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Is renal biopsy necessary for optimal management of the idiopathic nephrotic syndrome?

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Case presentation

A 60-year-old woman who previously had been in excellent health consulted her physician for periorbital and ankle edema and foamy urine that she had noticed for one month. Except for the edema, there were no other abnormal physical findings; the blood pressure was 150/80 mm Hg. A 24-hour urine collection contained 4.5 g of protein, the serum albumin was 2.7 g/dl, and the serum creatinine was 1.0 mg/dl. Furosemide was prescribed for edema and the patient was referred to the Nephrology Clinic at the New England Medical Center.

She had no history of renal disease, diabetes, hypertension, or hematuria, and protein had never been found in her urine previously. She had a history of "osteoarthritis" of the hands, but no other joints had been involved; there was no history of skin rash, chest pain, or alopecia. She had taken only aspirin as needed for the joint pain. Except for an occasional dose of Librium, she took no other medications and had no known exposure to toxins or hazardous chemicals. There was no family history of renal disease. She was a social drinker and had smoked 1 to 2 packs of cigarettes per day for many years.

On examination she was alert and in no distress. Blood pressure was 140/80 mm Hg; pulse was 72/min. There were some telangiectasias on the face and chest, and bilateral palmar erythema was present. The optic fundi were normal; the tongue was not enlarged. Examination of the heart and lungs was normal. The breasts contained no masses. No organs were palpable in the abdomen, and percussion revealed a normal-sized liver. Rectal, pelvic, and neurologic examinations were normal. Peripheral pulses were normal. There was 3+ pretibial edema bilaterally.

Laboratory studies revealed the following data: urinalysis showed a specific gravity of 1.030, 3+ protein, a pH of 5, and no glucose. The urine sediment contained 4 to 6 red blood cells, 1 to 3 white blood cells, and many coarse granular casts per high-power field. The hemoglobin, hematocrit, white blood cell count, and differential were normal. Serum creatinine was 1.4 mg/dl; BUN, 31 mg/dl; serum calcium, 7.2 mg/dl; serum phosphorus, 4.2 mg/dl; and serum albumin, 2.2 g/dl. Serum electrolytes, liver function studies, and clotting tests were normal. Serum immunoelectrophoresis showed a decrease in immunoglobulins. Total serum hemolytic complement was 224 units, and C3 was 1.34 mg/ml (both within normal limits). Protein excretion was 6.6 g/24 hours.

Three options were considered: *(1)* treating the patient with 125 mg of prednisone on alternate days for 2 months without performing a renal biopsy; *(2)* carrying out a renal biopsy and treating with the same program of steroids only if the patient was found to have either the "minimal-change" lesion or membranous nephropathy; or *(3)* treating the patient only with diuretics and avoiding both biopsy and steroid therapy.

Discussion

DR. JEROME P. KASSIRER *(Professor and Associate Chairman, Department of Medicine, Tufts University School of Medicine, and Associate Physician-in-Chief, New England Medical Center, Boston):* Performing a renal biopsy in adults with the idiopathic nephrotic syndrome (INS) is a diagnostic tradition from which few physicians deviate [1–4]. Indeed, there seems to be little justification for breaking with that tradition. With modern techniques, biopsy is a safe procedure that reliably provides glomeruli for study, and the glomerular lesions of INS can be classified neatly into accepted histopathologic entities. More important, the biopsy results determine whether the patient should be treated: certain histopathologic entities tend to respond to treatment, whereas others tend not to. Given the unreliability of clinical features in accurately predicting the histopathology, renal biopsy has seemed the only rational approach to the management of INS.

Despite the satisfying logic of this traditional approach, many thoughtful nephrologists harbor lingering doubts about the current practice. Is it really necessary that one be certain about the histopathologic variety of INS before recommending steroid therapy? Is steroid therapy so dangerous that we should use it only for patients with lesions known to be steroid responsive? Is the risk of renal biopsy small enough to justify doing a biopsy in all patients? Does the value of biopsy justify its risk and expense? Is a "blind trial" of steroids an appropriate alternate approach, or would it yield poorer results?

The findings of the renal biopsy, because they identify the histopathologic variety of INS, merely alter the likelihood of a

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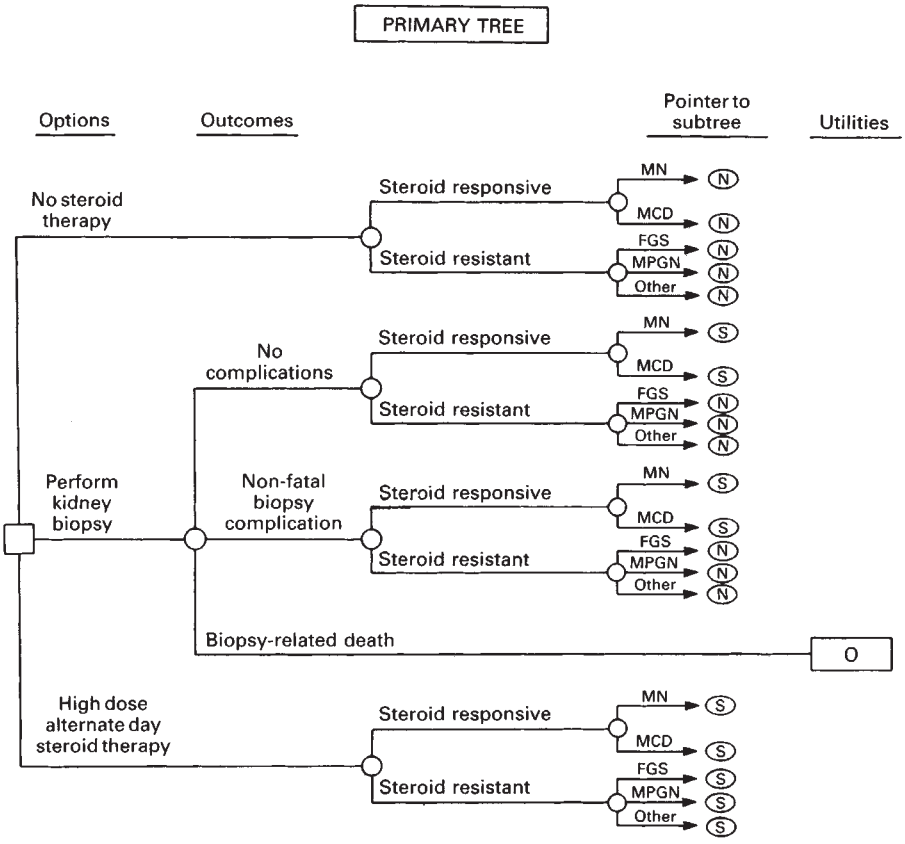

Fig. 1. Primary decision tree *for the 60-year-old woman with idiopathic nephrotic syndrome (INS) discussed in this Forum.* The choices considered for the patient are those that emanate from the square (decision) node, and the outcomes of these choices are chance events that are represented by circular nodes. The choices are: supportive therapy only, top branch; steroid therapy only for the lesions thought to be steroid responsive on biopsy (middle branch); and treatment with steroids for all patients without biopsy (bottom branch). The presence or absence of a complication of renal biopsy is represented on the center branch. Branches that point to (N) link to the nephrotic syndrome subtree in Figure 2; those that point to (S) link to the steroid therapy subtree in Figure 3. The following abbreviations are used: MN, membranous nephropathy; MCD, minimal-change disease; FGS, focal glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; Other, all other histopathologic varieties of INS.

steroid-responsive renal lesion. At first blush, the reduction in uncertainty gained by biopsying the kidney seems highly desirable: most would agree that it is always better to know a diagnosis with certainty rather than to be left guessing. Even if renal biopsy were totally risk free and totally cost free, however, this logic would hold true only if the outcome for biopsy-directed treatment was better on average than the outcome for the other choices, namely, blind steroid treatment or no treatment at all. If the choice of biopsy-directed treatment is not clearly preferable, then the expense, discomfort, and inconvenience of renal biopsy are not justified [5]. No available clinical study has addressed this question. The carefully controlled studies of INS have been designed to determine whether steroid therapy is better than no treatment for specific histopathologic lesions. In such studies, all patients are subjected to renal biopsy. It is impossible to determine the value of renal biopsy without employing a quantitative approach, because the competing values and risks of the biopsy-directed approach and of "blind" treatment with steroids are too disparate to compare them qualitatively.

