

Diagnostic Accuracy Study of Urine Dipstick in Relation to 24-Hour Measurement as a Screening Tool for Proteinuria in Lupus Nephritis

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ABSTRACT. *Objective.* Early detection of renal involvement in lupus prevents poor outcomes. Although published guidelines recommend urine dipstick as an appropriate screening test and evidence suggests a majority of American rheumatologists use dipstick to screen for proteinuria, the performance of this diagnostic approach in lupus has not been reported. We examined the validity of qualitative urine dipstick versus quantitative 24-hour measurement to accurately detect proteinuria, including low-level proteinuria. *Methods.* We performed a diagnostic accuracy study using paired samples from the Johns Hopkins University School of Medicine and the Ohio State University School of Medicine lupus cohorts. All qualitative urine dipstick values were obtained within 1 day of a 24-hour urine collection. *Results.* We analyzed the performance of 3 urine dipstick assays to detect proteinuria compared to 24-hour protein/creatinine ratios, using 2224 dipstick measures from 296 patients. The sensitivity of a $\geq 1+$ dipstick result to detect quantitative proteinuria (≥ 0.50 g protein/g creatinine) was 82.7% for the Clinitek, 97.7% for the Atlas, and 85.5% for the Bayer assay. The corresponding sensitivity to detect low-level proteinuria, (0.50–0.99 g protein/g creatinine) was 63.1%, 96.4%, and 80.7%, respectively. The specificity to correctly exclude proteinuria (< 0.50 g protein/g creatinine) with negative/trace results was 86.1%, 62.2%, and 59.4%. There was considerable variability in the range of protein/creatinine ratios detected at each dipstick level of proteinuria. *Conclusion.* Urine dipsticks demonstrate substantial variability and often poor validity to accurately detect proteinuria at quantitative levels; this warrants further diagnostic evaluation. Clinicians should consider quantified proteinuria assays as a more accurate screening tool in the diagnostic evaluation of lupus nephritis. (First Release Dec 15 2007; J Rheumatol 2008;35:84–90)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
DIAGNOSTIC CRITERIA

NEPHRITIS
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Systemic lupus erythematosus (SLE) is a multisystem disease that affects the kidneys in up to 60% of patients over the course of their disease^{1,2}. Proteinuria is the most common pre-

senting feature and an inevitable consequence of lupus nephritis³. As many as 75% of patients with lupus nephritis experience a decline in renal function (glomerular filtration rate < 80 ml/min) and 10%–15% will develop endstage renal disease^{4,5}. However, early detection and appropriate treatment of renal dysfunction can prevent significant morbidity and mortality⁶. Therefore, detection of proteinuria, particularly in the early stages of disease, is crucial to prevent adverse outcomes in lupus nephritis.

Although many screening assays for proteinuria are available, published recommendations and accepted standards frequently advocate use of the qualitative urine dipstick. For example, the American College of Rheumatology (ACR) classification criteria for SLE utilize a dipstick threshold of 3+ to classify renal involvement or a quantitative measure of > 0.5 g/24 h⁷. A recent review advocates dipstick screening in the absence of known renal involvement³. Urine dipstick is also used in scoring instruments, including the British Isles Lupus Assessment Group and the Systemic Lupus Arthritis Measurement^{8,9}. Moreover, these guidelines appear to be closely followed in clinical practice. According to a recent survey we performed, 64% of practicing American rheuma-

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tologists reported using urine dipstick as their primary screening tool¹⁰. Finally, many protocols support use of qualitative tests, including at the US Food and Drug Administration, whose grading system of adverse events includes the dipstick as a primary measure of proteinuria¹¹.

Despite these recommendations and widespread use of these assays, there are disadvantages to the dipstick as a screening tool for proteinuria. Growing evidence in other disorders suggests these qualitative measurements might have poor validity when compared to quantitative assays¹²⁻¹⁷. Both highly concentrated urine and alkalinized urine might falsely elevate test results¹⁸. Moreover, because dipsticks measure albumin exclusively, there is a potential for underestimating the true extent of proteinuria¹⁹. Most importantly, there are no published reports of the comparative validity of dipstick screening compared to quantitative tests to detect proteinuria in lupus nephritis.

