ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Clinicopathological Aspects Of Renal Involvement In Systemic Vasculitis.

[1]Ahmed Salah Darwish, [2]Emad Mohamed El-Shebini*, [2]Sabry Abd-Allah Shoeib,

[1]Alexandria fever hospital.
[2]Rheumatology and Immunology Unit, Internal Medicine Department, Faculty of Medicine, Menoufia University, Egypt.

ABSTRACT

Study of different kidney affections in systemic vasculitides. The kidneys are affected by many forms of system vasculitis, which cause a wide variety of clinical manifestations which differ according to size of affected vessels**.** Medline databases (Pub Med, Meds cape, Science direct, Up-to-date). Short reviews were made on kidney involvement in systemic vasculitis. Systemic vasculitides are important group of hematological disorders that commonly affect the kidney. The renal manifestations may vary from asymptomatic urinary abnormalities to sever life threatening rapidly progressive renal injury, early detection and optimum therapeutic interventions prevent irreversible renal damage.

Keywords: Systemic vasculitis; renal involvement; renal biopsy; Immunosuppressive drugs

Corresponding author

ISSN: 0975-8585

INTRODUCTION

The term systemic vasculitis includes a group of autoimmune disorders characterized by inflammation and necrosis of blood vessels with a heterogeneous clinical presentations and unknown etiology. The size of the vessel affected varies among the different forms of vasculitis and it is used for the classification of the disease (table 1). There are three main subgroups: large vessel, medium vessel and small vessel vasculitis, although any size artery can be affected in all the major categories **[1, 2].**

Table (1): 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [2]

Large vessel vasculitis	
Takayasu arteritis	
Giant cell arteritis	
Medium vessel vasculitis	
Polyarteritis nodosa	
Kawasaki disease	
Small vessel vasculitis	
ANCA associated vasculitis :	* Microscopic polyangiitis (MPA)
	* Granulomatosis with polyangiitis (GPA)
	* Eosinophilic granulomatosis with polyangiitis (EGPA)
	* Renal limited vasculitis (RLV)
Immune complex vasculitis	
	* Anti-glomerular basement membrane disease.
	* Cryoglobulinemic vasculitis.
	* IgA vasculitis.
	* Hypocomplementemic urticarial vasculitis.
Secondary vasculitis	
	* Lupus vasculitis.
	* Rheumatoid vasculitis.
	* B and C associated vasculitis
	* Drugs associated vasculitis.
	* Cancer associated vasculitis.
Variable-vessel vasculitis	
	* Behçet syndrome
	* Cogan's syndrome

The kidneys are affected by many forms of system vasculitis, which cause a wide variety of sometimes confusing clinical manifestations. Large-vessel vasculitides, such as giant cell arteritis and Takayasu arteritis, can narrow the abdominal aorta or renal arteries, resulting in renal ischemia and endovascular hypertension. Vasculitides of the medium-sized vessels, such as polyarteritis nodosa and Kawasaki disease, also can reduce flow through the renal artery and may affect intrarenal arteries, resulting in infarction and hemorrhage. Small-vessel vasculitides, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, previously called Wegener granulomatosis), immunoglobulin A (IgA) vasculitis (Henoch- Schonlein purpura), and cryoglobulinemic vasculitis, frequently involve the kidneys and especially the glomerular capillaries resulting in glomerulonephritis**[3].**

Clinicopathological manifestations of kidney involvement in different types of systemic vasculitides

Injury to blood vessels lead to increased vascular permeability, vessel weakening that causes aneurysm formation or haemorrhage, and intimal proliferation and thrombosis that result in obstruction and local ischemia. Different clinical presentations resulted acoordind to the affected vessels.

