Cost-Effectiveness of Routine Surveillance Endomyocardial Biopsy After 12 Months Post–Heart Transplantation

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Background—Despite low risk of late rejection after heart transplant (HT), surveillance endomyocardial biopsies (EMBs) are often continued for years. We assessed the cost-effectiveness of routine EMB after 12 months post-HT.

Methods and Results—Markov model compared the following surveillance EMB strategies to baseline strategy of stopping EMB 12 months post-HT: (1) every 4 months during year 2 post-HT, (2) every 6 months during year 2, (3) every 4 months for years 2 to 3, and (4) every 6 months for years 2 to 3. Patients entered the model 12 months post-HT and were followed until 36 months. In all strategies, patients had EMB with symptoms; in biopsy strategies after 12 months, EMB was also performed as scheduled regardless of symptoms. One-way and Monte Carlo sensitivity analyses were performed. Stopping EMB at 12 months was dominant (more effective, less costly), saving $2884 per patient compared with the next best strategy (every 6 months for year 2) and gaining 0.0011 quality-adjusted life-years. Increasing the annual risk of asymptomatic rejection in years 2 to 3 from previously reported 2.5% to 8.5% resulted in the biopsy every 6 months for year 2 strategy gaining 0.0006 quality-adjusted life-years, but cost $4 913 599 per quality-adjusted life-year gained. EMB for 12 months was also no longer dominant when mortality risk from untreated asymptomatic rejection approached 11%; competing strategies still cost >$200 000 per quality-adjusted life-year as that risk approached 99%.

Conclusions—Surveillance EMB for 12 months post-HT is more effective and less costly than EMB performed after 12 months, unless risks of asymptomatic cellular rejection and its mortality are strikingly higher than previously observed. **(*Circ Heart Fail*. 2014;7:807-813.)**

Key Words: biopsy ■ cost-benefit analysis ■ heart transplantation

Improved patient and donor selection and long-term care of heart transplant (HT) recipients has resulted in 1-year survival of ≈90%.[1] Advances in immunosuppressive therapies, such as calcineurin inhibitors and mycophenolate mofetil, have decreased the incidence of significant treated rejection from nearly 70% to ≈30%, with most episodes occurring during the first year after transplantation.[2–4] Although most rejection is asymptomatic or minimally symptomatic at the time of diagnosis, it is still associated with an increased risk of allograft vasculopathy and loss.[5–7] Therefore, although the risk of rejection after 1 year is substantially lower than during the first 6 months post-HT, many centers continue routine rejection surveillance for up to 5 years following transplantation.[3]

Clinical Perspective on p 813

Endomyocardial biopsy (EMB) remains the gold standard for rejection monitoring. However, EMB is costly, associated with patient discomfort and inconvenience, and carries a small risk of potentially serious complications such as pericardial tamponade and severe tricuspid regurgitation.[8–10] Several transplant centers have retrospectively demonstrated the safety of symptom-driven biopsies only after the first post-transplant year, but in absence of a prospective trial confirming this, many centers remain reluctant to adopt this approach. Subsequently, the usefulness of routine surveillance EMB in all patients after 1 year remains a subject of debate and considerable variation exists between institutions in the frequency and duration of surveillance biopsies.[11] Current guidelines recommend surveillance EMB (every 4–6 months) for an extended period of time in transplant recipients at higher risk for late acute rejection, but do not comment on the routine use in all patients.[12]

The low yield of EMB after 1 year post-HT, its cost, and the small but real risk associated with the procedure call into question the cost-effectiveness of this strategy. This is an even more important consideration in an era of increased focus on healthcare cost containment. Here, we assess the cost-effectiveness of various EMB strategies after 1 year post-HT to (1) demonstrate whether we could model any potential clinical benefit to prolonged surveillance and (2) define the cost associated with prolonged surveillance biopsy strategies, which has not previously been reported.

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Methods

Model Design and Structure

A Markov model was constructed comparing various surveillance EMB strategies with a baseline strategy of stopping routine EMB at 12 months post-HT. Four alternative strategies were examined: continued routine EMB every 4 months during year 2 post-transplant (ie, EMB 16, 20, and 24 months post-HT), routine EMB every 6 months during year 2 post-HT, routine EMB every 4 months during years 2 and 3 post-HT, and routine EMB every 6 months during years 2 and 3 post-HT. Markov analysis was performed with TreeAge Pro 2013 Software (Williamstown, MA). No institutional review board approval was required for this study, because we used only literature data sources.

