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INVITED COMMENTARY

Commentary on the Current Guidelines for the Diagnosis of Lupus Nephritis Flare

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Abstract

Purpose of Review Lupus nephritis flare is a frequent complication in patients with systemic lupus erythematosus. Recognizing disease activity is crucial in lupus nephritis management. Proteinuria magnitude and urine sediment change are major clinical indicators of lupus nephritis activity. This work updates these insights in light of recent findings regarding proteinuria quantification and urine sediment analyses.

Recent Findings Currently, BILAG and SLEDAI estimate proteinuria magnitude based on the protein/creatinine ratio of "spot" (single void collections) or "intended" 24-h urine collections without specifying the extent to which the collection approaches a 24-h collection. As discussed here, and based on our recently published work, these approaches often incur serious errors that can adversely affect SLE patient management. Also incorporated into this work is a new analysis of the clinical significance of urine sediment hematuria and pyuria changes with regard to recent-onset SLE glomerulonephritis (GN) flare. This analysis is based on a prospective study of urine sediment changes in the Ohio SLE Study, which was an NIH-sponsored prospective observational study of SLE GN patients with SLE flare of recent onset.

Summary We propose that BILAG and SLEDAI renal flare criteria can be made more rigorous by incorporating recently published insights into proteinuria quantification using the protein/creatinine ratio of an intended 24-h urine collection that is at least 50% complete based on its creatinine content. Also proposed are new insights into the interpretation of urine sediment hematuria and pyuria based on findings from the Ohio SLE Study.

Keywords Lupus nephritis · Lupus nephritis flare · Proteinuria · Hematuria · Pyuria

It is well established that "heavy proteinuria" is a major manifestation of a severe lupus nephritis (LN) flare. However, current disease activity indices for adjudicating LN flare (BILAG and SELENA-SLEDAI) have not been updated to include the latest insights into accurately estimating proteinuria magnitude. This work addresses this shortcoming. In addition, we provide new insights into the analysis of the urine sediment changes of hematuria and pyuria, which accompany LN flare.

The specific shortcomings of the current LN flare indices with regard to proteinuria assessment are that they do not take into account the following:

1. In patients with glomerulopathy, the rate of urine protein excretion often varies greatly hour by hour, but the rate of urinary creatinine excretion is relatively constant. As a result, the variability of urine protein/creatinine ratio (PCR) is remarkably large as shown in Fig. 1 [1, 2]. Noteworthy is that these nephrotic patients were subjected to conditions that would minimize proteinuria variability. Specifically, their diet was constant, and they were at complete bed rest and were on no medications. The implications of the relationships shown in Fig. 1 are that the urine PCR of short urine collections, for example spot (single void) collections, reveals this variability. By

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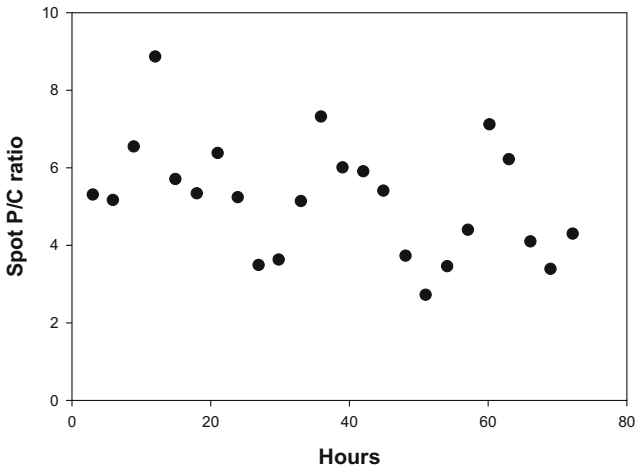


Fig. 1 Serial P/C ratios in a representative nephrotic patient who, starting the morning of day 1, was on strict bed rest for 3 days, a constant diet, and no medication. Note the highly variable sequential P/C ratios despite optimum conditions to stabilize proteinuria and creatinuria. P/C ratio variability was caused almost entirely by proteinuria rate variability. Creatinuria rate was relatively constant. Reprinted from Shidham and Hebert (2006), with permission from Elsevier

