COURSE OF ILLNESS AFTER THE ONSET OF CHRONIC REJECTION IN LUNG TRANSPLANT RECIPIENTS

By Mi-Kyung Song, RN, PhD, Annette De Vito Dabbs, RN, PhD, Sean M. Studer, MD, and Sarah E. Zangle, RN, BSN

Background Despite the overall negative impact of chronic rejection on quality of life and survival after lung transplant, the specific clinical indicators of deterioration have not been identified.

Objectives To describe the course of illness after the onset of chronic rejection, including demographic and transplant variables, morbidity, mortality, health resource utilization, and end-of-life care, and to identify clinical indicators of deterioration in health and limited survival after the onset of chronic rejection.

Methods The medical records of 311 recipients of lung transplants between 1998 and 2004 were reviewed retrospectively to identify 60 recipients who experienced chronic rejection.

Results Median survival after chronic rejection was 31.34 months. Time to rejection (mean, 26.05 months; SD, 16.85) was significantly correlated with overall survival without need of a retransplant ($r = 0.64$; $P < .001$). The earlier the onset of chronic rejection or the need for oxygen at home, the shorter was the period of survival after chronic rejection and the more frequent were hospital and intensive care unit admissions and prolonged stays. Of the 26 recipients who died, 65% died at the transplant center, and all but 1 died in the intensive care unit; 3 died after multiple attempts of cardiopulmonary resuscitation; life support was ultimately withdrawn in 69%.

Conclusions Lung transplant recipients who experience chronic graft rejection have high rates of morbidity, mortality, and health resource utilization; however, the course of illness after chronic rejection is highly variable. (*American Journal of Critical Care.* 2008;17:246-253)

L ung transplantation is an accepted procedure to prolong survival and quality of life for patients with end-stage pulmonary disease. However, the benefits of this procedure are often undermined by chronic graft rejection, which develops in 60% to 75% of recipients by year 5 after transplant and is the primary cause of death after the first year.[1-7] Recipients with chronic rejection may experience transient improvement and slower declines in graft function if immunosuppression is augmented; however, to date, treatments have been unsuccessful in sustaining remission or reversing chronic rejection.[8,9]

Ironically, although the development of chronic rejection is considered ominous because of its impact on quality of life and survival, the onset alone is not predictive of the course of illness or mortality. We hypothesized that the following factors are predictive of duration of survival after the onset of chronic rejection: number of readmissions, number of prolonged hospital stays (>10 days), number of readmissions to the intensive care unit (ICU), number of visits to the emergency department, length of hospital stay, and oxygen dependency. Clinicians may consider these variables known indicators of changes in recipients' health conditions, but the associations among these factors have not been documented.

A better understanding of the indicators of limited survival after the onset of chronic rejection would help recipients, their families, and clinicians avert decision-making crises by anticipating likely treatment decisions as the recipients' health declines, such as initiating life-sustaining treatments, withdrawing treatments deemed futile, opting for palliative care, and seeking retransplantation.[10]

Materials and Methods
Study Design and Sample

The medical records of the 311 adults who underwent lung transplantation at a hospital in western Pennsylvania between 1998 and 2004 were reviewed retrospectively to identify the cohort of 60 recipients in whom chronic graft rejection developed. Patients were included if they survived for at least 6 months after transplantation and experienced chronic graft rejection, defined as histological evidence of bronchiolitis obliterans (BO) or grade 2 or higher bronchiolitis obliterans syndrome (BOS; Figure 1). BOS grades were determined by using conventional diagnostic criteria[2]: forced expiratory volume in 1 second (FEV_1) 65% of baseline value or less without use of an inhaled bronchodilator and no confounding conditions (ie, infection, acute cellular rejection, or lymphocytic bronchitis/bronchiolitis). Grade 2 or higher BOS was selected because the life expectancy of lung transplant recipients with a pronounced reduction in FEV_1 is 2 years or less.[2]