Patients entered the model after 12 months of routine post-HT clinic visits. The Markov model cycle length was 1 month. In all strategies, patients had an EMB for any signs or symptoms associated with rejection (dyspnea on exertion or at rest, paroxysmal nocturnal dyspnea, orthopnea, palpitations, and syncope or near-syncope), instances in which graft function could be compromised (ie, infection), or an absolute decrease in left ventricular ejection fraction of >10% from baseline. In addition, patients received routine scheduled surveillance biopsies regardless of symptoms based on the strategy modeled.

Transitions during each monthly cycle for patients included remaining well, developing acute cellular rejection (ACR), developing hemodynamically significant ACR, developing antibody-mediated rejection, or death. Patients transitioned to other states based on the monthly relative likelihood of those events (Figure). The model cycled until 36 months post-HT. For example, patient A presents for their routine 24-month post-transplant clinic visit. In the baseline strategy, patient A would be evaluated clinically. If patient A reports symptoms of worsening dyspnea, orthopnea, palpitations or was found to have decrease in left ventricular systolic function, he would undergo an EMB. In the absence of any signs or symptoms of rejection, patient A would not undergo a biopsy. In the prolonged biopsy strategies, patient A would undergo a biopsy regardless of symptoms. If a biopsy was performed and demonstrated rejection, patient A would be treated accordingly. At the next monthly cycle, patient A would then either transition to another state or remain in his current state based on the relative probabilities of each event. If a biopsy was performed and did not demonstrate rejection, patient A would remain in the well state.

Costs

Costs, in 2010 US dollars, used in the model and ranges examined in sensitivity analyses are shown in Table 1. In our baseline model, patients with ACR without hemodynamic compromise were not hospitalized. Their treatment costs included methylprednisolone (1 g IV×3 days), IV infusion center cost, follow-up echocardiogram, and follow-up office visit. Because practice and resources available vary among transplant centers regarding inpatient or outpatient treatment of patients with ACR without hemodynamic compromise, sensitivity analysis included the possibility of hospitalization and its associated costs. Treatment costs for hemodynamically significant ACR included hospitalization, thymoglobulin (1.5 mg/kg IV× 3 days), T-cell subset laboratories, follow-up echocardiogram, and a follow-up office visit. Hospitalization costs for hemodynamically significant ACR were based on Healthcare Cost and Utilization Project median costs for *International Classification of Diseases, Ninth Revision* (ICD-9) code 996.83 (complications of transplanted heart) with a median length of stay of 5 days.

Antibody-mediated rejection treatment costs included hospitalization, plasmapharesis, catheter for plasmapharesis, intravenous immune globulin (2 g/kg IV for 2 days), donor-specific antibody testing, follow-up echocardiogram, and follow-up office visit. Because antibody-mediated rejection management typically involves more intensive and a longer duration of care, costs of hospitalization for its treatment were estimated using Healthcare Cost and Utilization Project data on the mean charges for *ICD-9* code 996.83 (complications of transplanted heart) with a mean length of stay of 8.4 days. Follow-up office visits for all types of rejection were billed as a level 4 established patient visit (current procedural terminology 99214).

Probabilities

The probabilities used in the baseline analysis and ranges examined in sensitivity analysis are shown in Table 2. The annual risk of developing asymptomatic ACR has previously been demonstrated to be ≈2.5%,[16] and this value was used in the baseline analysis. An additional analysis was done using an annual risk of asymptomatic ACR of 8.5% to evaluate the model under the greater pressure of increased undetected rejection risk.

The probability of having ACR given symptoms (dyspnea on exertion or at rest, paroxysmal nocturnal dyspnea, orthopnea, palpitations, and syncope or near-syncope) has previously been noted to be ≈12%.[16] However, patients are occasionally treated for ACR in the absence of an abnormal EMB based on symptoms or a change in graft function seen on noninvasive imaging. To capture the costs associated with symptomatic patients who may be treated despite a negative EMB, we used a rate of 25% for the probability of having ACR given symptoms. There is limited data available quantifying the risk of death with untreated asymptomatic rejection. One prior analysis of the natural history of moderate rejection showed no increased risk of short- or long-term mortality.[17] To assume that untreated asymptomatic rejection carries some mortality risk, we used a 5% risk in the baseline model with a wide range in sensitivity analysis.

