# Banff Schema for Grading Liver Allograft Rejection: An International Consensus Document

AN INTERNATIONAL PANEL **COMPRISED OF** ANTHONY J. DEMETRIS, KENNETH P. BATTS, AMAR P. DHILLON, LINDA FERRELL, JOHN FUNG, STEPHEN A. GELLER, JOHN HART, PEKKA HAYRY, WALTER J. HOFMANN, STEPHAN HUBSCHER, JOSEF KEMNITZ, GEORGE KOUKOULIS, RANDALL G. LEE, KLAUS J. LEWIN, JURGEN LUDWIG, ROD S. MARKIN, LIDIJA M. PETROVIC, M. JAMES PHILLIPS, BERNARD PORTMANN, JORGE RAKELA, PARMJEET RANDHAWA, FINN P. REINHOLT, MICHEL REYNÈS, MARIE ROBERT, HANS SCHLITT, KIM SOLEZ, DALE SNOVER, EERO TASKINEN, SWAN N. THUNG, G. WELDON TILLERY, RUSSELL H. WIESNER, D. G. DEREK WIGHT, JAMES W. WILLIAMS, and HIROHIKO YAMABE

**A panel of recognized experts in liver transplantation pathology, hepatology, and surgery was convened for the purpose of developing a consensus document for the grading of acute liver allograft rejection that is scientifically correct, simple, and reproducible and clinically useful. Over a period of 6 months pertinent issues were discussed via electronic communication media and a consensus conference was held in Banff, Canada in the summer of 1995. Based on previously published data and the combined experience of the group, the panel agreed on a common nomenclature and a set of histopathological criteria for the grading of acute liver allograft rejection, and a preferred method of reporting. Adoption of this internationally accepted, common grading system by scientific journals will minimize the problems associated with the use of multiple different local systems. Modifications of this working document to incorporate chronic rejection are expected in the future. (HEPATOLOGY 1997;25:658-663.)**

The success of hepatic transplantation has resulted in its widespread use for treatment of many patients with endstage liver disease; it is currently offered by more than 100 centers worldwide. One-year survival rates range from 70% to 90%; and long-term survival of 50% to 60% of patients is not uncommon.[1] Therefore, an increasing number of physicians, including pathologists, many of whom have no specific training in transplantation biology, will become involved in the care of organ allograft recipients.

Despite the good short-term and acceptable long-term survival after hepatic transplantation, the morbidity associated with long-term immunosuppression is significant and rejection remains a persistent, but usually manageable, problem. Clinical research to improve patient survival and lessen morbidity is, therefore, inherent to the clinical practice of hepatic transplantation. Because patient follow-up and successful application of developments could be simplified by a common scale of recognizing, naming, and grading the severity of acute liver allograft rejection, members of an international consensus panel recently agreed upon a common nomenclature and set of definitions.[2] The group next agreed to create an internationally acceptable grading system, which has already been developed for kidney,[3] heart,[4] and lung.[5] At the Third Banff Conference on Allograft Pathology, a group of specialists in liver transplantation from North America, Europe, and Asia met for this purpose.

## DEFINITION OF ACUTE REJECTION

In general, organ allograft rejection can be defined as, "an immunological reaction to the presence of a foreign tissue or organ, which has the potential to result in graft dysfunction and failure."[2] This report is specifically concerned with acute rejection, recently defined by the international consensus document on terminology for hepatic allograft rejection[2] as, "inflammation of the allograft, elicited by a genetic disparity between the donor and recipient, primarily affecting interlobular bile ducts and vascular endothelia, including portal veins and hepatic venules and occasionally the hepatic artery and its branches."[2] Early rejection, cellular rejection, nonductopenic rejection, rejection without duct loss, and reversible rejection are synonyms for acute rejection that appear in the literature, but their use is discouraged. The general clinical, laboratory, and histopathological abnormalities listed below were derived from the international consensus document.[2]

## CLINICAL AND LABORATORY FINDINGS

Viewed from a biological perspective, any recipient's immune system will likely be perturbed after transplantation, resulting in immune activation.[2] However, viewed from a clinical perspective, because of baseline immunosuppressive therapy only some recipients manifest clinical symptoms of allograft recognition with, in the case of liver transplantation, liver biochemical abnormalities (most often), or frank hepatic dysfunction.[2] Therefore, it is important to distinguish between "biological" and "clinically relevant" rejection. The latter may require additional immunosuppressive treatment, although the distinction is not always achievable and treatment philosophies differ at various centers. This is particularly true for hepatic allografts, which are widely acknowledged to be unique. They are more resistant than others to humoral rejection, and are accepted without immunosuppressive therapy in some small and large experimental animal species. Of potential importance for human transplantation is the observation that in all animals in which a liver allograft is eventually accepted without drugs, the allograft undergoes a transient acute rejection crisis.[6-9] Thus, it should be understood that the histopathological diagnosis of acute rejection may not automatically signal that treatment is indicated, particularly if it is low grade. Adoption of a standardized histopathological grading system possibly could help determine if, and at what point, the histopathological severity of rejection can predict the need for, and success of antirejection

Abbreviations: RFH, Royal Free Hospital; RAI, rejection activity index.