Decision analysis

Complex clinical decisions such as this typically have been made intuitively, frequently without full consideration of all the relevant outcomes. Developments over the past 10 years in the techniques of decision analysis have made it possible to deal with difficult clinical questions such as this by comparing management strategies quantitatively. Decision analysis is based on probability and utility theory. The method involves breaking down a problem into several elements: *(1) options* available to the decision makers; *(2) outcomes* of each option; *(3) probabilities* of all the outcomes; and *(4) values (utilities)* of all the outcomes. When the outcomes, probabilities, and utilities have been specified, one can calculate the average value (or "expected utility") of all the available options. The strength of decision analysis as a clinical tool is its quantitative basis. Although the probabilities required for defining the frequency of clinical outcomes often are not known with precision, the method allows one to use the best available approximations of such data, to specify the range over which these probabilities vary, and to test the impact on the decision of varying the probabilities over the specified range. This process, called sensitivity analysis, is equally applicable to the assessment of utilities.

The capacity of decision analysis to incorporate data of diverse types and from diverse sources is one of its potent advantages. Data describing prevalence of disease, life expectancy, complication rates of tests and treatments, efficacy of therapy, and quality of life can be synthesized into an integrated quantitative approach. The totally explicit nature of this method exposes the structure of a decision, the assumptions, and the data to open discussion and debate.

I will use decision analysis to assess whether a renal biopsy should be performed in the 60-year-old woman presented here today. I will not review the rationale of decision analysis, pragmatic details of the method, or arguments presented by its critics; these items can be found in the extensive literature on the subject [6–31].

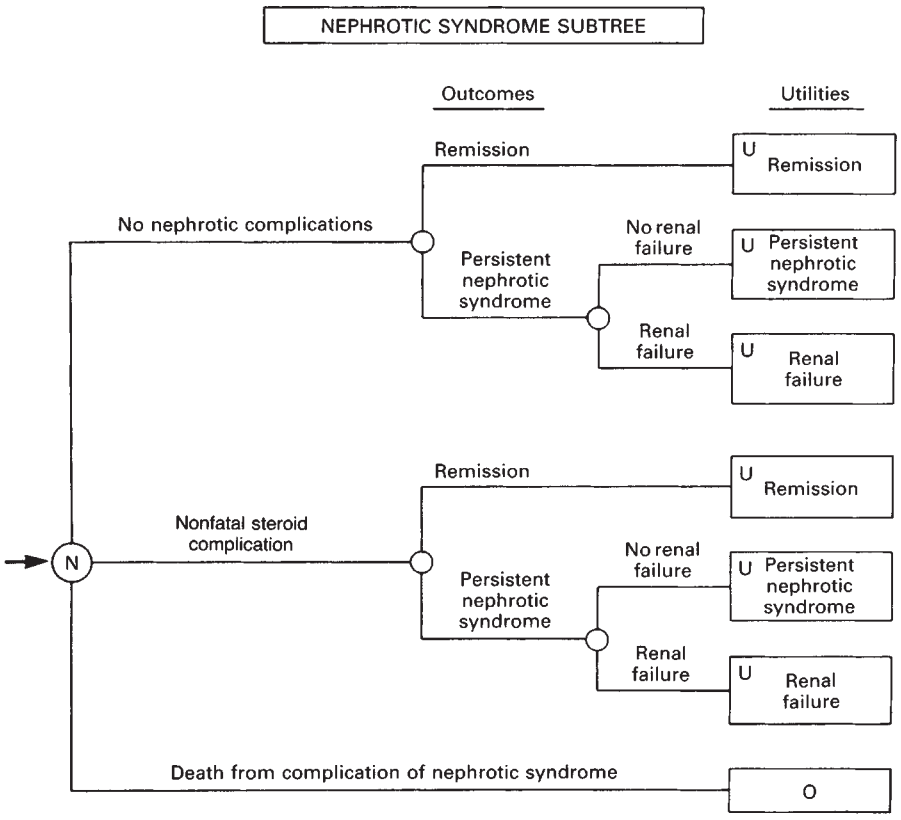

Fig. 2. Nephrotic syndrome subtree *that links to the primary tree in Figure 1 and to the steroid therapy subtree in Figure 3.* This subtree describes the possible outcomes of the nephrotic syndrome. Early complications are represented at the left, persistence or remittance of the nephrotic state in the center, and the outcome of renal function at the right. U refers to utility.

Structure of the problem

The "decision tree" for the problem posed by this patient is similar to one used in a recently published study [32] and is represented in Figures 1 through 3. Figure 1 displays the primary tree with its three major options, namely, treating all patients with steroids and not performing renal biopsy (bottom branch), biopsying the kidney and using the biopsy results to determine the therapeutic course (middle branch), and neither biopsying the kidney nor treating the patient with steroids (top branch). Figures 2 and 3 contain branched extensions (known as "subtrees") linked to the primary tree at several relevant points. Figure 2 contains the subtree that describes the possible outcomes in patients with the nephrotic syndrome. Figure 3 describes the possible outcomes in patients who receive steroid therapy. The points of attachment of each subtree to its several relevant positions on the primary tree are denoted by arrows. One can trace the logic of the decision tree by exploring the branches of the primary tree and subtrees. I will describe the data used to designate the outcomes for each subtree later.

Primary tree

For this analysis I have assumed that the possible histopathologic varieties of INS are membranous nephropathy (MN), minimal-change disease (MCD), focal glomerular sclerosis (FGS), membranoproliferative glomerulonephritis (MPGN), and a group of "other" lesions comprising all other disorders.

As already noted, three options are shown in Figure 1. In the option traditionally chosen, one first biopsies the kidney and then treats only patients who have either of the two steroid-responsive lesions, namely, MN and MCD. The middle branch of Figure 1 illustrates this option. For patients who have a renal biopsy, one of three possible consequences ensues: *(1)* no complications, *(2)* a nonfatal, biopsy-related complication, or *(3)* a fatal complication. If the patient has no complication or recovers from a nonfatal complication, steroid therapy is given for lesions known to be steroid responsive (MN and MCD) and not for those that tend to be steroid unresponsive (FGS, MPGN, and other). If the patient is not given steroids (top branch, Fig. 1), the outcomes are a function of the nephrotic state and the untreated primary renal lesion, whatever it may be, as illustrated in Figure 2. If the patient is treated with steroids without having a renal biopsy (bottom branch, Fig. 1), the outcome is dictated by the consequences of the nephrotic state, the primary renal lesion, the effect on the kidney of steroid therapy, and the complications of steroid therapy. The outcomes of steroid therapy are shown in the subtree in Figure 3.

Nephrotic syndrome subtree

Figure 2 illustrates the outcomes and utilities for the nephrotic syndrome subtree. I will describe the data for this subtree later. Irrespective of the renal histopathologic lesion, serious complications of the nephrotic state—such as thromboembolism, infection, and hypotension—can occur. If the patient survives one of these complications or has no complication, the nephrotic state either can disappear (upper branch, Fig. 2) or persist. If it disappears or if a partial remission ensues, the patient is not at risk for the development of renal failure or long-

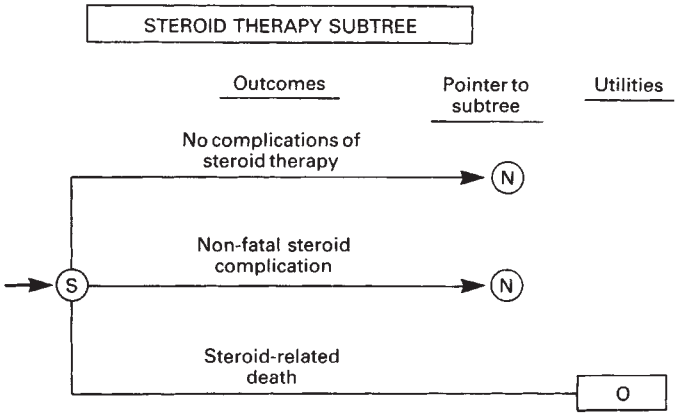

Fig. 3. Steroid therapy subtree *that links to both the primary tree and to the nephrotic syndrome subtree.* Symbols are the same as in Figure 1.

term complications of the nephrotic state (for example, accelerated arteriosclerosis), and life expectancy is considered normal. If the nephrotic state persists but the patient's renal function remains normal (second end branch from the top, Fig. 2), the patient is at risk only for the long-term complications of nephrotic syndrome. But if renal function deteriorates (third end branch), then the patient faces the unpleasant consequences of total renal failure. Because the patient under discussion today first developed INS at age 60 and would not be expected to develop total renal failure until 5 to 10 years later, she would not be an ideal candidate for transplantation at that time. For this reason we assume that her long-term therapy would consist only of dialysis if renal failure develops.

Steroid treatment subtree

The possible outcomes of steroid therapy are shown in Figure 3. I will describe the data for this subtree subsequently. If steroids are given, the patient might or might not suffer from a complication of therapy: if the patient either survives a serious steroid-related complication or has no such complication, the outcomes are the same as those described under the nephrotic syndrome subtree and as displayed in Figure 2. Thus, nonfatal complications of therapy are incorporated into the decision by a modification of the utility of each outcome.

