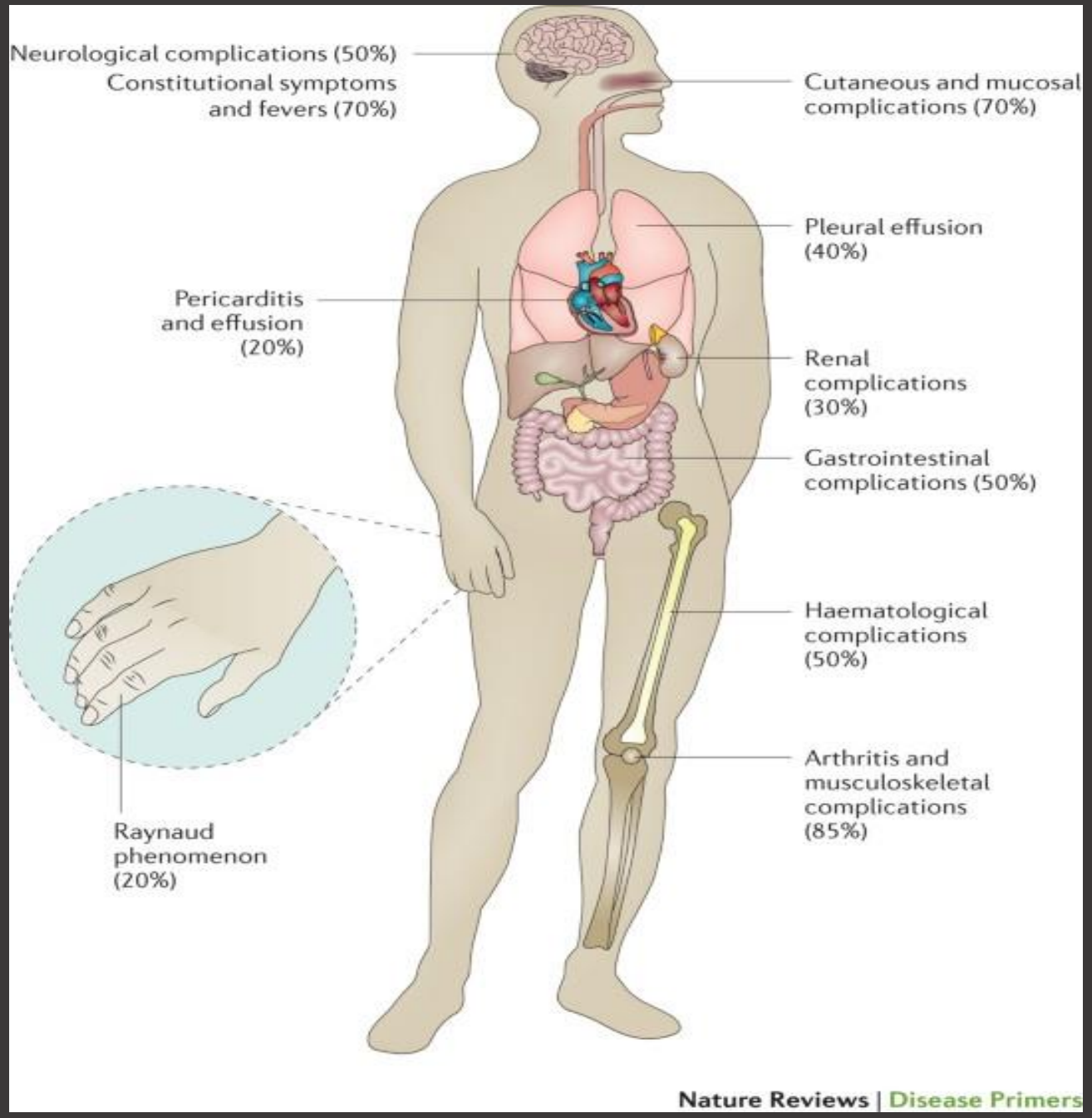
Lupus nephritis



SLE

is **an autoimmune disease in which the immune system attacks its own tissues**, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels.

Kidney involvement is common in systemic lupus erythematosus (SLE).

An **abnormal urinalysis** with or without an **elevated plasma creatinine concentration** is present in a large proportion of patients at the time of diagnosis of lupus nephritis (LN).

