A 25-year-old Haitian-born woman presents for her routine follow-up appointment. She was diagnosed with systemic lupus erythematosus (SLE) a year ago. Her disease features at presentation consisted of discoid skin lesions, photosensitivity, alopecia, oral ulcers, polyarthritis, leucopenia, lymphopenia, Coombs positive hemolytic anemia, and thrombocytopenia. Her serology was positive for ANA, anti-dsDNA, anti-Sm and anti-RNP antibodies. When first seen, she was found to have lower limb edema and her work-up showed a normal serum creatinine, low C3 and C4, hypoalbuminemia (30 g/L) and microscopic hematuria. A 24-hour urine collection revealed non-nephrotic range proteinuria (1.32 g/day). A kidney biopsy done at that time showed class III (A) lupus nephritis (LN) (Figure 1). The patient was started on high dose oral prednisone, mycophenolate mofetil (MMF), and hydroxychloroquine. Due to a severe skin reaction to MMF, treatment was changed to azathioprine.

Three months into her immunosuppressive therapy, she had improved significantly. Her skin lesions were healing and her lower leg edema had resolved. Her cell counts and complements had normalized, the albumin was improving (35 g/L), and anti-dsDNA titer was decreasing. The proteinuria was down to 500 mg/day. Due to her favourable evolution, her prednisone was gradually tapered and she continued to improve on her subsequent follow-up visits.

Her current presentation shows recurrence of significant lower limb edema. She is otherwise well; her blood pressure is normal. The blood work done today shows the following: normal complete blood count (CBC), normal serum creatinine, an albumin of 20 g/L, normal C3 and C4 and low titer positive anti-dsDNA (stable). Her urine dip is positive for trace blood and > 3 g/L of protein. A 24-hour urine collection now shows 9.4 g/day of protein. A second kidney biopsy is performed and findings are now compatible with pure class V LN (Figures 2 and 3).

Class V Lupus Nephritis
Membranous lupus nephritis (MLN) is characterized on histopathology by global or segmental continuous granular subepithelial immune deposits.1 Mesangial hypercellularity may be found, as well as mesangial immune deposits. When findings typical for MLN coexist with subendothelial immune deposits on light microscopy a diagnosis of combined LN should be made. The membranous variant of LN likely has a different immune pathogenesis compared to proliferative LN, as evidenced by our patient. She had a satisfying resolution of her immune complex disease and, at that point, rather suddenly developed MLN. A different pathogenetic mechanism, however, is not proven. In keeping with this there were some scattered subepithelial deposits in the first biopsy, as is not uncommonly seen in many cases of proliferative LN. Class V LN is present in up to 20% of renal biopsies in patients with lupus. In contrast to proliferative LN, the influence of ethnicity on response to therapy and long-term prognosis is not well characterized for MLN.

Clinical Features
Patients often present with nephrotic-range proteinuria, hypoalbuminemia, and edema. Serology is usually positive for ANA, but complements may be within normal limits and anti-dsDNA antibodies absent. Significant hematuria, cellular casts, low complement levels, elevated serum creatinine, and positive anti-dsDNA antibodies may all be found, but warrant consideration of proliferative nephritis. However, the concomitant mesangial cell proliferation seen in membranous lupus can be associated with microhematuria
and even red blood cell casts. Therefore, the finding of an “active” urine sediment does not necessarily imply that the patient has endocapillary proliferative LN.

Therapeutic Approach
The management of pure MLN is controversial. The available evidence mainly comes from case series and small, uncontrolled trials. Patients with MLN in combination with a proliferative form (class III + V, or IV + V) have a worse prognosis and should be treated as having proliferative LN. Patients with pure class V nephritis are reported to have a better outcome. Despite this, chronic kidney disease (CKD) and end-stage renal disease (ESRD) may develop in patients with MLN, especially in those with nephrotic-range proteinuria. Similar to patients with idiopathic membranous nephropathy, these patients are also at significant risk for thrombotic events and accelerated atherosclerosis. Pure class V nephritis should therefore not be regarded as a benign condition, especially when there is nephrotic-range proteinuria. Moroni et al recently published long-term outcome data on 67 patients with pure MLN, of whom 44.7% had nephrotic syndrome at presentation.2 Patients were followed over a mean of 13 years in two centres. After 15 years, 94.5% of patients were alive and 85% were free of chronic renal insufficiency.

Renal protective measures should be implemented in patients with LN. Blood pressure needs to be monitored regularly at home and anti-hypertensive therapy should be tailored to obtain blood pressure values ≤ 130/80.3 Salt restriction (< 2 g/day) should be strongly encouraged. It is quite common for patients on high doses of corticosteroid to develop volume-dependent hypertension. Often the blood pressure will not come under optimal control until the dose of steroid has been reduced, and so the clinician should not strive to necessarily bring the blood pressure down to target. In the meantime, since it is a volume-dependent hypertension as a result of mineralocorticoid-induced salt retention, dietary sodium restriction and thiazide diuretics can be very helpful. Weight control, establishment of a regular aerobic exercise program, smoking cessation, counselling on alcohol consumption, and treatment of dyslipidemia should be regarded as management priorities to improve blood pressure and the overall cardiovascular risk profile.4

Figure 1. Biopsy 1: Class III lupus nephritis (LN). Glomerulus shows segmental area of endocapillary hypercellularity with possibly small adjacent cellular crescent. The remaining capillary loops are patent. There is mild mesangial expansion due to the increase in matrix and cells (light microscopy, PAS staining 20X).