Assumptions

In constructing the decision analysis for the 60-year-old woman described here, many assumptions were made about the natural history of INS and its modification by therapy. The definition of INS was based on clinical findings, and obviously not on the results of a renal biopsy. For our purposes, a patient has INS if the history, physical examination, and laboratory studies disclose no secondary cause such as diabetes mellitus, lupus erythematosus, or drug or heavy-metal exposure. I have assumed that patients with INS can be categorized histopathologically into the five subgroups contained in the primary tree (MN, MCD, FGS, MPGN, and other). I further assume that percutaneous biopsy identifies the histologic subtypes of INS accurately. Complications of biopsy result either in death or short-term morbidity. For this analysis we assume no monetary expense of a renal biopsy.

Outcome measure

In every case the utilities of the outcomes are measured in terms of the patient's life expectancy and are adjusted for the quality of the patient's life. The following assumptions are made about the quality-adjusted life expectancy in years (QALY): *(1)* The worst outcome is early death from any cause (for example, a complication resulting from biopsy or steroid administration). This outcome is assigned a QALY of zero. *(2)* The best outcome is immediate and permanent remission of nephrotic syndrome without any complications from diagnostic or therapeutic procedures. This outcome is given the same value as the patient's age-, sex-, and race-adjusted life expectancy, in this case, 22.3 years [33]. *(3)* The early complications of steroid use, of the nephrotic state, and of biopsy all occur over a limited period and are incorporated into the decision by subtracting a short fixed period from the patient's QALY [34]. *(4)* Factors that reduce the quality of life over a long period are incorporated into the decision by reducing the QALY of the patient over time by a multiplicative factor [34]. If the patient has persistent nephrotic syndrome, for example, but has an otherwise uncomplicated course, and if the quality of life is judged to be reduced by 10% for the patient because of edema, accelerated arteriosclerosis, or other long-term complications, then the age-, sex-, and race-adjusted life expectancy of 22.3 years would be multiplied by 0.90 to obtain the QALY for this outcome of 20.1 years. *(5)* For each outcome, the life of a patient might be represented by only one segment (for example, permanent persistent nephrotic syndrome without renal failure) or by two segments (for example, a period in which the patient has persistent nephrotic syndrome followed by a period on dialysis). Each of these time intervals would be multiplied by a factor denoting the quality of life in that segment, and the two products would be added to obtain the QALY for that given outcome.

Definition of remission

A reduction in protein excretion to less than 200 mg/day is defined as complete remission, and to less than 2 g/day is defined as partial remission. Either type of remission can occur spontaneously or with steroid treatment. For the purpose of using a simplifying approximation, I will assume that remission can occur only within 2 years of treatment. Patients who experience either a complete or partial remission are considered to have the same long-term outcome, that is, a normal life expectancy and a normal quality of life thereafter.

Outcomes of persistent nephrotic syndrome

Patients who fail to achieve a complete or partial remission have persistent nephrotic syndrome, and over the long term, such individuals may or may not develop renal failure. Patients with relapsing heavy proteinuria are considered as having the same outcomes as do those with persistent proteinuria. The probabilities of the above outcomes (remission, persistent nephrotic syndrome, late development of renal failure) depend on the underlying renal pathology, on whether steroids are administered, and on the effectiveness of steroids.

Early complications of nephrotic syndrome (persistent edema, hypotension, acute renal failure) lead to short-term morbidity only. I assume that the risk of these complications is independent of pathologic subtype. Persistent nephrotic syn-

drome produces symptoms and thus reduces the quality of a patient's life.

Short-term prednisone therapy (125 mg every other day for 2 months) is the only treatment considered. Patients who do not respond to this regimen are assumed to be unresponsive to any therapy. Steroid responsiveness either hastens remission in patients with INS (and thus reduces the frequency of complications of nephrotic syndrome), reduces the likelihood of eventual renal failure, or both. Serious complications of steroid therapy result in either death or short-term morbidity. Some forms of INS relapse and require more than one course of prednisone therapy. The probability of complications is taken to be proportional to the number of courses of therapy.

The mean time to the development of renal failure in patients destined to develop uremia is not altered either by prior biopsy or steroid therapy. Life expectancy after onset of uremia is independent of pathologic subtype and previous steroid treatment; it depends only on the age at which uremia begins. The risk of renal failure is expressed as the probability of uremia within 10 to 15 years. I selected this interval because data concerning prognosis within this interval are available for most of the specific pathologic subtypes of INS. Indeed, there are few reports with longer follow-up.

Sources of data

As noted before, the data employed in the analysis will be described according to the tree or subtree in which they are used. The data consist of probabilities and utilities. In the following description, the source of these data and the justification for their use are provided.

Primary tree

Histopathologic varieties. Bayesian analysis was used to assess the probability of the various histopathologic varieties of INS in the patient under discussion today. Bayesian analysis usually is thought of as a method for combining data on the prevalence of a disease with that on the sensitivity and specificity of a diagnostic test to estimate the likelihood of a certain disease being present given a positive or negative test result [35]. Experience has shown, however, that Bayesian analysis has even wider applicability: by using other types of clinical information in addition to data on the sensitivity and specificity of diagnostic tests, it can be employed to revise a diagnostic assessment of a patient [10, 36, 37]. In this analysis I have used the method to calculate the probability of various histopathologic entities given data on the prevalence of the disorders that could be affecting the patient, the frequency of disease manifestations among these entities, and the clinical findings of the patient under discussion.

In this particular case, the set of diseases under consideration comprises 5 histopathologic entities (MN, MCD, FGS, MPGN, and other). The prevalence of these 5 entities, termed here the *prior probabilities,* was obtained from a review of several series of patients with INS reported in the literature [3, 38–40]: the data used for the prior probabilities are given at the top of Table 1. I selected clinical features of the nephrotic syndrome that might be useful in discriminating among these histopathologic entities. Experience in children indicates that these features do help distinguish among histopathologic varieties [3, 41–43]. I selected only clinical features, however, that appear to be independent and unrelated manifestations. They included the patient's age, sex, blood pressure, glomerular function, presence or absence of hematuria, and serum complement level. These features are not the only ones with diagnostic value, but I judged them the more important ones. The probability of finding each of these clinical manifestations in the 5 histopathologic entities is a *conditional probability* and is displayed in the center of Table 1. For the sake of brevity, the only conditional probabilities shown are those found in the patient under discussion (for example, blood pressure less than 160/95 mm Hg, and serum complement within normal limits). Again, these conditional probabilities were obtained from a review of the reported clinical manifestations of MN, MCD, and the other histopathologic categories.

Table 1. Bayesian analysis for patient described

Histopathology	MN	MCD	FGS	MPGN	Other
Prior probability	.50	.25	.15	.08	.02
Conditional probabilities					
Age, 45–60 years	.25	.20	.17	.14	.12
Sex, female	.43	.50	.34	.63	.40
Blood pressure, <160/95 mm Hg	.75	.85	.75	.60	.75
Serum creatinine, <1.5 mg/dl	.85	.95	.75	.60	.85
Hematuria, microscopic	.55	.25	.47	.60	.40
Complement, normal	.98	.98	.94	.35	.85
Posterior probabilities	.70	.19	.08	.02	.01

The revised or *posterior probabilities* of each of the five histopathologic varieties of INS for the patient under discussion are shown at the bottom of Table 1. Table 2 illustrates the method of calculating the posterior probabilities from the prior and conditional probabilities for a single clinical feature, microscopic hematuria. To obtain the posterior probability of each histologic entity given the presence of microscopic hematuria, the product of the prior probability of each entity and the conditional probability of microscopic hematuria in each is divided by the sum of all the products of the prior and conditional probabilities. After this result is obtained for microscopic hematuria, the process is repeated for the remaining conditional probabilities. Each time the process is repeated, the posterior probability of the previous analysis is used as the prior probability for the next analysis. The details of this process are described elsewhere [10, 36]. In this patient the probabilities of the various histopathologic entities used in Figure 1 are derived from the posterior probabilities shown at the bottom of Table 1.