ISSN: 0975-8585

Table 2: Clinical manifestations of different types of vasculitis [4-10]

Vasculitis	Organ involvement	Age	Clinical manifestations
Churg-Strauss syndrome	Respiratory tract, heart	50 to 60	Allergic rhinitis, asthma, peripheral eosinophilia
Cryoglobulinemic vasculitis	Skin, kidney	40 to 50	Recurrent palpable purpura, polyarthralgia, glomerulonephritis
Henoch-Schönlein purpura	Skin, gastrointestinal tract, kidney, joint	3 to 8	Purpura, arthritis, abdominal pain, gastrointestinal bleeding, glomerulonephritis
Microscopic polyangiitis	Skin, lung, heart, kidney, liver, gastrointestinal tract	50 to 60	Palpable purpura, pulmonary hemorrhage, glomerulonephritis
Wegener granulomatosis	Upper and lower respiratory tracts, kidney	40 to 50	Pneumonitis with bilateral nodular and cavitary infiltrates, mucosal ulceration of nasopharynx, chronic sinusitis, glomerulonephritis
Kawasaki disease	Coronary arteries, aorta and its branches	2 to 4	Fever, conjunctivitis, desquamating skin rash, enlarged cervical lymph nodes
Polyarteritis nodosa	Renal and visceral organs, spares lung	30 to 40	Fever, weight loss, hypertension, abdominal pain, melena, peripheral neuritis, renal ischemia
Giant cell arteritis	Extracranial branches of carotid artery, often involves temporal artery	50 to 60	Fever, visual disturbances, facial pain and headache (often along the course of superficial temporal artery)
Takayasu arteritis	Aorta and its major branches	30 to 40	Markedly lower blood pressure and weaker pulse in upper extremities, with coldness and numbness of fingers , visual disturbances, hypertension

1. Giant cell arteritis:

Extracranial vascular involvement occurs in 10–15 % of Giant cell arteritis (GCA) patients; renal manifestations are rare and include mild proteinuria and microhaematuria. Renal vasculitis have been described on kidney biopsy, including giant cell infiltration and a necrotizing small-vessel arteritis **[3].** Renovascular hypertension is uncommon. cases of renal failure have been attributed rarely to renal arteritis affecting the main renal artery or its major intraparenchymal branches **[11].**

Severe renal involvement with glomerulonephritis in patients with GCA are reported. In these cases, renal pathology shows focal segmental necrotizing glomerulonephritis with crescents **[12]**. Finally, cases of GCA-related renal and systemic AA-type amyloidosis have been reported **[13].**

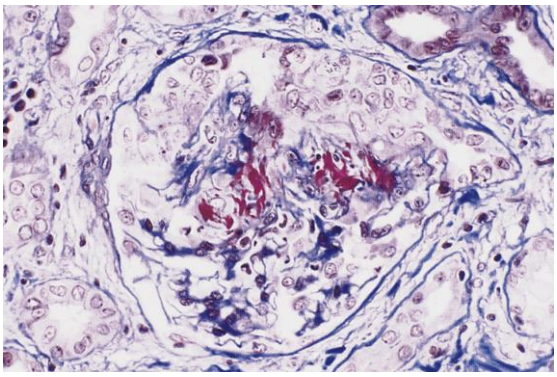

Fig 1: Glomerulus with segmental fibrinoid necrosis with red (esinophilic) fibrinous material and an adjacent cellular crescent, from a patient with antineutrophil cytoplasmic antibody small-vessel vasculitis (Masson trichrome stain).

2. Takayasu arteritis:

Renovascular hypertension is the most common renal manifestation of Takayasu arteritis (TA) caused by involvement of the main renal artery or its major branches. Proximal and unilateral but also bilateral stenosis is common. New onset hypertension is the presenting manifestation of TA in 45% of cases and its frequency over the disease course is up to 60 % **[14].**,Hypertension is sometimes in TA due to co-existing subclavian stenosis **[15].** Fibromuscular dysplasia (FMD) mimics TA-related renal artery stenosis which is a rare non-inflammatory, non-atherosclerotic (systemic) disorder that, like TA, often affects young women. FMD causes arterial stenosis, occlusion and aneurysm involved in 75–80 % of patients. Elevated acute-phase reactants can help distinguish the vasculitis disease from FMD, and imaging studies (especially PET-CT, angio-CT and MRI-angiography) show vessel wall inflammation, which rules out FMD **[15].**