Utilities (ie, Calculation of Quality-Adjusted Life-Years)

The utilities used in the baseline analysis and ranges examined in sensitivity analysis are shown in Table 3. Utilities for patients having a biopsy or with illness were calculated as the utility of the well state multiplied by the utility weight of the biopsy or illness state. The

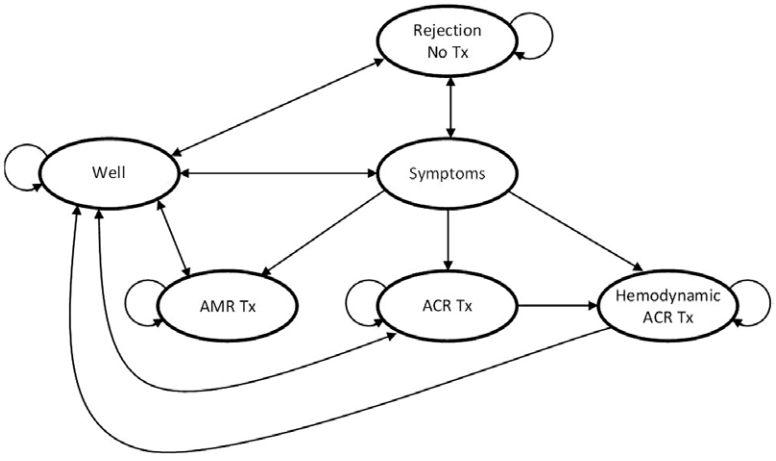

Figure. Markov model. Patients remain in a health state (circular arrows) or move from one health state to another (straight or curved arrows) on the basis of transition probabilities. As patients cycle through the model, they accumulate costs and utilities expressed as quality-adjusted life-years. The Markov cycle length is 1 month. Patients enter the model in either the well state or with signs or symptoms of rejection. During each cycle, patients can remain well, develop acute cellular rejection (ACR), develop hemodynamically significant ACR, develop antibody-mediated rejection (AMR), or die. For simplicity, the dead state is not shown in the figure. All states can transition to death.

Table 1. Costs (US$ 2010) Used in Baseline Analysis and Ranges Examined in Sensitivity Analysis

	Baseline	Range
Endomyocardial biopsy[13]	784	0–2000
AMR hospitalization[14]	28 995	2500–50 000
AMR treatment[13]	18 722	2000–30 000
Hemodynamic ACR hospitalization[14]	14 035	2500–30 000
Hemodynamic ACR treatment[13]	8350	1000–25 000
ACR hospitalization[14]	0	0–15 000
ACR treatment[13]	445	10–7500

ACR indicates acute cellular rejection; and AMR, antibody-mediated rejection.

utility of asymptomatic heart failure was used to represent nonhemodynamically significant rejection. The utility of New York Heart Association classes II and III heart failure was used as a surrogate for symptoms of rejection.

Sensitivity Analysis

One-way and multiway sensitivity analyses were performed. In the 1-way analyses, all variables were individually tested through the ranges shown in Tables 1 to 3. Monte Carlo (probabilistic) sensitivity analysis was performed for the multiway analysis. Monte Carlo analysis simultaneously varies all uncertain parameters over a range of values and probability distributions within that range producing a relative likelihood of resulting incremental cost-effectiveness ratios. Parameters were chosen randomly for 10 000 iterations of each biopsy strategy. Probability distributions were chosen based on the level of certainty of each parameter's distribution. Generally, these distributions were triangular with the baseline value used as the likeliest value, minimum value equal to 0.5 times the baseline, and the maximum value equal to 1.5 times the baseline. To evaluate greater uncertainty in the Monte Carlo analysis about the utility states and the frequency of rejection resolving with or without treatment, wider triangular distributions were used as shown in Table 4.

Table 2. Probabilities Used in Baseline Analysis and Ranges Examined in Sensitivity Analysis

	Baseline	Range
Developing rejection symptoms each month[15]	0.014	0.001–0.1
ACR		
Annual risk of asymptomatic ACR[16]	0.025	0.02–0.50
Likelihood of ACR given symptoms[16]	0.25	0.05–0.7
Probability of death with treated ACR[17]	0.02	0.01–0.9
Probability ACR resolves with treatment[18]	0.95	0.1–0.95
Hemodynamic ACR		
Likelihood of hemodynamic ACR given symptoms[19]	0.15	0.01–0.5
Probability of death with treated hemodynamic ACR[19]	0.06	0.01–0.9
Probability hemodynamic ACR resolves with treatment[18]	0.80	0.1–0.95
AMR		
Annual risk of asymptomatic AMR[20]	0.052	0.01–0.20
Likelihood of AMR given symptoms[19]	0.061	0.005–0.1
Probability of death with treated AMR[19]	0.20	0.01–0.8
Probability AMR resolves with treatment[20]	0.75	0.1–0.95
Untreated		
Probability of death with untreated asymptomatic rejection[17]	0.05	0.01–0.9
Probability asymptomatic rejection resolves without treatment[21]	0.25	0.0005–0.5

ACR indicates acute cellular rejection; and AMR, antibody-mediated rejection.