From the Department of Pathology—Division of Transplantation, University of Pittsburgh Medical Center, Pittsburgh, PA.

Received February 9, 1996; accepted October 17, 1996.

Address reprint requests to A. J. Demetris, M.D., Director, Division of Transplant Pathology, University of Pittsburgh Medical Center, E1548 Biomedical Science Tower, Pittsburgh, PA 15261.



0270-9139/97/2503-0028$3.00/0

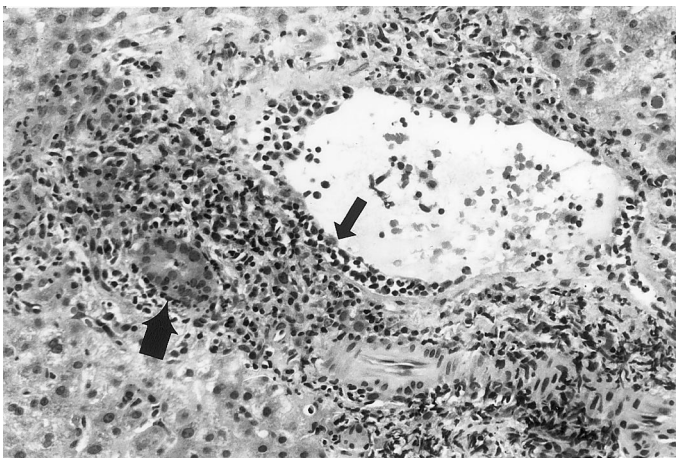

FIG. 1. Grading of acute rejection assumes the diagnosis has already been established: this portal tract shows all three of the typical histopathological features, two of which are required to make the diagnosis. There is: 1) a portal inflammatory infiltrate containing blastic lymphocytes and eosinophils; 2) subendothelial localization of the inflammatory cells in a portal vein branch (small arrow), and 3) inflammation and damage of small bile ducts (large arrow). If the subendothelial inflammation similar to this was present in most or all of the portal and/or hepatic venules, an RAI score of 2 for venous endothelial inflammation would be assigned.

therapy (see "Clinicopathological Correlation and Treatment of Acute Rejection").

When clinically apparent, acute rejection is usually first recognized between 5 and 30 days after transplantation. Earlier or later presentations can be seen in patients that receive less than therapeutic baseline immunosuppression. The clinical findings in early phases of mild acute rejection are often absent, although in late or severe cases, clinical findings include fever as well as swelling, cyanosis, and tenderness of the allograft. Bile often becomes pale in color and the flow is decreased. Occasionally, ascites develops because of liver swelling with increased intrahepatic pressure.[2]

Liver dysfunction, when present, usually manifests as concomitant nonselective elevations of the results of some or all of the standard liver injury tests, including total bilirubin, alanine aminotransferase, aspartate aminotransferase, $\gamma$-glutamyl transpeptidase, and alkaline phosphatase.[2] Leukocytosis and eosinophilia are also frequently present. Unfortunately, all clinical and laboratory findings lack sensitivity or specificity. The diagnosis is considered on clinical grounds and confirmed by examination of a core needle biopsy specimen. Some centers find that fine-needle aspirates of the allograft are useful adjunct.

## HISTOPATHOLOGIC FINDINGS

Most investigators have observed similar histopathological findings associated with acute rejection.[10-22] Core needle biopsy specimens may show the following: 1) mixed but predominantly mononuclear portal inflammation, containing blastic (activated) lymphocytes, neutrophils, and frequently eosinophils; 2) bile duct inflammation/damage; and 3) subendothelial inflammation of portal veins or terminal hepatic venules.[2] At least two of these three features are required for a histopathological diagnosis of acute rejection (Fig. 1 ). Biochemical evidence of liver damage manifests as increased results of tests for liver injury, usually elevation of serum $\gamma$-glutamyl transpeptidase and alkaline phosphatase activities, are also frequently present. The diagnosis is strengthened if $> 50\%$ of the ducts are damaged or if unequivocal endotheliitis of portal vein branches or terminal hepatic venules can be identified. Occasional cases show mild mononuclear inflammation of the perivenular regions with only focal portal tract changes. Additional findings such as ductopenia, spillover/piecemeal necrosis, eosinophilia, lobular inflammation, perivenular necrosis, arteritis, and inflammatory bridging, have been used in some systems for histopathological grading (see below).