Patients with TA have normal renal function with only mild proteinuria and/or haematuria. Renal failure is extremely rare. the most common glomerular lesion is Mild diffuse mesangial proliferative glomerulonephritis **[16].**

Mesangial deposits of immunoglobulins (Ig) , complement and **IgA** nephropathy have been observed.There are also rare descriptions of renal amyloidosis and cases of membranoproliferative glomerulonephritis, crescentic glomerulonephritis, and focal glomerulosclerosis **[17].**

3. Poly Arteritis Nodosa:

The most commonly affected visceral organ is The kidney in classic Poly Arteritis Nodosa **[18].**Earlierly, renal involvement was reported in 63–76 % of patients, whereas in more recent prospective studies its prevalence ranges between 26 and 44 % **[18, 19].** Renal involvement includes gross or microscopic haematuria, moderate proteinuria, slowly progressive renal failure and hypertension. Vasculitis of the renal and interlobar arteries, resulting in microaneurysm formation with consequent tissue infarction or haematomas causing kidney damage. kidney infarction can be silent. Renal involvement may includes loin pain, and new-onset hypertension or worsening of pre-existing hypertension secondary to intrarenal artery involvement occurs in up to 35 % of patients **[20,21].** Acute kidney failure with oligoanuria is uncommon **[22].**

Spontaneous renal hemorrhage or rupture is a rare complication and is typically unilateral **[23, 24].** Bilateral renal artery dissection has also been described in the context of PAN **[25].** Ureteral involvement with stenosis due to peri-ureteral vasculitis is another rare complication **[26].**

4. Microscopic polyangiitis and Granulomatosis with polyangiitis:

Renal involvement includes Microscopic polyangiitis and Granulomatosis with polyangiitis and is asymptomatic until advanced renal failure occurs. Therefore, renal involvement in AAV must be diagnosed through detection in urine of microscopic hematuria, erythrocytecasts and non-nephrotic proteinuria before the creatinine increase. Unfortionaly a missed or delayed diagnosis of renal involvement are life threatening as the survival and the risk of end-stage renal disease (ESRD) are associated with renal function at presentation **[27].**

The kidney involvement is characterized by a necrotizing and crescentic pauci-immune glomerulonephritis. The gold standard for diagnosis is renalbiopsy. Active disease include glomerular necrosis usually segmental without substantial endocapillary hypercellularity, segmental or circumferential crescents, disruption of Bowman's capsule and frequent periglomerularinfiltrates of leukocytes. There are a little or no histological abnormalities in the glomeruli without crescentic lesions. At immunofluorescence, there is no glomerular immune complex deposits or linear IgG deposits typical of anti-GBM disease. These histological features are defined as pauci-immune forms. The crescents change from cellular to fibrocellular to fibrotic phases. This process is accompanied by a comparable degree of progressive sclerosis of glomerular tuft, interstitial fibrosis and tubule atrophy. Arteriolar fibrinoid necrosis can be present in the renal specimen with associated mural and perivascular infiltration of neutrophils or mononuclear leukocytes lesions **(Fig.** I) . Mononuclear interstitial infiltration is frequently present in active phases of the disease **[28].** The course of MPA is characterized by acute and quiescent phases and finding in the same biopsy active and chronic lesions is not uncommon. The urinary manifestations are hematuria, oliguria, non-nephrotic proteinuria and erythrocyte casts. the most common cause for rapidly progressive glomerulonephritis (RPGN) with a very rapid decline of renal function is Pauciimmune glomerulonephritis. Deterioration of renal function often carries a poor prognosis, with a high rate of ESRD and mortality.**[29]**

5. Henoch–Schonlein purpura

HSP is the most common form of vasculitis in children, but occurs less commonly in adults. Renal involvement presents as IgA nephropathy and occurs in up to 40% of patients. The pathogenesis is driven by circulating immune complexes of IgG antibodies directed to hypogalactosylated IgA that are deposited in the renal mesangium **[30].** It appears that a fraction of serum IgA1 is hypogalactosylated, giving it immunopathogenic potential. Whether molecular mimicry between hypogalactosylated IgA and bacterial or viral glycoproteins accounts for triggering IgA nephropathy following infection is unknown and is under study. Progression to ESRD is rare and comprises 3% of patients with renal involvement; however, proteinuria and arterial hypertension are common sequelae **[31].** There is no specific evidence for the benefit of immunosuppressive treatment in glomerulonephritis caused by HSP However, there are anecdotal reports of the benefits of steroids, together with cyclophosphamide and plasma exchange in patients with crescentic glomerulonephritis **[32]**.

