Renal System and Rheumatology

14

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14.1 Introduction

Many rheumatic diseases can be associated with different complications in kidneys and urinary tract. The goal of this chapter is to provide a summary of renal manifestations in rheumatic diseases that is easily accessible by students, residents, and practitioners.

The material presented provides a simple approach to patients presenting with renal and rheumatic manifestations. It is not meant to be an exhaustive review.

It presents a stepwise approach to the evaluation of proteinuria and hematuria in patients with rheumatic diseases. It also provides a summary on the renal complications of rheumatic diseases. The chapter also discusses lupus nephritis (LN) in more detail as it is common and severe manifestation of systemic lupus erythematosus with increased risk of death and end-stage renal disease.

14.2 Objectives

By the end of this chapter, you should be able to:

1. Construct a diagnostic approach to patients with proteinuria or hematuria.
2. Diagnose and manage lupus nephritis (LN).
3. Discuss renal involvement in different rheumatic diseases.
4. Review the common side effects of antirheumatic medications on kidney function.

14.3 Proteinuria

Proteinuria screening among populations is based on measurement of albumin in random urine dipstick test. Most adolescents who have proteinuria through dipstick test do not have renal disease, and this proteinuria usually resolves on repeat testing. However, prolonged proteinuria is suggestive of kidney disease in patients with diabetes mellitus, hypertension, primary renal disease, SLE, or other systemic illnesses [1].

Proteinuria greater than 200 mg/24 h is considered abnormal. Urine protein excretion ranging between 200 and 3000 mg/24 h is termed

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sub-nephrotic range proteinuria. Nephrotic range proteinuria is typically more than 3000 mg/24 h.

Proteinuria is an important indicator of renal disease activity and progression. It reflects an underlying pathology causing a change in the permeability properties of the glomerular filtration barrier [1].

A stepwise approach that may help physicians detect and evaluate benign and pathological causes of proteinuria is illustrated in Fig. 14.1.

14.4 Hematuria

Microscopic hematuria refers to the presence of erythrocytes in urine that can be exclusively detected by microscopic exam or dipstick analysis. It is a frequent reason for referral to urology or nephrology. It is often asymptomatic and found incidentally on routine urine examination.

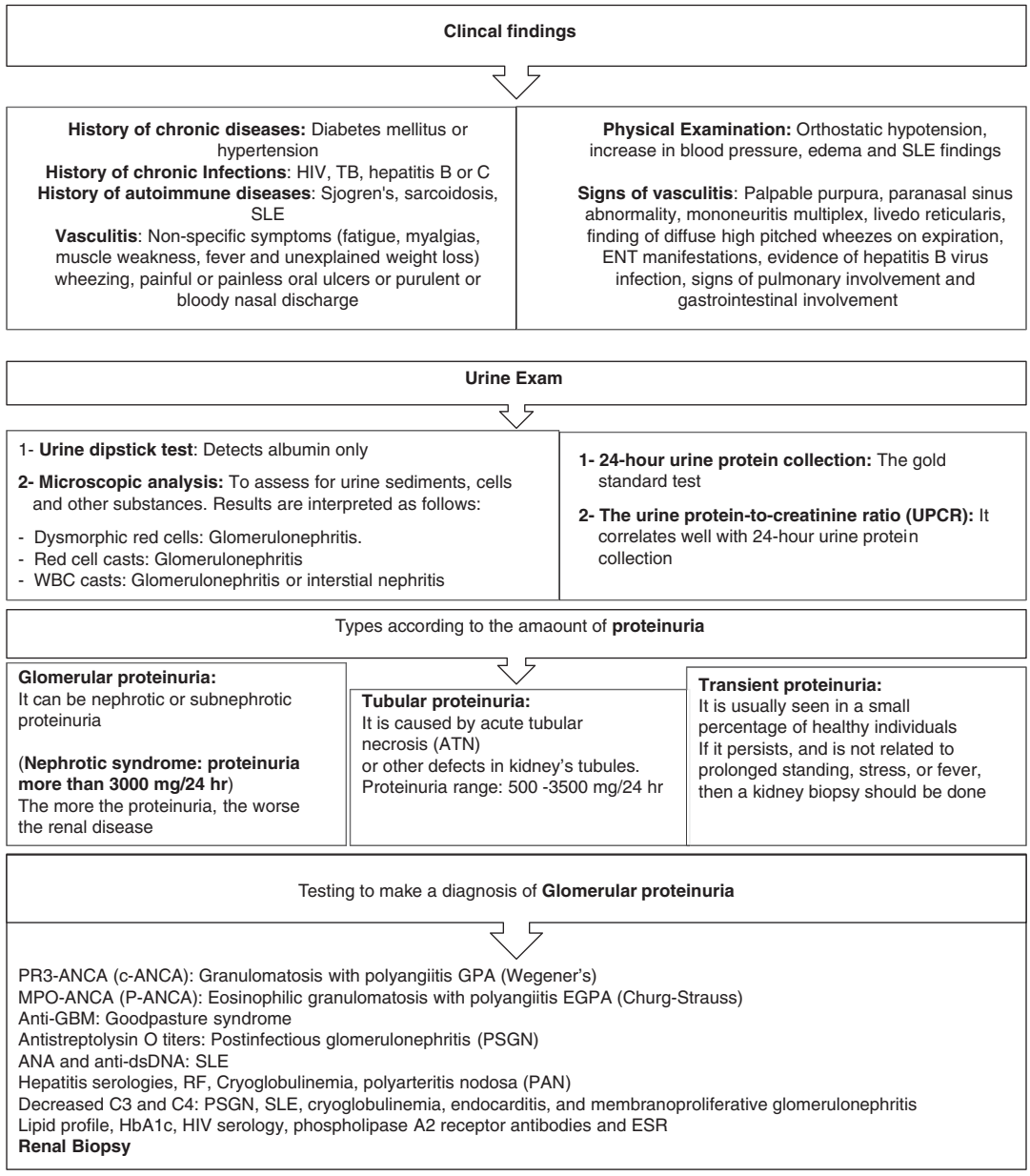

Fig. 14.1 Approach to a patient with proteinuria [1]

Macroscopic (grossly visible) hematuria is more commonly associated with malignancy than microscopic hematuria. For this reason, a full investigation, including upper tract imaging and cystoscopy for the lower tract, for all patients with macroscopic hematuria is usually required.

Opinions regarding which patients with microscopic hematuria should be evaluated and need to be investigated remain controversial [2, 3].

Figures 14.2 and 14.3 provide simplified approaches to detect and evaluate significant microscopic hematuria according the recent guidelines [2, 3].