The maintenance immunosuppression regimen for the cohort consisted of either cyclosporine or tacrolimus and prednisone, supplemented by azathioprine or mycophenolate mofetil. Induction therapy— that is, treatment with polyclonal antilymphocyte/ antithymocyte globulin or interleukin 2 receptor antagonist[11]—was used in some transplant patients after 2000.
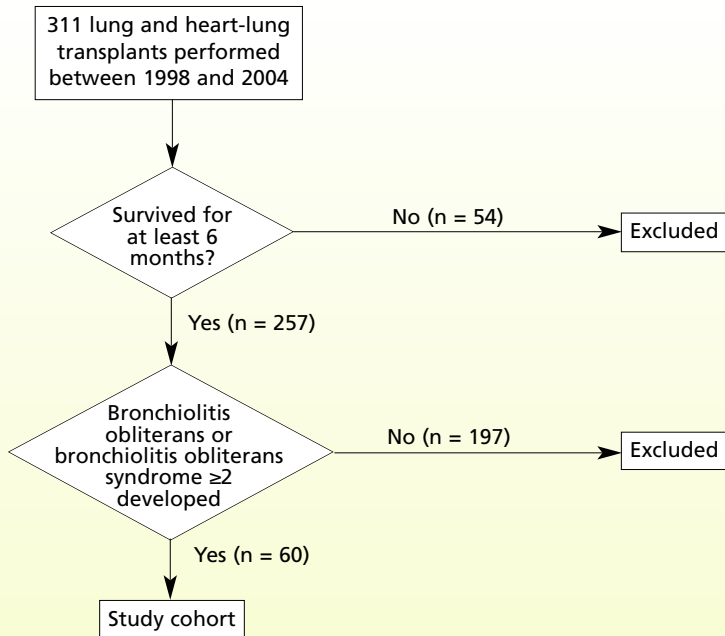
Acute allograft rejection (grade A2 or higher) and suspected chronic rejection were treated by augmenting immunosuppression, primarily with methylprednisolone (1.0 g/d for 3 days).[12] All recipients participated in an aggressive surveillance protocol, which included routine transbronchial biopsies within the first month after transplantation, then every 2 to 3 months during the first year, quarterly or semiannually during year 2, annually thereafter, and whenever rejection was suspected.[12] Recipients were encouraged to contact the transplant coordinator for changes that might indicate infection, rejection, or other complication, such as a change from their FEV_1 baseline value or a 10% decrease in FEV_1 during a week, a body temperature of 38.3°C (101°F) or higher, indications of fluid retention, blood pressure greater

Chronic rejection develops in 60% to 75% of lung transplant recipients by 5 years after transplant.

About the Authors
Mi-Kyung Song is an assistant professor in the School of Nursing at the University of North Carolina, Chapel Hill. **Annette De Vito Dabbs** is an assistant professor in the Department of Acute and Tertiary Care, University of Pittsburgh School of Nursing, Pittsburgh, Pennsylvania. **Sean M. Studer** is an assistant professor in the Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh School of Medicine, and **Sarah E. Zangle** is staff nurse in the emergency department, Children's Hospital of the University of Pittsburgh Medical Center.

Corresponding author: Mi-Kyung Song, PhD, Assistant Professor, School of Nursing, University of North Carolina at Chapel Hill, Carrington Hall, CB#7460, Chapel Hill, NC 27599-7460 (e-mail: songm@email.unc.edu).

Figure 1 Inclusion criteria.

Table 1
Transplant-related characteristics of the sample (n = 60)

Characteristic	No. of recipients (%)[a]
Pretransplant diagnosis	
Chronic obstructive pulmonary disease	18 (30)
Cystic fibrosis	12 (20)
Interstitial pulmonary disorders	10 (17)
Connective tissue disorders	10 (17)
α_1-Antitrypsin deficiency	5 (8)
Primary pulmonary hypertension	2 (3)
Other	3 (5)
Transplant type	
Bilateral lung	27 (45)
Single lung	31 (52)
Heart-lung	2 (3)
Diagnosis of chronic graft rejection	
Histological evidence of bronchiolitis obliterans first	31 (52)
Bronchiolitis obliterans syndrome ≥2 followed by evidence of bronchiolitis obliterans	13 (22)
Bronchiolitis obliterans syndrome ≥2 without evidence of bronchiolitis obliterans	16 (27)

a Because of rounding, not all percentages total 100.

than 160/100 mm Hg or less than 80/60 mm Hg, or tachycardia or bradycardia.[13] Other signs and symptoms in recipients were instructed to monitor and report to the transplant coordinator included persistent or productive cough, change in color or amount of sputum, worsening shortness of breath, and flu-like signs and symptoms.