6. Cryoglobulinemia

Within the spectrum of vasculitis caused by cryoglobulinemia, renal involvement occurs most often in type 2 essential mixed cryoglobulinemia. Renal biopsy generally shows a membrano-proliferative glomerulonephritis with subendothelial deposits, and occasionally crescent formation. ESRD occurs less commonly in cryoglobulinemia, affecting around 10% of patients **[33].** Many cases of cryoglobulinemia are related to underlying hepatitis C infection, although this appears less common in Northern Europe. For those with hepatitis C, treatment generally includes pegylated -interferon together with ribavirin. In patients with significantly reduced glomerular filtration rate (GFR), the dose of ribavirin may need to be reduced in order to prevent hemolytic anemia. In patients with RPGN, immunosuppressive therapy like prednisolone, cyclophosphamide and plasma exchange has been used. Recently, rituximab has been shown to confer clinical benefit in this group of patients **[34].**

7. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Renal manifestations occur in 25% of patients and range from isolated urinary abnormalities (e.g., microscopic hematuria, proteinuria) to rapidly progressive glomerulonephritis. Pauci-immune focal and segmental necrotizing glomerulonephritis are shown histologicaly, with or without crescents, which is often less severe than in other AAV **[35].**

8. Renal-limited vasculitis

Idiopathic RPGN like isolated pauci-immune necrotizing, crescentic glomerulonephritis, , has many features to suggest that it represents a renal-limited form of MPA, including the presence of circulating ANCA, mostly MPO-ANCA, in about 40–50% of cases**[36].** The histologic features of renal-limited pauci-immune crescentic glomerulonephritis are indistinguishable from those of pauci-immune crescentic glomerulonephritis that occurs as a component of systemic vasculitis. Histological classification OF AAV In 2010, a new histopathological classification based on the percent of normal glomeruli, cellular crescents or global sclerotic glomeruli was proposed for the purposes of predicting the renal prognosis **[37].**

Glomerular lesions proposed have four categories: focal, crescentic, mixed and sclerotic. Presence of more than 50% of normal glomeruli in the focal category; the crescentic category by more than 50% of glomeruli with cellular crescents, the mixed class by less than 50% of normal glomeruli and crescentic or sclerotic lesions, while the sclerotic class by more than 50% of glomeruli with global sclerosis. the sequence of categories in the validation study of Berden et al. was found to correspond to the order of severity of renal function loss at 1 year as well as at 5-year follow- up. Renal survival at 5 years was 93, 76, 61 and 50% respectively. With such promising results, many studies since 2010 have tested the value of the proposed classification. All studies agreed about the sclerotic class as having the worst prognosis **[38,39]** and many about the best prognosis of the focal class **[38,39,41,42].** The difference in survival between crescentic and mixed forms varies in several studies **[38, 39, 41-43]** . The renal survival at 5 years was worse in the crescentic subgroup compared to the mixed subgroup. This may be due to that in the crescentic subgroup we found only 12% of normal glomeruli and that more than half of the crescents present were circumferential. Moreover, the Kaplan–Meier curves estimating survival without development of ESRD did not show significant differences between the outcome of mixed and focal groups or between sclerotic and crescentic groups. Consequently, survival without ESRD was significantly better for the mixed and the focal groups in comparison to that of the sclerotic and the crescentic

groups. At multivariate analysis, independent predictors of ESRD were high serum creatinine and arterial hypertension at presentation and <20% of normal glomeruli at kidney biopsy. **[40].** Another matter of debate is that the classification is based on glomerular lesions only, while there are other lesions such as the chronic tubule-interstitial damage that can predict poor outcomes **[40]**.