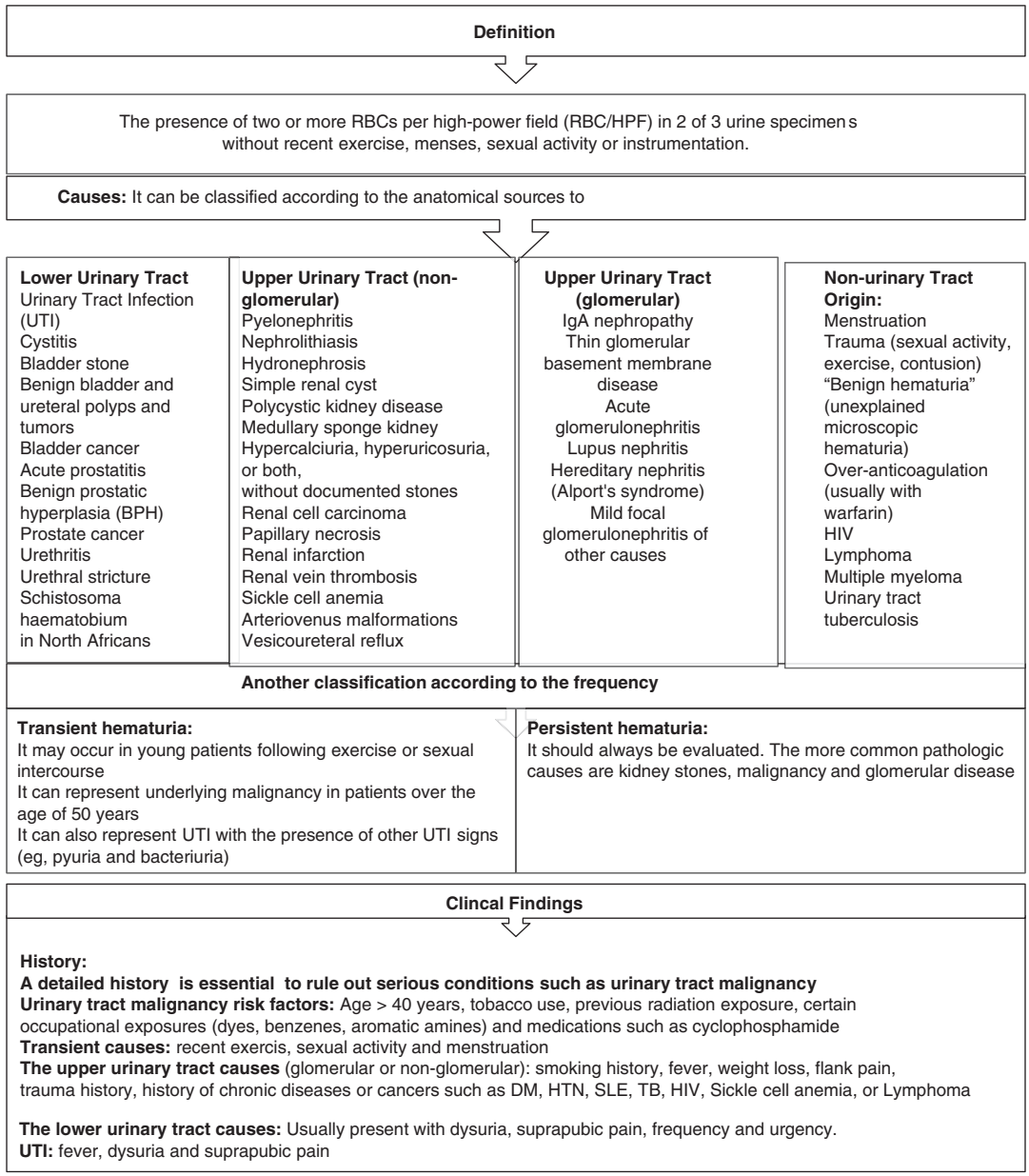

Fig. 14.2 approach to a patient with hematuria.

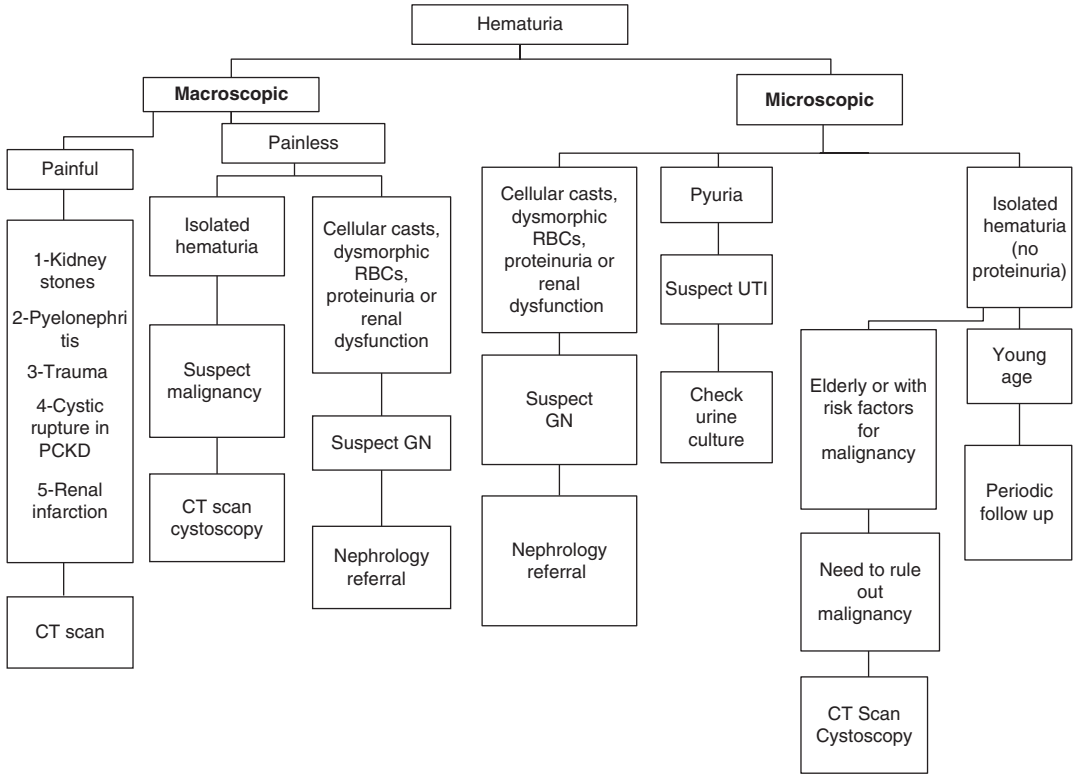

Fig. 14.3 Classification of hematuria

14.5 Renal Involvement in Different Rheumatic Diseases

Rheumatic diseases are frequently associated with renal complications. These complications include vascular, glomerular, and tubulointerstitial changes.

Drug-induced renal impairment should be included in the differential diagnosis of renal complications in a rheumatic patient.

Renal involvement clinically manifests in many different ways. The spectrum ranges from slight functional disorders such as slight erythrocyturia/proteinuria with normal renal function to rapidly progressive renal failure. Table 14.3 provides a summary of renal involvement in different rheumatic diseases.

14.6 Lupus Nephritis (LN)

Renal involvement is common in SLE. It is the leading cause of morbidity and mortality in patients with lupus, characterized by the loss of self-tolerance, production of autoantibody, and development of immune complexes that deposit in the kidney to induce nephritis. Proteinuria is one of the most commonly observed abnormalities in patients with lupus nephritis [6].

Figure 14.4 provides an overview of pathogenesis, clinical manifestations, and complications of lupus nephritis.

14.6.1 Diagnostic Criteria

Criteria for lupus nephritis in patients with SLE include any of the following conditions (Table 14.1):

1. **Persistent proteinuria.**
   - 500 mg/24 h protein
   - 3+ protein on urine dipstick
   - Spot urine protein/creatinine ratio > 0.5 mg/mg.
2. **Cellular casts.**
3. **Active urinary sediment** (> 5 red blood cells/high power field [RBC/hpf], > 5 white blood cells[WBC]/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts).
4. **Renal biopsy**: Immune complex-mediated glomerulonephritis compatible with lupus nephritis.
5. **Opinion of rheumatologist or nephrologist** [11]**.**

14.6.2 Treatment

The American College of Rheumatology (ACR) recommends treatment according to the International Society of Nephrology/Renal Pathology Society (ISN/ RPS) classification of lupus nephritis. (Check sect. 3 for full presentation of the recommendation for management guidelines). Response to treatment is based on several factors including age, gender, location, and race/ethnicity (Table 14.2) [14].

