When Rheumatic Diseases Affect the Kidney: Challenges for the Nephrologist

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- Kidneys are one of the most common organs involved in subjects with rheumatologic diseases
- Renal involvement can result either due to the direct effects of disease itself or as a result of complications of the therapy used to treat it
- Renal manifestations can vary from asymptomatic urinary abnormalities to severe life-threatening renal failure

- most cases of rheumatological diseases complicated with renal involvement warrant immunosuppressive therapy and have higher morbidity and mortality.
- The nephrologist along with rheumatologists plays a key role in the management of such patients:

  Establishing the diagnosis

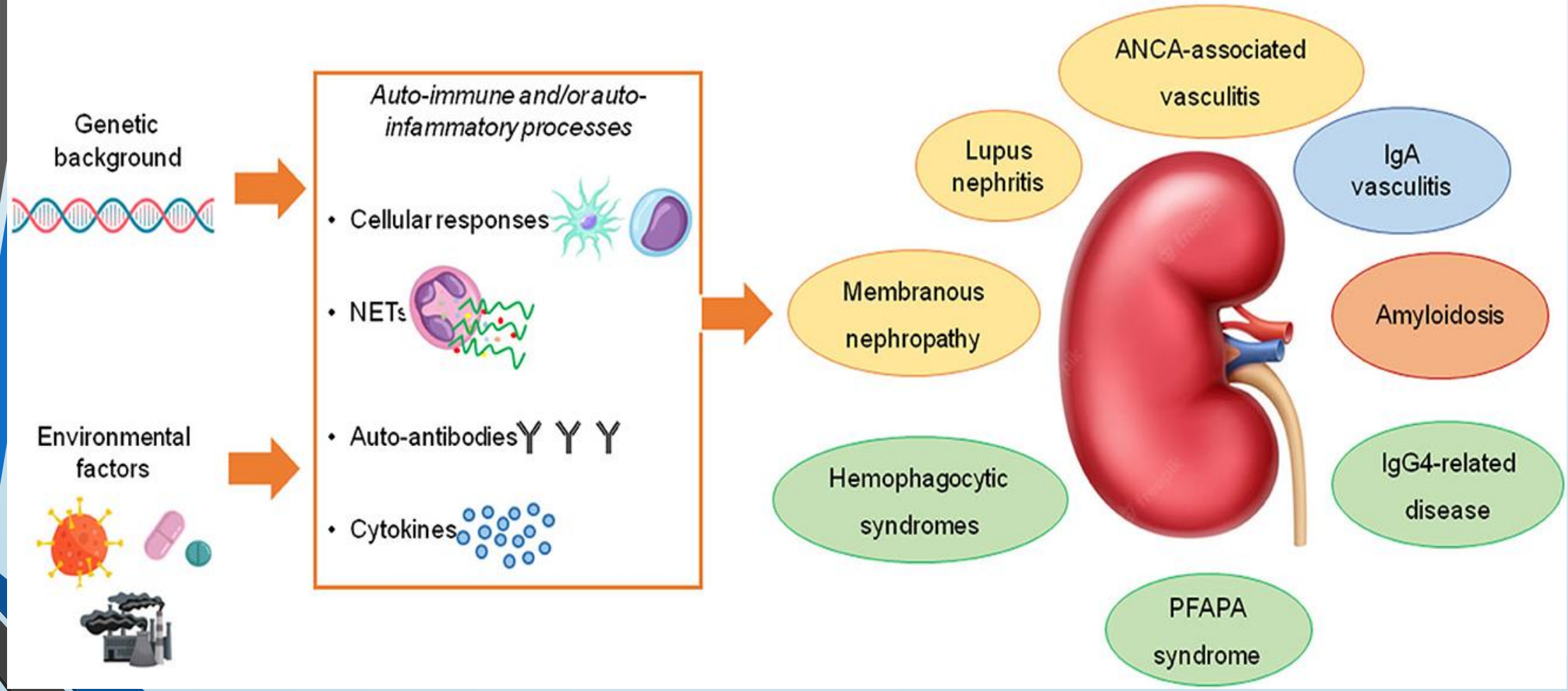
  Instituting appropriate therapies in the acute stage of illness

  Managing long-term complications of chronic kidney disease (CKD) and KRT

- **Pathophysiology Overview**

- Mechanisms of kidney injury in rheumatic diseases:
  - Immune complex deposition → glomerulonephritis (SLE)
  - Vasculitis → ANCA-associated renal injury
  - Chronic inflammation → secondary amyloidosis
  - Drug toxicity (NSAIDs, DMARDs, biologics)