Data Collection and Analysis

Demographic variables included age, sex, and race. Transplant-related characteristics included diagnosis before transplant, date and type of transplant, FEV_1 after transplant, results of transbronchial biopsy, and immunosuppression regimens. Morbidity and mortality data included hospital and ICU admitting diagnoses, patients' chief concern during emergency department visits, dates of readmissions and discharges, discharge disposition, oxygen dependency, and primary cause and location of death. Reasons for hospitalization were determined from either admission notes or discharge summaries. Oxygen dependency was defined as a requirement for continuous oxygen at home. Health resource utilization data included rehospitalizations, use of mechanical ventilation and other life-sustaining measures, ICU admissions, and number of attempts at cardiopulmonary resuscitation. Finally, data on end-of-life care included timing of do-not-resuscitate orders, use of advance directives, content and timing of end-of-life discussions, involvement of the palliative care team, provision of support to patients' family members, treatment withdrawals, and time from weaning from mechanical ventilation to death.

Descriptive statistics were used to characterize the sample, the pattern of complications, mortality, health resource utilization, advance care planning, and the end-of-life care. Univariate analyses were used to determine normality of data for the study variables. Nonparametric statistics (eg, rank test and Spearman rank correlation) were used to describe relationships among variables. Retransplantation because of graft failure was included with mortality in the analyses as defined by United Network for Organ Sharing outcome criteria.[14] The Kaplan-Meier method was used to estimate survival time after chronic rejection with no need for retransplant. Logistic regression was used to identify independent variables associated with death or retransplant after graft failure due to chronic rejection. The variables included in the model were selected on the basis of the univariate analyses and multicollinearity assessment.

Results
Characteristics of the Sample

The mean age of the sample (n = 60) was 48.21 years (SD, 12.29) at the time of transplant. More than 90% (n = 56) of the recipients were white, and 48% were men. Table 1 gives the transplant-related characteristics.

A total of 26 recipients (43%) with chronic rejection had died by the time of data collection (January 2006); for 9 surviving patients, the length

of follow-up between the onset of chronic rejection and the final data collection was less than 1 year. Approximately half of the recipients (n = 34) received their transplant after the year 2000; of those, 17 received induction therapy. Most of the recipients (65%) were prescribed tacrolimus as their primary immunosuppressant; another 27% were switched to cyclosporine because of side effects from tacrolimus. For more than half of the cohort, the diagnosis of chronic rejection was made on the basis of histological criteria alone. Seven patients had grade 3 BOS.