Treatment of acute rejection with additional immunosuppression before a biopsy specimen is obtained may make the histopathological diagnosis more difficult, because of subsequent loss of the subendothelial infiltration of veins and of eosinophils, and a relative decrease in the number of mononuclear inflammatory cells.

## GRADING OF ACUTE LIVER ALLOGRAFT REJECTION (CRITIQUE OF CURRENTLY POPULAR SYSTEMS)

The panel reviewed each system and agreed that the consensus scheme should fulfill the following criteria: scientific correctness, clinical relevance, simplicity, and reproducibility. They also recognized the need for flexibility and future modifications and therefore proposed a working formulation format for the current document.

The grading system used in Pittsburgh[23] is derived from those developed for kidney allograft.[24] It is based on the concept that serious injury from rejection is related to vascular compromise and ischemia, which can morphologically manifest as inflammatory or necrotizing arteritis and/or parenchymal necrosis and hemorrhage. The grading system developed in Minnesota by Snover et al.[19] is more specific to the liver and is based on a combination of an estimate of the severity of the inflammation and the presence and severity of damage or loss of key structures targeted for injury, such as the arterial vasculature or bile ducts. The above two systems have the advantage of simplicity[19, 23] and rely on pathophysiological concepts validated in renal transplantation. Prognostic significance has been shown at a single center.[19] Unfortunately, some of the features used in these schemes to define severe rejection are rarely found, poorly reproducible, or present so frequently in nonrejection complications that their usefulness in grading scheme is limited.[25] For example, while inflammatory or necrotizing arteritis[19, 23] represents a serious injury to the allograft, reproducibly identifying it in core needle biopsies is problematic.[25] In contrast, ballooning of perivenular hepatocytes[19] is frequently present in nonrejection graft syndromes and may not imply serious graft injury from an immunological insult. Bile duct loss, which has also been used to identify severe acute rejection more accurately reflects chronic rejection and possibly, a stage rather than a grade of rejection.

Kemnitz et al.[20,26] have devised a scheme similar to those mentioned above. However, increased emphasis is placed on precise numerical estimates of lobular injury, such as the percentage of necrosis, which may be difficult to reproduce and may not necessarily reflect rejection-related injury. Moreover, none of the systems was tested for reproducibility.

The European grading system for acute liver allograft rejection, developed by Hubscher and Dousset et al. at Birmingham[27-29], is based on a semiquantitative analysis of the diagnostic triad of Snover et al.[18] In this system, portal inflammation, bile duct damage, and venous endothelial inflammation are each graded semiquantitatively on a scale of 0 (absent) to 3 (severe). The individual scores are then added to produce an overall rejection score of 0 to 9, which is then converted to a rejection grade as follows: 0 to 2 = no rejection, 3 = borderline (consistent with), 4 to 5 = mild, 6 to 7 = moderate, and 8 to 9 = severe acute rejection. This system offers the attractive feature of quantifying the necro-inflammatory activity, as has recently become popular in the reporting and follow-up of patients with chronic hepatitis.[30-33] It also shows a good correlation between histological severity and clinical biochemical signs of graft dysfunction.[29] However, no obvious prognostic value has been shown.

The Royal Free Hospital, London (RFH) grading system[34] consists of a semiquantitative assessment of the diagnostic features of rejection, defined as immunosuppression responsive inflammation of rejection type, and identified by discriminant analysis. Mixed portal inflammation, eosinophils, endotheliitis, and bile duct damage were found to be independent, statistically significant contributors to the histological diagnosis of acute rejection. Each of the features are scored on a scale of 0 to 3, as in the European grading system, and a total score is derived by adding the individual scores together. Apart from the inclusion of eosinophils, which are of known diagnostic[35,36] and pathophysiological significance[37,38] as a separate variable in the RFH scheme, it is virtually identical to the European grading system. Like the European system, the RFH system offers a quantitative scale for the rejection-related activity, and is reproducible at the home institution.[34] However, neither the European system, nor the RFH system has been shown to have prognostic significance and the numerical cutoff points corresponding to the different degrees of rejection (and consequent therapeutic thresholds) need to be validated. In addition, there are no studies of inter-institutional scoring reproducibility.

The recently published scheme by the National Institute of Diabetes and Digestive Diseases and Kidney Diseases[39] had the advantages of being reproducible with prognostic significance documented at several centers. Unfortunately, the imprecise language used to explain the cutoffs for moderate and severe rejection makes the system difficult to follow, even for those experienced in the field.