9. Lupus associated vasculitis

The kidney is affected in 50% to 65% of SLE patients, with a high incidence of proliferative nephritis, accompanied on a few occasions by vasculitis. Focal segmental necrotizing glomerulonephritis with fibrinoid necrosis, which may lead to rapid progressive renal failureis the histological lesion of vasculitis **[44].** Necrotizing inflammation of the larger arteriole and small artery involvement may also be found associated with several renal diseases **[45].**

10. Rheumatoid vasculitis

Vasculitis is evident on renal biopsy in only a small number of patients with RA; it is characterized by either necrotizing glomerulonephritis or by destructive inflammation within the walls of renal arteries **[46].** Most renal disease in RA patients is non-vasculitic, such as acute tubular necrosis related to nonsteroidal antiinflammatory drug (NSAID) use, secondary amyloidosis due to the chronic inflammation, and nephrotic syndrome due to drug-related membranous nephropathy. These conditions have become even more infrequent with effective therapies, and the kidneys are much less likely to be involved in extraarticular RA, compared with the skin, peripheral nerves, and eyes **[47].**

11. Hepatitis B and C associated vasculitis

Renal manifestations were noted with HCV-related mixed cryoglobulinemic syndrome with glomerulonephritis had many clinical presentations which include Microscopic hematuria and subnephrotic proteinuria with or without chronic renal insufficiency (41 percent), Nephrotic syndrome with or without chronic renal insufficiency (22 percent), Acute glomerulonephritis (14 percent) , Chronic kidney disease without significant urinalysis abnormalities (13 percent) , Acute renal failure (9 percent), Hypertension (which can be severe - 65 percent**) [48].**

Histologic examination of the kidney reveals a membranoproliferative glomerulonephritis in over 80 percent of patients, with both thickening of the glomerular basement membrane and cellular proliferation, including a far greater influx of circulating macrophages than seen in other forms of proliferative glomerulonephritis **[49].**

Renal diseases most commonly associated with hepatitis B virus infection include membranous nephropathy, membranoproliferative glomerulonephritis, and polyarteritis nodosa

Membranoproliferative glomerulonephritis (MPGN) - HBV-associated MPGN, as with other forms of MPGN, presents with hematuria (often with dysmorphic red blood cells and/or red blood cell casts) and variable degrees of proteinuria, reduced glomerular filtration rate, and hypertension. The histologic deposition of circulating antigen-antibody complexes in the mesangium and subendothelial space **[50].**

Membranous nephropathy - HBV-associated secondary membranous nephropathy, as with other forms of membranous nephropathy, usually presents with proteinuria, which can be in the nephrotic range. Comparing patients who have idiopathic membranous nephropathy, with patients with HBV-associated membranous nephropathy are more likely to have microscopic hematuria, lower complement levels, and a negative anti-phospholipase A2 receptor antibody (anti-PLA2R) [51,52]. The histologic presence of mesangial or subendothelial immune deposits, in addition to the typical subepithelial localization, may be a clue to suggest secondary rather than primary membranous nephropathy.[53-55].

Polyarteritis nodosa: renal involvement leads to variable degrees of reduced glomerular filtration rate and hypertension. The clinical features of HBV-associated PAN are similar to idiopathic PAN.[56]

Treatment of renal involvement in systemic vasulitides:

Management requires balancing the burden of immune suppression with control of disease activity, Newer therapies have been shown great promise in the management of these disorders
sive glomerulonephritis.