The kidney in auto-immune and auto-inflammatory processes: definitions, mechanisms and biomarkers



Causes

- Renal involvement as a direct result of rheumatological disease
- Renal involvement as a complication of drugs used in the treatment of rheumatological diseases
- Rheumatological manifestations of kidney disease

Common Clinical Signs and Symptoms

- Proteinuria, ranging from mild to nephrotic levels
- Hematuria, often microscopic
- Elevated serum creatinine indicating impaired glomerular filtration rate (GFR)
- Hypertension secondary to renal dysfunction
- Edema related to hypoalbuminemia or fluid retention

Table 1 Causes of combined renal and rheumatological disorders

No.	Disease	Prevalence of kidney disease	Predominant pattern(s) of kidney injury
A.	Kidney involvement as a direct result of rheumatic disease		
1	Systemic lupus erythematosus	31–55%	Glomerulonephritis
2	Vasculitis		
	Large vessel vasculitis	20–90%	Renal artery stenosis
	Medium vessel vasculitis	50–75%	Renal artery microaneurysms, renal infarcts, renal parenchymal bleed, hypertension
	Small vessel vasculitis	50–90%	Proliferative glomerulonephritis
3	Systemic sclerosis	60–80%	Scleroderma renal crisis
4	Mixed connective tissue disorder	25–50%	Glomerulonephritis, renal vascular disease
5	Rheumatoid arthritis	20–50%	Amyloidosis
6	Primary Sjögren's syndrome	5–71%	Functional tubular defects, chronic interstitial nephritis
7	Sarcoidosis	1–50%	Granulomatous interstitial nephritis
8	Anti-phospholipid antibody syndrome	9–25%	Renal vascular disease, thrombotic microangiopathy
9	Inflammatory myopathies	20–25%	Pigment cast nephropathy, glomerulonephritis
B.	Drug induced kidney disease		Acute tubular necrosis, acute interstitial nephritis, minimal change disease
C.	Manifestations of kidney disease mimicking rheumatic disease		Dialysis-related amyloidosis, chronic kidney disease – mineral bone disorder

RENAL INVOLVEMENT AS ADIRECT RESULT OF RHEUMATOLOGICAL DISEASE

- Most common cause
- The disease process can involve different compartments of the kidneys:

Glomeruli (lupus nephritis)

Small vessels (small vessel vasculitis)

Large vessels (Takayasu arteritis)

Interstitial compartment (primary Sjogren's syndrome)

Long-standing chronic inflammatory state of these diseases (secondary amyloidosis or accelerated atherosclerosis)

Table 14.3 Summary of renal involvement in different rheumatic diseases

Rheumatic disease	Renal complications
Systemic lupus erythematosus	• Interstitial nephritis. • Necrotizing vasculitis. • Glomerulosclerosis. • Chronic kidney disease. • Nephritic syndrome. • Rapidly progressive renal failure .
Sjögren's syndrome	• Interstitial nephritis (may precede onset of sicca symptoms). • Renal tubular acidosis (types I and II) (in 11%). • Interstitial cystitis (rare). • Glomerulonephritis (rare). • Nephrolithiasis (rare).
Cryoglobulinemia	• Membranoproliferative glomerulonephritis (60 to 80%).
Henoch-Schönlein purpura (HSP) (IgA vasculitis)	• Hematuria with or without proteinuria. • Isolated hematuria. • Nephritic syndrome. • Renal insufficiency. • Hypertension. • End-stage renal failure.

Polyarteritis Nodosa	• Hypertension (common). • Variable degrees of renal insufficiency. • Rupture of renal arterial aneurysms can lead to perirenal hematomas. • Multiple renal infarctions (in severe vasculitis) .
Granulomatosis with polyangiitis GPA (Wegener's) and microscopic polyangiitis (MPA)	• Glomerulonephritis. • Acute kidney injury with hematuria and cellular casts. • Subnephrotic proteinuria. • Rapidly progressive glomerulonephritis.
Eosinophilic granulomatosis with polyangiitis EGPA (Churg-Strauss)	• Focal segmental glomerulonephritis common but renal failure rare. • Rapidly progressive or acute renal insufficiency. • Glomerulonephritis mainly with positive ANCA. • Hypertension. • Isolated proteinuria .
Rheumatoid arthritis (RA)	• Acute tubular necrosis related to nonsteroidal anti-inflammatory drug (NSAID) use. • Secondary amyloidosis due to the chronic inflammation; it is now relatively rare in RA. • Nephrotic syndrome secondary to membranous nephropathy. • Necrotizing glomerulonephritis. • Destructive inflammation within the walls of renal arteries.