Figure 2. Biopsy 2: Class V lupus nephritis. Glomerulus shows segmental mesangial expansion due to the increase in matrix and cells. The capillary loops are thickened with a rigid appearance (light microscopy, PAS staining 20X).

Figure 3. Biopsy 2: Class V lupus nephritis. Ultrastructural examination reveals numerous subepithelial immune-type electron dense deposits, mostly within stages 1 or 2. There is extensive foot process obliteration.
Ongoing proteinuria may lead to progression of CKD. Although no definite proteinuria threshold at which an antiproteinuric agent should be started has been established in LN, it is reasonable to start such an agent if proteinuria exceeds 0.5 g/day. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be used. Superiority of one class of medication over the other has not been demonstrated in systemic lupus erythematosus (SLE) patients. While the patient should be actively counselled against pregnancy during a flare of lupus, if they do conceive, these agents are considered teratogenic and should be discontinued.

Hydroxychloroquine therapy may decrease the incidence of renal flares. In addition, antimalarial therapy may provide other advantages. Reduced probability of renal damage accrual, favourable effects on lipid levels and glucose tolerance, and lowered risk of thrombosis are potential additional benefits to be gained from this class of drugs.

Who Should Be Started On Immunosuppressive Therapy?
As demonstrated in Table 1, no consensus has been reached on the indication and optimal treatment regimen to use in pure MLN. The decision to start an immunosuppressive agent in subjects with nephrotic-range proteinuria is rational, as spontaneous remission in this subgroup of patients is less likely to occur, and, as mentioned, carries a significant risk of thrombosis. For those with sub-nephrotic range proteinuria, no evidence exists that immunosuppressive drugs lower the risk of developing CKD and/or ESRD or improve survival. Hence, the decision to start such therapy needs to be individualized.

What Type of Immunosuppressive Agents Should Be Used?
There is a lack of well-designed studies addressing this question. The only randomized controlled trial comparing prednisone to combined immunosuppressive therapy in pure class V LN was done on a small single-centre cohort of SLE patients with heavy proteinuria (median proteinuria

### Table 1
Published Recommendations Regarding the Use of Immunosuppressive Therapies in Pure Class V Lupus Nephritis

<table>
<thead>
<tr>
<th>Statements</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American College of Rheumatology Guidelines</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td><strong>Nephrotic-range proteinuria:</strong></td>
</tr>
<tr>
<td>Prednisone (0.5 mg/kg/day) plus MMF 2-3 g/day</td>
<td>A</td>
</tr>
<tr>
<td>No consensus reached for the use of other therapies</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>European League Against Rheumatism (EULAR) / European Renal Association (ERA) - European Dialysis and Transplant Association (EDTA) Recommendations</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td><strong>Proteinuria &gt; 1g/day:</strong></td>
</tr>
<tr>
<td>Indication for immunosuppression</td>
<td>4C</td>
</tr>
<tr>
<td><strong>Nephrotic-range proteinuria; corticosteroids and MPA</strong></td>
<td></td>
</tr>
<tr>
<td>High-dose intravenous cyclophosphamide</td>
<td>2B</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>2A</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>3B</td>
</tr>
<tr>
<td>Rituximab</td>
<td>4C</td>
</tr>
<tr>
<td><strong>Non-nephrotic range proteinuria and no adverse clinical or histological prognostic factors:</strong></td>
<td></td>
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<tr>
<td>Azathioprine</td>
<td>4C</td>
</tr>
<tr>
<td><strong>Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td><strong>Non-nephrotic range proteinuria and normal kidney function:</strong></td>
</tr>
<tr>
<td>Antiproteinuric and antihypertensive medications; use corticosteroids and immunosuppressive agents if needed for non-renal SLE manifestations</td>
<td>2D</td>
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<tr>
<td><strong>Persistent nephrotic-range proteinuria; corticosteroids and Cyclophosphamide</strong></td>
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<tr>
<td>Calcineurin inhibitors</td>
<td>2C</td>
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<td>MMF</td>
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<tr>
<td>Azathioprine</td>
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of 5.4 g/day). A total of 42 patients were randomized to one of three treatment arms: alternate-day prednisone, alternate-day prednisone and bimonthly IV cyclophosphamide, and alternate-day prednisone combined with cyclosporin. Patients were treated and followed for 12 months at which point remission, based solely on the proteinuria level, was assessed. Patients in the two groups treated with adjunctive immunosuppressive agents achieved remission of proteinuria more frequently than in the prednisone-alone group (10/12, 9/15, and 4/15 in the prednisone and cyclosporin, prednisone and cyclophosphamide, and prednisone alone groups, respectively).

