

Reliability for Grading Acute Rejection and Airway Inflammation After Lung Transplantation

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Background: The Lung Rejection Study Group (LRSG) created a scheme for grading acute allograft rejection in 1990 and then revised it in 1996, but virtually no studies have evaluated the reliability of this formulation. This investigation assessed the reliability of the current LRSG system by determining inter- and intrareader agreement for grading transbronchial biopsy samples from lung transplant recipients.

Methods: Biopsy samples from a cohort of 204 recipients were reviewed and classified by a single pathologist who was blinded to original interpretations. The “A” and “B” rejection grades from this contemporary review were compared with original grades by the kappa statistic.

Results: For “A” grading, weighted kappa was 0.65 (95% confidence interval [CI] 0.60–0.70) for interreader agreement ($n = 529$ specimens) and 0.65 (95% CI 0.53–0.76) for intrareader agreement ($n = 97$ specimens). For “B” grading, weighted kappa was 0.26 (95% CI 0.14–0.39) for interreader agreement ($n = 164$ specimens) and 0.33 (95% CI 0.15–0.51) for intrareader agreement ($n = 58$ specimens).

Conclusions: On the basis of the analysis of the LRSG scheme, “A” grades exhibit very good reliability, but “B” grades have only fair reliability, and steps to improve this shortcoming should be taken. *J Heart Lung Transplant* 2005;24:652–7. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Acute rejection and lymphocytic bronchitis/bronchiolitis (LBB) are frequently encountered after lung transplantation and are important predictors for bronchiolitis obliterans syndrome (BOS) or chronic allograft rejection,¹ which remains the greatest deterrent to long-term success.² The pathologic correlates for acute rejection and LBB were established by the original Lung Rejection Study Group (LRSG) in 1990.³ The hallmark lesion of acute rejection is lymphocytic perivascular inflammation and is denoted by the “A” grade, which ranges between 0 (no rejection) and 4 (severe rejection) by the degree of perivascular inflammation.³ The LRSG provided mostly qualitative indicators to demarcate each grade, e.g., A2 should

display “expansion of the perivascular interstitium by inflammatory cells . . . no obvious infiltration by mononuclear cells into the adjacent alveolar septae or air spaces,” and A3 should be reserved for biopsy samples with “extension of the inflammatory cell infiltrate into perivascular and peribronchiolar alveolar septae and air spaces.” Grading of airway inflammation was simplified by the LRSG in 1996 and includes a similar system with the “B” grade, which ranges between 0 (no inflammation) and 4 (severe inflammation).⁴ When infectious processes can be excluded, airway inflammation in the form of LBB is postulated to be an immune-mediated attack on the allograft and a “possible harbinger” of BOS.⁴

Despite the LRSG’s attempt to standardize grading, the system still requires subjective interpretation. Reliability, also called agreement, is paramount when considering tests with subjective interpretation. Although the LRSG’s revised Working Formulation has been widely adopted, there has been a paucity of studies on its reliability between different pathologists (interreader)⁵ and no reports on its reliability for a single pathologist on different occasions (intrareader). The aim of this investigation was to judge the system’s reliability through determination of inter- and intrareader agreement for the current “A” and “B” grading schemes, on the basis of interpretations of a sizable collection of transbronchial biopsy samples from a large

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transplant center. Some of the preliminary results from this study were previously reported in abstract form.⁶

MATERIAL AND METHODS

We included transbronchial biopsy samples performed in the first 150 days after transplantation in 204 patients who underwent single lung, bilateral lung, or heart-lung transplantation at Barnes-Jewish Hospital and Washington University between January 1996 and December 2000. The Institutional Review Board of Washington University approved our protocol.