## INTERNATIONAL GRADING SYSTEM FOR ACUTE LIVER ALLOGRAFT REJECTION (RECOMMENDATIONS OF THE PANEL)

***Grading of Rejection.*** The grading of rejection, as with hepatitis,[33] is a measure of the severity of the necro-inflammatory process. In addition, because rejection is more vasculocentric and vasculodestructive than hepatitis, some estimate of vascular or ischemic damage is needed to assess the full extent of the insult. This can be accomplished either by a global assessment of the biopsy using a "gestalt"[25] approach, or semiquantitatively with the assignment of numerical scores to different histopathological parameters. No data support one approach over the other, and in practice the two methods yield similar results (see below). Moreover, the semiquantitative approach could complement the global assessment by offering a greater degree of precision, by forcing the pathologist to critically evaluate important histopathological features. Conversely, the global approach can temper the semiquantitative analysis in cases with active inflammation and high scores, in which there is little architectural damage.

The panel agreed that existing grading systems for acute liver allograft rejection are conceptually similar, and that like chronic hepatitis, frequent monitoring and reporting of disease activity is an important function of biopsy analysis.[30-33] Therefore, in coming to a consensus, the panel drew upon the strengths, hopefully avoided the pitfalls, and corrected the weaknesses of the currently available grading systems. Portal inflammation, bile duct damage, subendothelial inflammation of portal veins, and terminal hepatic venules, strictly defined inflammatory or necrotizing arteritis and eosinophils (in the proper context) are features that the panel members regard as diagnostic of acute rejection. Portal inflammation, bile duct damage, strictly defined arteritis, and possibly confluent perivenular necrosis associated with perivenular inflammation are features that may also have prognostic significance, based on previous publication,[19,39] or personal experience. However, arteritis, as well as other findings such as bile duct loss, interstitial hemorrhage, and perivenular necrosis without inflammation are not included in the scheme, because they are poorly reproducible findings, considered to be part of chronic rejection, or also encountered frequently in nonrejection-related complications, respectively. If strictly defined arteritis can be shown to be a reproducible observation and present in more than a rare case, the current system can be modified to include it.

**TABLE 1. Grading of Acute Liver Allograft Rejection**

| Global Assessment* | Criteria |
|---|---|
| Indeterminate | Portal inflammatory infiltrate that fails to meet the criteria for the diagnosis of acute rejection (see text) |
| Mild | Rejection infiltrate in a minority of the triads, that is generally mild, and confined within the portal spaces |
| Moderate | Rejection infiltrate, expanding most or all of the triads |
| Severe | As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis |

NOTE. Global assessment of rejection grade mode on a review of the biopsy and after the diagnosis of rejection has been established.

* Verbal description of mild, moderate, or severe acute rejection could also be labeled as Grade I, II, and III, respectively.

Being aware of the need for acceptability and thus simplicity, the panel agreed on a verbal grading of acute rejection based on the overall appearance of the biopsy according to the criteria listed in Table 1 (Fig. 2). It should be re-emphasized however, that any grading of acute rejection already presupposes that the diagnosis has been established. For example, use of the "indeterminate" category of acute rejection should be restricted to cases that have minor degrees of cellular infiltration that could possibly represent low grade or early acute rejection, but fail to meet the minimal diagnostic criteria. "Indeterminate" should not be used for cases in which one is unsure whether the inflammation is related to some other condition, such as chronic hepatitis C (see Complicating Conditions). After the global assessment, three specific features, portal inflammation, bile duct inflammation/damage, and venular inflammation, can be more critically evaluated and semiquantitatively scored on a 0 to 3 (mild, moderate, and severe) scale, according to the criteria listed in Table 2. The three are then added together to arrive at a final Rejection Activity Index (RAI) (Table 2), similar to the scoring developed for chronic hepatitis.[30-33] Modifications of the above system [19, 22, 29, 39] were made to arrive at a consensus scheme, so that features given the highest scores on the semi-quantitative analysis were the same as those shown to be of prognostic significance using the overall approach.

Potential problems using this method however, include: 1) the global assessment of rejection may under or overestimate the severity based on a semi-quantitative analysis and 2) the greater degree of "precision" achieved semiquantitatively may occur at the expense of reproducibility. We think that these pitfalls are unlikely to occur because both processes measure the same parameters or endpoints. Moreover, evaluation of a series of 50 posttransplantation liver allograft biopsy specimens using both methods by one of us (AJD) showed no significant differences between the systems. The reproducibility of the semiquantitative analysis will be the subject of future study by this group. The RAI, like other semiquantitative assessments of necro-inflammatory activity, is particularly attractive when evaluating new drugs or other treatment protocols and for comparison with previous biopsy specimens. Thus, it will be most valuable at academic centers involved with new developments in the field. Although strongly recommended for routine patient care, it is not required for day-to-day use if the pathologist chooses otherwise.