Complications of renal biopsy. With fluoroscopy or ultrasonography to localize the kidney, percutaneous needle biopsy yields renal tissue in 95% of patients. I have assumed that the tissue obtained by biopsy is suitable for pathologic analysis, that is, that the specimen contains sufficient glomeruli. Only one death was reported in combined data from 5 reports of more than 3000 patients undergoing percutaneous biopsy. In addition, 2 patients required exploratory surgery because of hemorrhage [44–48]. The risk of complications was not influenced by age or pathologic diagnosis. I also have assumed that the 5% of patients in whom adequate renal tissue is not obtained undergo a second percutaneous biopsy or an open surgical biopsy, yielding an adequate specimen. Finally, I have assumed that the

Table 2. Example of Bayesian analysis for one clinical feature (microscopic hematuria)

Histopathologic entity	Prevalence of each entity in a cohort of patients with INS (prior probability)	Frequency of microscopic hematuria in each entity (conditional probability)	Product of prior and conditional probability	Revised probability of each entity given microscopic hematuria (posterior probability)
MN	.50	.55	.2750	.59
MCD	.25	.25	.0625	.13
FGS	.15	.47	.0705	.15
MPGN	.08	.60	.0480	.17
Other	.02	.40	.0080	.02
		Sum	.4640	

Table 3. Complications

	Probabilities (First-order approximations)
Renal biopsy	
Death	0.0003
Serious nonfatal complications[a]	0.0006
Nephrotic syndrome[b]	
Death from early complications	0.001
Serious, nonfatal, short-term complications	0.050
Steroid therapy (per course)[c]	
Death	0.001
Serious nonfatal complications	0.050

[a] The ratios of serious nonfatal complications to death for nephrotic syndrome, steroid therapy, and biopsy shown here were kept constant in all sensitivity analyses.

[b] For patients with MCD who were treated with steroids, the probabilities of death and serious nonfatal complications are reduced 50% to account for the reduction in these complications with steroid-induced early remission.

[c] As noted in the text, probabilities for complications of therapy are obtained by multiplying the complication rates per course of treatment by the average number of courses of treatment for each histopathologic type. Average number of courses of steroids for the various histopathologic lesions are: MN, 1.3; MCD, 2.5; FGS, 1.1; MPGN, 1.1; Other, 1.3.

small probability that a second biopsy will be necessary will not increase the chance of serious complications. I have posited the risk of death to be 0.03% and of serious complications to be 0.06% (Table 3).

The only utility in the primary tree is that of biopsy-related death. This complication is considered to occur immediately and its utility (measured in years of survival, see above) is thus zero.

Nephrotic syndrome subtree

As noted, the nephrotic syndrome subtree is an extension of multiple branches of both the primary tree and the steroid therapy subtree. One uses the nephrotic syndrome subtree by obtaining specific values for probabilities and utilities for outcomes of each histopathologic variety of INS. In some instances the outcomes differ depending on the response to treatment. I now would like to explain how these data were derived (Table 4).

Outcomes of untreated INS. Approximately 25% of untreated patients with *MN* experience a complete or partial remission of the nephrotic syndrome within 2 years after the onset [38, 39, 49]. Approximately 40% of patients with persistent nephrotic syndrome secondary to MN develop progressive renal insufficiency; the average time before renal failure develops in this group is approximately 10 years [49, 50]. Approximately 50% of untreated adults with *MCD* achieve a spontaneous remission of proteinuria within 2 years [39, 50, 51]. Progression to renal failure in these patients is rare and is estimated at 1%. Typically, nephrotic syndrome in *FGS* is persistent, and in untreated patients progressive renal insufficiency results in renal failure in approximately 5 years on average [42, 52–57]. I estimate that only 10% of such patients sustain a spontaneous remission of the nephrotic syndrome and survive for prolonged periods without renal insufficiency. Like those with FGS, patients with *MPGN* have a poor prognosis; although normal renal function persists in some patients for many years, total renal failure develops on average in 5 years [3, 42, 58–61]. I estimated the spontaneous remission rate of MPGN to be the same as in FGS. Glomerular lesions other than those considered above (other) are rare causes of idiopathic nephrotic syndrome [40, 62–66]. Data are sparse in this group, but I have assumed the prognosis in untreated patients to be the same as in those with FGS and MPGN (see Table 4).

Complications of INS. Complications that occur *early* in the course of nephrotic syndrome result in short-term morbidity; these include infection, thromboembolism, vascular collapse, and acute renal failure. Although these complications are uncommon, each can lead to serious morbidity and even death. Data on the frequency of these complications are limited, but I have posited the risk of death and serious morbidity from early complications to be 0.1% and 5%, respectively (Table 3). For any individual who suffers one of the short-term, serious but nonfatal side effects, the quality of life was decreased by subtracting 0.1 QALY (Table 5). As noted before, the utility of death from any of these side effects is zero.

Long-term complications resulting from the metabolic derangements that accompany persistent nephrotic syndrome include persistent edema, accelerated arteriosclerosis, early bone demineralization, and side effects of diuretic therapy [67]. I incorporated the impact of the complications by decreasing the quality of life in all patients with persistent nephrotic syndrome by multiplying the time interval over which these patients are nephrotic by 0.90 (Table 5).

Development of total renal failure. In patients who develop total renal failure, the average time before renal failure develops

Table 4. Outcomes of nephrotic syndrome

Histopathology	MN	MCD[a]	FGS	MPGN	Other
Probability of sustained remission					
No steroid therapy	.25	.50	.10	.10	.10
Steroid therapy	.65	.50	.10	.10	.10
Probability of long-term preservation of normal renal function					
No steroid therapy	.60	.99	.10	.10	.80
Steroid therapy	.75	.99	.10	.10	.80

[a] The designation of MCD as a steroid-responsive lesion is based on criteria other than these long-term outcomes. For explanation, see text.

Table 5. Adjustments for quality of life

Short-term (subtractive)	Value (years)
Complications of renal biopsy	0.1
Complications of the nephrotic state	0.1
Complications of steroid therapy	0.1
Long-term (multiplicative)	**Factor**
Persistent nephrotic syndrome	0.90
Maintenance dialysis	0.75

is approximately 10 years in those with MN and 5 years in patients with all other histologic varieties of INS. Thus, if renal failure develops in the 60-year-old woman we are discussing, it would not occur until she is 65 or 70 years old, depending on the renal lesion. At either of these ages, I assume that maintenance dialysis would be the only treatment available to her. The life expectancy of a healthy 65- or 70-year-old woman is 18.4 years and 14.8 years respectively [33], but that of a patient of her age on dialysis is considerably reduced (6.3 years and 5.0 years respectively) [68]. Furthermore, the quality of life of a patient treated with maintenance dialysis is reduced. I have assumed a 25% reduction in quality (Table 5); this figure conforms to recent data obtained from such patients [69].

Steroid therapy subtree

The outcomes of steroid-treated INS versus untreated INS. In a randomized double-blind trial of short-term, alternate-day corticosteroid therapy (the "Collaborative Study"), patients received a course of 125 mg prednisone every other day for 2 months [38]. If an early partial or complete remission was followed by a relapse of proteinuria after the prednisone dosage was reduced, additional courses of therapy were given. The average number of courses of steroid treatment in patients with MN was 1.3 per patient. Within 2 years, 65% of patients with MN achieved a complete or partial remission (Table 4). The difference in frequency of renal failure in the initial report of the Collaborative Study between untreated and treated groups was 23% [38]. In other studies of untreated patients [39, 49], early progression to renal failure was less frequent than in the untreated group in the Collaborative Study. In an attempt not to overestimate the benefit of steroid therapy for MN, therefore, I took the difference in frequency of early renal failure to be 15%. Long-term results of the Collaborative Study are not yet available, but data from other studies indicate that long-term survival in patients treated with corticosteroids is approximately 50% [50, 52, 70–74]. Only one-half of the deaths are due to renal failure (25% of patients); the average time for progression to uremia is approximately 10 years [50]. Based on these data, if the 15% difference holds over 15 years, the fraction of patients with MN developing end-stage renal disease within this time would be approximately 40% in the untreated group and 25% in the treated group (Table 4).

A review of 9 series comprising 208 adults with MCD who were treated with daily steroid therapy (and in some cases cytotoxic agents also) showed that 95% of patients experienced early remission of proteinuria [51]. Two patients (1%) developed renal failure, and 21 (10%) died. Of the deaths, one-half probably resulted from complications of treatment. Preliminary findings of an ongoing trial suggest that alternate-day prednisone therapy (125 mg every other day for 2 months) is as effective as daily steroid therapy [51]. Of 11 patients with MCD treated with alternate-day steroids, 10 (91%) experienced complete remission of nephrotic syndrome; the remaining patient had a notable reduction in proteinuria. After 2 years, one-half had followed a relapsing course and received multiple courses of therapy. None had serious side effects of nephrotic syndrome, none developed renal failure, and none died. Thus, adults with MCD have an excellent prognosis in terms of survival and preservation of renal function, whether or not they are treated with steroids. Steroid therapy appears to hasten remission of nephrotic syndrome and reduce the frequency of early complications. Because of this steroid-induced reduction in short-term complications, MCD is considered a steroid-responsive lesion. I assumed that the likelihood of early complications of nephrotic syndrome was reduced by 50% in patients treated with alternate-day prednisone therapy (Table 3). Whether treatment prolongs life expectancy or reduces long-term morbidity in adults with MCD remains uncertain. I assume here that steroid therapy does not prolong life expectancy in MCD; thus the probability of sustained remission was taken to be 50% in treated as well as untreated patients (Table 4). I assumed that relapsing patients received on average 4 courses of therapy; thus, of all patients with MCD treated with steroids, on average 2.5 courses of therapy were given. The probability of progression to renal failure in patients with MCD was taken to be 1%. In those who do progress, the mean time to the onset of uremia was assumed to be 5 years.