Complications and Mortality

The time from transplant to the onset of chronic rejection for the cohort was 26.05 months (SD, 16.85; median, 21.82; interquartile range, 22.82; Table 2). The cohort experienced a total of 186 readmissions after the onset of chronic rejection. The most frequent reasons for rehospitalization were pulmonary infection and pneumonia (30 patients; 73 admissions), acute allograft rejection (18 patients; 38 admissions), chronic rejection (18 patients; 32 admissions), renal dysfunction (7 patients; 16 admissions), and gastrointestinal disorders (5 patients; 7 admissions). Less frequent reasons included cardiovascular complications (eg, coronary artery disease, stroke, deep vein thrombosis), malignant neoplasms, and fractures. The leading causes of prolonged hospitalizations (defined as >10 days) were infection and pneumonia (16 patients), chronic rejection (7 patients), respiratory failure (6 patients), renal insufficiency or failure (3 patients), and stroke (2 patients). The most frequent reasons for visits to the emergency department (28 patients; 169 visits) included shortness of breath (28 patients; 76 visits), fever with nausea and vomiting (19 patients; 27 visits), and abdominal pain (8 patients; 16 visits). Other reasons included arrhythmia, chest discomfort, hemodialysis access problems, and stroke.
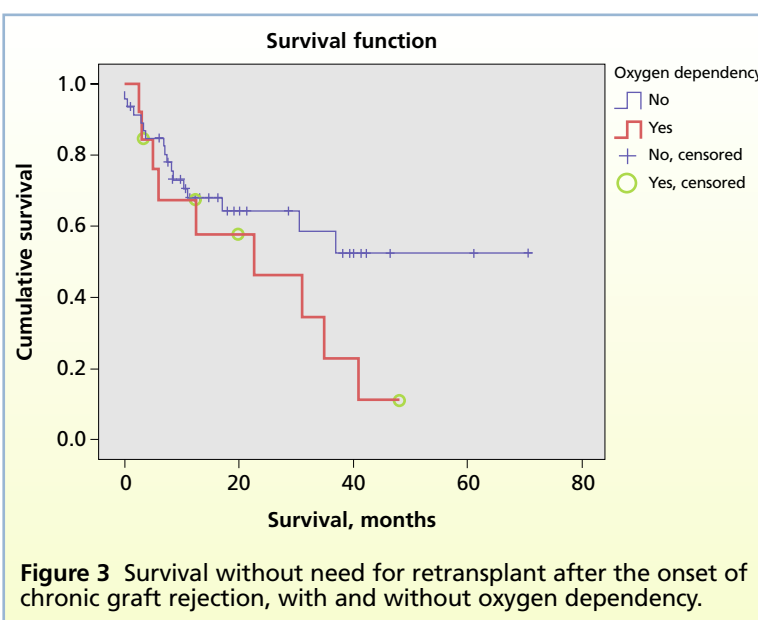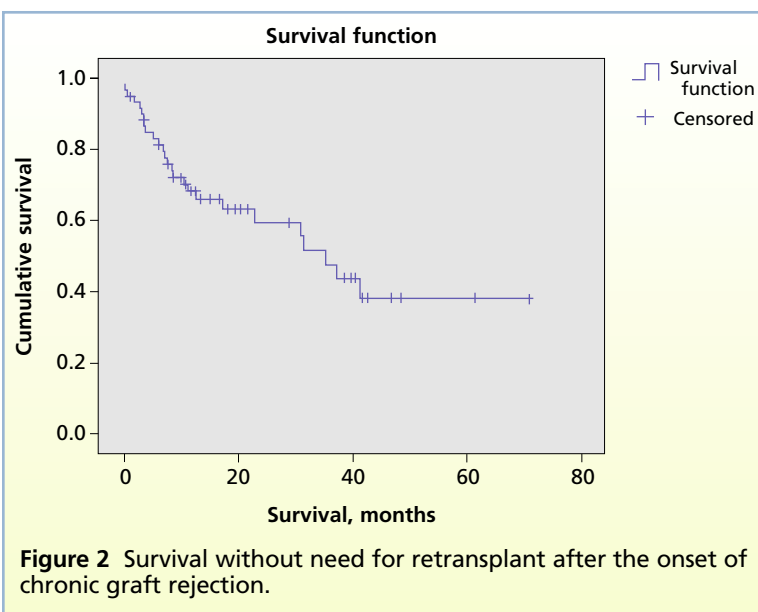
A total of 13 recipients (22%) required oxygen at home after chronic rejection; this number did not include recipients who required oxygen for hypoxemia during their final hospitalization. Among the 26 patients who died, 62% of the deaths were due to infection (8 patients) and chronic rejection (8 patients). Kaplan-Meier survival curves are shown in Figures 2 and 3. The median estimate of survival time without need for retransplant was 52.13 months (SE, 8.03; 95% confidence interval [CI], 36.40-67.87). The median estimate of survival time or time to retransplant after chronic rejection was 31.34 months (SE, 9.56; 95% CI, 12.63-50.11). When oxygen dependency was taken into account, the median survival estimates after the onset of chronic rejection were 37.27 months for those who were not
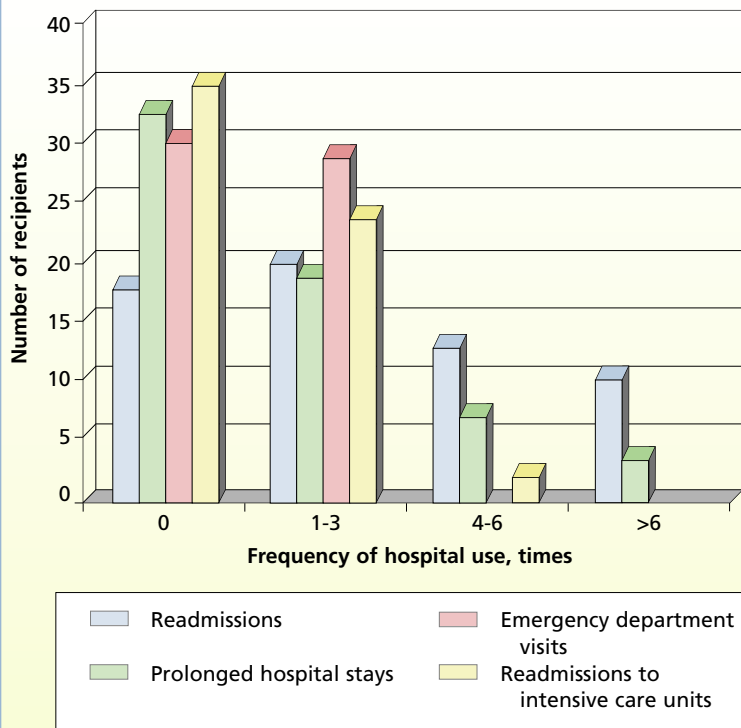
Table 2
Months to onset of chronic graft rejection, length of survival after onset of chronic rejection without need for retransplant, and overall survival after transplant among total cohort, survivors who did not need retransplant, and nonsurvivors[a]