Because early detection of proteinuria is crucial to prevent poor outcomes, achieving optimal accuracy in screening is critical. Moreover, the widespread use of dipstick assays by practicing rheumatologists necessitates an analysis of the utility of this predominant screening method. We compared the performance of the qualitative urine dipstick to a quantitative proteinuria assay in a population with lupus undergoing screening for proteinuria. We hypothesized that due to variability in urine concentration and the inherently qualitative properties of the test, dipsticks would exhibit poor sensitivity for detection of significant proteinuria in relation to a quantitative system.

MATERIALS AND METHODS

This study was reviewed and approved by the Johns Hopkins University School of Medicine and Ohio State University institutional review boards. Our study population included patients enrolled in the Johns Hopkins Lupus Cohort (JHLC), started in 1987 to study the pathogenesis of SLE²⁰, and the Ohio SLE Study (OSS), a prospective longitudinal study since 2001 of patients with confirmed SLE, 60% of whom have biopsy-proven immune-complex glomerulonephritis²¹.

We retrospectively identified all instances in the cohorts, between January 1995 and June 2004, when patients recorded both a qualitative urine protein dipstick and a quantitative 24-hour urine protein and creatinine measurement within 1 day of each other. At both institutions urine dipsticks were performed on urine samples obtained separately from those provided for the 24-hour collection. We included multiple datapoints from patients for whom multiple paired measurements existed. The quantitative measurement served as the gold standard of proteinuria. Quantitative proteinuria (reported as grams protein/grams creatinine) was calculated from the ratio of the 24-hour urine protein (mg/dl) to creatinine (mg/dl), an accepted estimate of proteinuria per 24-hours^{22,23}. We analyzed the 24-hour protein/creatinine ratio based on recent findings that this indicator is a more reliable measure of total proteinuria than the total 24-hour urine protein level²⁴. The improved reliability of this ratio is predominantly due to the frequent inadequacy of 24-hour urine collections²⁴. Further, recent ACR clinical trial response criteria support use of a protein/creatinine ratio as the primary measure of proteinuria²⁵.

The performance of 3 qualitative dipstick tests was compared to the quantitative measurement of proteinuria. Urinalyses conducted in the JHLC before December 2001 were performed with the Clinitek (Bayer, Elkhart, IN, USA) automated assay. Subsequent JHLC testing was performed using the automated Atlas (Bayer) assay. Dipstick results in the OSS cohort were measured

manually using Bayer Multistix 10SG (Bayer) by one of 3 physicians, who were unaware of the quantitative results.

Statistical analysis. Data analysis was conducted using Stata 9.0 (Stata Corp., College Station, TX, USA). We first compared the demographic characteristics of patients undergoing each screening test using chi-squared and ANOVA analysis. Next, we measured the sensitivity of the 3 dipstick assays at a $\geq 1+$ threshold to detect proteinuria of ≥ 0.50 g protein/g creatinine. We specifically chose a 1+ dipstick threshold for detection of proteinuria based on its use by a majority of American rheumatologists (56%) in a recent survey¹⁰; it is also a conservative marker of renal involvement in our clinical practice. We then measured the specificity of a negative or trace dipstick result to correctly rule out quantitative proteinuria ratios < 0.50 .

We next measured the sensitivity of a $\geq 1+$ dipstick result to detect proteinuria in the range of 0.50–0.99 g protein/g creatinine. The quantitative range of 0.50–0.99 g protein/g creatinine corresponds to the ACR threshold of 0.5 g. Our goal was to specifically assess the validity of dipstick at low levels of proteinuria, where early-stage disease might present²⁶.

In order to evaluate the appropriateness of the ACR $\geq 3+$ threshold as an indicator of renal involvement in lupus, we analyzed the sensitivity of a $\geq 3+$ urine dipstick result to detect proteinuria at various ranges of quantitative proteinuria. For this analysis, we categorized the quantitative results (0–0.49, 0.50–0.99, 1.00–1.99, 2.00–2.99, ≥ 3.0), and measured the proportion at each quantitative category detected by a $\geq 3+$ dipstick result, using each of the 3 dipstick assays. Finally, we compared the range of quantitative proteinuria corresponding to each dipstick value using Friedman 2-way nonparametric ANOVA testing.