Mixed connective tissue disease (MCTD)	• Glomerulonephritis. • Renal vasculopathy. • Malignant hypertension. • Immune complex-mediated nephritis. • Interstitial nephropathy. • Severe renal disease (rare) [4]
Scleroderma	• Renal impairment usually mild. • Scleroderma renal crisis rare (occurs in 1%–10%).
Ankylosing spondylitis	• Secondary renal amyloidosis. • Immunoglobulin A (IgA) nephropathy. • Membranoproliferative glomerulonephritis. • Treatment-associated nephrotoxicity. • Membranous glomerulonephritis (rare). • Focal glomerulosclerosis (rare). • Proliferative glomerulonephritis (rare) [5]

RENAL INVOLVEMENT IN RHEUMATOLOGICAL DISEASE AS A COMPLICATION OF THERAPY

Non-steroidal anti-inflammatory drugs

- One of the most commonly used drugs in rheumatological practice
- Act as cyclo oxygenase inhibitors and inhibit prostaglandins E2 and I2 which are potent vasodilators
- Potential to cause a dramatic fall in GFR
- Inhibit the important homeostatic actions of prostaglandins on the thick ascending limb of the loop of Henle and collecting ducts, reducing the medullary blood flow and causing apoptosis of medullary interstitial cells
- ATN, Acute TIN and MCD

DMARDs

- Methotrexate can precipitate in the renal tubules and cause AKI
- Methotrexate-induced nephrotoxicity has been reported to occur in ~2% of cases
- Gold, penicillamine or bucillamine: MGN in RA patients
- Gold and penicillamine : crescentic GN occasionally with ANCA positivity

Biological agents

- TNF-a blockers have recently been reported to be potentially nephrotoxic
- Direct injury to visceral epithelial cells and induction of anti-dsDNA antibodies leading to proteinuria and proliferative GN
- MGN has also been reported to occur with etanercept and adalimumab
- Etanercept have also been linked to occurrence of crescentic GN
- Use of these agents is associated with increased incidence of infections, which can also affect kidneys

Table 14.4 Renal side effects of commonly used drugs in rheumatic diseases

Drugs	Renal side effect
NSAIDs	- Acute tubular necrosis (ATN) - Acute interstitial nephritis (AIN) - Analgesic nephropathy: papillary necrosis and chronic interstitial nephritis - Minimal change disease - Membranous glomerulonephritis - Hyperkalemia - Hyponatremia - Salt and water retention - Renal tubular acidosis
Cyclooxygenase-2 (COX-2) selective inhibitors	Acute kidney injury Salt and water retention
Calcineurin inhibitors (cyclosporine and tacrolimus)	Acute kidney injury Hyperkalemia Chronic interstitial fibrosis and tubular atrophy Hypophosphatemia Hypomagnesaemia Global glomerular sclerosis Focal segmental glomerulosclerosis

Methotrexate	Crystal-induced AKI (mainly with high dose IV)
Sulfasalazine	Interstitial nephritis (rare) Nephrotic syndrome (rare)
Leflunomide	Interstitial nephritis (rare)
Gold	Membranous glomerulonephritis
Bisphosphonates	Acute tubular necrosis Focal segmental glomerulosclerosis Minimal change disease
Penicillamine	Membranous glomerulonephritis Minimal change disease
Azathioprine	Interstitial nephritis (rare)

RHEUMATOLOGICAL MANIFESTATIONS OF THE KIDNEY DISEASE

Long-standing kidney disease can lead to manifestations simulating primary rheumatological disorders.

- B2-microglobulin-related amyloidosis
- Hyperparathyroidism
- Uremic myopathy.