Although a number of patients with *FGS* can experience a temporary improvement in proteinuria after treatment, neither corticosteroids, cytotoxic agents, nor any other form of therapy appears to retard the progression to renal failure. A prospective controlled study of short-term, alternate-day steroid therapy in patients with FGS is in progress, but no data are yet available [38]. For this analysis I assumed the probability of remission in patients with FGS to be 10% whether or not steroid therapy is given, and I further assumed that all patients not in remission develop renal failure within 5 years on average. Sometimes patients with FGS follow a relapsing course after treatment with corticosteroids; I assumed this happens in 10% of steroid-treated patients, resulting on average in 1.1 courses of therapy per patient.

There is no evidence, at least from a pediatric study, that steroids alter the course of *MPGN* predictably or reliably [75]. Therefore, I assumed that MPGN is a steroid-unresponsive

Table 6. Time interval components of utilities (averages)[a]

	Years[b]
Age-, sex-, and race-adjusted life expectancy	22.3
Time until development of renal failure	
MN	10
All other histopathologic types	5
Life expectancy from onset of renal failure in patient treated only with maintenance dialysis	
Onset of renal failure after 5 years of INS	6.3
Onset of renal failure after 10 years of INS	5.0
Life expectancy of patient who dies immediately of complication of nephrotic state, biopsy, or steroid therapy	0

[a] These values apply only to the 60-year-old woman under discussion in this Forum.

[b] The cost of short-term complications and of long-term quality-of-life expectancy is not included in these figures.

histopathologic variety of INS; in steroid-treated patients I assumed that patients received 1.1 courses of therapy on average, that 10% of patients experienced a remission of nephrotic syndrome, and that, on average, the remaining patients progressed to renal failure in 5 years.

In the other disorders (*Other* in Fig. 1), steroid therapy is not usually effective in achieving a sustained reduction in urinary protein excretion or in preventing renal failure [61]. Thus this heterogeneous group of disorders was classified as steroid-unresponsive. I considered nephrotic syndrome persistent in 90% of these patients; I assumed that renal insufficiency occurs in approximately 20% and progresses to renal failure in 5 years. If treatment is given and the patient is in the small cohort that responds to treatment, I assumed that 30% of patients have a relapse of their disease; thus patients would receive, on average, 1.3 courses of therapy. Table 4 summarizes the data used to define the outcomes of these 5 histopathologic varieties.

Complications of steroid therapy. Gastrointestinal bleeding and urinary tract infection occurred in 2 of 34 patients with MN treated with 125 mg prednisone every other day for 2 months [38]. Because patients with MN received an average of 1.3 courses of therapy, the risk of serious complications per course of treatment was 5% (2 of 34 patients per 1.3 treatments per patient). In adults with MCD receiving alternate-day steroid therapy, 3 of 11 developed severe complications [51]. Assuming that these patients received an average of 2.5 courses of therapy, the risk of severe complications was 11% per treatment (3 of 11 patients per 2.5 courses of treatments per patient). The higher complication rate per treatment might result from cumulative toxicity of multiple courses of therapy.

Because data are limited regarding short-term, alternate-day prednisone therapy in the other histopathologic varieties of INS, I assumed the probability of complications from steroid therapy in these disorders to be similar to that observed in patients with MN and MCD. I made the simplifying assumption that in all pathologic subtypes of INS, the risk of death and serious complications per course of treatment was 0.1% and 5% respectively (Table 3). I assumed that the frequency and severity of complications depended only on the number of courses of therapy. I obtained the probability of a complication of therapy by multiplying these risks by the average number of courses of treatment for each histopathologic type (1.3 for MN, 2.5 for MCD, 1.1 for FGS, 1.1 for MPGN, and 1.3 for others).

A fatal complication of steroid therapy was assumed to occur immediately and was assigned a utility of zero. A nonfatal complication was considered a short-term morbidity, and the quality-of-life adjustment for this complication was performed by subtracting a fixed amount of time (0.1 QALY) from the quality-adjusted life expectancy. The data are displayed in Table 5.

Sample utility calculations

If a 60-year-old patient receives only supportive therapy, experiences a spontaneous remission of nephrotic syndrome, and escapes any serious complications due to the nephrotic syndrome, the utility expression for this outcome is simply $U_{\text{Remission}}$ = the age-, sex-, and race-adjusted life expectancy, or 22.3 years, because the "cost" of all complications is zero.

But let us consider a patient with MN who has no early complications of steroid therapy, biopsy, or the nephrotic state, who remains nephrotic, later develops total renal failure, and then is treated indefinitely by dialysis. Two quality-adjusted time intervals comprise the utility for a patient with these outcomes. The first is the product of a 10-year nephrotic period (Table 6) and a value of 0.9 for the quality of the nephrotic state (Table 5), or 9.0 QALY. The second interval is the product of a 5-year life expectancy with dialysis for a 70-year-old woman after the onset of end-stage renal disease (Table 6) and a value for the quality of life on maintenance dialysis of 0.75 (Table 5), or 3.8 QALY. Thus, the total utility for a patient with this complex, albeit common, outcome is 9.0 + 3.8, or 12.8 QALY.

Results of the analysis

The decision tree and its subtrees were constructed using the DECISION-MAKER computer program [76] and was run on a PDP 11/03 computer. The tree and all its subtrees contained a total of 381 nodes and 213 terminal branches. The calculation of expected utility for all three choices was carried out in slightly more than two minutes.

Expected utility calculations from baseline assumptions

The expected utilities of the three options are: *(1)* Administer no steroid therapy, 17.7 QALY; *(2)* Perform renal biopsy and treat (or not) depending on the histopathologic lesion found, 19.0 QALY; and *(3)* Give high-dose, alternate-day steroid therapy, 19.0 QALY. Note that the expected utility of no treatment is more than one year less than that of the other two options, but no difference exists in expected utility between treating "blindly" and using the biopsy-directed approach. According to these calculations, the decision is a toss-up; that is, there is no clear-cut best choice, yet there is a clear-cut worst choice: no treatment [5].

Sensitivity analysis

Effect of the probability of steroid-responsive nephrotic syndrome. This analysis was carried out by varying the probability of steroid-responsive nephrotic syndrome from 0 to 1 and calculating the expected utility of all three options. To perform this analysis, I kept the ratios among histopathologic varieties in both the steroid-responsive group and steroid-unresponsive group the same as those in the posterior probabilities (see Table 1). The sensitivity analysis was first carried out using baseline estimates of the risks of biopsy and steroid therapy. Figure 4A

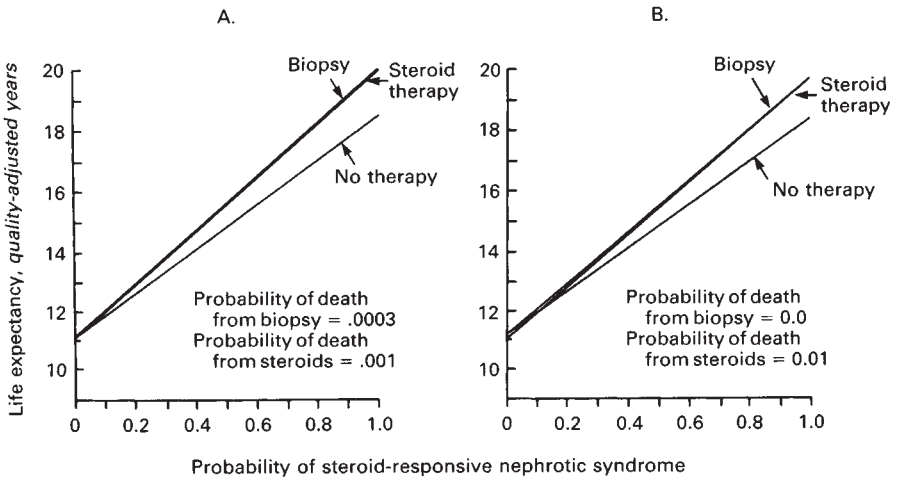

Fig. 4. *Sensitivity analyses showing quality-adjusted life expectancy for a range of probabilities of steroid-responsive nephrotic syndrome from 0.0 to 1.0.* The analysis using "baseline" probabilities of biopsy and steroid mortality rates is shown on the left (A). In this figure the lines depicting the expected utilities of the "biopsy" and "steroid therapy" options were superimposable and thus have been represented as a single line wider than the "no therapy" (i.e., supportive therapy only) line. This result indicates that the options of biopsy-directed steroid therapy and blind steroid therapy (i.e., treating all patients without biopsy) are nearly equivalent strategies (a "toss-up") no matter what the chance of steroid-responsive nephrotic syndrome. Both these options, however, are superior to withholding steroid therapy. The analysis is repeated for an exceptionally high steroid risk and zero biopsy risk in the figure on the right (B). Despite these unrealistic risk estimates, the optimal choice remains a toss-up between biopsy and "blind" steroid treatment at most probabilities of steroid-responsive nephrotic syndrome. No treatment (supportive therapy) is the least optimal choice, except for probabilities of steroid-responsive nephrotic syndrome less than 0.1, but at these low probabilities the choice among all three options is a close call.