Table 3. Utilities Used in Baseline Analysis and Ranges Examined in Sensitivity Analysis

	Baseline	Range
Well state (in a post-transplant patient)[22]	0.76	0.1–0.99
Endomyocardial biopsy[23]	0.97	0.1–0.999
ACR[24]	0.865	0.1–0.99
Hemodynamic ACR[25]	0.5	0.1–0.9
Antibody-mediated rejection[25]	0.5	0.1–0.9
Hospitalization[26]	0.65	0.1–0.9
Symptoms of rejection[27]	0.8	0.1–0.99

ACR indicates acute cellular rejection.

Results

In the baseline analysis, stopping EMB at 12 months was dominant (more effective and less costly), saving $2884 per patient compared with the next least costly strategy (every 6 months for year 2 post-HT) and gaining 0.0011 quality-adjusted life-years (QALYs) when using the previously reported 2.5% annual risk of asymptomatic ACR. When compared with a prolonged strategy of biopsies every 6 months for 5 years post-transplant, the baseline strategy would save $22.5 million annually in the United States. More frequent and longer durations of continued surveillance biopsies were associated with higher costs and lower effectiveness (Table 5). To ensure that the model was not biased by an underestimate of the risk of asymptomatic ACR, a second baseline analysis was done using an 8.5% annual risk. In doing so, the extended surveillance EMB strategies for 24 months were no longer dominated. The strategy of EMB every 6 months for year 2 now gained 0.0006 QALYs compared with baseline, but cost $4 913 599 per QALY gained (Table 5). Using the 8.5% annual

Table 4. Specific Probabilities Used in Monte Carlo Sensitivity Analysis

	Likeliest	Minimum–Maximum
Probability ACR resolves with treatment	0.95	0.60–0.98
Probability hemodynamic ACR resolves with treatment	0.9	0.4–0.95
Probability AMR resolves with treatment	0.75	0.25–0.99
Probability asymptomatic rejection resolves without treatment	0.25	0.1–0.5
Utility of well state	0.76	0.5–0.95
Utility of endomyocardial biopsy	0.997	0.5–0.999
Utility of ACR	0.865	0.5–0.95
Utility of hemodynamic ACR	0.5	0.3–0.9
Utility of AMR	0.5	0.3–0.9
Utility of hospitalization	0.65	0.3–0.9
Utility of symptoms of rejection	0.8	0.4–0.9

ACR indicates acute cellular rejection; and AMR, antibody-mediated rejection.

Table 5. Results of the Baseline Analyses (2010 US$)

Biopsy Strategy	ICER–2.5% Annual Risk Asymptomatic Cellular Rejection	ICER–8.5% Annual Risk Asymptomatic Cellular Rejection
Baseline (stop 12 mo post-HT)		
Every 4 mo for 12–24 mo post-HT	Dominated*	$4 913 599†
Every 6 mo for 12–24 mo post-HT	Dominated*	$4 975 254†
Every 4 mo for 12–36 mo post-HT	Dominated*	Dominated*
Every 6 mo for 12–36 mo post-HT	Dominated*	Dominated*

HT indicates heart transplant; and ICER, incremental cost-effectiveness ratio.
*More costly and less effective than the baseline strategy.
†Per quality-adjusted life-year gained.

risk of asymptomatic ACR, scheduled surveillance EMB strategies after 24 months remained less effective and more costly.

Sensitivity Analysis

Individually varying all parameters through the ranges described in Tables 1 to 3 resulted in only 2 parameters that significantly impacted the model results. As the annual risk of asymptomatic ACR approaches 7%, the year 2 post-HT biopsy strategies are no longer dominated. Yet, even with an implausible 50% annual risk of asymptomatic ACR, the strategy of EMB every 6 months for year 2 post-HT gained 0.0132 QALYs compared with baseline, but still cost $170 249 per QALY gained. EMB for 12 months was also no longer dominant when mortality risk from untreated asymptomatic rejection approached 11%. Using an 11% rate of death from untreated asymptomatic rejection created a model where EMB every 6 months for year 2 post-HT gained 0.0001 QALYs, costing >$28 million per QALY. Competing strategies continued to cost >$200 000 per QALY even when that risk approached 99%. In general, medical interventions costing >$100 000 per QALY gained are considered an expensive use of healthcare resources.[28,29]

Monte Carlo sensitivity analyses were done using both the 2.5% and 8.5% annual risks of asymptomatic ACR. With the baseline 2.5% annual risk of asymptomatic ACR, stopping EMB at 12 months was favored in 98.3% of model iterations with a willingness to pay threshold of $250 000. Using the higher 8.5% annual risk of asymptomatic cellular rejection still resulted in >97% of model iterations favoring stopping EMB at 12 months.

