

Role of Skin Biopsy to Confirm Suspected Acute Graft-vs-Host Disease

Results of Decision Analysis

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Objective: To estimate the value of skin biopsy in the evaluation of suspected acute cutaneous graft-vs-host disease (GVHD) after allogeneic stem cell transplantation.

Design: Decision analysis using parameters specified by expert opinion for skin biopsy characteristics, prevalence of acute GVHD, and value of potential outcomes. One-, 2-, and 3-way sensitivity analyses were performed.

Setting: Major stem cell transplantation centers in the United States.

Patients: Hypothetical cohort of patients with suspected acute cutaneous GVHD after stem cell transplantation.

Interventions: The following 3 interventions were compared: treat immediately for GVHD without performing a skin biopsy, perform a skin biopsy and treat immediately but stop treatment if skin biopsy specimen findings are inconsistent with GVHD, and perform a skin biopsy and await results of the skin biopsy specimen before treating.

Main Outcome Measures: Number of patients appropriately and inappropriately treated with each intervention, consistency of physician-reported behavior, in-

dividualized decision analyses, and preferred intervention based on the aggregate estimates of respondents.

Results: The decision to treat immediately for GVHD without performing a skin biopsy yielded the best clinical outcome for the specified clinical setting and under the parameters specified by expert opinion. One-way sensitivity analyses showed that these conclusions are robust if the prevalence of acute cutaneous GVHD in stem cell recipients with rash is greater than 50%, if the sensitivity of skin biopsy specimen is less than 0.8, and the specificity of skin biopsy specimen is less than 0.9. Only 25% of physicians interviewed chose an intervention consistent with their estimates of prevalence, test characteristics, and outcome evaluations, indicating an opportunity to improve management of this important clinical condition.

Conclusions: This decision analysis modeling technique predicts that in patient populations in which the prevalence of GVHD is 30% or greater (typical for allogeneic stem cell transplantation), the best outcomes were obtained with treatment for GVHD and no skin biopsy. In populations with prevalence of GVHD of 30% or less, obtaining a skin biopsy specimen to guide treatment was predicted to provide the best patient outcomes.

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ACUTE GRAFT-VS-HOST DISEASE (GVHD) in allogeneic stem cell transplantation (SCT) is a complex immunologic phenomenon involving donor T cells, cytokines, and host tissue reactions. Graft-vs-host disease is a frequent complication of SCT. Acute GVHD manifests in the first 3 months after transplantation, and the main target organs include the skin, the liver, and the gastrointestinal tract. Clinical features of acute cutaneous GVHD include a disseminated exanthem characterized by acral erythema and often a scarlatiniform eruption that may progress to erythroderma.¹ Clinically significant acute GVHD is estimated to occur in 6% to 90% of graft recipients,

depending on patient age, HLA type, and prevention protocols used.² A clinical staging system (grades 0 [best] to IV [worse]) based on degree of organ involvement has been used as an important prognostic indicator. The diagnosis of acute GVHD can have profound implications on prognosis;

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approximately 90% of patients with no or minimal (grade I) acute GVHD survive to day 100 compared with 60% of patients with grades II or III disease and 0% to 20% of patients with grade IV disease.³ Staging and grading criteria for acute GVHD used in this study are summarized in **Table 1**.

Table 1. Staging and Grading of Acute GVHD*

Acute GVHD	Organ Involvement		
	Skin	Liver, Bilirubin Level, mg/dL	Gastrointestinal Tract
Stage			
1+	Erythematous rash <25% of BSA	2-3	Diarrhea >500 mL/d or persistent nausea
2+	Erythematous rash 25%-50% of BSA	4-6	Diarrhea >1000 mL/d
3+	Erythematous rash >50% of BSA, and erythroderma	7-15	Diarrhea >1500 mL/d
4+	Generalized erythroderma with bulla formation	>15	Severe abdominal pain with or without ileus
Grade			
I	1+ to 2+	0	0
II	1+ to 3+	1+	1+
III	2+ to 3+	2+ to 3+	2+ to 4+
IV	4+	4+	NA

Abbreviations: BSA, body surface area; GVHD, graft-vs-host disease; NA, not available.

*Data from Przepiorka et al.⁴

Initially, the diagnosis of acute GVHD involving the skin is difficult to make because the eruption can be morphologically nonspecific, appearing as an erythematous macular rash. Differential diagnosis of an erythematous rash is broad in patients after SCT and includes cutaneous reactions to chemotherapy or radiation therapy, adverse drug reactions, and viral infections. In a patient with a skin eruption, the presence of extracutaneous GVHD is helpful in making the diagnosis and determining the need for therapy. However, hepatic and gastrointestinal tract involvement often are not present because the skin is the most common site of GVHD and frequently is the first organ to demonstrate clinical findings. Further workup usually includes obtaining a skin biopsy specimen.

Significant controversy involves the use and timing of skin biopsy in the diagnosis of acute cutaneous GVHD in SCT recipients. The value of obtaining a skin biopsy specimen after SCT depends on at least 2 schools of thought about acute GVHD management. Some clinicians assert that cautious use of immunosuppression therapy is warranted because of the high risk for sepsis in patients recovering from SCT. Others maintain that delaying appropriate therapy for GVHD can lead to rapid progression of the disease and that, therefore, immunosuppression therapy should be considered immediately in patients with a skin eruption when the probability of GVHD is high.⁵ This rationale is supported by the high prevalence of GVHD in patients who have an erythematous eruption involving more than 60% of the body surface area a few days after undergoing SCT.