	Total (n = 60)	Survivors, no retransplant (n = 31)	Nonsurvivors or retransplant (n = 29)
Onset of chronic rejection	26.05 16.85 (21.82; 22.82)	32.63 17.64 (30.00; 26.07)	19.02 12.86 (14.95; 14.57)
Survival after onset of chronic rejection	18.75 16.49 (12.63; 24.05)	24.73 17.92 (19.50; 29.10)	12.36 12.11 (7.50; 14.26)
Overall survival	44.80 20.99 (45.38; 30.38)	57.36 18.49 (55.60; 28.63)	31.38 14.17 (30.53; 26.48)

[a] Values are mean and standard deviation; values inside parentheses are median, interquartile range.

Figure 2 Survival without need for retransplant after the onset of chronic graft rejection.

Figure 3 Survival without need for retransplant after the onset of chronic graft rejection, with and without oxygen dependency.

Figure 4 Readmissions and emergency department visits after the onset of chronic graft rejection (n = 60). Data indicate health resource utilization that occurred at the transplant center only.

dependent on oxygen and 22.80 months for those who were oxygen dependent.

> The leading causes of prolonged hospitalizations were pulmonary infection and pneumonia.

Health Resource Utilization

Of the 60 recipients, 43 were hospitalized at the transplant center at least once and up to a maximum of 14 times after chronic rejection (interquartile range, 5; Figure 4). More than 67% of the 43 recipients experienced prolonged hospitalizations at least once (interquartile range, 1) and 56% required ICU admissions (interquartile range, 1.75). The pattern and timing of readmissions were unpredictable; recipients were hospitalized in acute settings just as often in the early stages of chronic rejection as in the later stages. Approximately one half of the sample sought care in the transplant center emergency department at least once and up to a maximum of 17 times (interquartile range, 2). All 3 patients who had retransplantation because of chronic rejection were alive at the close of data collection (survived 39.57, 41.00, or 64.13 months each since the first transplant); however, chronic rejection, renal failure requiring dialysis, or malignant neoplasm was diagnosed (n = 1 for each condition) within 2 months after retransplantation.

End-of-Life Care

Of the 26 recipients who died, 4 died at another health care facility and 2 died at home; the location of death for 3 recipients was unknown. Data on end-of-life care were available solely for the 17 recipients who died at the transplant center. Except for 1 recipient who died in the emergency department, all 16 recipients died in the ICU and 3 died after multiple attempts at cardiopulmonary resuscitation. Mechanical ventilation was ultimately stopped in 11 recipients; their median time of death was 3.5 hours after withdrawal of mechanical ventilation.

Advance directives were found in the medical charts of 2 patients. The primary type of end-of-life discussion documented in the medical record was a family conference led by the ICU attending physician (n = 13), although most end-of-life discussions (n = 8) were initiated by patients' families. Do-not-resuscitate orders were written for 12 recipients within 24 hours of their deaths. Attending physicians initiated discussions about do-not-resuscitate orders for 4 patients. For 5 recipients, a hospital chaplain was involved in the discussions. Timing of discussions varied from day 4 to day 97 after admission to the ICU. Palliative care consultations or referrals to hospice were made for 4 recipients; 2 of the 4 opted to spend their final days at home.

Relationships Among Variables

Time to the onset of chronic rejection was significantly correlated with overall survival after transplant ($r = 0.64$; $P < .001$). The earlier the onset of chronic rejection, the shorter was the period of survival after chronic rejection and the higher were the frequencies of rehospitalization ($r = -0.34$; $P = .01$), prolonged hospitalization ($r = -0.37$; $P < .001$), and number of ICU admissions ($r = -0.48$; $P < .001$). The 13 recipients who were oxygen dependent required rehospitalizations (median, 5; $P = .002$), ICU readmissions (median, 2; $P < .001$), and prolonged hospitalizations (median, 2; $P = .001$) more often than did recipients who were not oxygen dependent. Prolonged hospitalizations and ICU stays were highly correlated ($r = 0.72$; $P < .001$).