RESULTS

We analyzed data from 832 Clinitek assays, 557 Atlas assays, and 835 Bayer manual assays for a total of 2224 paired urine dipstick and 24-hour collections from 296 patients. Overall, the cohort was 92.2% female; mean age was 37.6 years. Urine samples for the 3 assays were collected from patients who were similar for sex and age (Table 1). However, there was a higher proportion of Caucasian participants in the OSS (Bayer manual assay) than in the JHLC (Clinitek and Atlas assays). Participants contributed a median of 5 urine dipsticks to the study (range 1–28).

Each qualitative dipstick assay was compared to a quantitative protein/creatinine ratio derived from the corresponding 24-h urine collection (Table 2). A total of 987 of the 2224 tests (44.4%) were defined as positive by the diagnostic standard (protein/creatinine ratio ≥ 0.50). The sensitivity of a $\geq 1+$ dipstick result to detect quantitative proteinuria of ≥ 0.50 g protein/g creatinine was 82.7% (343/415; 95% CI 78.7%–86.2%) for the Clinitek assay, 97.7% (208/213; 95% CI 94.6%–99.2%) for the Atlas assay, and 85.5% (307/359; 95% CI 81.4%–89.0%) for the Bayer manual assay. The speci-

Table 1. Demographic characteristics of 296 patients from the Johns Hopkins Lupus Cohort and Ohio SLE Study.

	Clinitek	Atlas	Bayer Manual	p
Matched urine samples	832	557	835	
Patients, n	108	104	84	
Sex, % female	94.4	91.3	90.4	0.54
Race, % Caucasian	43.5	37.5	60.2	<0.01
Age, mean yrs (SD)	36.0 (10.8)	38.8 (10.3)	38.2 (11.7)	0.15

Table 2. Comparison between dipstick proteinuria levels and protein/creatinine ratios (g protein/g creatinine) on specimens collected from patients with SLE.

	Clinitek Assay Protein/Creatinine Ratio					Total
	0–0.49	0.50–0.99	1.00–1.99	2.00–2.99	≥ 3.00	
Negative	285	16**	4*	0*	1*	306
Trace	74	29**	19*	2*	1*	125
1+	38 [†]	31	24	6	3	102
2+	14 [†]	33	31	7	11	96
≥ 3+	6 [†]	13	63	35	86	203
Total	417	122	141	50	102	832

	Atlas Assay Protein/Creatinine Ratio					Total
	0–0.49	0.50–0.99	1.00–1.99	2.00–2.99	≥ 3.00	
Negative	160	1**	0*	0*	1*	162
Trace	54	2**	0*	0*	1*	57
1+	90 [†]	23	4	0	0	117
2+	37 [†]	42	20	7	5	111
≥ 3+	3 [†]	15	40	15	37	147
Total	344	83	64	22	44	557

	Bayer Manual Assay Protein/Creatinine Ratio					Total
	0–0.49	0.50–0.99	1.00–1.99	2.00–2.99	≥ 3.00	
Negative	90	5**	0*	0*	6*	101
Trace	193	18**	7*	0*	16*	234
1+	112 [†]	23	19	1	4	159
2+	58 [†]	44	37	14	7	160
≥ 3+	23 [†]	29	55	26	48	181
Total	476	119	118	41	81	835

* False-negative results. ** False-negative values in range of low-level proteinuria. [†] False-positive results.

ficity of a < 1+ dipstick (trace or negative) result to correctly exclude significant proteinuria, as measured by a protein to creatinine ratio < 0.50, was 86.1% (359/417; 95% CI 82.4%–89.3%) for the Clinitek assay, 62.2% (214/344; 95% CI 56.9%–67.4%) for the Atlas assay, and 59.4% (283/476; 95% CI 54.9%–63.9%) for the Bayer manual dipstick assay. Thus, although the Atlas test had the lowest false-negative rate (2.3%; 5/213), it had a substantial false-positive rate (37.8%; 130/344). In addition, although the Clinitek had a lower sensitivity than the Atlas, it exhibited a relatively higher specificity. Finally, the Bayer manual assay appeared to be the least valid of the 3 measures, performing as poorly as the Clinitek in terms of sensitivity and as poorly as the Atlas in terms of specificity.