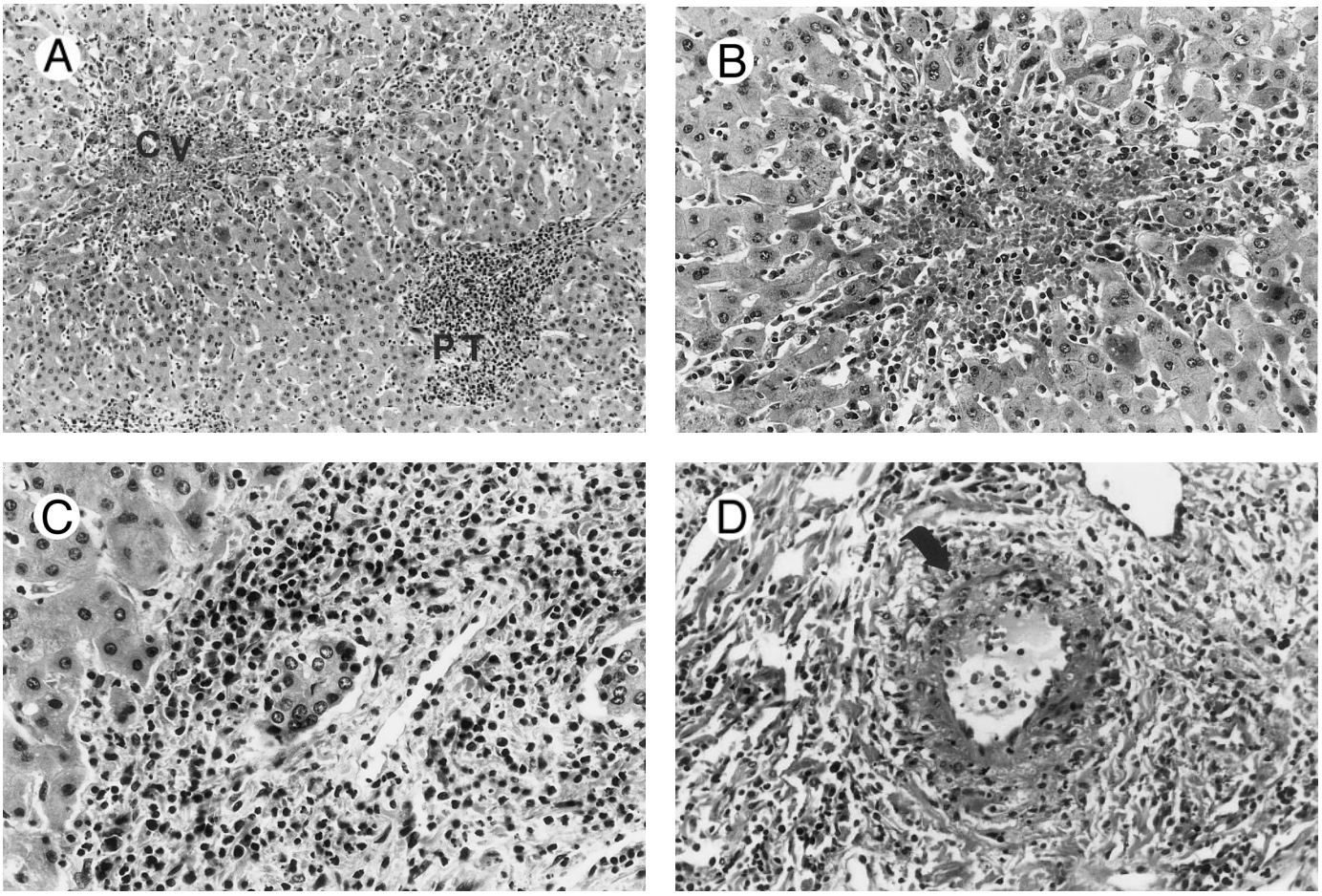


FIG. 2. (A) Low power photomicrograph of a failed liver allograft with severe acute rejection. Note the prominent portal tract (PT) and central vein (CV) inflammation, associated with confluent perivenular necrosis, which is shown at a higher magnification in (B). These findings would elicit a diagnosis of severe acute rejection. (C) In the same liver allograft, the bile duct inflammation and damage was widespread, and there was focal lumenal disruption, eliciting an RAI score of 3 for bile duct damage (Table 2). Both the portal and venous endothelial inflammation were also scored as severe, or "3," resulting in a total RAI score of 9/9. (D) Sections from the hilum of this failed allograft also revealed clear cut necrotizing arteritis (arrow), which is rarely detected with certainty in needle biopsies.

***Staging of Rejection.*** Staging of a biological phenomenon is performed in an attempt to codify a process that is largely unidirectional and evolves in a predictable pattern over a relevant period of time. Acute liver allograft rejection is, for the most part, widely considered to be a completely reversible phenomenon. In the uncommon event of allograft failure from acute rejection, the evolution is relatively rapid. Therefore, acute rejection is not readily amenable to staging. Chronic rejection on the other hand, usually evolves more slowly and is often, but not always,[40,41] unidirectional or irreversible. At this time it is not clear whether acute and chronic rejection represent the ends of a spectrum of alloreactivity, or if they are completely different biological processes. Considerable data suggest the former, because both processes appear to be triggered by alloreactivity, and persistent or severe acute rejection can result in allograft failure from chronic rejection.