Most patients with systemic lupus erythematosus will have clinical evidence of kidney disease, usually an abnormal urinalysis, at some point in the course of their disease.

- ✓ Lupus nephritis typically develops early in the disease course.
- ✓ Clinically evident kidney disease eventually occurs in up to one-half of patients with SLE
- ✓ up to 10 percent of patients with LN will develop end-stage kidney disease

PATHOGENESIS

Although lupus nephritis is considered to be a classic form of immune complex glomerulonephritis, the pathogenesis of LN is complicated. The pathogenesis may involve the expression of genes, both in the peripheral blood as well as in the kidneys, leading to neutrophil activation and increased expression of interferon and upregulation of myeloid cell and proinflammatory transcriptomes

The pattern of glomerular injury seen in SLE (and in other immune complex-mediated glomerular diseases) is generally related to the site of formation of the immune deposits, which are primarily due to anti-double-stranded DNA (anti-dsDNA or anti-DNA) antibodies.

CLINICAL FEATURES

The most frequently observed abnormality in patients with lupus nephritis is **proteinuria**.

Other common clinical manifestations include:

- ✓ microscopic hematuria with or without red cell casts
- ✓ kidney function impairment
- ✓ nephrotic-range proteinuria or nephrotic syndrome
- ✓ hypertension

DIAGNOSIS

When to suspect LN

The presence of lupus nephritis should be suspected in patients with known systemic lupus erythematosus who develop an **active urinary sediment** with persistent hematuria (five or more red blood cells, most of which are dysmorphic, per high-power field) and/or cellular casts, proteinuria, and/or an elevated serum creatinine (or decrease in estimated glomerular filtration rate [eGFR]).

Elevated anti-double-stranded-DNA (anti-dsDNA) titers and low complement (C3 and C4) levels often indicate active SLE, particularly LN, although the utility of serological assessment differs among patients.

Establishing the diagnosis

The diagnosis of LN is ideally confirmed by a **kidney biopsy**

We generally perform a kidney biopsy in patients who have one or more of the following clinical manifestations:

- Urine protein excretion greater than **500 mg/day.**
- **An active urinary sediment with persistent hematuria** (five or more red blood cells per high-power field, most of which are dysmorphic) and/or cellular casts. The urine may be contaminated with vaginal blood in menstruating women or with bladder red cells with urinary tract infections. Red cells from this source are not dysmorphic.
- A **rising serum creatinine** that is not clearly attributable to another mechanism.

When to repeat the biopsy

The indications for a repeat biopsy include:

- ✓ the emergence of an active sediment in someone with previously quiescent disease
- ✓ a new elevation in serum creatinine
- ✓ and/or worsening of proteinuria despite treatment

Table 1. ISN/RPS Classification of Lupus Nephritis

Class	Description
I	Minimal mesangial
II	Mesangial proliferative
III	Focal
IV	Diffuse
V	Membranous
VI	Advanced sclerosing

ISN/RPS: International Society of Nephrology/Renal Pathology Society.
Source: Reference 4.

Minimal mesangial LN (class I) — This class of lupus nephritis is rarely, if ever, diagnosed because **these patients typically have a normal urinalysis, no or minimal proteinuria**, **and a normal serum creatinine**. As a result, a biopsy is not usually performed. Patients with class I disease have only mesangial immune deposits that are identified by immunofluorescence alone or by both immunofluorescence and electron microscopy, but such patients do not have light microscopic abnormalities. Minimal mesangial LN (class I) represents the earliest and mildest form of glomerular involvement.

Mesangial proliferative LN (class II)

The histologic changes with class II disease are manifested **clinically by microscopic hematuria and/or proteinuria**. Hypertension is uncommon, and nephrotic syndrome and kidney function impairment are virtually never seen.

Focal LN (class III)

Patients with class III lupus nephritis (LN) usually **have hematuria and proteinuria, and some patients will also have hypertension, a decreased GFR, and/or nephrotic syndrome**. Class III disease is defined histologically by the following:

- Less than 50 percent of glomeruli are affected by light microscopy. If more than 50 percent are involved, then the disease would be defined as diffuse LN (class IV). Although less than 50 percent of glomeruli are affected on light microscopy, immunofluorescence microscopy (for IgG and C3) reveals almost uniform involvement

- Active or inactive endocapillary or extracapillary glomerulonephritis is almost always segmental (ie, involves less than 50 percent of the glomerular tuft). Electron microscopy usually reveals immune deposits in the subendothelial space of the glomerular capillary wall as well as the mesangium.