Although the sensitivity and specificity of a skin biopsy specimen in suspected acute GVHD has not been established, clinicians continue to obtain skin biopsy specimens when considering the possibility of acute GVHD after SCT. Previous studies have established that certain histologic changes evident in patients with acute GVHD, such

as lymphocytic infiltrate at the basement membrane with exocytosis and spongiosis, are pathologically indistinguishable from common differential diagnoses of rash after SCT, including irradiation dermatitis and drug reactions.^{6,7} Another study demonstrated that in 80% of rash skin biopsy specimens obtained after SCT the findings were interpreted by pathologists as nonspecific and unequivocal, 76% of patients were treated empirically before biopsy specimen results were available, and in only 5.5% of patients was treatment changed based on biopsy specimen results.⁸ A recent retrospective analysis showed that skin biopsy specimen findings are poorly correlated with the clinical severity of rash suggestive of acute GVHD early after SCT.⁹ This study found no significant difference between patients with positive biopsy specimen findings and those with negative biopsy specimen findings, either in the clinical severity of acute GVHD or in the likelihood of receiving treatment for GVHD. They found that the decision to treat suspected acute GVHD depended on clinical suspicion, not on biopsy specimen findings, and, therefore, suggested that skin biopsy has a limited role in the management of eruptions in the early period after SCT.

Inasmuch as the optimal management intervention likely hinges on the pretest probability of acute GVHD, the test characteristics of the skin biopsy specimen to confirm acute GVHD (sensitivity and specificity), and the relative consequences of appropriate and inappropriate treatment, we performed a decision analysis to investigate the interaction between these factors. Decision analysis is a method to aggregate diverse considerations pertinent to a decision so that the best clinical choice can be made in the absence of clear experimental or observational data.^{10,11} Hence, this approach enables simultaneous consideration of the risks and benefits of skin biopsy after SCT: appropriate treatment of GVHD, missed or delayed treatment of GVHD in patients with negative skin biopsy specimen findings, and inappropriate treatment in patients without GVHD but with positive skin biopsy specimen findings. A traditional decision analysis model would use survival curves, receiver operating characteristic curves, and other evidence-based data. An extensive literature search failed to provide data necessary for the model, including sensitivity and specificity of skin biopsy specimens and occurrence of adverse outcomes. Therefore, this modeling approach used expert opinion to estimate test characteristics of skin biopsy specimens and to provide valuations for the relative benefit-risk ratio of appropriate vs inappropriate treatment of GVHD. Our results should be used to guide further research to better understand the role of skin biopsy after SCT.

METHODS

STUDY DESIGN

A computerized decision model was created to reflect the following 3 interventions of interest: treating immediately for acute GVHD without performing a skin biopsy; performing a skin biopsy, treating immediately for GVHD, and stopping treatment if skin biopsy specimen findings were inconsistent with GVHD; and performing a skin biopsy and treating based on results (**Figure 1**). A comprehensive literature review (MEDLINE