Giant Cell Arteritis

Corticosteroids causes rapid and dramatic improvements in general well-being, specific symptoms, and laboratory abnormalities. The recommended initial dosage of prednisone is 40-60 mg/day **[56].** Renal failure resulting from GCA without glomerulonephritis has been previously reported to respond well to steroid therapy alone or in combination with cyclophosphamide **[57].**

Takayasu arteritis

During the acute stage, TA usually responds well to high dose corticosteroids (e.g., prednisone 1 mg/kg/day), followed by steroid maintenance for several months depending on disease activity. Occasionally, patients with more severe disease may benefit from other medications including azathioprine, methotrexate, leflunomide, cyclophosphamide, mycophenolate mofetil, and tumour necrosis factor (TNF) blockers **[58].** When the sclerotic phase has developed, residual morbidity may result from stenosis of previously inflamed arteries. In these cases, balloon angioplasty may be used to dilate stenotic lesions of the aorta and renal arteries. Renal artery angioplasty effectively reverses hypertension in up to 56 % of the patients, but re-stenosis is observed in one-fifth of the cases. Rarely, surgical revascularization may be necessary. The overall mortality is low, but relapse rates can be very high **[59].**

Poly Arteritis Nodosa

Patients usually treated with corticosteroids. If relapses occur during steroid tapering or if remission cannot be achieved, immunosuppressive agents are added to prednisone in order to induce remission. Cyclophosphamide is used for remission induction for 4–12 months **[61].**

Henoch schonlein purpra

Patients with >0.5 g/day of proteinuria treated with ACE inhibitors or ARBs to reduce proteinuria, unless contraindicated. Proteinuria of >750 mg to 1 g/day, nephrotic syndrome, evidence of crescentic glomerulonephritis on renal biopsy necessitates a six-month, tapering course of glucocorticoid; pulse IV methylprednisolone at a dose of 500 mg to 1 g daily for three days, followed by oral prednisone 60 mg daily or 120 mg every other day. Monitoring urine protein excretion and serum creatinine every two weeks for one month and then monthly for the first six months.**[62]**

Granulomatosis with polyangiitis and Microscopic polyangiitis

Rituximab or Cyclophosphamide 2 mg/kg orally daily or pulsed monthly and high doses of corticosteroids (1 mg/kg orally daily, tapered during 6 to 12 months) are effective medications for induction of remission with improved outcomes . Other options Methotrexate (up to 25 mg/week) and corticosteroids **[63].**

Cryoglobinemia

Rituximab appears to provide effective therapy in patients with the mixed cryoglobulinemia syndrome **not** associated with chronic HCV infection. Intravenous methylprednisolone 7.5 to 15 mg/kg per day is given for one to three days based upon the severity of the illness. This is followed by oral prednisone, 1 mg/kg per day (maximum dose of 80 mg/day) for two to four weeks, then 40 mg/day for two weeks, and then 20 mg/day for another two to four weeks. Plasma exchange is beneficial in selected cases **[64].**

Rheumatoid vasculitis

Glucocorticoids, Cyclophosphamide or Rituximab**[65].**

Lupus associated vasculitis

Cyclophosphamide, glucocorticoids, azathioprine, or mycophenolate Mofetil.**[66]**

Hepatitis B and C

New direct Antiviral drugs for hepatitis C demonstrated efficacy in treatment of renal involvement Rituximab is well tolerated and is used for patients with severe renal disease. Plasmapheresis is used in cases with kidney or life threatening disease. **[67,68].**

Table 3: Clinical picture of kidney affection by different types of systemic vasculitides [7, 8, 10]

Disease	Common renal manifestations	Less common
Giant cell arteritis	No specific	Mild proteinuria micro-haematuria
Takayasu disease	Renovascular hypertension,	Proteinuria, Progressive renal failure
Chronic Periaortitis	Hydronephrosis Renovascular hypertension	ESRD
Poly artitis nodosa	Haematuria, moderate proteinuria, slowly progressive renal failure and hypertension.	Oligoanuria Spontaneous renal haemorrhage or rupture
Granulomatosis with poly angitis	Oliguria,hematuria, erythrocyte casts andnon-nephrotic proteinuria**,** ESRD	No specific
Henoch–Schonlein purpura	Proteinuria and arterial hypertension	ESRD
Cryoglobulinemia	Hypertension,Microscopic hematuria and subnephrotic proteinuria	ESRD
Esinophilic granulomatosis with polyangitis	Microscopic hematuria, proteinuria	RPGN
Lupus associated vasculitis	Focal segmental necrotizing glomerulonephritis with fibrinoid necrosis	Rapid progressive renal failure
Rheumatoid vasculitis	Necrotizing glomerulonephritis	ESRD
Hepatitis B & C	Hypertension Microscopic hematuria and subnephrotic proteinuria	ESRD