Dialysis-related amyloidosis

- Deposition of b2-microglobulin in bones and joints leading to carpal tunnel syndrome, chronic arthropathy, destructive spondyloarthropathy and cystic bone lesions
- Most frequently in patients on long-term hemodialysis, it has also been reported to occur in patients on peritoneal dialysis and in CKD patients not on dialysis
- This is characterized by pain, restriction of movements, most commonly in the shoulders, hips and knees
- Involvement is usually bilaterally symmetrical and pain is relieved by rest
- The deposition of b2 microglobulin occurs initially at the cartilage surface, and then extends to involve the joints and tendons

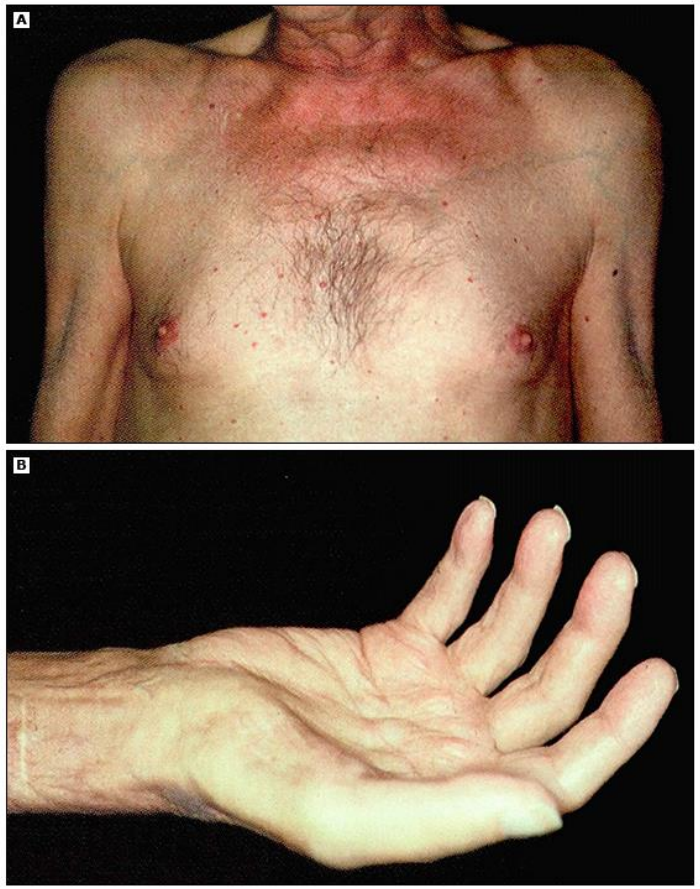
Clinical manifestations

- Shoulder pain due to scapulohumeral periarthritis
- Carpal tunnel syndrome (CTS)
- Trigger finger (flexor tenosynovitis)
- Spinal pain due to destructive spondyloarthropathy
- Pathologic fractures due to rapidly enlarging bone cysts

Diagnosis

- Dialysis for ≥5 years + presence of typical clinical manifestations and characteristic imaging findings.
- Although tissue biopsy is generally not needed to diagnose DRA and is rarely performed, biopsy is the definitive diagnostic test for beta2-m amyloidosis.