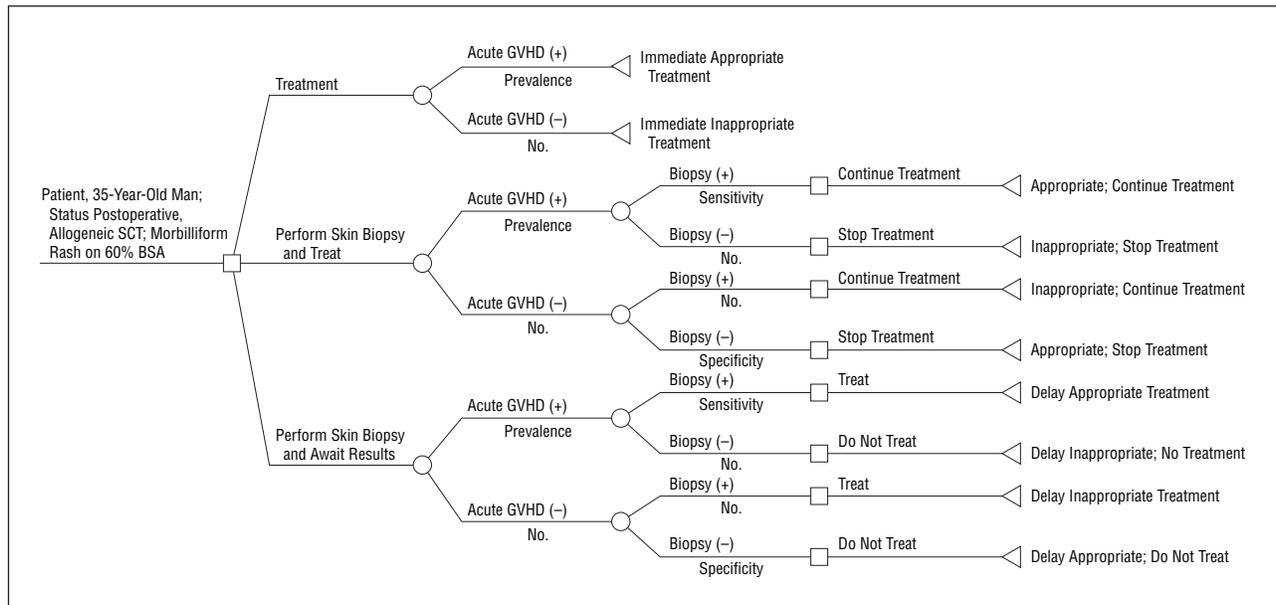


Figure 1. Decision tree for skin biopsy constructed for this model shows the following 3 main branch points: treatment, perform skin biopsy and treat, and perform skin biopsy and await results. BSA indicates body surface area; GVHD, graft-vs-host disease; and SCT, stem cell transplantation.

search, review of references) failed to provide data needed for the model. Specifically, we sought the prevalence of acute GVHD after SCT in patients with rash, the sensitivity and specificity of the skin biopsy specimen to confirm acute GVHD, and survival curves for undertreatment in patients with GVHD and overtreatment in patients without GVHD. Therefore, expert opinion was obtained, a method used when there is lack of data for decision models.^{12,13}

SURVEY

A questionnaire was developed to elicit expert opinion for the prevalence of GVHD and the sensitivity and specificity of skin biopsy. A pilot questionnaire was used in 5 test subjects excluded from the final sample. Minor modifications in wording were made, and an e-mail was sent to several academic centers to request participation from experts in the field. We identified a convenience sample of 17 oncologic opinion leaders and 26 dermatologic opinion leaders to participate in the study. Fifteen-minute telephone interviews were conducted with 6 dermatologists and 10 oncologists who agreed to participate. Participating institutions included Oregon Health Sciences University, Corvallis; City of Hope, Duarte, Calif; Fred Hutchinson Cancer Research Center, Seattle, Wash; University of Minnesota, Rochester; M. D. Anderson Cancer Center, Houston, Tex; Dana-Farber Cancer Institute, Boston, Mass; National Institutes of Health, Bethesda, Md; University of Michigan, Ann Arbor; Duke University, Durham, NC; University of Arkansas, Little Rock; and University of Nebraska, Omaha.

The first part of the questionnaire assessed physician characteristics, namely, years in practice and approximate number of patients with GVHD seen per year. The second part presented a clinical scenario involving a patient in whom a rash developed 14 days after SCT, with the differential diagnosis including drug eruption or acute cutaneous GVHD. This clinical scenario was chosen to assess expert opinion about the utility of obtaining a skin biopsy specimen in the most controversial setting, that is, early after SCT when skin biopsy seems to be least helpful. Physicians were asked if they would choose to treat for acute GVHD, obtain a skin biopsy specimen and await results, or obtain a skin biopsy specimen and treat immediately but adjust therapy based

on skin biopsy specimen results. They were asked to estimate the probability that the patient has acute GVHD or the prevalence of GVHD, and their understanding of the sensitivity and specificity of obtaining a skin biopsy specimen in this setting. High sensitivity of skin biopsy was defined as skin biopsy specimen findings highly suggestive of GVHD if the patient in fact had GVHD. High specificity was defined as skin biopsy specimen findings not suggestive of GVHD if the patient in fact did not have GVHD. Measures of internal consistency were included in the questionnaire to ensure that individual estimates of test characteristics were reliable.

Physicians were also asked to rate the desirability of different clinical outcomes using a direct rating method. Six health states in patients with a rash after SCT were described: no GVHD, immediate treatment of GVHD, delayed treatment of GVHD, no treatment in a patient with GVHD, full and inappropriate treatment in a patient without GVHD, and inappropriate but abbreviated treatment in a patient without GVHD. We decided to use a direct rating method rather than elicit utilities for each specific health state using time trade-off or standard gamble techniques. Direct rating methods, including category rating and visual analog scales, require judges to assign a value to each health state, usually on a scale of 0 (least desirable or death) to 100 (most desirable or perfect health). The clinicians in this study were asked to rate the 6 health states on a scale of -10 to +10, with -10 representing the worst clinical outcome; 0, not clinically material; and +10, the best clinical outcome. The values were normalized to a scale of 0 to 1, with 0 representing the least desirable outcome and 1 the most desirable outcome; however, these values should not be interpreted as true utilities for the outcomes assessed.

STATISTICAL ANALYSIS

A 2-sided *t* test was used to test for significant differences in the clinical experience of dermatologists and oncologists in the field (Stata software, version 8; StataCorp LP, College Station, Tex). Internal consistency between stated and inferred values for test characteristics was evaluated with the Wilcoxon signed rank test for matched pairs.

Table 2. Baseline Characteristics of Respondents*

Baseline Characteristic	Oncologists	Dermatologists	P Value†
No. of SCT recipients seen per year	102 (73)	60 (77)	.31
No. of patients with GVHD seen per year	42 (24)	42 (60)	.98
No. of patients with stage 3+ cutaneous GVHD seen per year	16.5 (15)	26.5 (40)	.58
No. of years in practice	18 (6)	22 (13)	.55

Abbreviations: GVHD, graft-vs-host disease; SCT, stem cell transplantation.

*Data are given as mean (SD).