ESRD: End stage renal disease. **RPGN**: Rapid progres

CONCLUSION

The systemic vasculitis are important group of hematological disorders that commonly affect the kidney. The renal manifestations may vary from asymptomatic urinary abnormalities to sever life threatening rapid progressive renal failure. Steroid therapy is always indicated, Very few cases required cyclophosphamide and plasma exchange. One variable to consider is the use of anti-CD 20 (Rituximab) therapies in severely ill patients failing to respond to steroids or PEX.

REFERENCES

[1] Jennette JC et al (1994) Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthr Rheum 37:187–192

[2] Jennette JC et al (2013) 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthr Rheum 65(1):1–11

[3] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65:1.

[4] Gabriel SE, O'Fallon WM, Achkar AA, et al. The use of clinical characteristics to predict the results of temporal artery biopsy among patients with suspected giant cell arteritis. J Rheumatol 1995; 22:93.
[5] Miller NR. Visual manifestations of temporal arteritis. Rheum Dis Clin North Am 2001; 27:781.
[6] Yoneda S, Nukada T, Tada K,et al. Subclavian steal in Takayasu's arteritis. A hemodynamic study by means of ultrasonic Doppler flowmetry. Stroke 1977; 8:264.
[7] Sung RY, Ng YM, Choi KC, et al. Lack of association of cervical lymphadenopathy and coronary artery complications in Kawasaki disease. Pediatr Infect Dis J 2006; 25:521.
[8] Neumann I, Regele H, Kain R, et al. Glomerular immune deposits are associated with increased proteinuria in patients withANCA-associated crescentic nephritis. Nephrol Dial Transplant 2003; 18:524.
[9] Sinico RA, Bottero P. Churg-Strauss angiitis. Best Pract Res Clin Rheumatol 2009; 23:355
[10] Noth I, Strek ME, Leff AR. Churg-Strauss syndrome Lancet 2003; 361:587
[11] Scarpioni R et al (2003) Isolated renal giant cell arteritis, not so rare a cause of renal failure? Am J Kidney Dis 41(3):720
[12] Truong L et al (1985) Temporal arteritis and renal disease. Case report and review of the literature. Am J Med 78(1):171–175
[13] Moraga S et al (2001) Giant cell arteritis and renal amyloidosis: report of a case. Clin Nephrol 56(5):402–406.
[14] Vanoli M et al (2005) Takayasu's arteritis: a study of 104 Italian patients. Arthritis Rheum 53(1):100–107
[15] Lagneau P, Michel JB (1985) Renovascular hypertension and Takayasu's disease. J Urol 134(5):876–879
[16] Lai KN, Chan KW, Ho CP (1986) Glomerulonephritis associated with Takayasu's arteritis: report of three cases and review of literature. Am J Kidney Dis 7(3):197–204
[17] de Pablo P et al (2007) Kidney involvement in Takayasu arteritis. Clin Exp Rheumatol 25(1 Suppl 44):S10–S14
[18] el-Reshaid K et al (1997) The spectrum of renal disease associated with microscopic polyangiitis and classic polyarteritis nodosa in Kuwait. Nephrol Dial Transplant 12(9):1874–1882
[19] Cohen RD, Conn DL, Ilstrup DM (1980) Clinical features, prognosis, and response to treatment in polyarteritis. Mayo Clin Proc 55(3):146–155
[20] Gorriz JL et al (1997) Renal-limited polyarteritis nodosa presenting with loin pain and haematuria. Nephrol Dial Transplant 12(12):2737–2739
[21] Wang AY et al (1996) Acute renal failure induced by angiotensin converting enzyme inhibitor in a patient with polyarteritis nodosa. Ren Fail 18(2):293–298.
[22] Ladefoged J et al (1969) Acute anuria due to polyarteritis nodosa. Am J Med 46(5):827–831
[23] Schlesinger M et al (1989) Perirenal and renal subcapsular haematoma as presenting symptoms of polyarteritis nodosa. Postgrad Med J 65(767):681–683
[24] Romijn JA et al (1989) Bilateral kidney rupture with severe retroperitoneal bleeding in polyarteritis nodosa. Neth J Med 35(5–6):260–266
[25] Hekali PE et al (1984) Bilateral renal artery dissections: unusual complication of polyarteritis nodosa. Eur J Radiol 4(1):6–8
[26] Glanz I, Grunebaum M (1976) Ureteral changes in polyarteritis nodosa as seen during excretory urography. J Urol 116(6):731–733
[27] Sinico RA et al (2013) Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis. Autoimmun Rev 12(4):477–482
[28] Kallenberg CG (2014) The diagnosis and classification of microscopic polyangiitis. J Autoimmun 48–49:90–93
[29] Jennette JC, Olson JL, Schwartz MM, Silva FG (eds) (1998) Heptinstall's pathology of the kidney, 5th edn. Lippincott- Raven publishers, Philadelphia, pp 625–656
[30] Barratt J, Eitner F, Feehally J, et al. Immune complex formation in IgA nephropathy: a case of the "right" antibodies in the "wrong" place at the "wrong" time? Nephrol Dial Transplant 2009; 24:3620–3.
[31] Sanders JT, Wyatt RJ. IgA nephropathy and Henoch– Sch¨onlein purpura nephritis. Curr Opin Pediatr 2008; 20:163–70.
[32] Brogan P, Eleftheriou D, Dillon M. Small vessel vasculitis. Pediatr Nephrol 2010; 25:1025–35.
[33] Fabrizi F, Lunghi G, Messa P, et al. Therapy of hepatitis C virus-associated glomerulonephritis: current approaches. J Nephrol 2008; 21:813–25.
[34] De Vita S, Quartuccio L, Isola M, et al. A randomized, controlled, trial of rituximab for treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum 2011 Dec 6. doi: 10.1002/art.34331.
[35] Sinico, R.A.; di Toma, L.; Maggiore, U.; Tosoni, C.; Bottero, P.; Sabadini, E.; Giammarresi, G.; Tumiati, B.; Gregorini, G.; Pesci, A.; et al. Renal involvement in Churg-Strauss syndrome. Am. J. Kidney Dis. **2006**, 47, 770–779.
[36] Radice A et al (2013) Anti-neutrophil cytoplasmic autoantibodies: methodological aspects and clinical significance in systemic vasculitis. Autoimmun Rev 12(4):487–495