***Clinicopathological Correlation and Treatment of Acute Rejection.*** As alluded to in the introductory sections, the histopathological diagnosis of acute rejection does not necessarily imply that the rejection is clinically significant or requires treatment with increased immunosuppression. In fact, Schlitt et al.[42] have shown that up to 40% of patients in whom a biopsy shows acute rejection, according to the criteria of Snover et al.[18,19] did not have clinically apparent graft malfunction or significant elevations of results of liver injury tests, and did not require additional immunosuppressive therapy. Similar conclusions were also reached in a study from Birmingham, in which 70% of histologically mild rejection episodes received no additional immunosuppression, without any adverse outcome.[28,29] A survey of the panel members showed no clear-cut consensus on the therapeutic approach to mild acute rejection (RAI $\leq$ 4) as defined in this report. In contrast, most centers report that patients with histopathological moderate or severe rejection (RAI $\geq$ 6) experience significant elevations of liver injury tests and the vast majority probably should, and usually are treated with additional immunosuppression. At present, no therapeutic recommendations can be inferred from the mild acute rejection grade, although some centers have exercised the option of routinely obtaining a follow-up biopsy after 1 to 2 weeks.

***Complicating Conditions.*** Liver allografts are frequently affected by more than one condition. In the first few weeks after transplantation, preservation-related changes and mechanical problems with the vascular and/or biliary tree are the conditions that most commonly co-exist with acute rejection. Separation of the necro-inflammatory and ischemic damage of rejection from the same type of nonrejection insults is at times problematic, but achievable for the most part. For example, perivenular necrosis can occur in both preservation injury and severe rejection. However, the concomitant presence of mononuclear perivenular inflammation, portal changes of rejection, and absence of perivenular necrosis in a prior biopsy, are features that help to distinguish between the two. In contrast, more than several months after

**TABLE 2. Rejection Activity Index**

| Category | Criteria | Score |
|---|---|---|
| Portal Inflammation | Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads | 1 |
| | Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils | 2 |
| | Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma | 3 |
| Bile Duct Inflammation Damage | A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells | 1 |
| | Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium | 2 |
| | As above for 2, with most or all of the ducts showing degenerative changes or focal lumenal disruption | 3 |
| Venous Endothelial Inflammation | Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules | 1 |
| | Subendothelial infiltration involving most or all of the portal and/or hepatic venules | 2 |
| | As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis | 3 |

NOTE. Total Score = Sum of Components. Criteria that can be used to score liver allograft biopsies with acute rejection, as defined by the World Gastroenterology Consensus Document.

transplantation, chronic viral hepatitis and recurrence of autoimmune chronic inflammatory disorders pose considerable difficulties in differential diagnosis and with grading or scoring of rejection related activity.

The problem of differentiating duct damage associated with complicating conditions such as viral hepatitis C from that seen in acute rejection can be minimized by applying strict diagnostic criteria: damage of more than an occasional bile duct, the presence of unequivocal endotheliitis, and absence of significant lobular disarray and necro-inflammatory activity favor a diagnosis of acute rejection. However, problematic cases will still be encountered, and implicit in any grading scheme for acute rejection (including this one), is the notion that grading can be reliably applied to biopsies only when rejection is thought to be the sole or predominant cause of graft damage. Therefore, in cases where other causes of cellular infiltration are suspected, neither the overall grade nor the scores can be reliably applied. In such cases, it is left to the judgment of the pathologist whether apportioning the necro-inflammatory activity to rejection or other concurrent conditions is appropriate.

## CONCLUSIONS AND RECOMMENDATION

Although the adequacy of any particular biopsy is ultimately left to the judgment of the pathologist, the panel recommends that at least two hematoxylin and eosin stained sections from at least two different levels, of a core needle biopsy containing at least five triads be examined. The adequacy of the biopsy in the absence of any diagnostic findings when fewer than five portal tracts are identified, is again left to the pathologist's judgment.