Comparing negative and positive predictive values for each of 3 assays (Table 3), we found a similar tradeoff between the Clinitek and Atlas assays. The Clinitek assay had the highest positive predictive value at 85.5%, versus 61.5% for the Atlas assay and 61.4% for the Bayer manual assay. However, the Atlas assay had the highest negative predictive value at 97.7%, versus 83.3% for the Clinitek and 84.5% for the Bayer manual assay. As with sensitivity and specificity

data, the predictive value results suggest that the Bayer manual assay is the least valid of the 3 dipstick measures.

We next focused our attention on the quantitative proteinuria range of 0.50–0.99 (g protein/g creatinine), where early and clinically significant disease might present. The sensitivity of a ≥ 1+ dipstick to detect quantitative proteinuria in this range was 63.1% (77/122; 95% CI 53.9%–71.7%) for the Clinitek assay, 96.4% (80/83; 95% CI 89.8%–99.2%) for the Atlas Assay, and 80.7% (96/119; 95% CI 72.4%–87.3%) for the Bayer manual dipstick assay (Table 2). Further, as shown in Figure 1, the Clinitek assay had a false-negative rate of 36.9% for detecting low-level proteinuria. Remarkably, 13.1% of those with quantitative proteinuria in this range had a negative dipstick, while 23.8% had a trace result using the Clinitek assay. In contrast, the Atlas assay had only a 3.6% false-negative rate in that quantitative range of proteinuria. The Bayer manual assay had a false-negative rate of 19.3%.

We also determined the quantitative levels of proteinuria corresponding to each dipstick value (Figure 2). The median level (interquartile range) of proteinuria corresponding to a 1+ dipstick result was 0.74 (0.39–1.18), 0.26 (0.14–0.43), and

Table 3. 2 × 2 result table comparing proteinuria dipstick assays with a quantified 24-hour protein (Pr)/(Cr) creatinine ratio (g protein/g creatinine) as the gold standard. A positive protein/creatinine ratio is defined as 24-hour urine ratio > 0.50. A positive urine dipstick is defined as a result ≥ 1+.

	Clinitek Dipstick			Atlas Dipstick			Bayer Dipstick	
	+	-		+	-		+	-
Pr:Cr +	343	72	Pr:Cr +	208	5	Pr:Cr +	307	52
Ratio -	58	359	Ratio -	130	214	Ratio -	193	283
	Sensitivity 82.7%	PPV 85.5%		Sensitivity 97.7%	PPV 61.5%		Sensitivity 85.5%	PPV 61.4%
	Specificity 86.1%	NPV 83.3%		Specificity 62.2%	NPV 97.7%		Specificity 59.4%	NPV 84.5%

PPV: positive predictive value; NPV: negative predictive value.