14.6.3 Adjunctive Treatments

1. Hydroxychloroquine for all patients with SLE unless contraindicated.
2. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers if proteinuria ≥500 mg/24 h [15]
3. Statin therapy if LDL cholesterol >100 mg/dL (2.6 mmol/L).
4. Control hypertension at a target of ≤130/80 mm Hg [11]

Note: Patients with lupus should remain on antimalarial therapy even during disease quiescence as it was shown to be associated with associated with reduced risk of renal damage, improved survival, and decreased incidence of lupus flares [16].

14.7 Sjögren's Syndrome

Sjögren's syndrome is a chronic inflammatory disorder characterized by lymphocytic infiltration of the lacrimal and salivary glands which result in dryness of the eyes and mouth [17]. Systemic features may include arthritis, renal, hematopoietic, pulmonary involvement, and vasculitis (Fig. 14.5). These manifestations are secondary to vasculitis, autoantibody-mediated mechanisms, or lymphocytic infiltration of the target organs. The prevalence of renal involvement ranges from 2 to 67% [22].

14.8 Cryoglobulinemic Syndrome (CG)

Cryoglobulinemic vasculitis is an immune-complex-mediated disease caused by the deposition of cryoglobulins in the small- and medium-sized arteries and veins. Renal involvement is noted in around 20% of patients with mixed cryoglobulinemic vasculitis and usually diagnosed 2.5 years after the disease onset. Membranoproliferative glomerulonephritis is reported in around 80% of patients [23]. Figure 14.6 provides an overview of renal involvements in CG.

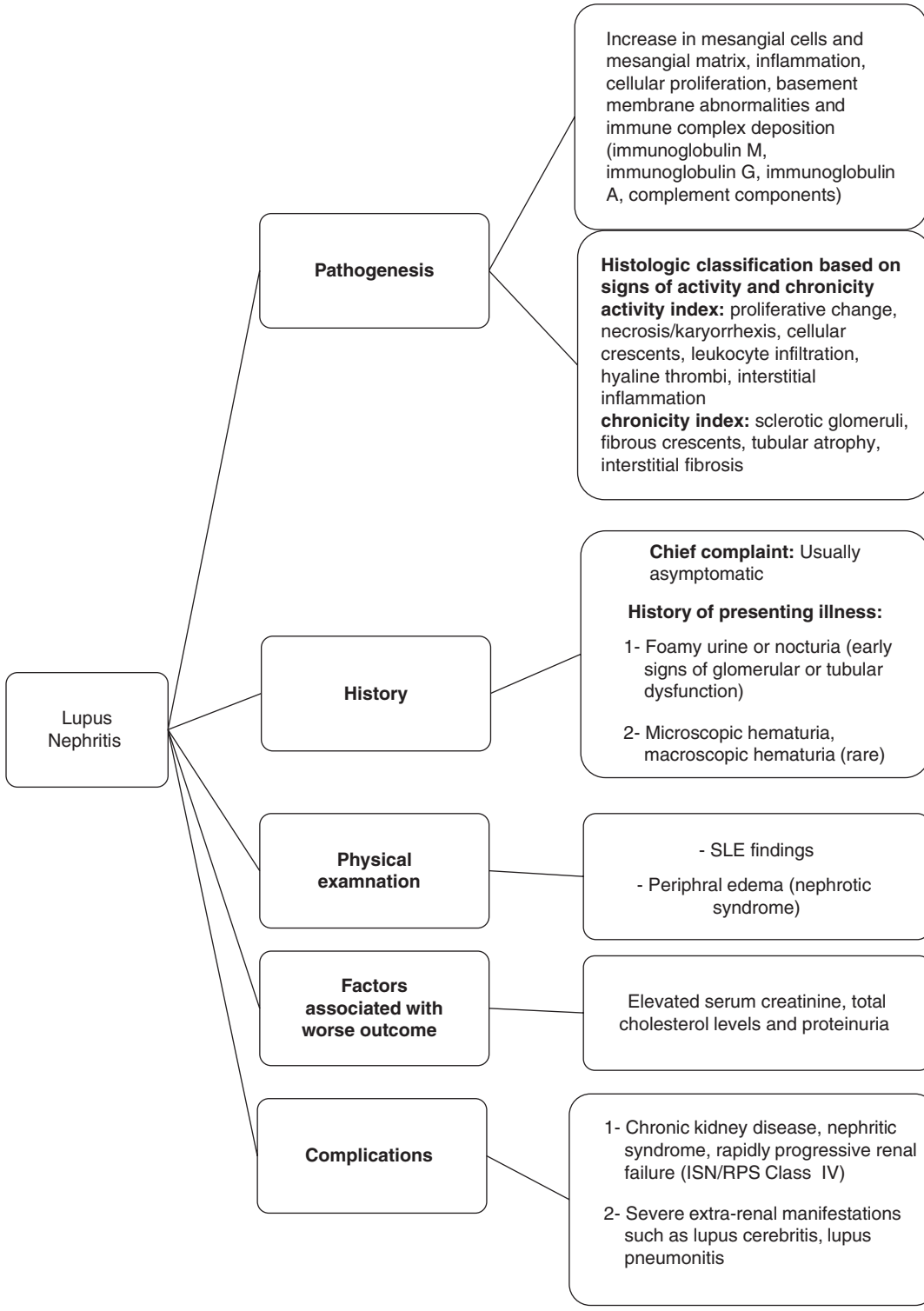

Fig. 14.4 Overview of pathogenesis, clinical manifestations, and complications of lupus nephritis [7–9]

Table 14.1 Recommended workup for suspected lupus nephritis

Tests	Findings	Analysis
	Serum creatinine	To evaluate renal functions [6]
	Antinuclear antibodies (ANA)	Frequently positive in patient with connective tissue disease and high sensitive for SLE and drug-induced lupus [6]
	Anti-double-strand DNA antibodies (anti ds-DNA)	High in patient with LN, it plays an important role in induction of tissue damage, and it correlates with disease activity [6]
	Antiphospholipid antibodies (APLA)	To evaluate autoimmune disease especially SLE**,** its presence means increase risk of thrombosis [6]
	Anti-C1q antibodies	It is sensitive and specific to diagnosis of lupus nephritis and evaluating the disease activity [10]
	Complement 3 (C3) and complement 4 (C4)	Lack of C3 and C4 may indicate lupus nephritis because the presences of these complement components exert a protective effect against disease onset, although it may be normal [6]
Urine studies	**Persistent proteinuria**	- Increases incrementally within severity classes - >500 mg/24 h protein - >3+ protein on urine dipstick - Spot urine protein/creatinine ratio > 0.5 [6, 11]
	Dysmorphic erythrocytes	- Indicate inflammatory glomerular disease [6, 11]
	RBC or WBC cells	- (> 5 red blood cells/high power field [RBC/hpf], > 5 white blood cells[WBC]/hpf in the absence of infection - Indicate glomerulonephritis or tubulointerstitial disease [6, 11]
	Cellular casts	- RBC or WBC casts which indicate inflammatory glomerular disease [6, 11]
	Lipiduria	- May result from abnormal glomerular permeability [6, 11]
Renal biopsy	**Indications**	**American College of Rheumatology (ACR) recommendations**
	1 to confirm suspected nephritis 2 to evaluate disease activity and damage 3 to determine appropriate therapy 4 to make sure that the type, duration, and intensity of treatment matches the severity of disease 5 to predict outcome and identify the alternative causes of renal disease	- Biopsy is highly recommended in patients with systemic lupus erythematosus with the following: Increasing serum creatinine without alternative cause (such as sepsis, hypovolemia, or medication induced). Confirmed proteinuria ≥1000 mg/24 h (either 24-hr urine specimens or spot protein/creatinine ratios). Combinations of following (confirmed in ≥2 tests done within short period and in the absence of alternative causes). Proteinuria ≥500 mg/24 h plus hematuria (≥ 5 red blood cells per high power field). Proteinuria ≥500 mg/24 h plus cellular casts. All patients with clinical evidence of active lupus nephritis, previously untreated, should have renal biopsy to classify glomerular disease by current International Society of Nephrology/Renal Pathology Society (ISN/ RPS) classification (unless biopsy is strongly contraindicated) [11] **Second biopsy:** To detect disease progression **Indications:** 1. When the patient does not respond to therapy 2. In case of worsening of renal function [12]