The following format for the grading and reporting of acute liver allograft rejection is recommended, although all of this information is not needed in every case. The type of specimen and time after transplantation, if available, should be listed first. This is followed by the histopathological diagnosis(es). Although not necessary, some pathologists may prefer to list first the diagnosis perceived to be of greatest significance, followed by the second most important, and so forth. However, a comment on the presence or absence of acute rejection should be given for every biopsy, either in the diagnosis or comment section. This is followed by reporting of an RAI. The presence of chronic injury, such as bile duct loss or obliterative arteriopathy should also be listed. Lastly, a comparison with the most recent previous biopsy should be made if the pathologist feels that such a comparison is warranted. The following are several examples:

1. Liver allograft, needle biopsy (7 days posttransplantation)
   (a) Moderate preservation injury
   (b) No evidence of rejection (RAI = 0)
   (c) No previous biopsy for comparison
2. Liver allograft, needle biopsy (10 days posttransplantation)
   (a) Acute rejection, moderately active (RAI = 7)
   (b) Significantly worse than previous biopsy (S95-999 of 02/06/95{RAI = 2})
3. Liver allograft, needle biopsy (10 weeks posttransplantation)
   (a) Acute hepatitis, viral type C
   (b) No rejection (RAI = 0)
4. Liver allograft, needle biopsy (18 months posttransplantation)
   (a) Chronic hepatitis, viral type B, moderately active (HAI = 14)
   (b) Acute rejection, mildly active (RAI = 4)
   (c) Duct loss in 5/9 portal triads, suggestive of chronic rejection

We believe that this system will be easy to use and useful for physicians caring for allograft recipients. There already are data available to suggest that it will be both reproducible and have prognostic significance,[39] yet flexible enough to incorporate future development like the inclusion of chronic rejection or staging of rejection. We urge scientific journals to adopt this reporting system, classification, and grading of liver allograft rejection, to overcome the obstacles presented by the multiple schemes that currently exist and facilitate comparisons among different centers.

## REFERENCES

1. Belle SH, Beringer KC, Detre K. Trends in liver transplantation in the United States 1993. In: Terasaki PI, Cecka JM, eds. Clinical Transplants. Los Angeles: UCLA Tissue Typing Laboratory, 1994: 19-36.
2. International Working Party. Terminology for hepatic allograft rejection. HEPATOLOGY 1995;22:648-654.
3. Solez K, Axelsen RA, Benediktsson B, Burdick JF, Cohen AH, Colvin RB, Croker BP, et al. International standardization of nomenclature and criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology. Kidney Int 1993; 44:411-422.
4. Billingham ME, Cary NRB, Hammond ME, Kemnitz J, Marboe C, McAllister HA, Shover DC, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection. Heart rejection study group. J Heart Transplant 1990;9:587-593.
5. Yousem SA, Berry GJ, Brunt EM, Chamberlain D, Hruban RH, Sibley RK, Stewart S, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection. Lung rejection study group. J Heart Transplant 1990;9:593-601.
6. Starzl TE. Experience in Hepatic Transplantation. Philadelphia: Saunders, 1969.
7. Calne RY, Sells RA, Pena JR, Davis DR, Millard PR, Herbertson BM,