Biopsy specimens were classified by the indication for the bronchoscopy. Scheduled surveillance bronchoscopy was performed in stable patients during the first, second, third, sixth, and 12th months after transplantation. Clinical bronchoscopy was conducted at any given time for the evaluation of new symptoms or signs of respiratory disease, including unexplained decline in FEV₁ of $\geq 10\%$ from baseline. Follow-up bronchoscopy was undertaken to assess therapeutic response to a previous abnormal finding or to monitor a previously untreated episode of minimal (A1) acute rejection.

During bronchoscopy, bronchoalveolar lavage and transbronchial biopsy samples were performed. Our standard practice is to obtain 8 to 12 samples via biopsy from the right middle and lower lobes or left lower lobe and lingula under fluoroscopic guidance. Specimens were stained with hematoxylin and eosin, and additional stains (Gomori methenamine silver, acid-fast, immunoperoxidase for cytomegalovirus [CMV]) were performed if needed. Staff pathologists with experience in transplant pathology originally interpreted the specimens between 1996 and 2000 by means of the revised LRS guidelines (first reading).

While blinded to original interpretations, a lung transplant pathologist (JR) reviewed the specimens for a contemporary reading. If specimens from a procedure were adequate,⁴ "A" and "B" scores were assigned (second reading). Specimens with CMV pneumonitis (i.e., intranuclear or intracytoplasmic viral inclusions on hematoxylin and eosin stain or a positive CMV immunoperoxidase stain) were excluded. "A" and "B" grades from the first and second readings were compared. If a pathologist other than JR had performed the first reading, the specimen was assigned to the interreader analysis. If JR had provided the first reading, the specimen was used in the intrareader analysis. Inter- and intrareader analyses for both categories were mutually exclusive.

Because minimal acute rejection (A1) from surveillance bronchoscopy is usually not treated, we dichotomized the "A" grading system for surveillance biopsy samples into 2 clinically relevant categories: A ≤ 1 and A ≥ 2 . Because minimal airway inflammation (B1) is rela-

Table 1. Patient Demographics*

Characteristic	Value
Age (years) (mean $\pm$ SD)	49 $\pm$ 12
Male sex, <i>n</i> (%)	106 (52)
Indication for transplantation, <i>n</i> (%)	
COPD	129 (63)
Cystic fibrosis	35 (17)
Pulmonary fibrosis	14 (7)
Bronchiectasis	10 (5)
Other	16 (8)
Type of transplant, <i>n</i> (%)	
Bilateral lung	172 (84)
Single lung	30 (15)
Heart lung	2 (1)
Year of transplantation, <i>n</i> (%)	
1996	27 (13)
1997	45 (22)
1998	47 (23)
1999	39 (19)
2000	46 (23)

*COPD, chronic obstructive pulmonary disease.

tively common and often below the threshold for altering immunosuppression, we dichotomized the "B" grading system for all biopsy samples to either B ≤ 1 or B ≥ 2 .

Continuous data are reported as means ($\pm$ SD) and categorical data as proportions. Distributions of "A" and "B" grades from the first and second readings were compared by the Wilcoxon signed-rank test for paired samples. We constructed 5×5 tables to differentiate the possible pairings from the first and second readings for analyses that used the complete grading scheme. Similarly, 2×2 tables were assembled for characterizing the pairings between the first and second readings for analyses with a dichotomized system. Concordance rates were calculated as the percentage of pairings with the same grade from the first and second readings relative to total number of pairings. Inter- and intrareader agreement was quantified by the kappa statistic, which ranges between -1.0 (perfect disagreement) and $+1.0$ (perfect agreement), with 0 representing chance agreement. A weighted kappa (K_w) was computed for tables with more than 2 strata, whereas a simple kappa (K_s) was calculated for tables with only 2 strata. A 2-tailed *p* value ≤ 0.05 was used to establish statistical significance. Statistical analyses performed with SPSS 10.0 (SPSS, Chicago, IL) and SAS 8.2 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the 204 recipients who formed the cohort are displayed in Table 1. During the first 150 days after transplantation, 730 bronchoscopies with transbronchial biopsies were per-

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