Table 14.2 Summary of the classification and treatment of lupus nephritis [11, 13]

Classifications of lupus nephritis	Treatment
Class I (minimal mesangial LN) and class II (mesangial proliferative LN)	Treated as dictated by the extra-renal clinical manifestations of lupus
Class III LN (focal LN) and class IV LN (diffuse LN)	**Initial therapy**: Corticosteroids (1 mg/kg, to be tapered according to clinical response) combined with either cyclophosphamide (500 mg IV every 2 weeks for 6 doses) or mycophenolate mofetil (up to 3 g per day as tolerated) **Maintenance therapy**: Mycophenolate mofetil (1–2 g/d in divided doses) or azathioprine (1.5–2.5 mg/kg/d) and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent)
Class V LN (membranous LN)	**Non-nephrotic-range proteinuria**: Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Corticosteroids and immunosuppressive therapy use is dictated by the presence of extrarenal manifestations of lupus **Persistent nephrotic-range proteinuria:** Corticosteroids plus an additional immunosuppressive agent—(Cyclophosphamide, tacrolimus, cyclosporine), mycophenolate mofetil or azathioprine
Class VI LN (advanced sclerosis LN)	Treated with corticosteroids and immunosuppressive therapy only as dictated by the extra-renal manifestations of lupus. Discussion of renal replacement therapy (dialysis vs kidney transplant)

14.9 Scleroderma

Scleroderma is manifested by widespread progressive fibrosis of the skin and internal organs due to accumulation of collagen. Renal involvement occurs in around half of the patients and is manifested as mild proteinuria, worsening kidney function, and/or hypertension (Fig. 14.7) [26]. Scleroderma renal crisis is the most serious renal manifestation which occurs in 5 to 10% of patients with systemic sclerosis, more commonly in diffuse cutaneous systemic sclerosis [27].

14.9.1 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a systemic inflammatory disorder of unknown etiology that primarily involves the joints. It has been reported that the annual incidence of rheumatoid arthritis is around 40 per 100,000. Females are affected two to three times more often than males, and the peak onset is between 50 and 75 years of age [28]. An observational study has shown that the incidence of impaired kidney function is higher in patients with rheumatoid arthritis; these changes were anticipated by many factors like cardiovascular disease, dyslipidemia, elevated sedimentation rate in the first year of rheumatoid arthritis, and NSAIDs use [29]. Figure 14.8 provides an overview of renal involvement in RA.

14.9.2 Renal Involvement in Vasculitis

14.9.2.1 Polyarteritis Nodosa (PAN)

It is a systemic necrotizing vasculitis of medium-sized and occasionally small vessels [34]. It is a rare disease and characterized by the absence of antineutrophil cytoplasmic antibodies (ANCA) [34]. Any organ can be affected including the kidneys (renal artery involvement is common and leads to stenosis, hypertension, and eventually chronic kidney disease) (Fig. 14.9). This disease spares the lungs [34]. Most cases are idiopathic; however, 33% of cases are associated with chronic HBV infection [34]. Renal disease is the most common cause of death. It is fatal if left untreated, but has favorable response to treatment [34].

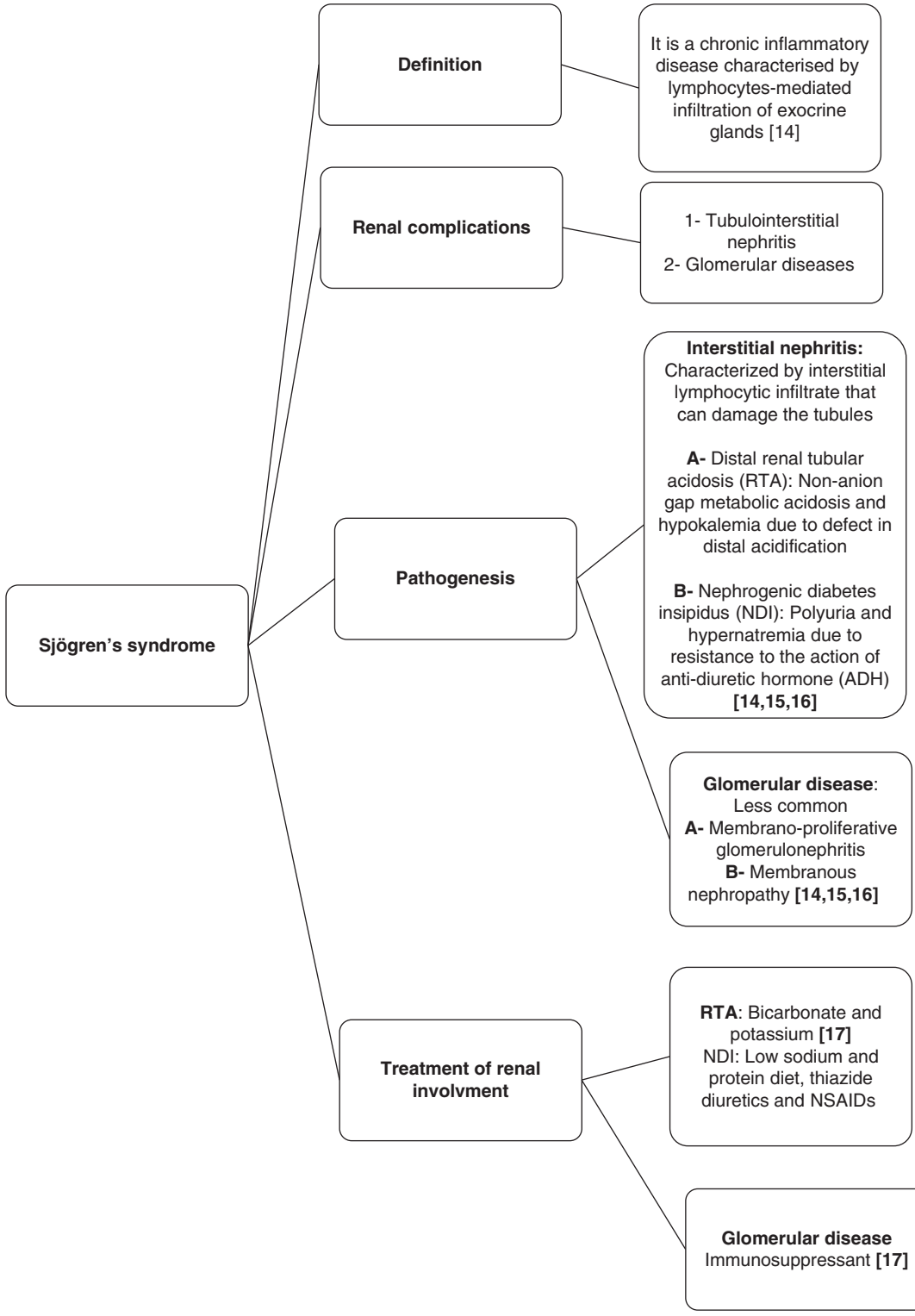

Fig. 14.5 Renal involvement in Sjögren's syndrome: [18–21]