†Two-sided *t* test comparing oncologists and dermatologists.

Table 3. Estimates of Skin Biopsy Characteristics*

Skin Biopsy Characteristic	Estimates	Calculated Estimates	P Value†
Sensitivity	0.73 (0.24)	0.77 (0.20)	.74
Specificity	0.66 (0.20)	0.60 (0.21)	.09
Positive predictive value	0.75 (0.15)	0.76 (0.22)	.61
Negative predictive value	0.57 (0.24)	0.65 (0.25)	.30
Prevalence	0.58 (0.27)	NA	NA

Abbreviation: NA, not available.

*Data are given as the mean (SD).

†Wilcoxon signed rank test for matched pairs.

DECISION ANALYSIS AND SENSITIVITY ANALYSIS

Means (SD) of the prevalence, test characteristics, and outcome ratings were calculated and entered in the final decision model (TreeAge Software, Williamstown, Mass). First, the optimal decision under the specified clinical scenario was obtained based on expert estimates. Second, because the quantities incorporated in the decision tree are based on best estimates from expert opinion, we performed a sensitivity analysis. Sensitivity analysis examines parameter uncertainty; it varies the estimates of certain parameters and evaluates whether the optimal decision would change as parameter estimates change. Each parameter may be varied individually (1-way analysis) or together (2-way and 3-way analyses). One-, 2-, and 3-way sensitivity analyses were performed on 3 variables in the model, namely, prevalence of disease and test characteristics, sensitivity, and specificity, to determine whether the decision to obtain a skin biopsy specimen would change for certain parameter values. Third, estimates from each physician were entered in individual decision trees to calculate each respondent's optimal decision, given his or her estimates of disease prevalence and skin biopsy test characteristics. This calculated decision for each physician was then compared with the physician's stated preference to obtain a skin biopsy specimen in the clinical setting given. This was performed to determine whether physician decision making correlated with opinions on skin biopsy as a discriminatory test.

RESULTS

The baseline characteristics of the physicians interviewed are given in **Table 2**. There were no statistically significant differences between dermatologists and oncologists for any baseline characteristics, namely, years in practice or number of patients with GVHD seen per year. The physicians interviewed had been in practice on average for 19 years, reflecting substantial clinical experience. In addition, physicians evaluated on average 86 SCT recipients per year and estimated that clinically relevant GVHD developed in approximately 50% of these patients.

Based on the hypothetical clinical scenario given to the physicians, the prevalence of GVHD in a patient with a rash after SCT was 58% (SD, 27%). Only 25% of physicians stated that they would not perform a skin biopsy and would treat immediately with immunosuppressive agents; 31% would perform a skin biopsy and await results be-

fore treating; and 44% would treat and perform a skin biopsy concomitantly, modifying therapy when biopsy specimen results became available. Each physician's estimates were entered in individual decision trees and a calculated decision was compared with their stated decision to perform a skin biopsy or not. Of all of the physicians evaluated, 25% gave estimates that predicted their real decision to perform a skin biopsy or not. In other words, one fourth of the physicians made a decision in clinical practice that was consistent with the best-calculated decision, given their ideas of skin biopsy test characteristics and consequences of clinical decision making.

The mean (SD) values of the parameters entered in the model are given in **Table 3**. On average, the physicians interviewed rated the sensitivity of the skin biopsy specimen higher than the specificity. Both values for sensitivity and specificity were estimated to be less than 80%, an important parameter after considering the sensitivity analysis. Inferred estimates for sensitivity and specificity were derived by calculating these values from stated false-positive and false-negative estimates. The questionnaire showed internal consistency because none of the inferred estimates for skin biopsy characteristics were substantially different from stated values of sensitivity and specificity of the skin biopsy specimen.

Results from the decision analysis show that the decision to treat immediately would result in appropriate treatment of GVHD in 58% of patients vs treatment in 42% of patients without GVHD. In the skin biopsy and treatment arm, fewer patients with GVHD would receive appropriate treatment (43% vs 58%), 16% with acute GVHD would not receive therapy, and 27% without GVHD would not receive treatment. In this scenario, fewer patients without GVHD (14% vs 42%) would receive immunosuppressive therapy inappropriately.

The outcome ratings as specified by the physicians and entered in the decision model are given in **Table 4**. A scale of -10 (poorest outcome) to +10 (best outcome) was used. Physicians thought that immediately treating GVHD yielded the best clinical outcome (7.9), whereas misdiagnosing GVHD and therefore not treating was the worst clinical outcome (-8.7). The consequence of overtreating in a patient without GVHD was not perceived as poorly (+0.19) as undertreating in a patient with GVHD (-2.4).