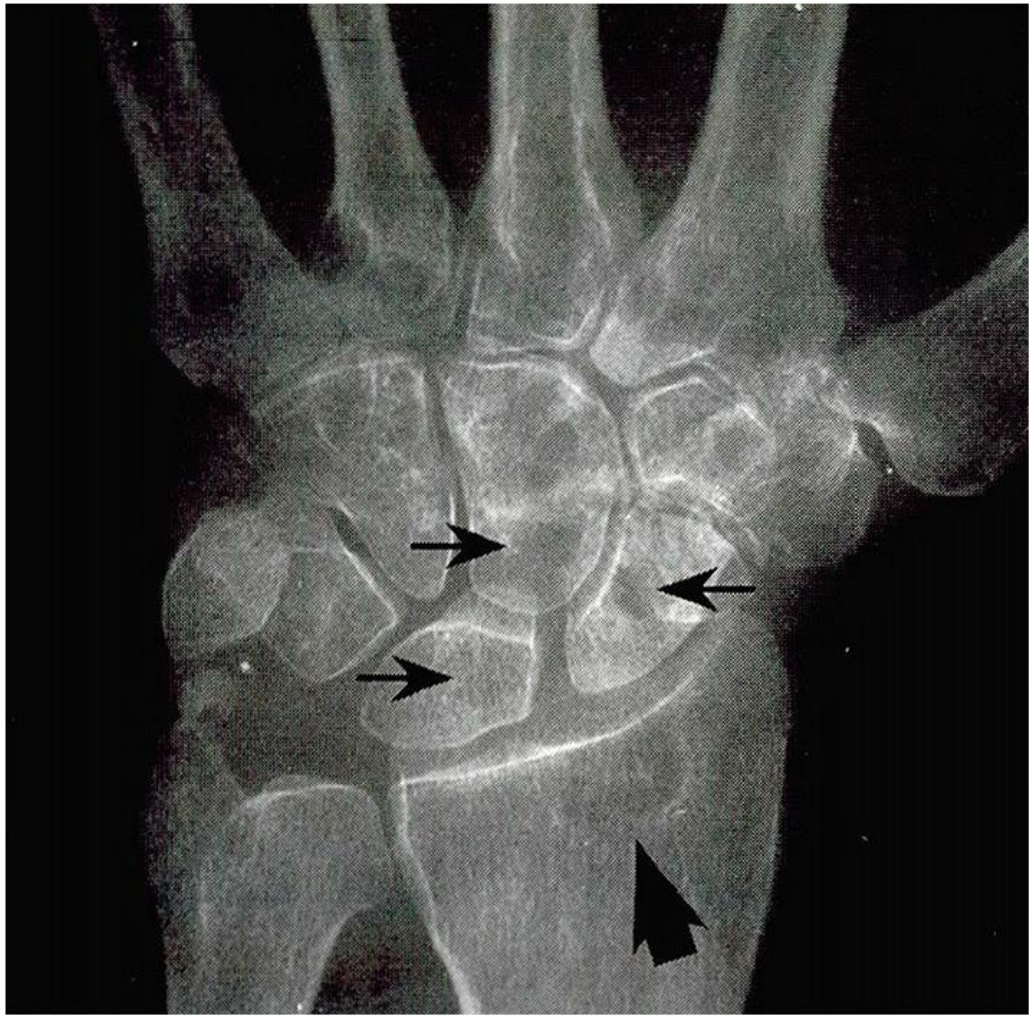
Shoulder pad sign and wrist and hand amyloid deposits in a patient with beta$_2$-m amyloidosis



(A) Bilateral shoulder pads in a patient with beta$_2$-microglobulin amyloidosis who was receiving long-term hemodialysis.

(B) Fixed flexion contractures of the fingers due to beta$_2$-microglobulin amyloid deposits in the hand of a patient receiving long-term hemodialysis. Amyloid deposits, appearing as soft tissue fullness around the wrist, resulted in carpal tunnel syndrome and atrophy of the thenar muscle.

Wrist radiograph of a patient with beta$_2$-microglobulin amyloidosis



Wrist radiograph of a patient with beta$_2$-microglobulin amyloidosis who was on long-term hemodialysis, showing cysts in the carpal bones (small arrows) and the distal radius (large arrow).

Treatment

Dialysis modification – Our approach to dialysis modification depends on dialysis modality.

- **Hemodialysis** – we suggest a biocompatible, high-flux membrane rather than a bioincompatible or low-flux membrane (Grade 2C). we suggest increasing the duration and frequency of dialysis (Grade 2C).
- **Peritoneal dialysis** – we suggest switching to hemodialysis (Grade 2C)

Symptom management – Symptoms of DRA are managed in part by analgesics, which help to reduce periarticular and bone pain. A variety of surgeries also may improve DRA symptoms.

Impact of transplantation

- Kidney transplantation is the definitive therapy for DRA in patients with end-stage kidney disease.
- Successful kidney transplantation reduces plasma beta2-m levels to normal, and joint pain usually resolves soon after the kidney allograft has begun to function.
- We do not use hemodiafiltration solely for the treatment of DRA.

Chronic kidney disease-mineral bone disorders (CKD-MBD)

- Bony pains and proximal muscle weakness mimicking rheumatological illness
- Start at advanced stages of CKD (stage 3 and above) and occur frequently in dialysis-dependent patients

- Both high and low turnover bone disease can lead to these symptoms
- Diagnosis rests on the demonstration of altered levels of serum calcium, phosphate, and parathyroid hormone (PTH), extraosseous calcification, skeletal X-rays, ultrasound of the neck, parathyroid scan and in selected cases, bone histomorphometry.
- Therapy depends on the specific combination of disorders present and includes phosphate binders, vitamin D, calcimimetics and parathyroid ablation or parathyroidectomy.