Discussion

This study demonstrates that when using typical rates of ACR, surveillance EMB for 12 months post-HT is more effective and less costly than strategies where EMB is performed after 12 months. As would be expected, increasing the risk of asymptomatic ACR and risk of dying from untreated asymptomatic rejection resulted in a net improvement in effectiveness of the longer surveillance EMB strategies, but at considerable costs per QALY gained. Using an 8.5% annual risk of asymptomatic ACR, which is >3 times higher than previously published reports, resulted in a small benefit of surveillance biopsy strategies extending to 24 months. However, this was at a cost of almost $5 million per QALY gained. Additionally, when the risk of death from untreated asymptomatic rejection approached 11%, the longer surveillance biopsy strategies provided a small benefit but at a cost of >$28 million per QALY gained. Even as this risk approached 99%, the cost per QALY gained remained >$200 000.

Introduced in the early 1970s by the Stanford group, the modern use of routine EMB for monitoring cardiac allograft rejection has been adopted by nearly all HT centers.[30] There are small, but real, procedural risks associated with repeated EMB. Potential complications of EMB include severe tricuspid regurgitation, cardiac tamponade, arrhythmias, accidental arterial puncture, and bleeding.[8–10] Additionally, in patients requiring anticoagulation for other medical conditions, there are risks associated with interruption or bridging of this therapy to allow for biopsies. The rationale for surveillance biopsies and accepting this small risk is that early recognition and treatment of high-grade rejection (International Society for Heart & Lung Transplantation grade ≥2R) will decrease the risk of future allograft dysfunction or mortality. However, this practice was established in an era of less effective immunosuppression. With current immunosuppression regimens, the risk of significant rejection is ≈30% in the first year. This risk peaks at 1 month after transplant and then rapidly declines during the subsequent 5 months reaching a low near-constant rate by the end of the first year.[15] Therefore, the mean number of rejection episodes per patient decreases from 1.2 to 1.8 in the first year to 0.18, 0.13, and 0.02 in the second, third, and fourth years post-HT, respectively.[31] Additionally, between 60% and 85% of moderate grade rejection episodes (ie, International Society for Heart & Lung Transplantation 1990 grade 2 and some grade 3A or International Society for Heart & Lung Transplantation 2004 grade 1R and some 2R) resolve spontaneously without intensified immunosuppression and those that progress to higher grades of rejection generally occur within the first 6 months post-HT.[17,21] Untreated asymptomatic cellular rejection has also not been associated with an increase in mortality,[17] and previous studies have demonstrated no difference in mortality using a symptom-driven biopsy strategy.[16] In the setting of previously described low rates of asymptomatic rejection after 12 months post-HT, our model illustrated that prolonged EMB strategies are more costly and less effective than a symptom-driven approach. To demonstrate any effectiveness of a routine surveillance biopsy strategy after 1 year with our model required using rates of asymptomatic cellular rejection and an attendant mortality that are significantly higher than have been reported in published series.

Despite tremendous progress during the past 3 decades in the care of the transplant patient, there still is a lack of consensus on how to risk stratify patients and hence tailor post-transplant surveillance for rejection and graft dysfunction. Beyond the presence of histological evidence for rejection on an EMB, there are numerous other factors that programs consider when devising a post-transplant surveillance strategy. Our analysis did not include individual risk factors for rejection such as a shorter time since transplant, history of rejection, younger age, and black ethnicity. Patients with a higher risk of rejection therefore may derive greater benefit from routine surveillance EMB, and biopsy strategies may need to be individualized or modified based on the patient demographics of a particular transplant center. In particular, black

patients are at risk for hemodynamically significant rejection and worsened mortality and may benefit from continuing biopsy surveillance for up to 5 years post-transplant.[3,12] However, although nonblacks with risk factors are at a higher risk of late rejection, it may take ≥200 biopsies to prevent 1 hemodynamically significant episode without any clear survival benefit,[3] and our analysis may assist centers in deciding which surveillance strategy to use.

The diagnosis of rejection and the decision to treat often are made in the face of negative or inconclusive biopsies. Such patients may be treated for rejection if they have profound hemodynamic perturbations or worsening systolic dysfunction. This is particularly evident with antibody-mediated rejection, where only recently have consensus diagnostic pathology criteria been published.[32] The routine assessment of donor-specific antibodies is becoming more commonplace, and hence, the interpretation of donor-specific antibodies and the decision to alter therapy could potentially be affected by the findings on biopsy. Finally, the management of some patients may be affected by the invasive hemodynamics that are typically obtained in conjunction with the EMB. Hemodynamic perturbations not only can heighten the suspicion for rejection, but may also suggest restrictive physiology or aid in the management of patient's volume status. Although an invasive surveillance strategy may take all of this data into account, the bulk of patients who present for routine surveillance biopsies are asymptomatic and have normal hemodynamics, bland biopsy findings, and no donor-specific antibodies. Our data would suggest that continuing such an invasive strategy is not cost effective for the vast majority of transplant patients, but our knowledge of how to delineate the truly high-risk patient remains incomplete and will likely continue to evolve over time.