Diffuse LN (class IV)

Class IV LN is the most common histologic pattern and most severe form of lupus nephritis . **Hematuria and proteinuria are present in virtually all patients with active class IV disease, and nephrotic syndrome, hypertension, and reduced GFR are all frequently seen**. Affected patients typically have significant hypocomplementemia (especially C3) and elevated anti-dsDNA levels, especially during active disease .

Class IV LN is defined histologically by the following:

- More than 50 percent of glomeruli are affected by light microscopy. If less than 50 percent are involved, then the disease would be defined as focal LN (class III).
- Affected glomeruli display **endocapillary with or without extracapillary glomerulonephritis**. **Mesangial abnormalities** may also be observed. Electron microscopy reveals subendothelial deposits, at least during the active phase

Lupus membranous nephropathy (class V)

Lupus membranous nephropathy is present in **10 to 20 percent of patients with LN**. Patients with class V LN typically present with signs of the **nephrotic syndrome**, similar to that in primary membranous nephropathy. Microscopic hematuria and hypertension may also be seen at presentation, and the creatinine concentration is usually normal or only slightly elevated.

Class V disease is characterized by diffuse thickening of the glomerular capillary wall on light microscopy and by subepithelial immune deposits (either global or segmental involvement) on immunofluorescence or electron microscopy. Mesangial involvement may also be seen.

Advanced sclerosing LN (class VI)

Patients with **advanced sclerosing glomerulonephritis** usually display slowly progressive kidney dysfunction in association with proteinuria and a relatively bland urine sediment.

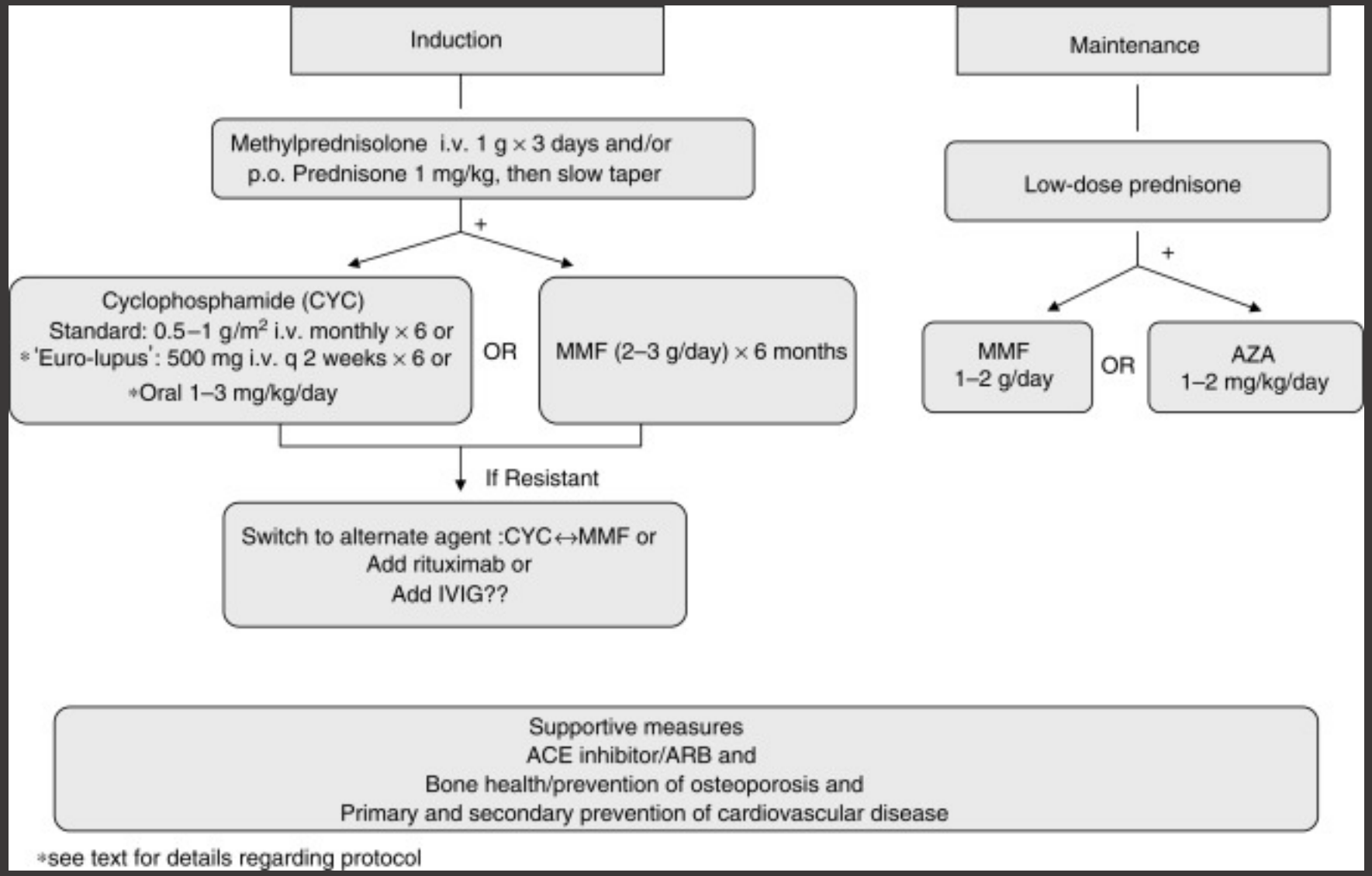
Class VI disease is characterized by global sclerosis of more than 90 percent of glomeruli. It represents healing of prior inflammatory injury, as well as the advanced stage of chronic class III, IV, or V lupus nephritis (LN).