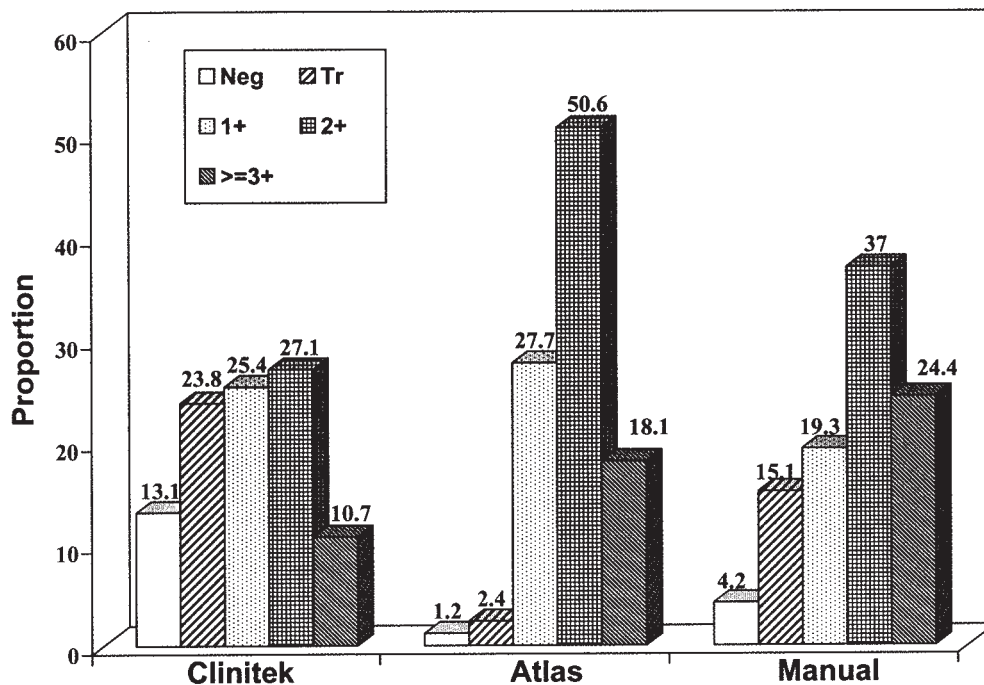


Figure 1. Proportion of quantitative low-level proteinuria (0.50–0.99 g protein/g creatinine) detected by dipstick results for each of 3 urine dipstick assays. Negative (Neg) or trace (Tr) qualitative results are false-negative.

0.30 (0.17–0.57) g protein/g creatinine for the Clinitek, Atlas, and Bayer manual assays, respectively ($p < 0.0001$).

Finally, we analyzed the performance of the $\geq 3+$ threshold as defined by the ACR classification criteria for SLE (Figure 3). The ability of a $\geq 3+$ dipstick result to detect proteinuria > 0.50 (g protein/g creatinine) was 47.5% (197/415; 95% CI 42.6%–52.4%) for the Clinitek assay, 50.2% (107/213; 95% CI 43.3%–57.1%) for the Atlas assay, and 44.0% (158/359; 95% CI 38.8%–49.3%) for the Bayer manual assay. In the range of 0.50–0.99 (g protein/g creatinine) the sensitivity of $\geq 3+$ to detect proteinuria was 10.7% (13/122; 95% CI 5.8%–17.5%) for the Clinitek assay, 18.1% (15/83; 95% CI 10.4%–28.0%) for the Atlas assay, and 24.4% (29/119; 95% CI 17.0%–33.1%) for the Bayer manual assay. Remarkably, the sensitivity of a $\geq 3+$ dipstick result to cor-

rectly detect ≥ 3.0 (g protein/g creatinine), a higher level of proteinuria, was also surprisingly low, only 84.3% (86/102; 95% CI 75.8%–90.8%) for the Clinitek assay, 84.1% (37/44; 95% CI 69.9%–93.4%) for the Atlas assay, and 59.3% (48/81; 95% CI 47.8%–70.1%) for the Bayer manual assay.

DISCUSSION

Early and accurate assessment of proteinuria is a priority of clinical care in patients with lupus. This is particularly true for proliferative lesions, including ISN class III and IV, which often have a fulminant course requiring early and aggressive intervention. Since proliferative lupus nephritis might initially present with low levels of proteinuria (500 to 1000 mg/day), it is critical that diagnostic detection methods have adequate precision in this range²⁶. Importantly, the majority of