Due to the small number of patients and to the fact that, after 12 months, treatment given was no longer protocolized, this study does not allow direct comparison of cyclosporin and cyclophosphamide’s efficacy in terms of relapse prevention. However, the study is consistent with those in idiopathic nephrotic syndrome, where cyclophosphamide is associated with a more sustained remission than in those who receive a calcineurin inhibitor. However, this study used alternate-day prednisone rather than daily corticosteroid, and the data was collected over the span of two decades. A recent meta-analysis of studies on immunosuppressive therapy for MLN reporting remission outcome came to a similar conclusion. Response rate, defined as the sum of complete and partial remission rates, was contrasted between patients treated with at least one nonsteroidal immunosuppressive medication (n = 349; nonsteroidal agents used: azathioprine, mycophenolate mofetil, enteric coated mycophenolate sodium, chlorambucil, cyclophosphamide, cyclosporine, and tacrolimus) vs. those receiving corticosteroids alone (n = 136). Patients on nonsteroidal immunosuppressive medications showed a higher response rate than those on corticosteroid monotherapy (81% vs. 60%, respectively), even after heterogeneity and bias compensation (76% vs. 60%, respectively). Similar response rates were obtained for azathioprine (88%), cyclophosphamide (75%), cyclosporin (84%), and mycophenolate mofetil (82%). Despite methodological limitations, these studies seem to indicate that adjunctive immunosuppressive therapy may lead to higher remission rate.

Radhakrishnan et al. performed a pooled analysis of 84 subjects with pure class V LN from two large RCTs comparing induction therapy with intravenous cyclophosphamide vs. MMF in LN. At 24 months, no significant difference between the two drugs was noted in terms of improvement in proteinuria and serum creatinine level. Due to the favourable safety profile of MMF, it is likely to be preferred to cyclophosphamide unless there are doubts about adherence to therapy. Unfortunately, no data is available on the long-term outcome of these patients, so it is not known if the relapse rate will differ over time. Other trials have reported on the use of calcineurin inhibitors as an adjunct to corticosteroids for initial treatment, or for relapsing and refractory cases. Here again, limitations imposed by small sample sizes, non-RCT designs, short follow-up time, and the inclusion of proliferative or combined LN in the studied population prevent firm conclusions. A potential added benefit of using calcineurin inhibitors in MLN may be the antiproteinuric effect induced by this class of medication which seems to be independent of their immunosuppressive action. Finally, rituximab has been reported in uncontrolled studies to reduce proteinuria to non-nephrotic levels, mainly for refractory or relapsing cases. Also, a recent pooled analysis of European cohorts of LN patients treated with rituximab reported complete or partial response in 11/17 MLN subjects at 12 months. It is challenging to sort out the true efficacy of rituximab as it has mainly been used as a rescue therapy and/or used concomitantly with other immunosuppressive agents. Similar to what plagues all studies of treatment of glomerulonephritis, there may be a significant lag time between therapy and response. If a patient is treated with Agent A, and then is switched to Agent B six months later, and goes into remission, it is uncertain whether the response was the result of Agent B, or a delayed response to Agent A. Furthermore, in all these studies, only short-term follow-up data is available.

Back to the Case: Cyclosporin, a loop diuretic and an ACE inhibitor were added to the patient’s treatment regimen. The prednisone weaning continued. The patient improved gradually. At her last follow-up visit, 18 months after her membranous nephritis flare, her albumin has increased to 32 g/L and her proteinuria has decreased to 1.5 g/day.

References
4. Reich HN, Gladman DD, Urowitz MB, et al. Persistent proteinuria and
tasks such as completing a tax return. Consider the role of contributing factors such as medications, insomnia, fatigue, and mood disorders.

7. Cognitive distortions, particularly fear of further injury and catastrophizing, prevent functional improvements. People with persistent pain should be screened for fear avoidance and catastrophizing using self-assessment tools such as the Tampa Scale for Kinesiophobia (TSK) and the Pain Catastrophizing Scale (PCS). A referral for cognitive behaviour therapy should be considered when you suspect cognitive distortions may be impeding functional recovery.

8. Although pain self-management programs can improve biological, psychological, and social contributors to persistent pain, readiness to accept this approach varies. Using approaches such as Prochaska’s Stages of Change model, assess each individual for readiness to change. Different approaches are needed to motivate change: educational approaches to make people aware of the need to try self-management, and cognitive behavioural approaches to overcome barriers once that need is recognized.

9. Pain-modifying agents should target both persistent pain and contributing conditions.

Tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) appear to reduce abnormal pain processing. TCAs also improve neuropathic pain and sleep; SNRIs improve neuropathic pain, anxiety, and depression. Pregabalin can improve neuropathic pain and sleep. Tramadol and tapentadol have both opioid and TCA-like effects.

10. Opioids can increase pain and inhibit hormonal function. Opioid-induced hyperalgesia should be suspected if patients develop increasingly diffuse pain and allodynia despite increasing doses of opioids. High doses of opioids, particularly over 200 mg of oral morphine equivalents per day, may contribute to problems of hypogonadism, adrenal dysfunction, and other hormonal disturbances.

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