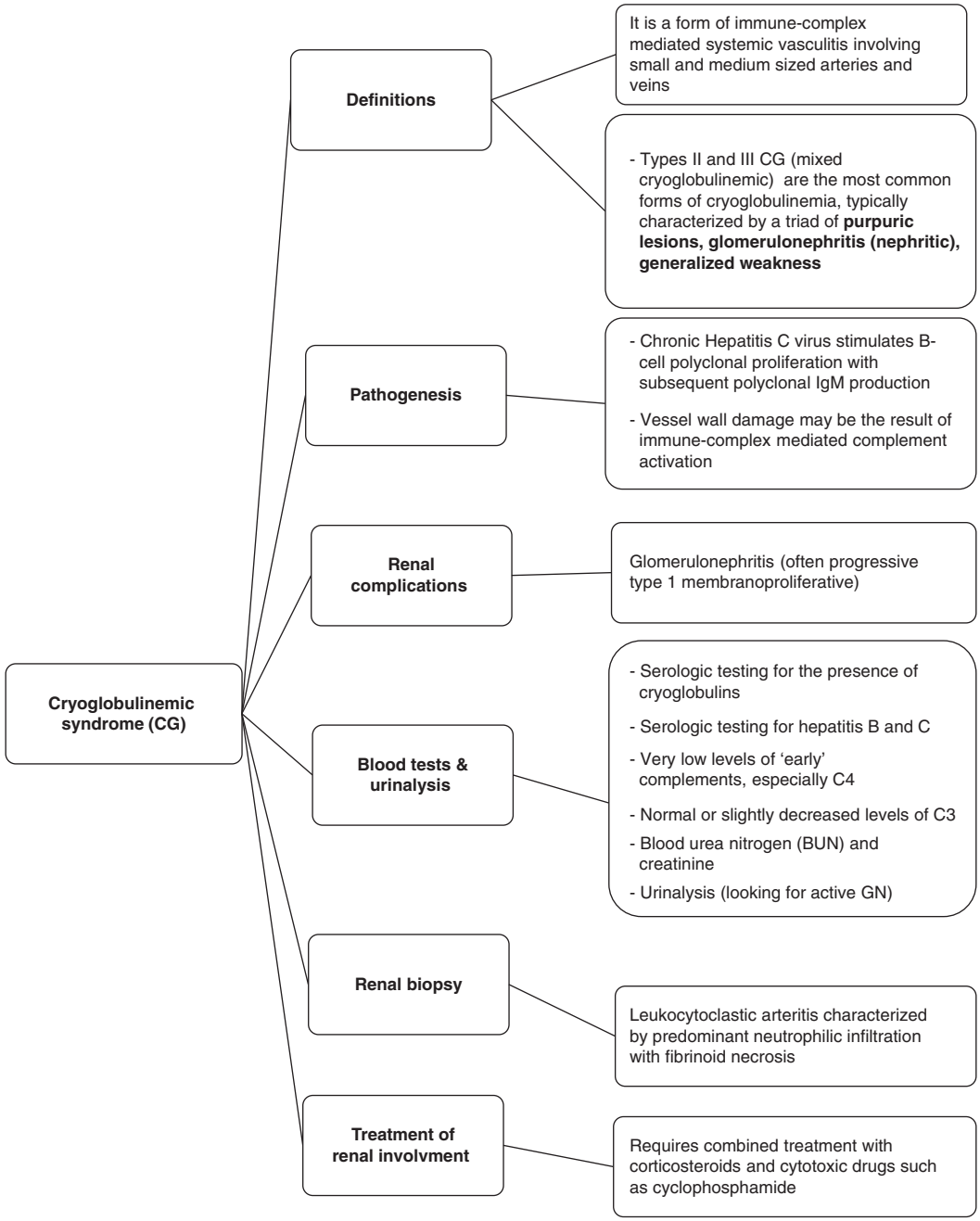

Fig. 14.6 Overview of renal involvements in CG [23]

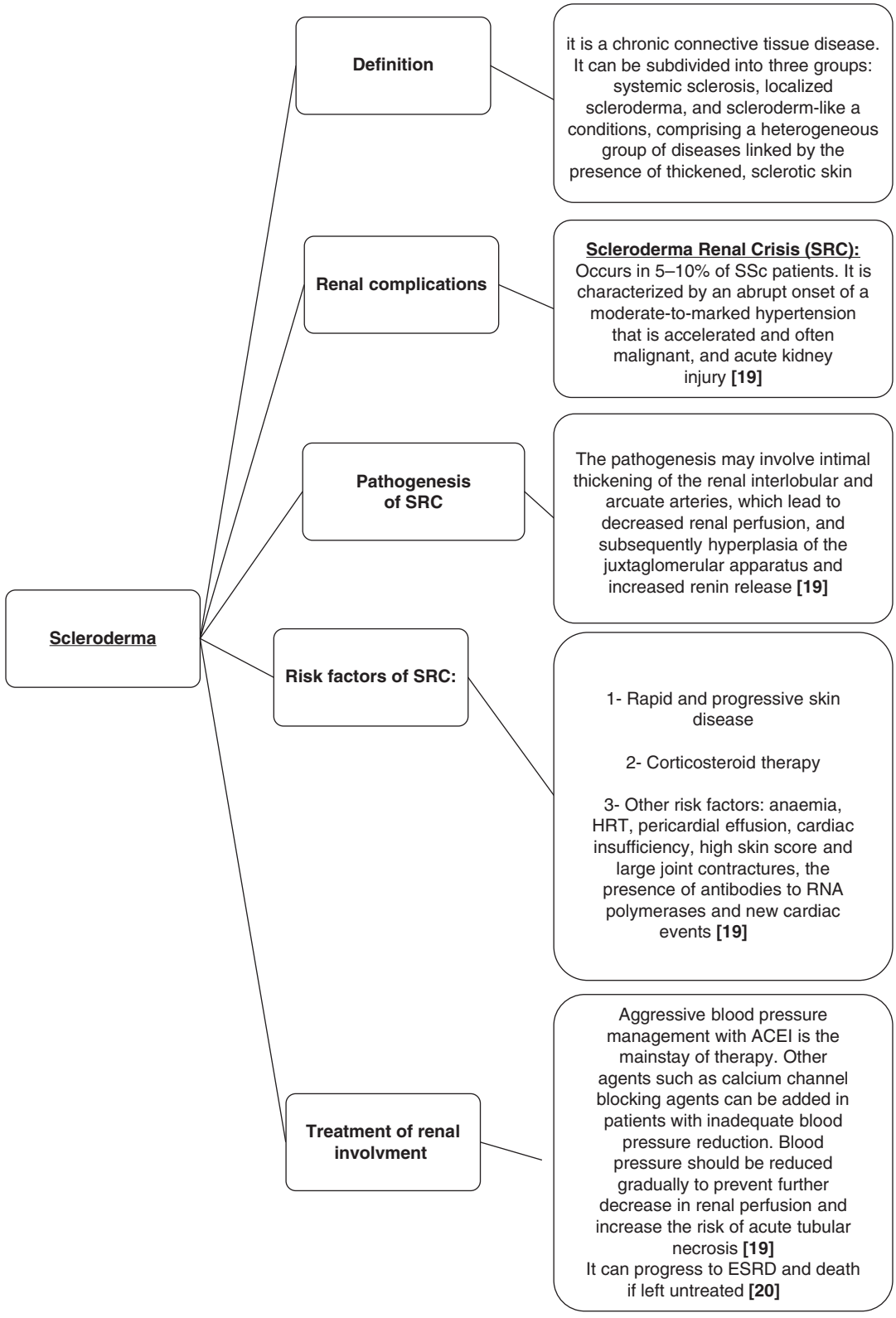

Fig. 14.7 Renal involvement in scleroderma [24, 25]