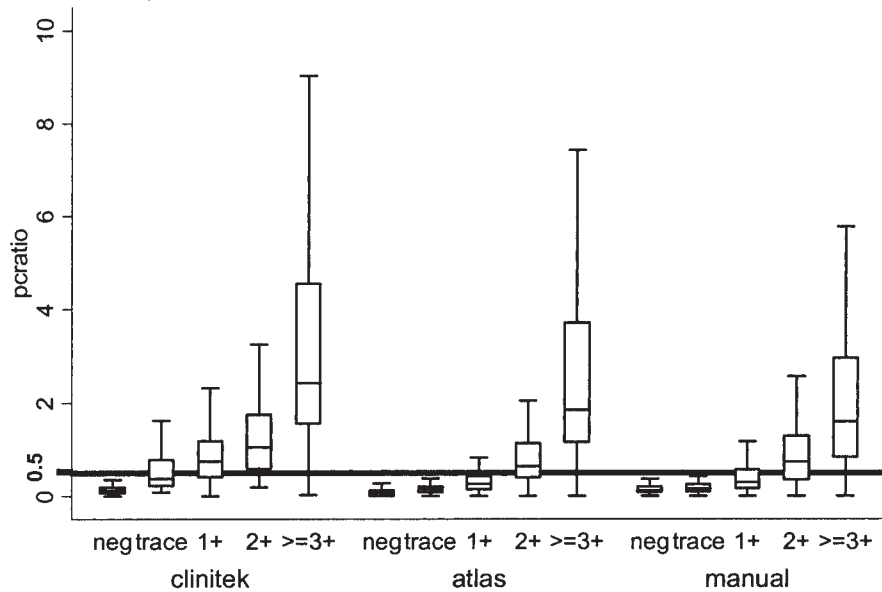


Figure 2. Quantitative ranges of the protein/creatinine ratio corresponding to 3 dipstick assays used to detect proteinuria. Boxes represent interquartile ranges for each distribution. Horizontal lines within boxes represent median values. Whisker lengths represent outliers up to 1.5 times interquartile range. Outliers beyond the whiskers are omitted from this figure. Y-axis line crosses at 0.50.

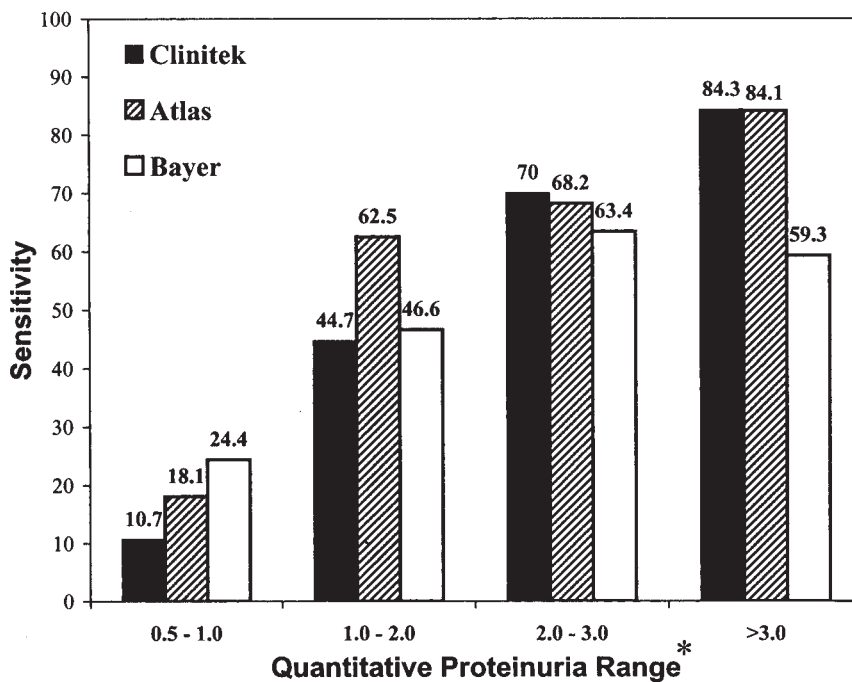


Figure 3. Sensitivity of a $\geq 3+$ urine dipstick result to detect abnormal quantitative proteinuria across a broad range of levels. *Results from 24-hour collection are calculated in g protein/g creatinine.

American rheumatologists use the qualitative urine dipstick as the primary method of screening¹⁰. However, our results suggest that urine dipstick is not an optimal screening tool for proteinuria in this population. Each of the 3 qualitative assays we examined has significant shortcomings. With false-nega-

tive rates of 36.9% and 19.3%, respectively, the Clinitek and Bayer manual assays have poor sensitivity to detect sub-nephrotic-range proteinuria in the range of 0.50–0.99, where early disease may present. Therefore, use of these dipstick systems might give an erroneous result, a missed diagnosis, in

as many as one in 3 patients with lupus, subjecting them to delayed investigations and delayed institution of treatment.

In contrast, the Atlas assay, although 97.7% sensitive, falsely classifies 38.5% of those without significant proteinuria as being positive. Bayer manual dipsticks also exhibited poor specificity, with a false-positive rate of 40.6%. The large proportion of false-positive results with the Atlas and Bayer manual assays necessitates use of a second, quantitative measurement of proteinuria to guide clinical decision-making regarding biopsy and treatment. Return visits in those falsely identified as positive impose an unnecessary diagnostic burden that may cause increased cost, patient anxiety, and potential iatrogenicity in those without true disease.