Cardiac transplantation remains the treatment of choice for patients with end-stage heart failure. It results in improved survival and quality of life. Current 1-year post-HT survival approaches 90% and the median survival is >10 years, making cardiac transplantation a critical therapeutic option for select patients. However, heart transplantation is inherently costly. The billed charges for the heart transplantation procedure alone are ≈$780 000 and they have increased disproportionately relative to inflation since 1983.[33] Charges for the first year post-HT approach $1 000 000.[34] Additionally, long-term costs of post-transplant care such as careful monitoring of immunosuppression, screening for rejection and transplant vasculopathy, and treating episodes of rejection can be as high as $70 000 per year.[35] Consequently, heart transplantation cannot be fairly evaluated using a $50 000 or $100 000 per QALY gained benchmarks that are generally used in cost-effectiveness analyses.[28,29] Society has largely accepted heart transplantation despite the high costs because of the lack of alternative treatments for generally young patients with a life-limiting illness. With the considerable initial costs associated with transplantation, it is sensible to continue significant investments in post-HT care and surveillance. However, with increasing pressures to contain costs, we must still attempt to minimize unnecessary or extreme costs. Although the incidence of serious complications related to EMB is <1%,[11] its diagnostic yield after 12 months post-HT is low, results in patient discomfort, and adds to the significant costs associated with transplantation. In our model, prolonged surveillance EMB was less effective than shorter duration surveillance, because of the loss of QALYs associated with repeated EMB outweighing the gains associated with the procedure. In the setting of higher than previously demonstrated rates of asymptomatic cellular rejection and death from untreated asymptomatic rejection, routine surveillance EMB was only minimally effective for ≤24 months. Even then, its costs were well beyond what would be considered economically reasonable, millions of dollars per QALY gained. Therefore, routine surveillance EMB after 1 year post-HT are not cost effective and their use should be reconsidered.

Limitations

Our analysis has several limitations. First, although most of our data inputs were based on prior studies of heart transplantation, these studies are generally small to moderate in size consisting of at most only a few hundred patients. Because of limited data in certain instances, such as the rate of ACR given symptoms of rejection and the risk of death given untreated rejection, expert opinion was used. In particular, the 2.5% risk of asymptomatic ACR was based on a series of patients who were treated during a different era of maintenance immunosuppression.[13] These patients were typically maintained with cyclosporine, azathioprine, and prednisone. With improved maintenance immunosuppression, it is possible that the risk of asymptomatic ACR is even lower and our analysis underestimated the cost associated with prolonged surveillance EMB. Second, treatment patterns for rejection (and therefore costs) vary among transplant centers. Less costly treatments, such as oral prednisone for ACR, may result in a more favorable cost-effectiveness analysis. Third, many centers now use gene expression profiling tests to monitor for rejection after 12 months post-HT. We did not evaluate the use of these tests and only assessed the cost of biopsy surveillance compared with no routine surveillance. However, gene expression profiling may not offer any cost benefit over EMBs for prolonged surveillance.[36] Finally, our model did not account for outcomes after 36 months and therefore may underestimate any delayed benefits of detecting asymptomatic rejection after 12 months post-HT. There may be a relationship between asymptomatic rejection and coronary artery vasculopathy; however, the impact of discontinuing surveillance biopsies after 1 year on the rates of vasculopathy could not be determined with this study and would require much longer term follow-up. However, asymptomatic rejection after 3 years remains rare and there continues to be controversy about whether rejection that occurs this late after HT has long-term negative effects.[37]

Conclusions

Given currently accepted rates of rejection, using surveillance EMB for only the first 12 months post-HT is more effective and less costly than strategies where surveillance EMB is performed after 12 months. Even in the setting of improbably high rates of asymptomatic rejection and mortality, the costs per QALY remain exceedingly high for performing surveillance EMB after 1 year. The role of surveillance EMB for cardiac transplant patients after 1 year should be reassessed.

Disclosures

None.