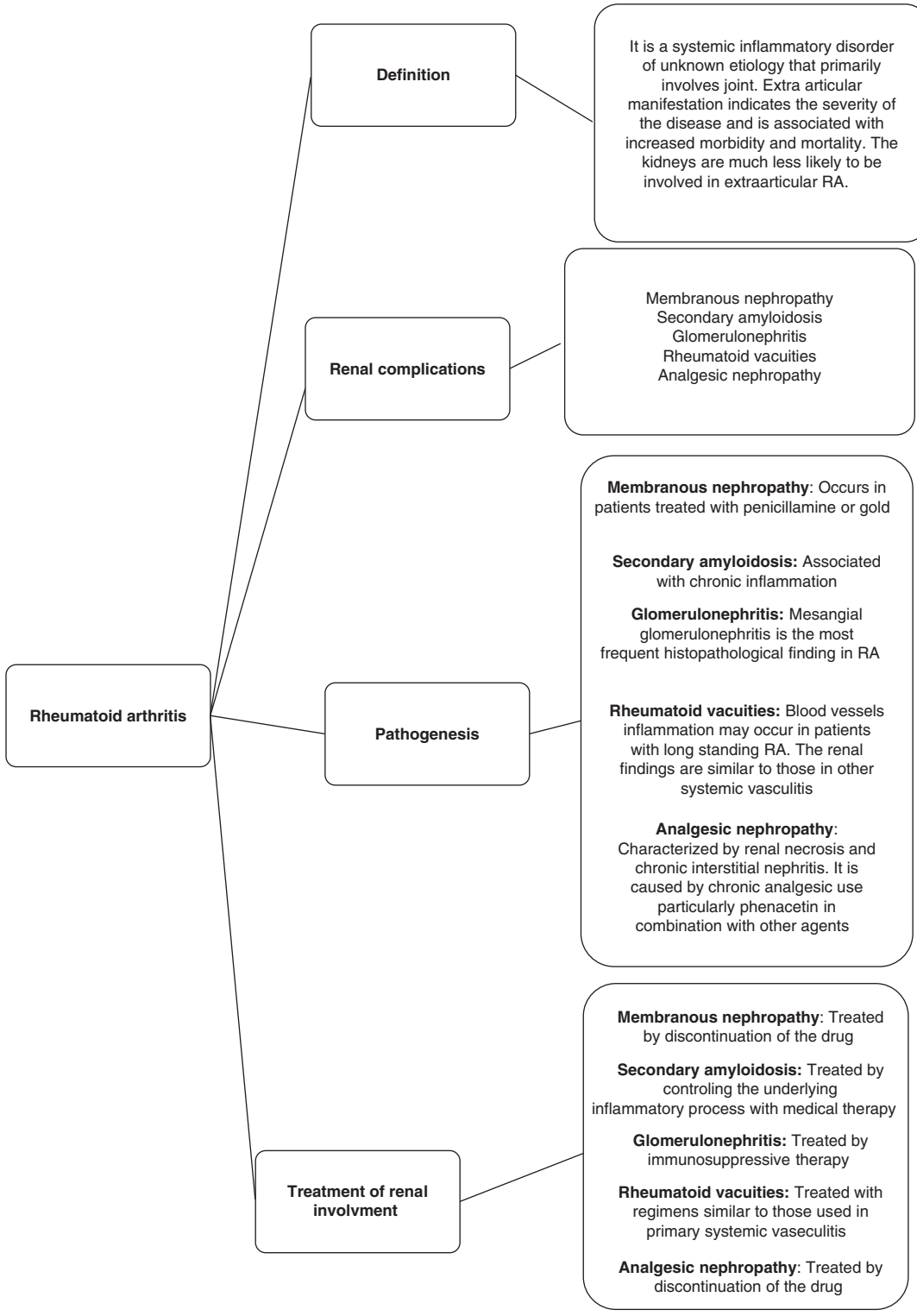

Fig. 14.8 Overview of renal involvement in RA [30–33]