The logistic regression model for identifying variables associated with risk of death or retransplantion after chronic rejection (controlling for the differences in duration of follow-up; goodness-of-fit $\chi^2 = 3.45$; $df = 8$; $P = .90$) indicated that time to the onset of chronic rejection and oxygen dependency were significant factors associated with overall survival without need for retransplant. For every month of delay in the onset of chronic rejection, recipients had a 14% increase in the likelihood of survival

without need for retransplant (odds ratio, 0.86; 95% CI, 0.79-0.95). The need for oxygen at home (24 h/d) radically increased chances for death or retransplant (odds ratio, 26.19; 95% CI, 2.69-255.9).

Discussion

Although others have described patterns of chronic graft rejection[15,16] and its negative effect on allograft function,[2,17] quality of life,[4,6,18] health care costs,[19-23] and survival,[5,24-26] our results further our understanding of the course of illness after the onset of chronic rejection and indicate additional factors associated with the patterns of chronic rejection.[27] As we hypothesized, numbers of readmissions, prolonged hospitalizations, and ICU admissions were significantly associated with the time from transplant to the onset of chronic rejection; length of hospital stay and number of emergency department visits were not. The earlier the onset of chronic rejection after transplant, the more often recipients had complications, sought care in the emergency department, were readmitted to the hospital, experienced more prolonged hospital stays and more frequent ICU admissions, and had reduced overall survival rates. Furthermore, the need for oxygen at home was an ominous predictor of deterioration in health and of limited survival. Our findings may seem obvious to many clinicians; however, empirical evidence of the clinical course after the onset of chronic rejection has been lacking.

Of the 257 recipients who survived 6 months or longer after transplant, 113 met criteria for at least grade 1 BOS (20%-34% decrease in FEV_1 from the best FEV_1 after transplant). However, we defined chronic rejection conservatively (BOS grade ≥2) because patients with this degree of impairment are more likely to have multiple hospitalizations, frequent treatment dilemmas, and a limited life expectancy.[2] Despite reports of the low sensitivity of transbronchial biopsies for detection of BO,[1,28] more than half of the cohort had histological evidence of chronic rejection. This finding may reflect the fact that the study transplant center is one of the centers in which transbronchial biopsies are a routine part of rejection surveillance protocols well beyond the first 2 years after transplantation.[29]

Chronic rejection was diagnosed, on average, within 3 years after transplant. The median survival time or time to retransplant for graft failure after the onset of chronic rejection was approximately 2.5 years. These results are consistent with previously reported hazard ratios (3.89 and 11) for recipients surviving more than 3 months after transplant with grades 2 and 3 BOS, respectively.[5] The primary causes of death in our sample were pulmonary infection and rejection, the same as the primary reasons for rehospitalizations.

Evidence[30] suggests that over time recipients develop insight about reporting changes in signs and symptoms to the transplant team so that serious complications can be averted. In contrast, the recipients in our study made visits to the emergency department throughout the course of their illness regardless of the length of time since transplant. This finding suggests that even longer-term recipients need to sustain vigilant monitoring of signs and symptoms and report subtle changes to the transplant team early in order to reduce health care utilization by managing problems in less costly settings.

Oxygen dependency was significantly associated with the length of survival after the onset of chronic rejection, and its predictive value for relative risk for death or retransplant may be a useful indicator for clinical management and may prompt clinicians to review goals of care with recipients and recipients' family members. Although retransplantation may be considered a treatment option for chronic rejection, only a few recipients with chronic rejection meet the stringent selection criteria, such as being ambulatory and not requiring ventilatory support and an interval of more than 2 years from the time of initial transplantation.[31,32] In addition, at best, the survival rate 1 year after retransplant is 50%.[32,33] The scarce supply of donor organs makes this option even more unrealistic for many recipients with chronic rejection.

Our study has several limitations. Sampling bias may affect the findings because the cohort was drawn from a single transplant center, and the center's management practices may vary from those of other centers. However, characteristics (eg, age, sex, race, pretransplant diagnosis, transplant type) of the cohort were comparable to characteristics reported in national data.[34] Also, some of the recipients with chronic rejection were not managed exclusively at the host transplant center, a situation that limited access to records for those who were managed and/or died at other health care facilities. Finally, the retrospective study design and shortcomings of relying on data documented in the medical record limited our ability to fully examine the course of illness after the onset of chronic rejection.