A sensitivity analysis was performed on the parameters in the model to determine whether the decision would change based on varying estimates for sensitivity and specificity of skin biopsy specimen results and for prevalence of disease. This was warranted because the parameters in the model were based on expert opinion. It also enables individual readers to evaluate the optimal decision based on parameter values that pertain to their specific institutions; that is, if they consider the sensitivity of the skin biopsy specimen result to be very high at their institution, then the decision may change accordingly. One-way sensitivity analysis (**Figure 2**) showed that treating immediately was the best option, given the clinical scenario, if the prevalence of GVHD in SCT recipients with rash is greater than 50%. With prevalence between 30% and 50%, performing a skin biopsy and treating was the best option, whereas performing a skin biopsy and awaiting results was best if the prevalence of GVHD was less than 30%. With a prevalence of 58%, treating immediately was the best decision if the sensitivity of the skin biopsy specimen was less than 0.8 and the specificity of the skin biopsy specimen was less than 0.9. The baseline estimates for sensitivity and specificity according to expert opinion were 0.73 and 0.66, respectively. Overall, the decision to simultaneously perform a skin biopsy and treat, with revision of treatment according to skin biopsy specimen results, yielded the best clinical outcome only if the sensitivity and specificity of the skin biopsy specimen are very high.

Two-way sensitivity analyses were used to evaluate the effects of changing prevalence and individual test characteristics simultaneously (**Figure 3**). We found that for a low prevalence of GVHD (<30%), sensitivity of the skin biopsy specimen result did not matter and that the decision to perform a skin biopsy and await results seemed to be best. For high prevalence of GVHD (>50%), sensitivity of the skin biopsy specimen result also did not seem to matter, and the decision to treat immediately seemed to be best. For intermediate values of GVHD prevalence (30% < prevalence < 50%), the sensitivity of the skin biopsy specimen result affected the treatment strategy; for high sensitivity, to perform a skin biopsy and treat was the decision, and for low sensitivity, to treat immediately was the decision. For GVHD prevalence greater than 55%, specificity of the skin biopsy specimen result did not affect results and the option to treat immediately seemed better. For lower GVHD prevalence, to perform a skin biopsy and treat was better if the specificity was high; otherwise to perform a skin biopsy and await results was better. When varying the sensitivity and specificity of the skin biopsy specimen result simultaneously, the option to perform a skin biopsy and treat was only optimal if both sensitivity and specificity were very high.

Three-way sensitivity analyses confirmed these conclusions. For high prevalence of GVHD, only when values for sensitivity and specificity were very high was the option to perform a skin biopsy and treat optimal; otherwise, the option to treat immediately was better. For intermediate prevalence of GVHD, high sensitivity and specificity made the option to perform a skin biopsy and treat optimal (**Figure 4A**). For low prevalence of GVHD, if both sensitivity and specificity were high, the option to per-

Table 4. Outcome Ratings

Values of Outcomes by Rating Scale	Mean (SD)	Adjusted Scale, 0-1 (Range)
Appropriately treating GVHD immediately	7.9 (2.6)	1.00 (0.75-1.00)
Avoiding treatment in a patient with rash but without GVHD	5.1 (3.9)	0.81 (0.55-0.93)
Rapid taper of steroid therapy in a patient with rash but without GVHD	0.19 (2.1)	0.54 (0.41-0.66)
Initiating treatment late in a patient with GVHD	-2.4 (4.8)	0.38 (0.15-0.61)
Full course of steroid therapy in a patient with rash but without GVHD	-6.5 (2.3)	0.13 (0.08-0.30)
No treatment in a patient with GVHD	-8.7 (1.7)	0.00 (0.00-0.16)

Abbreviation: GVHD, graft-vs-host disease.

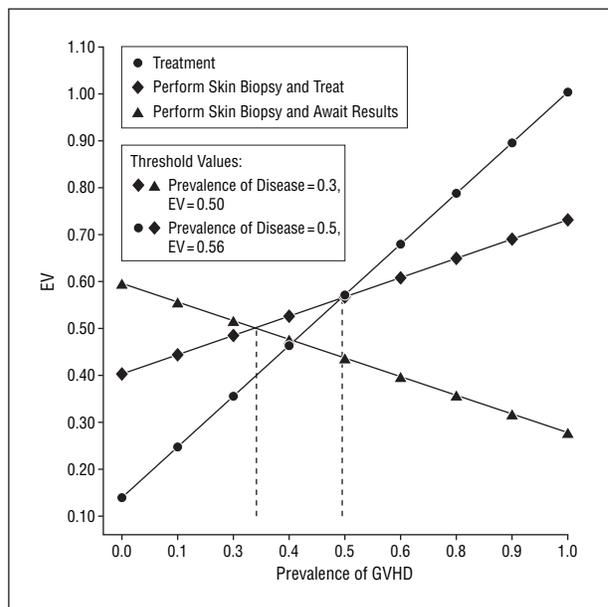


Figure 2. One-way sensitivity analysis of prevalence of acute graft-vs-host disease (GVHD) in stem cell recipients has an effect on the treatment decision. For low prevalence (<30%), performing a skin biopsy and awaiting results is the best option; for intermediate prevalence (30% < prevalence < 50%), performing a skin biopsy and treating is best; for high prevalence (>50%), treating immediately is best. EV indicates expected value. First dashed line indicates the point at which the biopsy and await results and biopsy and treat are equivalent options. Second dashed line, point at which treatment vs biopsy and treat options are equivalent.

form a skin biopsy and await results was optimal (**Figure 4B**).