Table 2. Medications Used for the Treatment of Lupus Nephritis

Medication	Dosing
INDUCTION THERAPY	
MMF	2-3 g IV/po daily × 6 mo
Cyclophosphamide	"Euro-Lupus": 500 mg IV every 2 wk × 6 doses High dose: 500-1,000 mg/m² IV monthly × 6 doses
Methylprednisolone	Pulse: 500-1,000 mg IV daily × 3 doses, followed by 0.5-1 mg/kg/day of oral glucocorticoid tapered to minimal effective dose
MAINTENANCE THERAPY	
MMF	1-2 g po daily × 3 y
Azathioprine	2 mg/kg po daily × 3 y*
ADJUNCTIVE TREATMENT	
Hydroxychloroquine	200-400 mg po daily

**Length of treatment computed from the American College of Rheumatology's recommendation for maintenance treatment with MMF. MMF: mycophenolate mofetil. Source: Reference 2.*

Treatment


Induction
Methylprednisolone i.v. 1 g × 3 days and/or
p.o. Prednisone 1 mg/kg, then slow taper
+
Cyclophosphamide (CYC)
Standard: 0.5–1 g/m² i.v. monthly × 6 or
*'Euro-lupus': 500 mg i.v. q 2 weeks × 6 or
*Oral 1–3 mg/kg/day
OR
MMF (2–3 g/day) × 6 months
If Resistant
Switch to alternate agent :CYC↔MMF or
Add rituximab or
Add IVIG??
Maintenance
Low-dose prednisone
+
MMF
1–2 g/day
OR
AZA
1–2 mg/kg/day
Supportive measures
ACE inhibitor/ARB and
Bone health/prevention of osteoporosis and
Primary and secondary prevention of cardiovascular disease
*see text for details regarding protocol

- **Partial response:** in patients with ≥3.5g/24h, decreased proteinuria <3.5g/24h. In patients with baseline proteinuria <3.5g/24h, >50% reduction in proteinuria as compared to initial values. In both situations, stabilisation (±25%) or improvement in serum creatinine with regard to initial values.

- **Complete response:** Serum creatinine <1.2mg/dl (or decrease to initial values or ±15% of baseline value in patients with creatinine ≥1.2mg/dl), proteinuria ≤0.5g/24h, inactive urinary sediment (≤5 red blood cells, ≤5 leukocytes, 0 red blood cell casts) and serum albumin >3g/d.