illustrates the results of this analysis. Note that no matter how low the probability of steroid-responsive nephrotic syndrome, the option not to treat never becomes the preferred choice. Also note that the expected utilities of the other two options, "blind" treatment and biopsy first, are inseparable at any probability of steroid-responsive disease. Thus, no matter how likely steroid-responsive nephrotic syndrome is in this 60-year-old woman, the choice between treatment with steroids and the biopsy-directed approach is a toss-up.

Effect of high risk of steroid therapy and no risk of biopsy. If the probability of death ensuing from a 2-month course of high-dose, alternate-day steroid therapy is arbitrarily set at 0.01 (an unreasonably high value) instead of the baseline value of 0.001, and if the probability of death from renal biopsy is set at 0.0, the expected utilities of the three options are: *(1)* Administer no steroid therapy, 17.70 QALY; *(2)* Perform renal biopsy and treat according to histopathologic lesion found, 18.73 QALY; and *(3)* Give high-dose, alternate-day steroid therapy, 18.72 QALY. The conclusion is the same as that described earlier: biopsy and "blind" steroid therapy are virtually equivalent, but each is better than no treatment at all.

If the sensitivity analysis on the probability of steroid-responsive nephrotic syndrome is performed as described using exceptionally high steroid risk and low biopsy risk (Fig. 4B), the expected utility of the biopsy option is either equal to, or only slightly higher than, the expected utility of the next best option, but the difference in utility between biopsy and the next best strategy is always small. Despite the high complication rate, steroid therapy has a higher expected utility than does no treatment, except for probabilities of steroid-responsive nephrotic syndrome less than 0.1. The largest difference between the option with the highest expected utility and the next highest is 0.12 QALY, equivalent to approximately 6 weeks. This gain, compared to an expected utility between approximately 10 and 20 QALY for any probability of steroid-responsive nephrotic syndrome, is sufficiently small that the choice still should be considered a toss-up.

Effect of better results of the treatment of MCD. The analyses described were carried out under the assumption that steroid therapy had no influence on the remission rate in patients with MCD. In this sensitivity analysis, the rate of sustained remission in MCD was varied between 0.5 (the baseline value) and 1.0, and the analysis was repeated. The expected utility of the blind treatment and the biopsy-directed approaches remained virtually identical and always better than the no-treatment option.

Effect of timing of steroid-induced complications. I performed this analysis using baseline assumptions. I first assumed that when a steroid-induced complication occurred, steroid administration had to be discontinued and that the patient did not derive any benefit from treatment. I then repeated the analysis assuming that although the complication occurred, the patient still achieved full benefit of treatment. Although the expected utility of the treatment option improved if the complication occurred only after therapy, the change was insignificant. The choice between "blind" treatment and the biopsy-directed approach remained a close call.

General comments

The decision tree used to analyze the optimal approach in this patient could be made applicable to any patient with INS, but the results of the analysis are germane only to the patient under discussion today. Although most nephrologists would insist on carrying out a renal biopsy in this patient before embarking on a course of steroid therapy [1–4], the analysis provides convincing evidence that this view is unwarranted. Extensive sensitiv-

ity analysis shows that the biopsy-directed approach, namely, treating the patient only if she were shown to have a histopathologic lesion known to be responsive to steroid therapy, is no better than treating her with steroids without knowing the histology [5]. Indeed, no matter how I biased the analysis to exaggerate the risks of steroids and underplay the risks of biopsy, the result was always the same: biopsy-directed and "blind" treatment were virtually equivalent strategies. Even when the probability of steroid-responsive nephrotic syndrome was varied from very high to very low levels, the expected utilities of the two strategies were still virtually the same. Except when the probability of steroid-responsive INS was very low, however, the option of withholding treatment was substantially worse than the other two choices. This analysis confirmed the common attitude that withholding steroid therapy is not the optimal approach.

What approach should one take in a patient, such as the one under discussion today, when the choice between biopsy and "blind" steroid therapy is a toss-up? This question can best be answered if we examine the biases of the assumptions used in formulating the analysis. Two such assumptions are pertinent: first, that biopsy precisely identifies the histopathologic varieties of INS, and second, that biopsy carries with it no financial expense. Although I assumed that the histologic type of INS is always identifiable, even expert renal pathologists disagree about the classification of renal lesions in patients with INS [77]. For this reason, errors are inevitable when a biopsy is interpreted, and such errors reduce the expected utility of the biopsy option. Second, the expense of renal biopsy must be considered. Although the patient under discussion had third-party coverage and would not have directly paid for the biopsy, any expenses of renal biopsy reduce its value to the patient. At present, the charges for a 2- to 3-day admission for an uncomplicated renal biopsy at the New England Medical Center are approximately $2500 to $3000. Thus, if the choice between biopsy and "blind" steroid treatment is a close call, the error in biopsy interpretation as well as the associated expense would reduce the value of the biopsy option and leave "blind" steroid therapy as the optimal choice. This conclusion would be even stronger if the patient were at a hospital in which the pathologists were less expert and at which the risks of biopsy were not as low as those used in this analysis.

It is interesting that the choice between biopsy and "blind" treatment is a toss-up for this patient no matter what the chance of the patient having steroid-responsive nephrotic syndrome, that is, either MN or MCD. This conclusion implies that the same result might be obtained for any patient with INS. This question will require a more extensive analysis using a decision tree similar to that used here, but applied to patients of both sexes and of various age groups. For younger patients, the renal failure branch would require expansion to encompass changes in life expectancy associated with cadaver donor and living donor transplants. My colleagues and I are in the process of performing such a study now.

If, as seems likely, the results of a generic analysis of all patients with INS prove similar to the conclusions for this patient, what can we deduce about the traditional practice of biopsying the kidney before treating? The reduction of diagnostic uncertainty by a relatively safe test (biopsy) comforted physicians with the knowledge that they were treating only the responsive forms of the syndrome and avoiding unnecessary therapy in patients who would not benefit from steroids. The theory was rational, but the observation that treatment with steroids on an every-other-day basis was as effective but safer than daily steroid therapy [38, 51] might have been used as a basis for adopting the "blind" steroid therapy approach. Clinicians did not alter their management approaches, however, perhaps because the tradition of biopsying first had become firmly entrenched, and perhaps because physicians are uncomfortable with uncertainty. Obviously, it is disquieting to be treating all patients with a drug to which only some will respond.

Some clinicians argue that a need for "baseline" data necessitates renal biopsy early in a patient's course. This argument implies that although early decision-making would not be affected by the information gained at biopsy, important therapeutic decisions later would depend on such information. I doubt that this assertion is valid. Let us follow a "what-if" examination of patients treated "blindly" with steroids and try to imagine what advantage specific histopathologic data might confer. *(1)* If we blindly treat a patient who has INS with steroids, and proteinuria remits, we would taper the steroids and stop treatment. We would do this no matter what the histopathology. *(2)* If proteinuria remits while the patient is taking steroids but the proteinuria then recurs, we again would treat with steroids no matter what the lesion. *(3)* If a patient's disease fails to remit, we would stop giving steroids after the 2-month course, no matter what the lesion. *(4)* If, later in the patient's course, progressive renal failure develops, we would not treat the patient again with steroids; there is no evidence that this approach has any value. Again, this decision would not depend on the renal lesion. *(5)* Finally, one could argue that still later in the course the histologic data could be useful in choosing between dialysis and transplantation. Certain types of renal lesions, such as focal glomerulosclerosis, do have a tendency to recur after transplantation, and others do not. But again I doubt that the histologic information would change the decision between dialysis and transplantation. Most patients choose between these two treatment modalities on the basis of other factors, and most nephrologists regard transplantation in patients with focal glomerulosclerosis as a reasonable option even though there is an increased chance of recurrence in the transplanted kidney. Only when the patient and physician are undecided about this choice would such information be helpful. In such circumstances a renal biopsy performed when the patient is already uremic would be of little diagnostic value, because the advanced histologic changes of chronic renal disease might well obscure the diagnosis. Nonetheless, I believe that these dilemmas are rare. I do not believe that the information from renal biopsy is sufficiently valuable later in the patient's course to justify performing the test when the patient first presents with the syndrome.