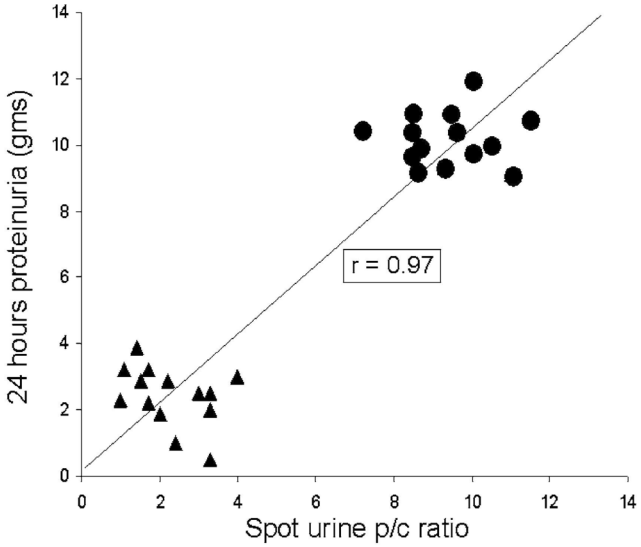


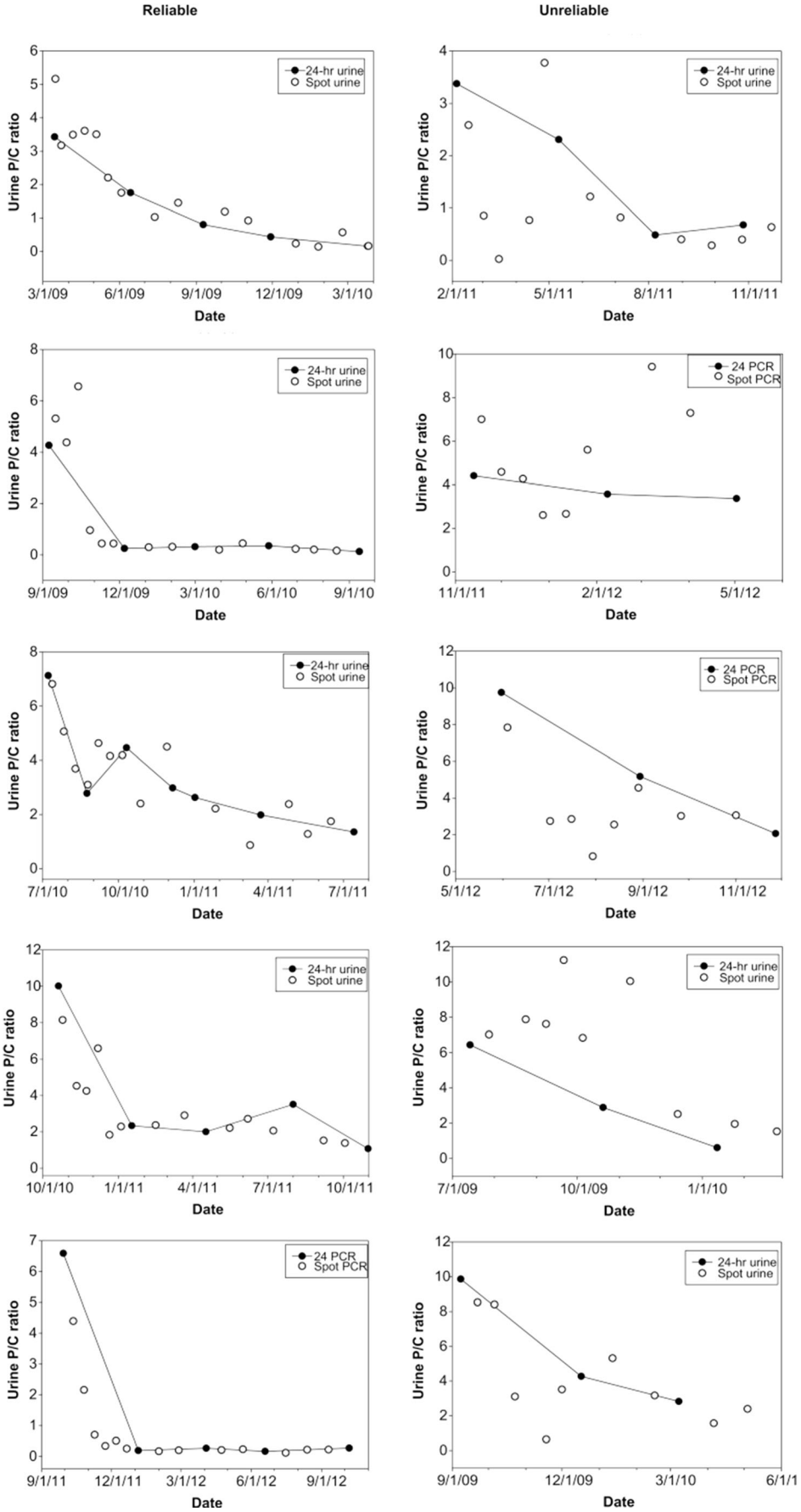
Fig. 2 Hypothetical comparison of two different methods to assess proteinuria rate: spot testing (urine P/C ratio) versus 24-h testing (24-h proteinuria). Circles, hypothetical patients with high proteinuria rates; triangles, hypothetical patients with low proteinuria rates. A striking correlation ($r = 0.97$) is present. However, closer inspection shows there is no significant correlation between spot and 24-h urine testing in patients with low-level proteinuria (the slope of the regression drawn through the points would not be different from 0). The same is true of patients with high-level proteinuria. Therefore, spot urine P/C ratio shows high correlation with 24-h proteinuria rates only because these populations are combined in the same regression. Reprinted from Shidham and Hebert (2006), with permission from Elsevier