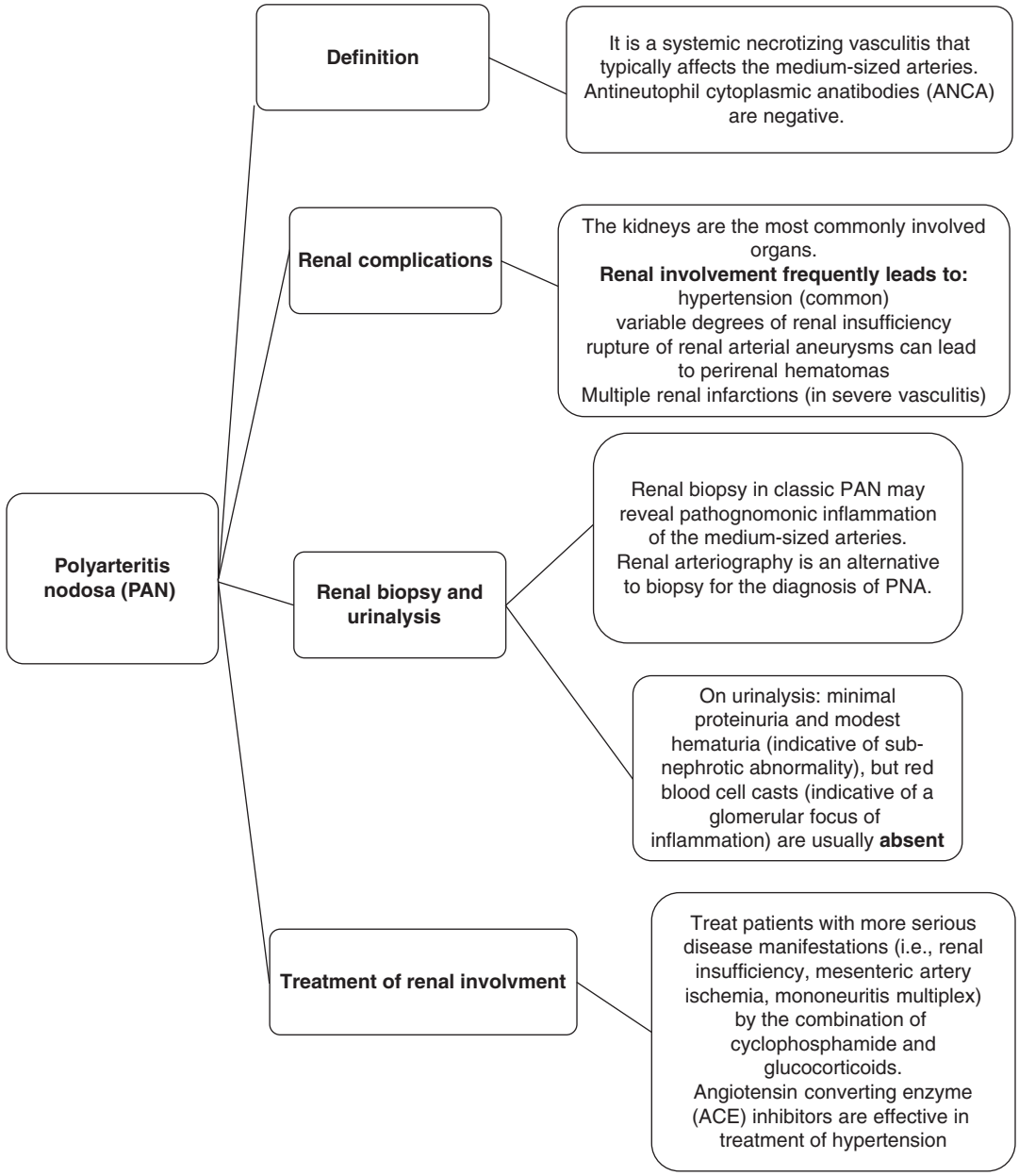

Fig. 14.9 Medium vessel vasculitis: polyarteritis nodosa (PAN) [34]

14.9.3 Eosinophilic Granulomatosis with Polyangiitis EGPA (Churg-Strauss)

It is a systemic necrotizing vasculitis that affects small-sized muscular arteries [35]. It is a rare disease and characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA) [35]. Asthma, peripheral eosinophilia, and granulomas on histology are common associations with this disease [35]. Renal involvement can lead to pauci-immune rapidly progressive glomerulonephritis (Fig. 14.10) [35].

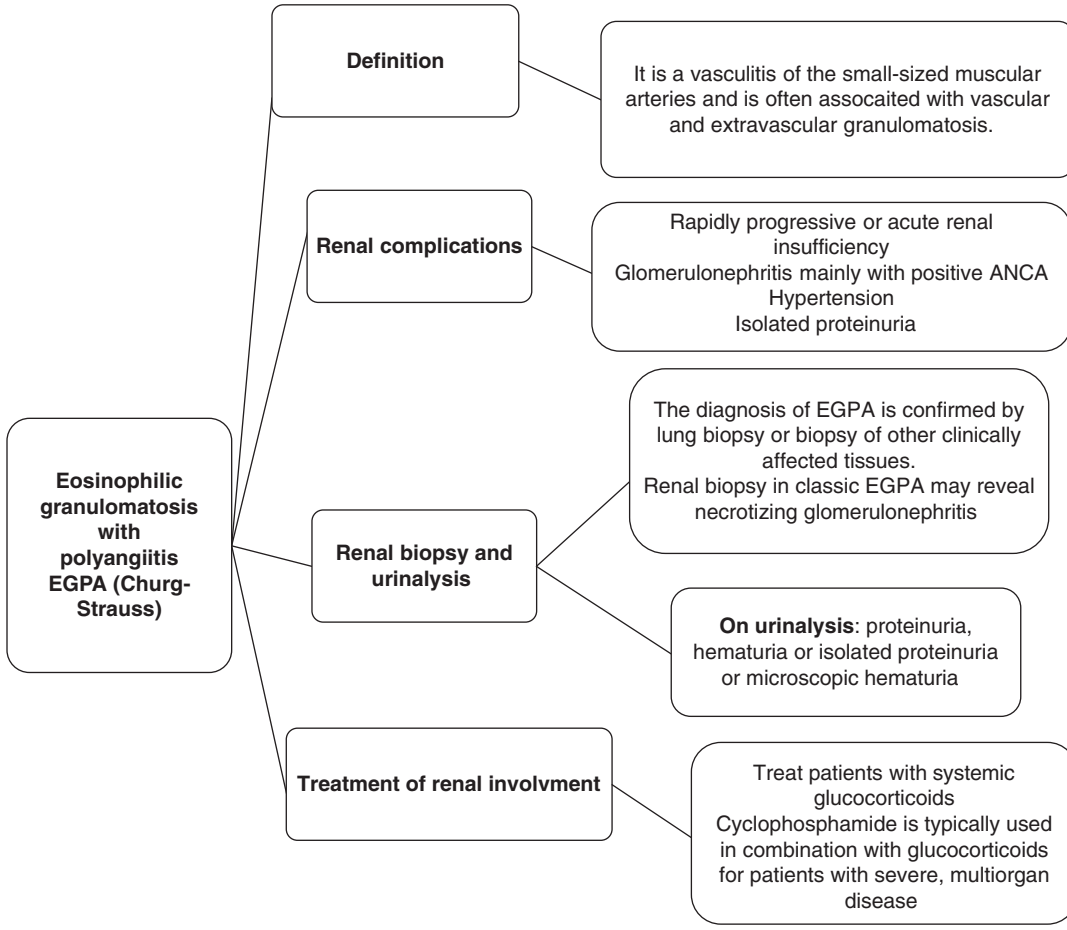

Fig. 14.10 Eosinophilic granulomatosis with polyangiitis EGPA (Churg-Strauss) [35]

14.9.4 Granulomatosis with Polyangiitis GPA (Wegener's) and Microscopic Polyangiitis (MPA)

These are systemic vasculitides of the medium- and small-sized arteries, as well as the venules and arterioles [29]. They are known to cause many renal complications, e.g., glomerulonephritis, acute kidney injury, and proteinuria (Fig. 14.11) [29, 30].

Rapidly progressive glomerulonephritis is a common and severe feature with Wegener's granulomatosis or proteinase-3 (PR3)-ANCA vasculitis, and it might lead to end-stage renal diseases [29, 30]. In addition, necrotizing granulomatous inflammation is the histopathologic hallmark of GPA [29, 30]. Microscopic polyangiitis or myeloperoxidase (MPO)-ANCA vasculitis are associated with chronic renal injury more than glomerulonephritis [29, 30].

14.9.5 Henoch-Schönlein Purpura (HSP) (IgA Vasculitis)

It is a systemic vasculitis of the small-sized blood vessels (the post-capillary venules), characterized by the deposition of IgA-containing immune complexes [40].

IgA vasculitis is considered the most common systemic vasculitis in children [40]. Renal involvement occurs in 20% to 100% of patients. HSP nephritis is common and generally mild in children (particularly young children) (Fig. 14.12). It is mainly presented with microscopic hematuria or proteinuria [40] (Table 14.3).

