm for dealing with acute rejection manifest primarily or exclusively as perivenular or subendothelial inflammation of the hepatic venules. This finding, also known as *central venulitis* or *central perivenulitis*, is recognized as a manifestation of acute rejection (*16,61–64*), but only some of these patients will require treatment. Because we have shown that such findings can be associated with the development of perivenular fibrosis in subsequent biopsies, consideration should be given to appropriate treatment. However, more study on the natural evolution of this lesion is required.

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