contrast, long urine collections conceal this variability because the long collections can be viewed as the integrated mean of the individual spot collections. First morning void PCR is sometimes used in clinical trials employing SLEDAI criteria. First morning void PCR testing can be a satisfactory estimate of proteinuria magnitude; however, there are limitations, as we have previously described. They include exaggerated effects of diet taken the evening of the collection (high in salt or protein), variation in depth of sleep, nocturia, and contamination of the urine with semen, which has a very high albumin concentration [3].

2. The notion that spot urine PCR testing is a reliable estimate of 24-h proteinuria has been widely accepted based on numerous publications showing that the correlation coefficient between spot urine PCR and 24-h proteinuria is very significant. However, this interpretation is misleading because as shown in Fig. 2 the correlation coefficient is highly sensitive to the proteinuria range in which the comparisons have been made [2]. As discussed in the legend for Fig. 2, the high correlation coefficient is the result of examining these relationships over a wide range of values. Over more restricted ranges, including ranges that are clinically relevant, the correlation between spot urine PCR and 24-h proteinuria is poor.
3. Using spot PCR testing serially to assess for proteinuria trend is often highly unreliable and varies considerably from patient to patient [4]. This "unreliability" was shown using a unique dataset obtained from the ACCESS trial in which 103 patients with severe glomerulonephritis were followed for up to 18 months with concurrent spot PCR testing (done at each clinic visit) and 24-h proteinuria (done every 3 months) [5]. In about 40% of the patients, the spot PCR testing provided reliable estimates of proteinuria trend based on the gold standard, an intended 24-h urine collection that is at least 50% complete based on the creatinine content [4]. However, in about 60% of the patients, the spot PCR testing was an unreliable estimate of proteinuria trend, to the extent that if clinical decisions had been made based on the spot PCR testing, then those decisions likely would lead to mismanagement [4]. To make matters worse, baseline measures could not differentiate those who had "unreliable" spot PCR from those who had "reliable" spot PCR. As a consequence, none of the spot PCR trends identified by prospective testing could be trusted in clinical decision making. It is only in retrospect that the true proteinuria trend is revealed.