Nonetheless, our findings provide more information on the complicated clinical course of illness

> The mean time from transplant to the onset of chronic rejection was 26 months.

> The need for home oxygen was an ominous predictor of deterioration and limited survival.

and high health care utilization after chronic rejection. Compared with other recipients, recipients who experience chronic rejection and its pervasive complications require more comprehensive and coordinated care. Although Kurz[35] reported that recipients' families play an essential role in the recipients' recovery and outcomes, data are lacking on the experiences and needs of recipients and their families, particularly after the onset of chronic rejection, when long-term survival is in jeopardy.

The findings of this study expand our understanding of significant use of health care resources to treat complications and prolong life, as described in a previous study.[36] Although an approach focused on aggressive treatment does not preclude the inclusion of palliative care, in our study, timely assessment for goals of care to identify patient's needs for palliative care and making referrals when appropriate were rarely documented. Further research is needed to examine the prevalence and characteristics of lung recipients currently referred for palliative care services; this information can be used to determine the best practice for integrating aggressive and palliative care in a complementary way to promote better quality of life after chronic rejection. Because the impact of chronic rejection among recipients varies widely, a review at each ICU admission or clinic visit of the clinical indicators we identified might help clinicians, transplant recipients, and recipients' families anticipate treatment choices that promote the best quality of survival.

> To reduce health care utilization, recipients must monitor symptoms vigilantly and report subtle changes to the transplant team early.

> Palliative care should be integrated with aggressive care to promote recipients' quality of life after chronic rejection.

SEE ALSO
To learn more about transplantation in high acuity and critical care, visit **http://ccn.aacnjournals.org** and read the archived special issue on transplantation and organ donation (*Critical Care Nurse,* April 2006).

eLetters
Now that you've read the article, create or contribute to an online discussion about this topic using eLetters. Just visit **www.ajcconline.org** and click "Respond to This Article" in either the full-text or PDF view of the article.

REFERENCES
1. Boehler A, Kesten S, Weder W, Speich R. Bronchiolitis obliterans after lung transplantation: a review. *Chest.* 1998;114(5):1411-1426.
2. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant.* 2002;21(3):297-310.
3. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. *Am J Respir Crit Care Med.* 1999;160(1):265-271.
4. Gross CR, Raghu G. The cost of lung transplantation and the quality of life post-transplant. *Clin Chest Med.* 1997;18(2):391-403.
5. Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. *J Heart Lung Transplant.* 1998;17(12):1255-1263.
6. Lanuza DM, Lefaiver C, McCabe M, Farcas GA, Garrity E Jr. Prospective study of functional status and quality of life before and after lung transplantation. *Chest.* 2000;118(1):115-122.
7. Verleden GM, Dupont LJ, Van Raemdonck DE. Is it bronchiolitis obliterans syndrome or is it chronic rejection: a reappraisal? *Eur Respir J.* 2005;25(2):221-224.
8. Hertz MI. Immunosuppression for prevention of bronchiolitis obliterans. *Curr Opin Organ Transplant.* 2000;5(4):402-406.
9. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med.* 2005;172(6):772-775.
10. Butler J, McCoin NS, Feurer ID, et al. Modeling the effects of functional performance and post-transplant comorbidities on health-related quality of life after heart transplantation. *J Heart Lung Transplant.* 2003;22(10):1149-1156.
11. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report—2007. *J Heart Lung Transplant.* 2007;26(8):782-795.
12. DeVito Dabbs A, Hoffman LA, Iacono AT, et al. Pattern and predictors of early allograft rejection after lung transplantation. *Am J Crit Care.* 2003;12(6):497-507.
13. CT Transplant Group. *Discharge Instructions: Patient Education After Cardiothoracic Transplantation.* Pittsburgh, PA: University of Pittsburgh Medical Center; 2002.
14. United Network for Organ Sharing. Thoracic-lung data collection form. http://unos.org/SharedContentDocuments/Thoracic-Lung_Transplant_Recipient_Follow-Up.pdf. Published 2004. Accessed February 22, 2008.
15. Nathan SD, Ross DJ, Belman MJ, et al. Bronchiolitis obliterans in single-lung transplant recipients. *Chest.* 1995;107(4):967-972.
16. Sundaresan S, Trulock EP, Mohanakumar T, Cooper JD, Patterson GA. Prevalence and outcome of bronchiolitis obliterans syndrome after lung transplantation. Washington University Lung Transplant Group. *Ann Thorac Surg.* 1995;60(5):1341-1346.
17. Studer SM, Levy RD, McNeil K, Orens JB. Lung transplant outcomes: a review of survival, graft function, physiology, health-related quality of life and cost-effectiveness. *Eur Respir J.* 2004;24(4):674-685.
18. van den Berg JW, van Enckevort PJ, TenVergert EM, Postma DS, van der Bij W, Koëter GH. Bronchiolitis obliterans syndrome and additional costs of lung transplantation. *Chest.* 2000;118(6):1648-1652.
19. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. An economic evaluation of lung transplantation. *J Thorac Cardiovasc Surg.* 2002;123(3):411-420.
20. Ramsey SD, Patrick DL, Albert RK, Larson EB, Wood DE, Raghu G. The cost-effectiveness of lung transplantation: a pilot study. University of Washington Medical Center Lung Transplant Study Group. *Chest.* 1995;108(6):1594-1601.
21. van Enckevort PJ, Koopmanschap MA, TenVergert EM, et al. Lifetime costs of lung transplantation: estimation of incremental costs. *Health Econ.* 1997;6(5):479-489.