Bone abnormalities of CKD-MBD

- Three parameters are used to assess bone pathology (renal osteodystrophy): bone turnover, mineralization, and volume (TMV system).
- TMV characteristics of the major CKD-related bone diseases are as follows :

• Osteitis fibrosa cystica (high turnover due to secondary hyperparathyroidism)

• Adynamic bone disease (low turnover due to excessive suppression of the parathyroid glands) (most common)

• Osteomalacia (low bone turnover in combination with abnormal mineralization)

•Mixed uremic osteodystrophy (high or low bone turnover and by abnormal mineralization)

Uremic myopathy

- Changes in muscle structure and function that are present in patients with advanced kidney disease, including sarcopenia, cachexia, protein energy wasting and muscle atrophy
- The clinical presentation of uremic myopathy includes cardiomyopathy, muscle wasting, weakness, low endurance and fatigue
- Muscle wasting can lead to insulin resistance, accelerated cardiovascular disease, longer hospital stays and increased mortality in patients with kidney disease

Multiple mechanisms may contribute to uremic myopathy in kidney disease patients including:

- Inflammation
- Exposure to elevated levels of reactive oxygen species (ROS)
- Malnutrition
- Metabolic acidosis
- Impaired mitochondria metabolism play a central role

- Muscle loss is more prevalent in patients with CKD than the non-CKD population and prevalence increases as kidney disease progresses to ESRD
- Around **7%** of the elderly population over **65** meet the definition of frailty while frailty affects up to **70%** of ESRD patients over age **65** years old and affects **47%** of younger adults (**18–64** years old) on dialysis

Management

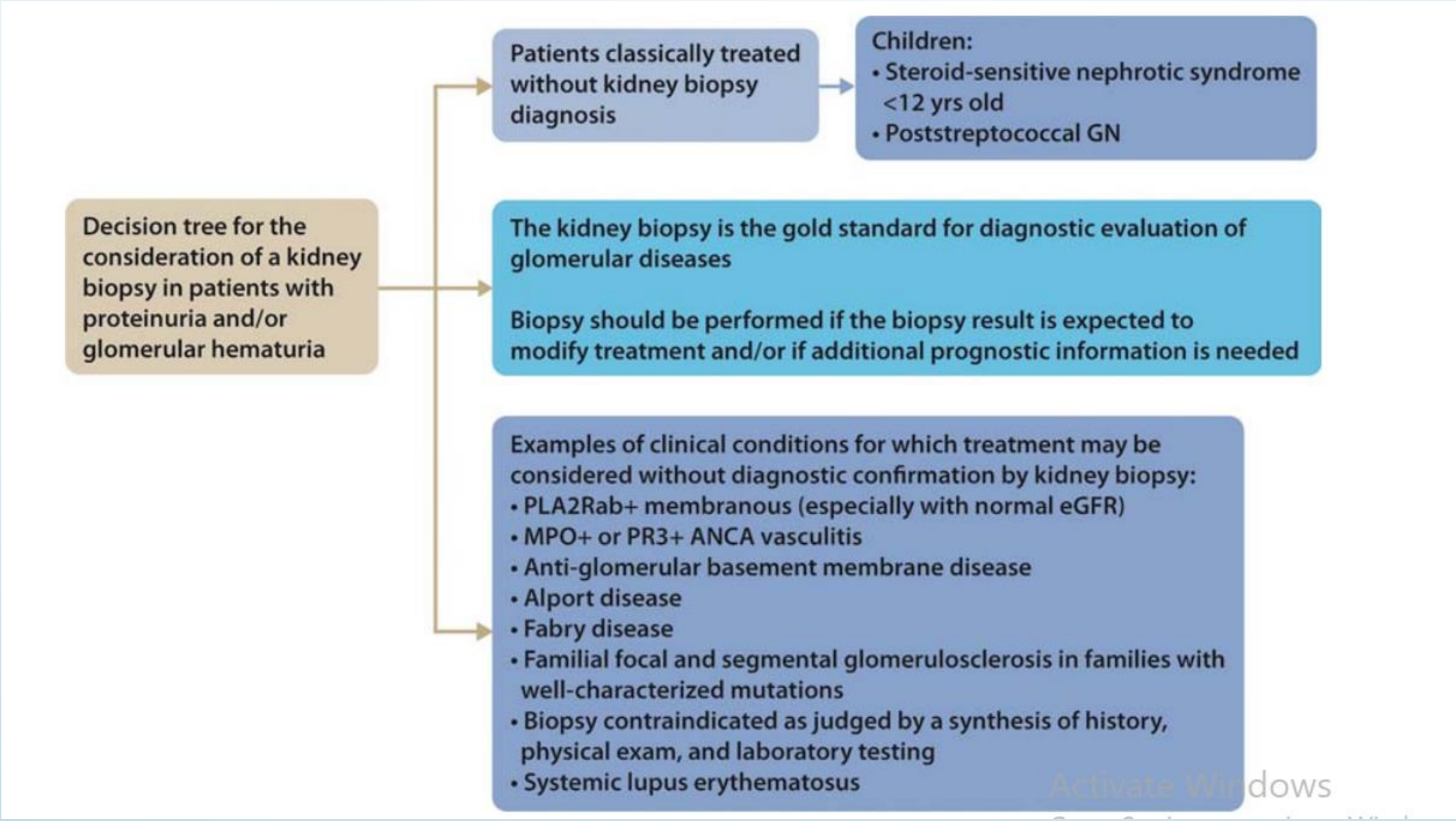
- Optimal treatment of vitamin D deficiency and anemia
- Adequate nutrition
- Exercise regimen
- Testosterone replacement therapy (Grade 2C)