References

1. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Yusen RD, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report–2013; focus theme: age. *J Heart Lung Transplant*. 2013;32:951–964.
2. Kobashigawa J, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R, Costanzo M, Eisen H, Dureau G, Ratkovec R, Hummel M, Ipe D, Johnson J, Keogh A, Mamelok R, Mancini D, Smart F, Valantine H. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. *Transplantation*. 1998;66:507–515.
3. Stehlik J, Starling RC, Movsesian MA, Fang JC, Brown RN, Hess ML, Lewis NP, Kirklin JK; Cardiac Transplant Research Database Group. Utility of long-term surveillance endomyocardial biopsy: a multi-institutional analysis. *J Heart Lung Transplant*. 2006;25:1402–1409.
4. Gradek WQ, D'Amico C, Smith AL, Vega D, Book WM. Routine surveillance endomyocardial biopsy continues to detect significant rejection late after heart transplantation. *J Heart Lung Transplant*. 2001;20:497–502.
5. Radovancevic B, Konuralp C, Vrtovec B, Radovancevic R, Thomas CD, Zaqqa M, Vaughn WK, Frazier OH. Factors predicting 10-year survival after heart transplantation. *J Heart Lung Transplant*. 2005;24:156–159.
6. Raichlin E, Edwards BS, Kremers WK, Clavell AL, Rodeheffer RJ, Frantz RP, Pereira NL, Daly RC, McGregor CG, Lerman A, Kushwaha SS. Acute cellular rejection and the subsequent development of allograft vasculopathy after cardiac transplantation. *J Heart Lung Transplant*. 2009;28:320–327.
7. Brunner-La Rocca HP, Schneider J, Künzli A, Turina M, Kiowski W. Cardiac allograft rejection late after transplantation is a risk factor for graft coronary artery disease. *Transplantation*. 1998;65:538–543.
8. Baraldi-Junkins C, Levin HR, Kasper EK, Rayburn BK, Herskowitz A, Baughman KL. Complications of endomyocardial biopsy in heart transplant patients. *J Heart Lung Transplant*. 1993;12(1 pt 1):63–67.
9. Bhat G, Burwig S, Walsh R. Morbidity of endomyocardial biopsy in cardiac transplant recipients. *Am Heart J*. 1993;125:1180–1181.
10. Williams MJ, Lee MY, DiSalvo TG, Dec GW, Picard MH, Palacios IF, Semigran MJ. Biopsy-induced flail tricuspid leaflet and tricuspid regurgitation following orthotopic cardiac transplantation. *Am J Cardiol*. 1996;77:1339–1344.
11. Hamour IM, Burke MM, Bell AD, Panicker MG, Banerjee R, Banner NR. Limited utility of endomyocardial biopsy in the first year after heart transplantation. *Transplantation*. 2008;85:969–974.
12. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J; International Society of Heart and Lung Transplantation Guidelines. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2010;29:914–956.
13. Centers for Medicare & Medicaid Services. CMS physician fee schedule search. http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx. Accessed May 21, 2013.
14. Agency for Health Research Quality. *HCUP National Statistics on All Stays*. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed May 21, 2013.
15. Kubo SH, Naftel DC, Mills RM Jr, O'Donnell J, Rodeheffer RJ, Cintron GB, Kenzora JL, Bourge RC, Kirklin JK. Risk factors for late recurrent rejection after heart transplantation: a multiinstitutional, multivariable analysis. Cardiac Transplant Research Database Group. *J Heart Lung Transplant*. 1995;14:409–418.
16. Orrego CM, Cordero-Reyes AM, Estep JD, Loebe M, Torre-Amione G. Usefulness of routine surveillance endomyocardial biopsy 6 months after heart transplantation. *J Heart Lung Transplant*. 2012;31:845–849.
17. Winters GL, Loh E, Schoen FJ. Natural history of focal moderate cardiac allograft rejection. Is treatment warranted? *Circulation*. 1995;91:1975–1980.
18. Eisen HJ, Jessup M. Acute cardiac allograft rejection: treatment. In: Hunt S, ed. *UpToDate*. http://www.uptodate.com/contents/acute-cardiac-allograft-rejection-treatment. Updated July 8, 2013.
19. Shahzad K, Aziz QA, Leva JP, Cadeiras M, Ho EK, Vlad G, Vasilescu ER, Latif F, Sinha A, Burke E, Addonizio LJ, Restaino SW, Marboe CC, Suciu-Foca N, Naka Y, Mancini D, Deng MC. New-onset graft dysfunction after heart transplantation–incidence and mechanism-related outcomes. *J Heart Lung Transplant*. 2011;30:194–203.
20. Kfoury AG, Snow GL, Budge D, Alharethi RA, Stehlik J, Everitt MD, Miller DV, Drakos SG, Reid BB, Revelo MP, Gilbert EM, Selzman CH, Bader FM, Connelly JJ, Hammond ME. A longitudinal study of the course of asymptomatic antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant*. 2012;31:46–51.
21. Brunner-La Rocca HP, Sütsch G, Schneider J, Follath F, Kiowski W. Natural course of moderate cardiac allograft rejection (International Society for Heart Transplantation grade 2) early and late after transplantation. *Circulation*. 1996;94:1334–1338.
22. Moreno SG, Novielli N, Cooper NJ. Cost-effectiveness of the implantable HeartMate II left ventricular assist device for patients awaiting heart transplantation. *J Heart Lung Transplant*. 2012;31:450–458.
23. Wong JB, Sonnenberg FA, Salem DN, Pauker SG. Myocardial revascularization for chronic stable angina. Analysis of the role of percutaneous transluminal coronary angioplasty based on data available in 1989. *Ann Intern Med*. 1990;113:852–871.
24. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. *J Am Coll Cardiol*. 2004;43:1019–1026.
25. Morton RL, Howard K, Webster AC, Wong G, Craig JC. The cost-effectiveness of induction immunosuppression in kidney transplantation. *Nephrol Dial Transplant*. 2009;24:2258–2269.
26. Rosen VM, Taylor DC, Parekh H, Pandya A, Thompson D, Kuznik A, Waters DD, Drummond M, Weinstein MC. Cost effectiveness of intensive lipid-lowering treatment for patients with congestive heart failure and coronary heart disease in the US. *Pharmacoeconomics*. 2010;28:47–60.
27. Kühr EM, Ribeiro RA, Rohde LE, Polanczyk CA. Cost-effectiveness of supervised exercise therapy in heart failure patients. *Value Health*. 2011;14(5 suppl 1):S100–S107.
28. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med*. 2003;163:1637–1641.
29. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008;46:349–356.
30. Caves PK, Stinson EB, Graham AF, Billingham ME, Grehl TM, Shumway NE. Percutaneous transvenous endomyocardial biopsy. *JAMA*. 1973;225:288–291.
31. Kirklin JK, Naftel DC, Bourge RC, White-Williams C, Caulfield JB, Tarkka MR, Holman WL, Zorn GL Jr. Rejection after cardiac transplantation. A time-related risk factor analysis. *Circulation*. 1992;86(5 suppl):II236–II241.
32. Berry GJ, Burke MM, Andersen C, Bruneval P, Fedrigo M, Fishbein MC, Goddard M, Hammond EH, Leone O, Marboe C, Miller D, Neil D, Rassl D, Revelo MP, Rice A, Rene Rodriguez E, Stewart S, Tan CD, Winters GL, West L, Mehra MR, Angelini A. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant*. 2013;32:1147–1162.
33. Evans RW. Aggregate Annual Health Care Expenditures Associated with Heart Transplantation in the United States: 1980:2011. *J Heart Lung Transplant*. 2013;32:S159.
34. UNOS. *Costs of Transplantation*. http://www.transplantliving.org/before-the-transplant/financing-a-transplant/the-costs/. Accessed November 20, 2013.
35. Mark DB. Economics and cost effectiveness in cardiology. In: O'Rourke RA, Fuster V, Alexander RW, eds. *Hurst's the Heart Manual of Cardiology*. 13th ed. New York, NY: McGraw Hill; 2011:2389–2408.
36. Heidenreich PA, Pham MX, Teuteberg JJ, Kfoury AG, Starling RC, Deng MC, Cappola TP, Kao A, Anderson AS, Cotts WG, Ewald GA,