What are the implications for the research efforts currently underway to determine the optimal approach to INS? Even if a generic analysis shows that the choice between biopsy and "blind" treatment is a toss-up for all patients with INS, the conclusion that the biopsy-directed approach offers no benefit over "blind" treatment would be applicable only to patients being treated by physicians not engaged in this research. Research efforts to identify optimal therapeutic approaches

must continue, because more effective treatment regimens will be devised through such efforts. Indeed, such regimens could be assessed by how much they widen the life expectancy in treated and untreated groups.

The analysis discloses several features about the management of INS that are worthy of comment. First, the risk of both steroid therapy and biopsy is very small, but given the low risk of alternate-day steroid therapy, little harm is done by treating all patients, thus exposing the patients with steroid-unresponsive lesions to unnecessary therapy. On average, inappropriate therapy in steroid-unresponsive patients is a small price to pay for the remissions induced in the steroid-responsive patients. Of course it is true that the risk of renal biopsy is also small, and one could argue equally cogently that a renal biopsy should be done in all patients: even though the patients who ultimately receive steroid therapy anyway will be biopsied unnecessarily, there is some benefit to be gained—that is, the avoidance of steroid therapy—in the patients found to have one of the lesions that generally do not respond to steroids. Given the low risks and modest benefits with both renal biopsy and "blind" steroid therapy, the choice between the two options is a close call.

The finding that "blind" steroid therapy is at least as good as the biopsy-directed approach in the patient under discussion today, no matter what the chance of a steroid-responsive lesion, is surprising; one would expect that "blind" therapy would be preferable for patients with a high probability of steroid-responsive INS, that is, those highly likely on clinical grounds to have either MN or MCD, and one would predict the biopsy-directed approach to be preferable in patients with a small chance of having steroid-responsive INS. Indeed, these preferences are revealed in the analysis, but the differences in expected utility between the two options are extremely small no matter what the chance that the patient has a steroid-responsive lesion. Whether the differences will remain as narrow when the analysis is extended to patients of both sexes and all age groups remains to be assessed.

Finally, every part of the analysis presented here is open for discussion and scrutiny. The difference between this Forum and the usual discussions we have about the value of renal biopsy is that here I have stated specifically all my assumptions, all my biases, all the outcomes that I consider relevant, and all the data I used to solve the problem. There are hundreds of assumptions, most of them based on published data on INS and some on my own perceptions and prejudices about outcomes of the syndrome, and they are all displayed here. Indeed, one of the most attractive features of decision analysis is its explicitness. If there is disagreement about any of the data or the assumptions, we can simply rerun the computer program using different, but still explicit, estimates and determine whether the decision for this patient changes.

Questions and answers

DR. JOHN T. HARRINGTON: Dr. Herrin, what do you think would be the impact of following Dr. Kassirer's analysis on the pediatrician's approach to nephrotic syndrome?

DR. JOHN T. HERRIN *(Chief, Pediatric Nephrology, Massachusetts General Hospital, Boston):* An analysis such as that outlined by Dr. Kassirer would not change the common pediatric practice of treatment with steroids, reserving renal biopsy for those patients who fail to respond, relapse frequently, or are steroid dependent. The high probability of minimal-change lesion in childhood nephrotic syndrome is likely to weigh the result even more favorably to "blind" steroid trial in childhood than in adulthood.

It might be reasonable to look at selectivity of proteinuria as a guide to the need for renal biopsy before treatment. Highly selective proteinuria generally is associated with steroid response, whereas patients with nonselective proteinuria rarely respond to steroid therapy. Maybe it would be reasonable to use nonselective proteinuria as an indication for biopsy. Patients with highly selective or moderately selective proteinuria then could be given a steroid trial, and biopsy could be reserved for those who fail to respond.

DR. KASSIRER: My analysis does not address whether protein selectivity is a useful test for all patients with INS, but in the patient analyzed in today's Forum, the presence or absence of selective proteinuria would not have had an effect on the decision. The only effect the result of such an analysis of urine protein has is altering the probability of steroid-responsive nephrotic syndrome. As Dr. Herrin correctly asserted, the finding of selective proteinuria increases the probability of a steroid-responsive lesion, and the finding of nonselective proteinuria reduces it. For this patient, the choice between biopsy versus "blind" steroid therapy was insensitive to the probability of a steroid-responsive lesion; that is, the biopsy and treatment options were of equivalent value no matter what the chance of a steroid-responsive lesion. Given this result, the measurement of protein selectivity would provide no additional information that would influence the decision, and in this patient we could find no justification for doing the test.

If a generic analysis of INS eventually shows a definite preference for biopsy in patients with a moderate to high probability of steroid-responsive nephrotic syndrome, then diagnostic tests that help discriminate among the various histopathologic varieties of INS, such as protein selectivity studies, will be useful because they will increase or reduce our belief that the lesion is a responsive one.

DR. NICOLAOS E. MADIAS: Of the various factors tested in the sensitivity analysis, which was the most important in affecting the outcome?

DR. KASSIRER: If I took what I considered extreme estimates for the risks of steroids and biopsy, and extreme estimates for the steroid responsiveness of the various lesions, the results were still the same. Figure 4B shows an example of this kind of analysis for a high-steroid and low-biopsy risk. If you take unreasonable values for the risk of steroids, for example, you can demonstrate, as you might expect, that one of the other options becomes preferable.

DR. HARRINGTON: What would the risk of steroid therapy have to be for one to decide in favor of biopsy? What value for the risk of steroids would be required to obtain a one-year difference in quality-adjusted survival between "blind" steroid therapy and the next best option?

DR. KASSIRER: The steroid mortality rate would have to be approximately 10% to obtain a one-year difference in quality-adjusted life expectancy between the "blind" steroid therapy option and the next best alternative, which is withholding therapy. This is clearly an unreasonably high value.

DR. JOSEPH LAU *(Fellow, Clinical Decision-Making Division, NEMC):* We performed another analysis that addresses this

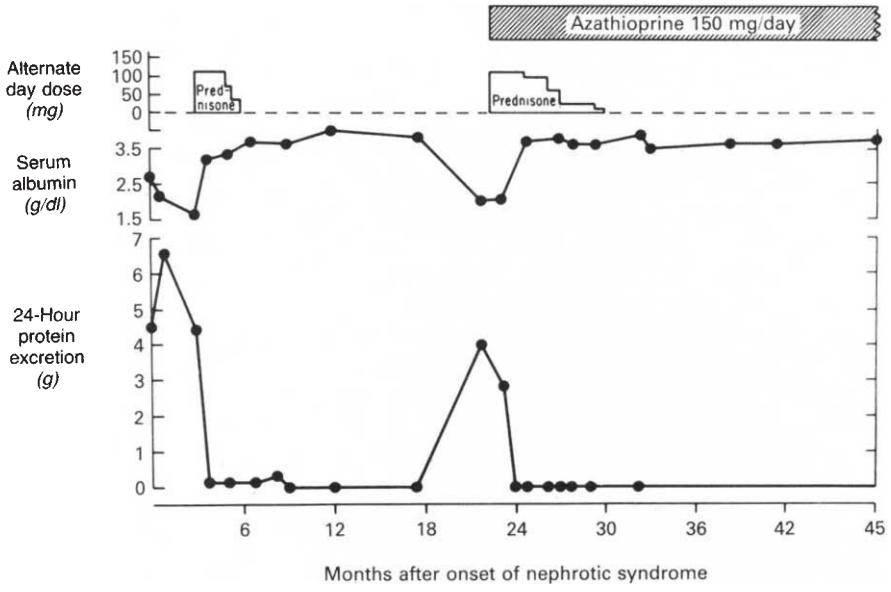

Fig. 5. *Course of the 60-year-old patient with INS presented in this Forum.* Note that although the renal biopsy showed focal glomerulosclerosis, prednisone therapy produced a complete remission of the nephrotic syndrome; when a relapse occurred 16 months later, prednisone again eliminated proteinuria. The biopsy result in the patient was misleading; initially she was not treated with steroids because FGS was found, but steroids were given when severe edema became unmanageable. The result (complete remission) was surprising.

issue indirectly by examining the impact of daily rather than alternate-day steroid therapy. In that analysis we assumed a mortality rate of 0.1% and an overall complication rate of 10% for such therapy. Even in that extreme case, we found little difference between biopsy and a trial of steroid therapy. In fact, a therapeutic trial still was slightly preferable. We performed this analysis to investigate the origin of the tradition of renal biopsy; maybe in an era with higher steroid-related morbidity, biopsy might have been preferable. However, to our surprise, this was not the case.