The poor performance of these qualitative tests prevents any single assay or threshold from serving as a reliable measure of proteinuria at levels where clinicians might consider further diagnostic evaluation. Therefore, we do not recommend the use of urine dipstick to screen for proteinuria in patients with lupus. Moreover, the ACR classification criteria might warrant reconsideration for ascertainment of renal disease. The current guidelines state that kidney involvement is classified by a quantified value of 500 mg/24 h or $\geq 3+$ proteinuria on dipstick. Our results indicate a significant inconsistency between these 2 criteria. Specifically, the sensitivity of the $\geq 3+$ level to detect proteinuria > 0.50 ranged from 44.0% to 50.2% for the 3 assays. Further, only 10.7% to 24.4% of those with significant, subnephrotic-range proteinuria, and as few as 59.3% with those near or greater than nephrotic-range proteinuria (> 3.0 g protein/g creatinine) were detected by dipstick value $\geq 3+$. Our data therefore suggest that a 3+ cutoff is an insensitive threshold for clinically significant proteinuria in those with lupus. We propose that a quantified measure of proteinuria serve as a more appropriate screening method and that use of dipsticks be reconsidered in future iterations of the ACR classification criteria.

It is also important to recognize that the dipstick is a poor tool to follow patients with established glomerulonephritis longitudinally, because diagnosis and monitoring of a flare depend to a great extent on a change in the level of proteinuria. Our results in lupus are consistent with studies in other disease states. Specifically, a number of reports in the obstetrics literature document the poor validity of dipstick to detect subnephrotic proteinuria, including a recent metaanalysis¹²⁻¹⁴. Moreover, other investigators have concluded that dipsticks not be used to detect early hypertensive or diabetic nephropathy^{16,17}. Our results add to the growing body of evidence that questions the appropriateness and validity of urine dipstick as a screening test.

The most important shortcoming of our study is the use of different urine samples to compare the 3 qualitative and quantitative diagnostic tests. However, to minimize the temporal discordance between the qualitative dipstick and 24-hour quantitative collection, we limited the interval between paired urine collections to a maximum of 1 day. Another limitation

was the analysis of multiple paired samples per patient and the inherent relatedness of more than a single specimen from a given patient. We were limited by cohort sample size and chose to increase our study power by including more data-points. An additional advantage of our methodology, however, was the measurement of proteinuria across a broad range of values, from minimal proteinuria through the nephrotic range. Another limitation is that we studied only a limited number of dipstick assays. Nevertheless, the Bayer, Atlas, Clinitek, and manual assays are the most widely used tests for proteinuria assessment. Importantly, we did not study the Multistix Pro Strips (Bayer, Elkhart, IN, USA), a new dipstick assay providing protein/creatinine results. This assay deserves further study.

Ultimately there are many considerations when choosing a screening method for proteinuria. Cost and convenience must be incorporated into the decision-making process. In the 20 years since protein/creatinine ratios were first reported as a reliable marker for proteinuria²², the methodology has been validated and recommended by investigators within and beyond the field of rheumatology². Recent response criteria guidelines by the ACR recommend use of a spot protein/creatinine ratio for detection of proteinuria in lupus nephritis²⁵. The National Kidney Foundation has also recommended the use of the protein/creatinine ratio to follow the course of chronic kidney disease²⁷. In our study, protein/creatinine ratios were calculated from 24-hour collections alone. The utility of the protein/creatinine ratio from spot (random single) urine collections in screening for lupus nephritis was not assessed, and deserves to be examined.

Our results suggest that urine dipsticks as a measure of proteinuria fail to attain the necessary precision to promptly and accurately detect significant proteinuria in patients with lupus nephritis. It might be prudent to reexamine guidelines that recommend using urine protein dipstick as a screening tool, both in this patient population and in other disease states in which low-level proteinuria might signal significant disease. We believe our findings discourage continued use of qualitative dipsticks as a screening tool for lupus nephritis. The use of quantitative testing has come of age.

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