22. Vasiliadis HM, Collet JP, Penrod JR, Ferraro P, Poirier C. A cost-effectiveness and cost-utility study of lung transplantation. *J Heart Lung Transplant.* 2005;24(9):1275-1283.

23. Vasiliadis HM, Collet JP, Poirier C. Health-related quality-of-life determinants in lung transplantation. *J Heart Lung Transplant.* 2006;25(2):226-233.

24. Brugière O, Pessione F, Thabut G, et al. Bronchiolitis obliterans syndrome after single-lung transplantation: impact of time to onset on functional pattern and survival. *Chest.* 2002;121(6):1883-1889.

25. Date H, Lynch JP, Sundaresan S, Patterson GA, Trulock EP. The impact of cytolytic therapy on bronchiolitis obliterans syndrome. *J Heart Lung Transplant.* 1998;17(9):869-875.

26. Jackson CH, Sharples LD, McNeil K, Stewart S, Wallwork J. Acute and chronic onset of bronchiolitis obliterans syndrome (BOS): are they different entities? *J Heart Lung Transplant.* 2002;21(6):658-666.

27. Iacono AT, Corcoran TE, Griffith BP, et al. Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. *Eur Respir J.* 2004;23(3):384-390.

28. Chamberlain D, Maurer J, Chaparro C, Idolor L. Evaluation of transbronchial lung biopsy specimens in the diagnosis of bronchiolitis obliterans after lung transplantation. *J Heart Lung Transplant.* 1994;13(6):963-971.

29. Levine SM; Transplant/Immunology Network of the American College of Chest Physicians. A survey of clinical practice of lung transplantation in North America. *Chest.* 2004;125(4):1224-1238.

30. Dabbs Ade V, Hoffman LA, Swigart V, et al. Striving for normalcy: symptoms and the threat of rejection after lung transplantation. *Soc Sci Med.* 2004;59(7):1473-1484.

31. Kotloff RM. Lung retransplantation: all for one or one for all? *Chest.* 2003;123(6):1781-1782.

32. Strueber M, Fischer S, Gottlieb J, et al. Long-term outcome after pulmonary retransplantation. *J Thorac Cardiovasc Surg.* 2006;132(2):407-412.

33. Hertz MI, Taylor DO, Trulock EP, et al. The Registry of the International Society for Heart and Lung Transplantation: nineteenth official report—2002. *J Heart Lung Transplant.* 2002;21(9):950-970.

34. US Organ Procurement and Transplantation Network. 2005 Annual report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003. http://www.optn.org/data/annualReport.asp. Accessed March 3, 2008.

35. Kurz JM. Experiences of well spouses after lung transplantation. *J Adv Nurs.* 2001;34(4):493-500.

36. Song MK, De Vito Dabbs AJ. Advance care planning after lung transplantation: a case of missed opportunities. *Prog Transplant.* 2006;16(3):222-225.

Course of Illness after the Onset of Chronic Rejection in Lung Transplant Recipients

Mi-Kyung Song, Annette De Vito Dabbs, Sean M. Studer and Sarah E. Zangle

Subscription Information
http://ajcc.aacnjournals.org/subscriptions/

Information for authors
http://ajcc.aacnjournals.org/misc/ifora.xhtml

Submit a manuscript
http://www.editorialmanager.com/ajcc

Email alerts
http://ajcc.aacnjournals.org/subscriptions/etoc.xhtml