Dr. Albert Fournier *(Chief, Nephrology Unit, Centre Hospitalo-Universitaire, Amiens, France):* Some nephrologists believe that the response rate in MN is lower than that found in the Collaborative Study [38]. If so, would your conclusion change?

Dr. Kassirer: When I ran the computer program assuming that no long-term benefit was derived from steroids in MN, I found that the "no therapy" option was preferable by a small margin (approximately 0.2 QALY) and that again the biopsy and "blind" treatment approaches were virtually equal. Thus more studies are needed to clarify the benefits of steroid therapy in the so-called steroid-responsive varieties of INS.

Dr. Jeanine Carlson *(Fellow, Division of Nephrology, NEMC):* On the basis of this Forum, it would appear that you would not have recommended a biopsy for the patient presented today. Was a biopsy performed and, if so, could you tell us what it showed, how the patient was treated, and the eventual outcome?

Dr. Kassirer: This patient was first examined several years ago. She was managed according to the traditional approach and was admitted to the New England Medical Center for renal biopsy shortly after having been seen in the Nephrology Clinic. Biopsy was carried out without complications. On light microscopy, one glomerulus was totally sclerotic, 19 others were segmentally sclerotic, and others appeared normal. Immunofluorescent microscopy showed focal segmental deposition of IgM, complement, and fibrinogen in the glomeruli, and focal deposits of C3 in tubular basement membranes and small arterioles. Electron microscopy revealed extensive glomerular epithelial foot process fusion and focal areas of glomerular capillary collapse and sclerosis. No deposits were seen. All findings were consistent with the diagnosis of focal glomerular sclerosis.

Given the unequivocal diagnosis of FGS, steroid therapy was not given and attempts were made to reduce the edema, which was making the patient uncomfortable. Initially the diuretic program was successful, but the patient became intolerant to both furosemide and ethacrynic acid. In a few weeks despite maximum doses of metolazone, spironolactone, mannitol, and albumin, no further diuretic response could be obtained. In the hope that steroid therapy might improve the patient's diuretic responsiveness either by reducing protein excretion or by a mechanism independent of proteinuria, she was started on prednisone, 125 mg on alternate days. Her response to this regimen was surprising. As noted in Figure 5, she had a dramatic response to steroid therapy. Even though one would have predicted from the biopsy findings that there would be no response, proteinuria disappeared. Indeed, steroids had the same effect on a second occasion after the nephrotic syndrome recurred. Even though this response to steroids is unusual in FGS, this patient would have benefited from "blind" treatment if that approach had been accepted as the usual therapy when she first presented.

Dr. Lau: Dr. Kassirer, you didn't refer to the decision analysis on idiopathic nephrotic syndrome reported by Hlatky in the *Lancet* in December 1982.

Dr. Kassirer: I omitted a discussion of Hlatky's paper [78] because I believe the study to be seriously flawed. It really isn't a report of decision analysis, only of a probability analysis; and because he took this approach, he did not represent all outcomes such as remissions and complications on the same scale, as I did. As a consequence, it is impossible to compare the values of each management approach. Hlatky concluded that "blind" treatment was better than renal biopsy-directed therapy, but because of the lack of a commensurate utility scale, it is not possible to ascertain whether the two choices are a toss-up.

I am also unhappy with his assessment of the response to steroid therapy. He took the benefit of treatment in children as a percent reduction in mortality compared to older studies and extrapolated these results to adults. This assumption is questionable.

Finally, he used the response rate after 2 months as the only benchmark of successful therapy. I doubt that many nephrologists accept this assumption.

DR. ANDREW S. LEVEY *(Division of Nephrology, NEMC):* A minority of patients with lesions traditionally classified as steroid-unresponsive have been reported as having remissions of proteinuria, or improvement in renal function or glomerular pathology after steroid therapy. In view of these findings, some nephrologists would try a short course of steroid therapy even if the biopsy demonstrated focal sclerosis or MPGN. Would you comment on how this strategy would alter the outcome of the analysis for this patient?

DR. KASSIRER: Because the biopsy option and the "blind" treatment option are equivalent for virtually any probability of steroid response in nephrotic syndrome, that approach sounds rational for the patient we are discussing today, but I am not comfortable about extrapolating this notion to all patients with INS unless the analysis is extended to include patients of all ages. Recall that our group has not done a generic analysis for all of INS. In the analysis today, I haven't included long-term outcomes in patients who would receive renal transplants; all I have considered is what happens in patients who develop renal failure and are treated only with dialysis. If the results of an analysis of the entire population of adults with nephrotic syndrome turns out the same as the one here, then what you are suggesting would be rational.

DR. MARTIN GELMAN *(Renal Division, St. Elizabeth's Hospital, Boston):* I was struck by the fact that there was only a one-year difference between no treatment and treatment. For patients like the one presented, I would have assumed that a satisfactory response to steroids would extend the life expectancy considerably longer than that. Could you comment on this apparent discrepancy?

DR. KASSIRER: Indeed, if the patient we discussed today had responded to steroids and had had a permanent remission of nephrotic syndrome, her quality-adjusted life expectancy would be the optimal value of 22.3 years. If she had not responded to steroids, had continued to have persistent nephrotic syndrome, had had one or more serious complications, and had developed renal failure after a few years, she would have had one of the bad outcomes, a life expectancy of only 4 or 5 years. But in a decision analysis, the expected utility of an option represents an average value of each of the choices factored for the probability of each outcome. For this reason the difference in *average* value, or expected utility, between two therapeutic choices will be much narrower than that between the best and worst outcomes. So we shouldn't be confused between the average life expectancy given the choices for a cohort of similar patients and individual outcomes.

DR. MADIAS: Have you considered the impact of the prognostic information derived from renal biopsy on the patient's quality of life?

DR. KASSIRER: We could incorporate the prognostic value of biopsy results into the analysis by adjusting the quality of life of a patient who has access to the result. For any patient who has had a renal biopsy and is found to have one of the favorable lesions, such as MCD or MN, we could temporarily increase the quality of the patient's life to reflect the patient's knowledge that the long-term prognosis is good. Of course, we would have to temporarily reduce the quality of life for the biopsied patients who do not have a steroid-responsive lesion. I haven't carried out such an analysis, but it is difficult to imagine that this modification would change the result.

Actually, considerable information is obtained from steroid therapy. If the patient responds to steroids, there is a good chance that the patient's long-term outlook is excellent. If the patient fails to respond, the chance that normal renal function will be preserved for many years is considerably reduced.

DR. HERRIN: I would agree that in fact we obtain better information from steroid therapy than from biopsy. By that I mean that a patient with any lesion does better if the lesion is steroid responsive.

DR. JERRY MCCAULEY: *(Nephrology Division, NEMC):* You have presented rather convincing evidence against renal biopsy in idiopathic nephrotic syndrome. In most forms of secondary nephrotic syndrome, little additional information is provided by biopsy. Do you believe that renal biopsy should be relegated to a research tool in nephrotic syndrome?

DR. KASSIRER: From the data I presented today, I would not be willing to extrapolate that far. We need to expand the analysis to a larger spectrum of patients before coming to grips with your interesting question. As your question anticipates, however, I am not convinced that renal biopsy provides much information that is critical from a therapeutic standpoint in many disorders including acute renal failure, lupus nephritis, and nephrotic syndrome. But I would not be willing to make this assertion with confidence without carrying out an analysis of these different disorders.

DR. LEVEY: Biopsy does not appear to be a valuable tool for this patient because our tests and therapies are neither very good nor very harmful. If, for example, we had a magic bullet that could cure focal sclerosis, but this treatment had important toxicities, it would be important to find every patient with focal sclerosis and to withhold this treatment from those with other histologic types. Biopsy would then be a critical determinant of therapy. The lack of utility for the biopsy in this case is simply a reflection of the limited number of safe but effective therapeutic modalities available for treating nephrotic syndrome.

DR. KASSIRER: Your point is well taken. It is an addendum to a comment that I made in my discussion with regard to research efforts in the field. There is no question that we need better treatment for various types of nephrotic syndrome.

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