COMMENT

The skin biopsy has limited specificity as a single test in the diagnosis of acute cutaneous GVHD. When considered in the context of other target organ dysfunction and evaluation of the individual patient, skin biopsy findings can help rule out other diagnoses. Our decision analysis based on expert estimates of the prevalence of acute

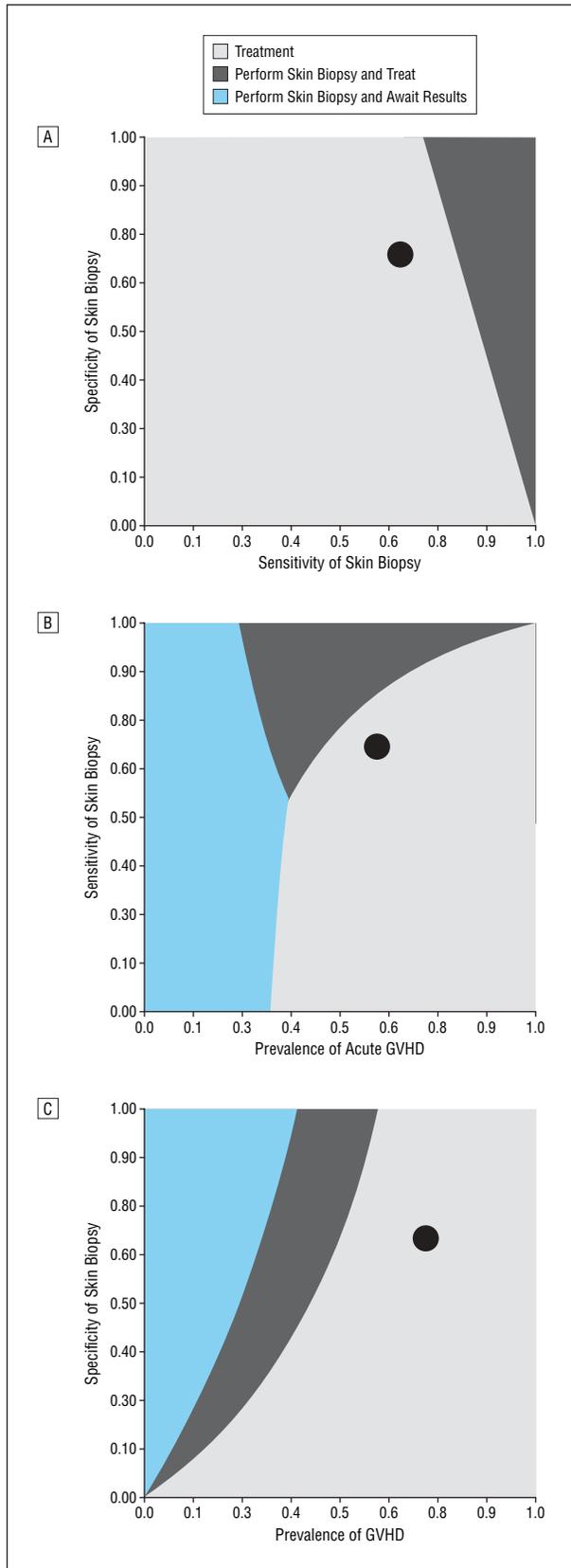


Figure 3. Impact of skin biopsy specimen characteristics on medical decision making. A, Two-way sensitivity analysis of sensitivity and specificity of skin biopsy. Black dot shows the mean expert estimates for sensitivity (0.73) and specificity (0.66) of skin biopsy specimen results. Based on these estimates, the treat-immediately option prevails. Varying both specificity and sensitivity together affects the treatment decision. If both are high, performing a skin biopsy and treating is the best option; if they are both less than 0.8, as the experts have estimated, treating immediately is best; if sensitivity of skin biopsy is very high, performing a skin biopsy and treating is best even if specificity is very low. B, Two-way sensitivity analysis of prevalence of graft-vs-host disease (GVHD) and sensitivity of skin biopsy. Black dot shows the mean expert estimates for prevalence of GVHD (58%) and sensitivity of skin biopsy (0.73). Prevalence and sensitivity of skin biopsy, when varied together, affect the treatment decision. For low prevalence of GVHD (<30%), sensitivity of the skin biopsy specimen result matters little and the biopsy and await results option is best. For high prevalence of GVHD (>50%), sensitivity of a skin biopsy specimen result matters little and the treat-immediately strategy is best. For intermediate values of prevalence of GVHD, the sensitivity of the test affects the treatment strategy: for high sensitivity, a skin biopsy and treating is best; for low sensitivity, treating immediately is best. C, Two-way sensitivity analysis of prevalence of GVHD and specificity of skin biopsy. Black dot shows the mean expert estimates for prevalence of GVHD (58%) and specificity of skin biopsy (0.66). Prevalence and specificity of a skin biopsy result, when varied together, affect the treatment decision. For prevalence greater than 55%, specificity of the skin biopsy specimen result matters little and the treat-immediately option is best. For lower prevalence values, performing a skin biopsy and treating is best if the specificity is high; otherwise, performing a skin biopsy and awaiting results is best.

GVHD and test characteristics of skin biopsy suggests that use of skin biopsy findings to guide treatment of GVHD does not provide the best clinical outcome in a patient in whom a rash develops 14 days after SCT. For this study

we chose a specific clinical scenario in which the patient did not have other organ dysfunction that would help guide the clinician. Our results are driven by the high pretest probability of acute GVHD when a rash devel-

ops after SCT and by the perception that undertreatment of acute GVHD is much worse than overtreatment in a patient without GVHD. Physicians interviewed for this study estimated acute cutaneous GVHD prevalence of 58% (SD, 27%). Ideally, a test with very high sensitivity and specificity that can accurately confirm or exclude the diagnosis would improve on a management strategy of treating every patient with suspected GVHD.