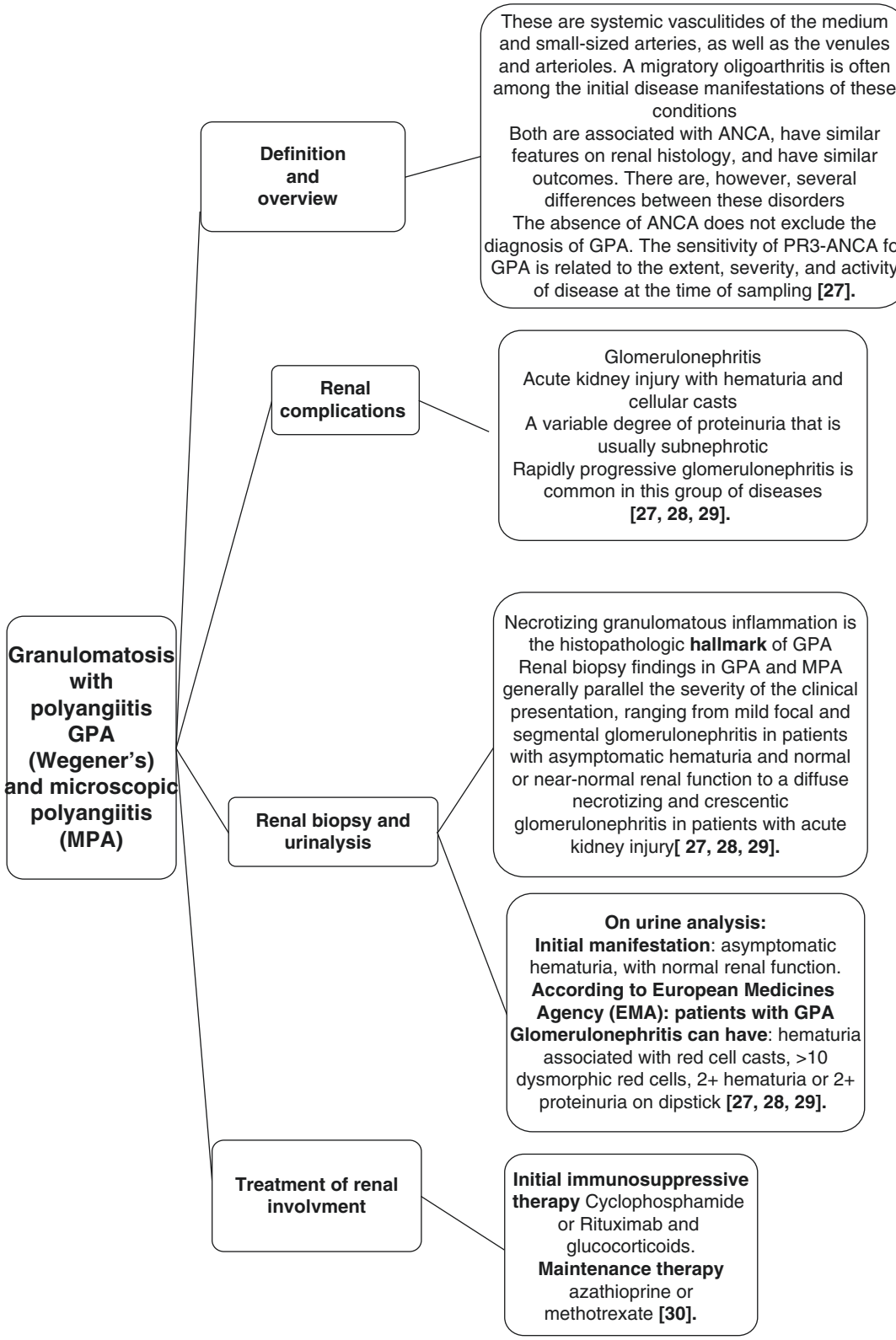

Fig. 14.11 Granulomatosis with polyangiitis GPA (Wegener's) and Microscopic Polyangiitis (MPA) [36–39]

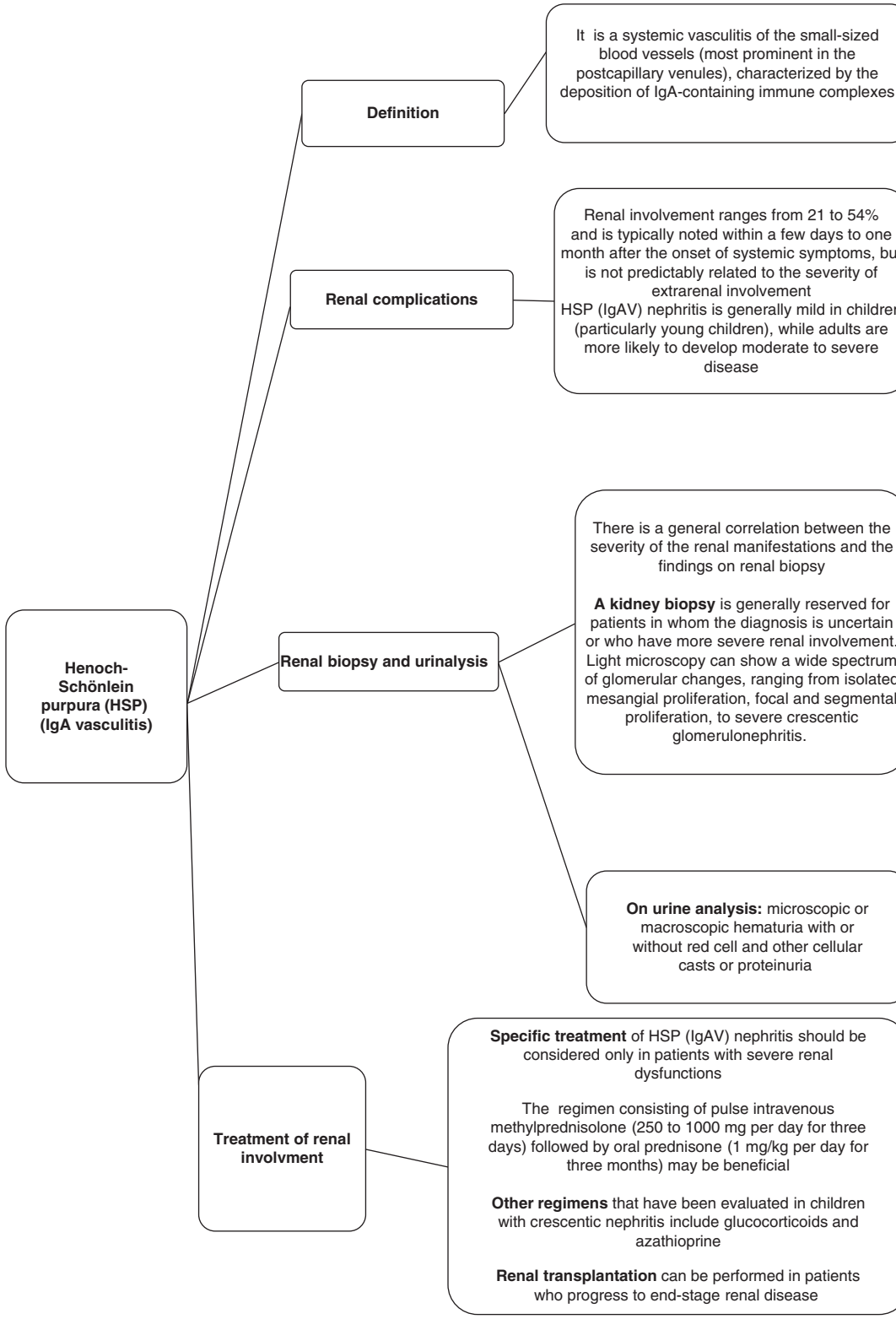

Fig. 14.12 Henoch-Schönlein purpura (HSP) (IgA vasculitis) [40]

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]

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)

14.9.6 Renal Side Effects of DMARDs and NSAIDs

Renal toxicity of disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) varies depending on the age and the kidney function of the patient. Side effects are commonly observed in elderly patients with compromised kidney function. Therefore, the use of NSAID should be avoided in patients with chronic kidney disease. Cyclosporine, gold, and penicillamine are associated with more serious renal side effects. Fortunately, gold and penicillamine are now very rarely used for the treatment of rheumatic diseases. Others like methotrexate, azathioprine, antimalarials, sulfasalazine, and leflunomide are safer with relatively less renal toxicity [35, 36]. Table14.4 summarized the renal side effects of commonly used drugs in rheumatic diseases.

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