A biopsy is sometimes deferred in the following scenarios:

- **If other findings and serologic testing strongly support diagnostic and therapeutic decision making and the risk outweighs the benefit**

- **If the duration of the increased creatinine is not known and may have been longer than three months, particularly if kidney imaging suggests chronicity.**

- **If there is a recent hospitalization and an associated AKI without complete recovery.**



The kidney biopsy is the "gold standard" for the diagnostic evaluation of glomerular diseases. However, under some circumstances, treatment may proceed without a kidney biopsy confirmation of diagnosis

Why Awareness of Renal Involvement Matters

- Early detection improves renal survival
- Persistent proteinuria or delayed therapy → CKD progression
- Multidisciplinary care improves long-term outcomes

Key Takeaways

- Rheumatic kidney disease is heterogeneous and complex.
- Early recognition and biopsy are essential.
- Treatment requires balancing disease control vs renal safety.
- Collaboration between nephrologists and rheumatologists is critical.

A Three-Headed Approach to Kidney Involvement in Rheumatic Diseases

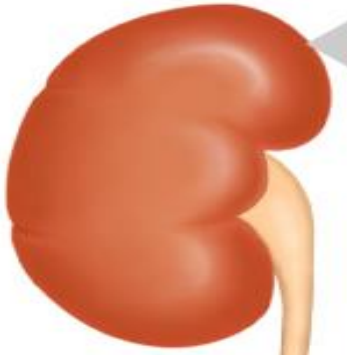
- Optimal approach to renal involvement in rheumatic diseases will remain a 3-headed one that includes a nephrologist, a rheumatologist, and a renal pathologist
- Kidney biopsy report not only suggests or confirms a pathologic diagnosis but can also provide information on the severity of the injury, activity versus chronicity of the lesion, and the presence of other, significant renal or vascular abnormalities.

Therapeutic Challenges

- Balancing immunosuppression and infection risk
- Avoiding nephrotoxic drugs
- Managing comorbidities: hypertension, CKD, cardiovascular risk
- Coordination with rheumatologists for systemic disease control

With Sincere Thanks for Your Attention

Causes of hematuria



Renal
- Benign renal mass (angiomyolipoma, oncocytoma, abscess)
- Malignant renal mass (renal cell carcinoma, transitional cell carcinoma)
- Glomerular bleeding (IgA nephropathy, thin basement membrane disease, Alport syndrome)
- Structural disease (polycystic kidney disease, medullary sponge kidney)
- Pyelonephritis
- Hydronephrosis/distension
- Hypercalciuria/hyperuricosuria
- Malignant hypertension
- Renal vein thrombus/renal artery embolism
- Arteriovenous malformation
- Papillary necrosis (sickle cell disease)

Mimics of hematuria
- Menstruation
- Drugs (pyridium, phenytoin, rifampin, nitrofurantoin)
- Pigmenturia
- Beeturia

Ureter
- Malignancy
- Stone
- Stricture
- Fibroepithelial polyp
- Post-surgical conditions (ureteroiliac fistula)