It seems that most physicians, specifically, 75% in this study, follow a management strategy that is inconsistent with their statements about previous probability of disease and performance of diagnostic tests. Although skin biopsy is a reasonable test with potentially low risk after SCT, it is most justified if sensitivity and specificity are high. That physicians interviewed rated the sensitivity of a skin biopsy specimen higher than specificity indicates that they consider skin biopsy more a screening test than a confirmatory test for GVHD. On average, physicians thought that skin biopsy was neither highly sensitive nor specific and that undertreating GVHD yielded the worst clinical outcome. However, most still obtained a skin biopsy specimen and some also waited for the skin biopsy specimen results before initiating treatment. Careful assessment of the decision analysis results suggests that the decision to perform a skin biopsy and to treat vs to treat immediately hinges on 2 issues. First, the high positive value for treating GVHD appropriately overrides the negative effects of overtreatment with steroid agents in patients with false-positive results. Second, the negative value for missing a patient with GVHD warrants a test with high sensitivity so that fewer patients with true-positive results remain untreated.

These conclusions must be interpreted within the context of study limitations. First, the physician sample providing estimates used in the model was small, although from several major academic centers and representing years of clinical experience. Their estimates should be considered point estimates rather than measures of the true sensitivity and specificity of skin biopsy in acute GVHD. Because data on test characteristics for skin biopsy were unavailable from a large study, we relied on expert opinion to inform the models and compute post-test probabilities. Clinicians may have a tendency to underestimate the sensitivity and specificity of skin biopsy in this clinical scenario. This in turn may be due to the variability in pathologists reporting a diagnosis of acute GVHD in the same clinical scenario. Carefully designed prospective studies with blinded pathologic review and careful assessment of clinical outcomes are necessary to confirm the test characteristics of skin biopsy in acute GVHD. The results suggest that for clinicians to accurately assess the usefulness of skin biopsy in clinical practice, specific values for the sensitivity and specificity of skin biopsy must be determined, especially inasmuch as these parameters have not been established.

Second, the valuations placed on possible clinical outcomes were not on a scale of 0 to 100, as is conventionally used for expected values when eliciting utilities.¹⁴ Rather, we used a scale of -10 to +10. This rating method was chosen over utility assessments for various reasons. Clinicians and patients have difficulty understanding standard gamble or time trade-off techniques used to create

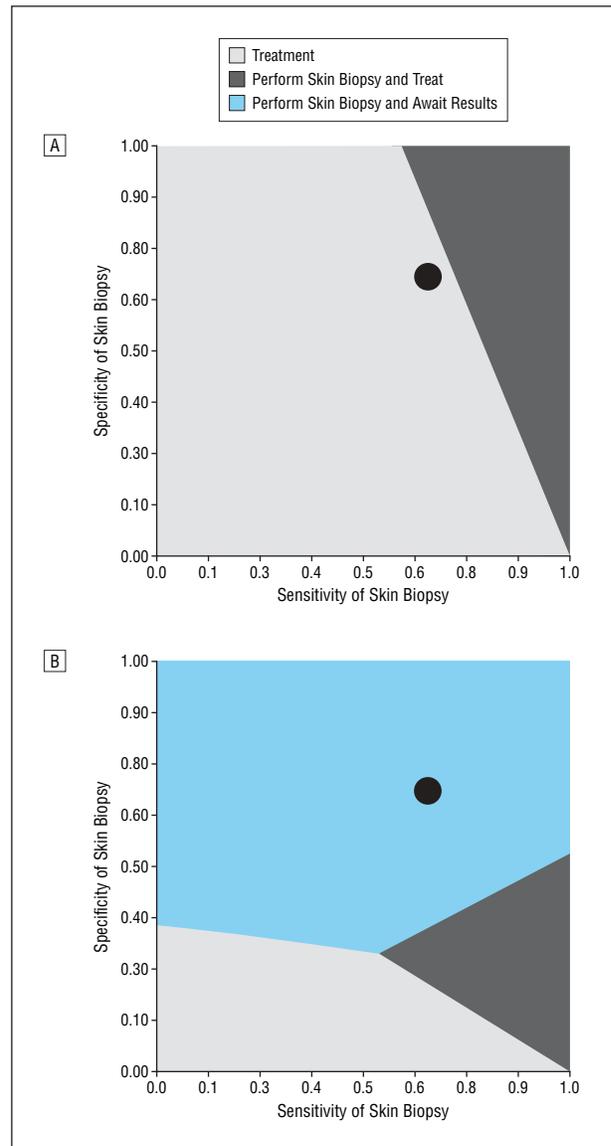


Figure 4. Impact of graft-vs-host disease (GVHD) prevalence on medical decision making. A, Three-way sensitivity analysis for intermediate prevalence of GVHD (50%). If both sensitivity and specificity are high, the skin biopsy and treating option is best. B, Three-way sensitivity analysis for low prevalence of GVHD (20%). The skin biopsy and awaiting results option is best if sensitivity and specificity of the skin biopsy specimen are high. Black dot shows the mean expert estimates for sensitivity and specificity of skin biopsy specimen results.

utility scales, especially for the possible clinical outcomes assessed in this study. Rating scale methods are easier to understand and much easier to administer.¹⁵ Moreover, there was consensus on rank ordering of the 6 different health states from worst outcome to best outcome. Because preliminary sensitivity analyses did not indicate that the magnitude of the established order changed the results significantly, we decided to adopt the less complicated rating scale. Readers may agree with the values our respondents assigned during the study or may assign their own relative values for overtreatment vs undertreatment of GVHD.