Binns RM, et al. Induction of immunological tolerance by porcine liver allografts. Nature 1969;233:472-474.
8. Kamada N. The immunology of experimental liver transplantation in the rat. Immunology 1985;55:369-389.
9. Qian S, Demetris AJ, Murase N, Rao AS, Fung JJ, Starzl TE. Murine liver allograft transplantation: tolerance and donor cell chimerism. HEPATOLOGY 1994;19:916-924.
10. Porter KA. Pathology of the orthotopic homograft and heterograft. In: Starzl TE, ed. Experience in Hepatic Transplantation. Philadelphia: Saunders, 1969:422-471.
11. Portmann B, Wight DGD: Pathology of liver transplantation. In: Calne RY, ed. Liver Transplantation, 2nd ed. London: Grune & Stratton, 1987: 435-470.
12. Wight DGD: Pathology of liver transplantation. In: Calne RY, ed. Liver Transplantation. London: Grune & Stratton, 1983:247-277.
13. Eggink HF, Hofstee N, Gips CH, Krom RAF, Houthoff HJ. Histopathology of serial graft biopsies from liver transplant recipients: liver homograft pathology. Am J Pathol 1984;114:18-31.
14. Vierling JM, Fennell RH, Jr. Histopathology of early and late human hepatic allograft rejection. Evidence of progressive destruction of interlobular bile ducts. HEPATOLOGY 1985;4:1076-1082.
15. Williams JW, Peters TG, Vera SR, Britt LG, van Voorst SJ, Haggitt RC. Biopsy-directed immunosuppression following hepatic transplantation in man. Transplantation 1985;39(6):589-596.
16. Hubscher SG, Clements D, Elias E, McMaster P. Biopsy findings in cases of rejection of liver allograft. J Clin Pathol 1985;38:1366-1373.
17. Demetris AJ, Lasky S, Van Thiel DH, Starzl TE, Dekker A. Pathology of hepatic transplantation: A review of 62 adult allograft recipients immunosuppressed with a cyclosporine/steroid regimen. Am J Pathol 1985;118(1): 151-161.
18. Snover DC, Sibley RK, Freese DK. Orthotopic liver transplantation: a pathologic study of 63 serial liver biopsies from 17 patients with specific reference to the diagnostic features and natural history of rejection. HEPATOLOGY 1984;4:1212-1222.
19. Snover DC, Freese DK, Sharp HL, Bloomer JR, Najarian JS, Ascher NL. Liver allograft rejection. An analysis of the use of biopsy in determining outcome of rejection. Am J Surg Pathol 1987;11(1):1-10.
20. Kemnitz J, Ringe B, Cohnert TR, Gubernatis G, Choritz H, Georgii A. Bile duct injury as part of diagnostic criteria for liver allograft rejection. Hum Pathol 1989;20:132-143.
21. Reynes M. Anatomie pathologique du greffon hepatique in Transplantation d'organes et greffes de tissus. In: Herve P, Riffle G, eds. Paris-London: J Libbey, 1996:(in press).
22. Hubscher SG. Pathology of liver allograft rejection. Transplant Immunol 1994;2:118-122.
23. Demetris AJ, Qian SG, Sun H, Fung JJ. Liver allograft rejection: an overview of morphologic findings. [Review]. Am J Surg Pathol 1990;1:49-63.
24. Porter KA. Pathological changes in transplanted kidneys. In: Starzl TE, ed. Experience in Renal Transplantation. Philadelphia: Saunders, 1964: 299.
25. Demetris AJ, Belle SH, Hart J, Lewin K, Ludwig J, Snover DC, Tillery GW, et al. Intraobserver and interobserver variation in the histopathological assessment of liver allograft rejection. The Liver Transplantation Database (LTD) Investigators [see comments]. HEPATOLOGY 1991;14(5):751-755.
26. Kemnitz J, Gubernatis G, Bunzendahl H, Ringe B, Pichlmayr R, Georgii A. Criteria for the histopathologic classification of liver allograft rejection and their clinical significance. Transplant Proc 1989;21:2208-2210.
27. Hubscher SG. Histological findings in liver allograft rejection—new insights into the pathogenesis of hepatocellular damage in liver allografts (comment). Histopathol 1991;18:377-383.
28. Dousset B, Hubscher SG, Padbury RT, Gunson BK, Buckels JA, Mayer AD, Elias E, et al. Acute liver allograft rejection-is treatment always necessary. Transplantation 1993;55:529-534.
29. Hubscher S. Diagnosis and grading of liver allograft rejection: a European perspective. Transplant Proc 1996; 28:504-507.
30. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, et al. Formulation and application of a numerical scoring system for assessing histologic activity in asymptomatic chronic active hepatitis. HEPATOLOGY 1981;1:431-435.
31. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. HEPATOLOGY 1994; 19:1513-1520.
32. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13:372-374.
33. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, et al. Histologic grading and staging of chronic hepatitis. J Hepatol 1995; 22:696-699.
34. Datta Gupta S, Hudson M, Burroughs AK, Morris R, Rolles K, Amlot P, Scheuer PJ, et al. Grading of cellular rejection after orthotopic liver transplantation. Hepatology 1995;21:46-57.
35. Foster PF, Sankary HN, Hart M, Ashmann M, Williams JW. Blood and graft eosinophilia as predictor of rejection in human liver transplantation. Transplantation 1989;47:72-74.
36. Sankary H, Foster P, Hart M, Ashmann M, Schwartz D, Williams JW. An analysis of the determinants of hepatic allograft rejection using stepwise logistic regression. Transplantation 1989;47:74-77.
37. de Groen PC, Kephart GM, Gleich GJ, Ludwig J. The eosinophil as an effector cell of the immune response during hepatic allograft rejection. HEPATOLOGY 1994;20(3):654-662.
38. Martinez OM, Ascher NL, Ferrell L, Villanueva J, Lake J, Roberts JP, Krams SM, et al. Evidence for a nonclassical pathway of graft rejection involving interleukin 5 and eosinophils. Transplantation 1993;55(4):909-18.
39. Demetris AJ, Seaberg EC, Batts KP, Ferrell LD, Ludwig J, Markin RS, Belle SH, et al. Reliability and predictive value of the NIDDK liver transplant database nomenclature and grading system for cellular rejection of liver allografts. HEPATOLOGY 1995;21:408-416.
40. Freese DK, Snover DC, Sharp HL, Gross CR, Savick SK, Payne WD. Chronic rejection after liver transplantation: a study of clinical, histological and immunological features. HEPATOLOGY 1991;13:882-891.
41. Hubscher SG, Neuberger JM, Buckels JAC, Elias E, McMaster P. Vanishing bile-duct syndrome after liver transplantation—is it reversible? Transplantation 1991;51:1004-1110.
42. Schlitt HJ, Nashan B, Krick P, Ringe B, Wittekind C, Wonigeit K, Pichlmayr R, et al. Intragraft immune events after human liver transplantation. Correlation with clinical signs of acute rejection and influence of immunosuppression. Transplantation 1992;54(2):273-278.