Figure 3 shows examples of patients who manifest reliable spot PCR or unreliable spot PCR. The format used in these displays is that the proteinuria trend line is composed of the PCRs of intended 24-h urines in which the creatinine content

Fig. 3 Representative ACCESS patients in whom spot PCR was deemed ▶ to be reliable or unreliable based on the degree to which the patient's spot PCR values follows the patient's proteinuria trend line (the line joining the patient's 24 PCR value). Reprinted from Shidham et al. (2018), with permission from Elsevier


Reliable
Unreliable
Urine P/C ratio
Date
24-hr urine
Spot urine
24 PCR
Spot PCR
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6/1/09
9/1/09
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Table 1 Current guideline for the determination of renal flare in SLE nephritis based on proteinuria

	Current guidelines	Recommended change to guidelines
BILAG[1]	Urine dipstick protein Urine albumin–creatinine ratio	• Dipstick testing should not be used to estimate proteinuria magnitude
	Urine protein–creatinine ratio 24-h urine protein	• Proteinuria magnitude should be based on the protein/creatinine ratio (PCR) of intended 24-h urine collections that are at least 50% complete based on the creatinine content of the collection[3]
SLEDAI[2]	Proteinuria > 0.5 g/24 h	

[1] British Isles Lupus Assessment Group (BILAG 2004)

[2] Systemic Lupus Erythematosus Disease Activity Index, 2000 (SLEDAI)

[3] Cockraft-Gault equation can be used to estimate the expected creatinine content of a complete 24-h urine collection according to the patient's age, sex, race, and weight [6]

was at least 50% of that expected in a complete 24-h collection. The PCR of such collections produces a reliable estimate of proteinuria magnitude [4]. Therefore, the trend line formed from serial 24-h PCR testing is a reliable estimate of proteinuria trend.

Urine dipstick is not specific for proteinuria. The urine can be concentrated or highly alkaline producing a false-positive test for proteinuria 1 to 2+. The dipstick detects mainly albumin which is about two-thirds of glomerular proteinuria. Hence, the dipstick may underestimate total proteinuria magnitude. Also, the dipstick does not take into account urine concentration leading to risks of over- or underestimated interpretations.

In summary, we suggest that the BILAG and SLEDAI proteinuria criteria for renal flare should be updated as shown in Table 1.

With regard to the significance of pyuria as a manifestation of nephritis flare, we would caution that pyuria is a common finding in LN women in the absence of flare and often may represent "periurethral washout." The latter should be suspected if the urine sediment also shows numerous squamous epithelial cells. Nevertheless, we have examined this issue in the Ohio SLE Study, and have found that significant pyuria (WBC > 5/HPF) can be seen in the absence of significant hematuria (RBC > 5/HPF) at the time of renal flare (Fig. 4, unpublished data). However, this is unusual.

Finally, it should be recognized that major LN flare based on serum creatinine, proteinuria, and histology can occur without evidence of nephritic sediment. On the other hand, active urine sediment can be seen in mild LN flare. Thus, active sediment is neither a sensitive nor a specific indicator for LN flare or its severity.

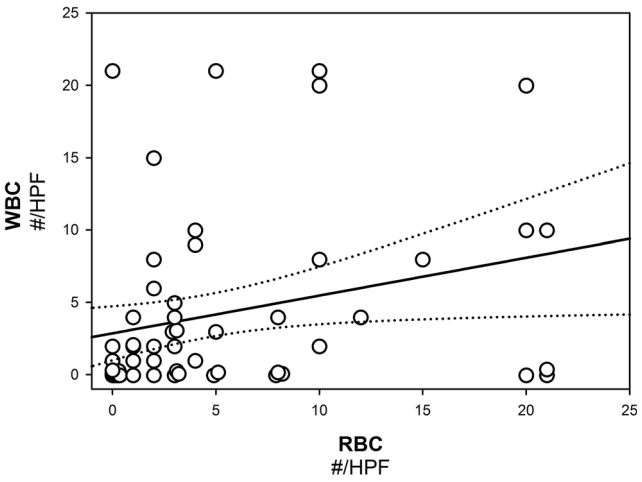

Fig. 4 Relationship between urine red blood cells per high-power field (RBC/HPF) and white blood cells per high-power field (WBC/HPF) at renal flare in LN patients followed in Ohio SLE Study

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- •• Of major importance

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