Last, our decision model reflects only one possible presentation of rash after allogeneic SCT and is a snapshot

of real clinical practice. The clinical scenario described to clinicians in this study was specific and may not apply to all patients with GVHD. For example, we restricted clinicians to the notion of a single biopsy at one point in time rather than serial skin biopsies performed during a few days, which may yield different information. Some clinicians may also think the decision model did not accurately represent true clinical practice because it did not allow for dynamic assessment of the rash and alternative choices during the course of therapy. Our model only addresses the best initial management strategy and whether skin biopsy findings improve decision making; it does not account for changes in therapy made on the basis of evolving clinical status or subsequent skin biopsy specimen findings.

This preliminary decision analysis using expert estimates suggests that within the specified clinical scenario, skin biopsy performed because of rash early after allogeneic SCT may not meet required test characteristics to provide meaningful data with technology available today. Performing a skin biopsy may have other uses in the evaluation of suspected acute cutaneous GVHD in addition to evaluation of the diagnosis. Performing a skin biopsy may help consolidate the diagnosis in the presence of other tests, such as liver function tests or intestinal biopsy; provide insight into potential evolution to chronic GVHD; and provide information about a particular patient at a given time, allowing comparison of future skin biopsy findings when the condition evolves. Many of the parameters on which this decision analysis hinges, namely, skin biopsy characteristics and prevalence of GVHD in SCT recipients, need to be evaluated before definitive recommendations can be made about the usefulness of skin biopsy in SCT recipients. We hope that readers will assess the parameters and clinical outcomes that are relevant to their own institution and consider the implications of false-negative and false-positive results to evaluate their decision-making strategy.

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REFERENCES

- Aractingi S, Chosidow O. Cutaneous graft-vs-host disease. *Arch Dermatol.* 1998; 134:602-612.
- Voic-Platzer B, Stingl G. Cutaneous graft versus host disease. In: Ferrara J, Deeg J, Burakoff S, eds. *Graft-Versus-Host Disease*. New York, NY: Marcel Dekker Inc; 1991:245-254.
- Deeg HJ. Graft-versus-host disease: pathophysiological and clinical aspects. *Annu Rev Med.* 1984;35:11-24.
- Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant.* 1995;15:825-828.
- Nghiem P. The "drug vs graft-vs-host disease" conundrum gets tougher, but there is an answer: the challenge to dermatologists. *Arch Dermatol.* 2001;137:75-76.
- Drijckoningen M, De Wolf-Peeters C, Tircot G, Degreef H, Desmet V. Drug-induced skin reactions and acute cutaneous graft-versus-host reaction: a comparative immunohistochemical study. *Blut.* 1988;56:69-73.
- LeBoit PE. Subacute radiation dermatitis: a histologic imitator of acute cutaneous graft-versus-host disease. *J Am Acad Dermatol.* 1989;202, (pt 1):236-241.
- Barksdale SK, Oberlender SA, Barnhill RL. "Rush" skin biopsy specimens in a tertiary medical center: diagnostic yield and clinical utility. *J Am Acad Dermatol.* 1998;38:548-554.
- Zhou Y, Barnett MJ, Rivers JK. Clinical significance of skin biopsies in the diagnosis and management of graft-vs-host disease in early postallogeic bone marrow transplantation. *Arch Dermatol.* 2000;136:717-721.
- Richardson WS, Detsky AS; Evidence-Based Medicine Working Group. Users' guides to the medical literature, VII: how to use a clinical decision analysis, A: are the results of the study valid? *JAMA.* 1995;273:1292-1295.
- Hunink M, Glasziou P, Siegel J, et al. *Decision Making in Health and Medicine: Integrating Evidence and Values*. Cambridge, England: Cambridge University Press; 2001.
- Weinstein MC, Fineberg HC, Elstein AS, et al. *Clinical Decision Analysis*. Philadelphia, Pa: WB Saunders Co; 1980.
- Weinstein MC, Stasson WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med.* 1977;296:716-721.
- Sox HC, Blatt MA, Higgins MC, Marton KI. Measuring the outcome of care. In: *Medical Decision Making*. Boston, Mass: Butterworth Publishers; 1988:201-237.
- Gold MR, Patrick DL, Torrance GW, et al. Identifying and valuing outcomes. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996:82-134.

Announcement

Calendar of Events: A New Web Feature

On the new Calendar of Events site, available at <http://pubs.ama-assn.org/cgi/calendarcontent> and linked off the home page of the *Archives of Dermatology*, individuals can now submit meetings to be listed. Just go to <http://pubs.ama-assn.org/cgi/cal-submit/> (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.