Baran DA, Bogaev RC, Elashoff B, Baron H, Yee J, Valantine HA. Economic Impact of Monitoring Heart Transplant Recipients With Gene Expression Profiling to Detect Rejection: an IMAGE Analysis. *J Card Fail*. 2010;16:911–912.

37. Klingenberg R, Koch A, Schnabel PA, Zimmermann R, Sack FU, Haass M, Dengler TJ. Allograft rejection of ISHLT grade >/=3A occurring late after heart transplantation–a distinct entity? *J Heart Lung Transplant*. 2003;22:1005–1013.

CLINICAL PERSPECTIVE

Rejection monitoring strategies are a subject of debate both within and between transplant centers. Despite low rates of rejection and retrospective studies demonstrating the safety of a symptom-driven biopsy strategy after the first year post-transplant, many transplant centers continue routine surveillance biopsies for ≤5 years post-transplant. The motivation for this strategy is that early recognition and treatment of rejection may decrease future adverse events. Yet, endomyocardial biopsies are associated with a small, but real, risk of complications and add considerable cost to the already expensive post-transplant management. We modeled the cost-effectiveness of prolonged biopsy strategies versus a baseline strategy of stopping biopsies at 1 year post-transplant. Our results demonstrate that in the absence of markedly higher rates of asymptomatic cellular rejection and its mortality than previously described, prolonged biopsy strategies are less effective and more costly than a strategy of stopping biopsies after 1 year. With a randomized trial of biopsy strategies unlikely to happen, our model adds to the existing evidence about the safety and possible clinical disadvantage of prolonged biopsy strategies. To our knowledge, our study is also the first to quantify the cost associated with prolonged biopsies. We think this is valuable information to add to the conversation within the transplant community and at individual centers about what is the appropriate length of time to continue routine surveillance biopsies.

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