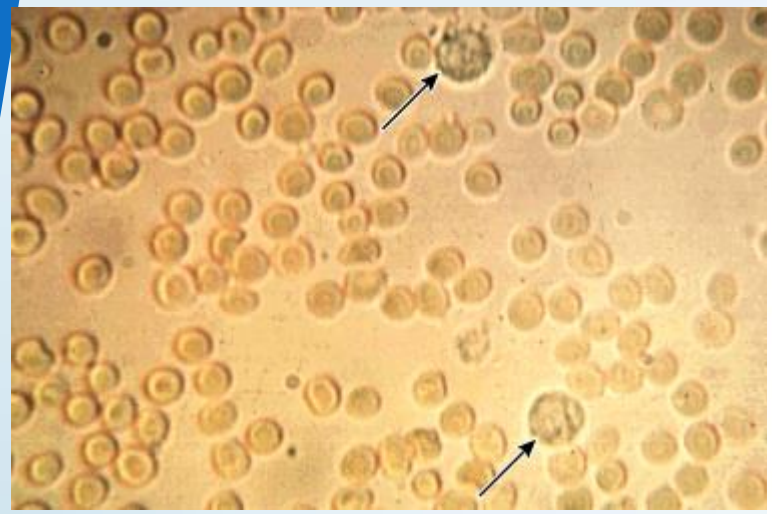
Renal and/or upper or lower collecting system:
- Infection (bacterial, fungal, viral)
- Malignancy
- Urolithiasis
- Tuberculosis
- Schistosomiasis
- Trauma
- Recent instrumentation including lithotripsy
- Exercise-induced hematuria
- Bleeding diathesis/anticoagulation*

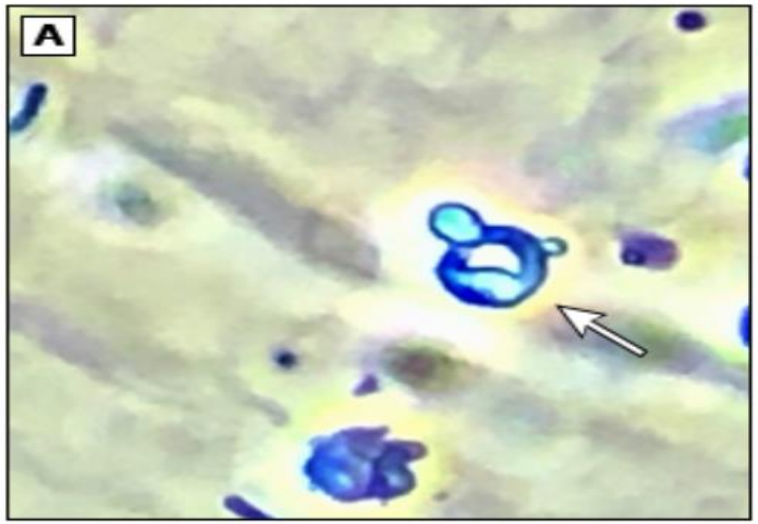
Upper collecting system

Lower collecting system

Bladder
- Malignancy (transitional cell carcinoma, squamous cell carcinoma)
- Radiation
- Cystitis
- Bladder stones

Prostate/urethra
- Benign prostatic hyperplasia
- Prostate cancer
- Prostatic procedures (biopsy, transurethral resection of the prostate)
- Traumatic catheterization
- Urethritis
- Urethral diverticulum

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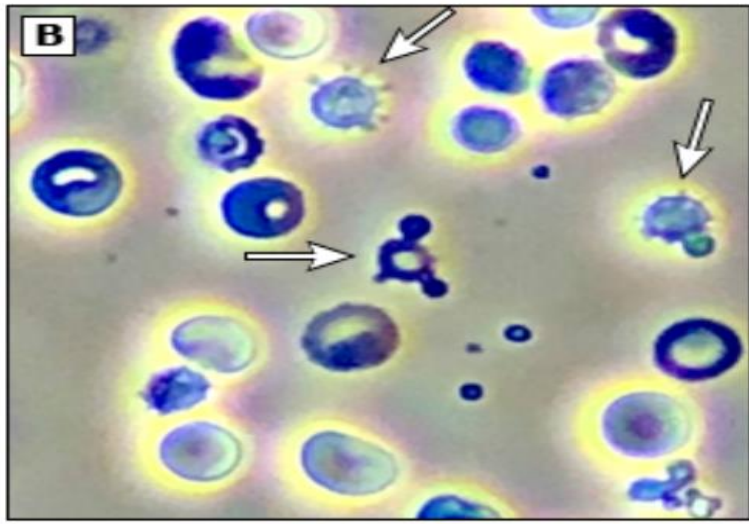
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