[37] Berden AE et al (2010) Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 21(10):1628–1636
[38] Chang DY et al (2012) Re-evaluation of the histopathologic classification of ANCA-associated glomerulonephritis: a study of 121 patients in a single center. Nephrol Dial Transplant 27:2343–2349
[39] Muso E et al (2013) Evaluation of the newly proposed simplified histological classification in Japanese cohorts of myeloperoxidase- anti-neutrophil cytoplasmic antibody associated glomerulonephritis in comparison with other Asian and European cohorts. Clin Exp Nephrol 17(5):659–662
[40] Moroni G et al (2015) Predictors of renal survival in ANCAassociated vasculitis. Validation of a histopathological classification schema and review of the literature. Clin Exp Rheumatol 33(2 Suppl 89):S56–S63
[41] Tanna A et al (2015) Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors. Nephrol Dial Transplant 30:1185–1192
[42] Hilhorst M et al (2013) Improved outcome in anti-neutrophil cytoplasmic antibody (ANCA)- associated glomerulonephritis: a 30-year follow-up study. Nephrol Dial Transplant 28:373–379
[43] Quintana LF et al (2014) ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-associated glomerulonephritis. Nephrol Dial Transplant 29:1764–1769
[44] D'Cruz D. Vasculitis in systemic lupus erythematosus. Lupus. 1998;7(4):270–4.
[45] Bacon PA, Carruthers DM. Vasculitis associated with connective tissue disorders. Rheum Dis Clin N Am. 1995;21(4):1077–96.
[46] Boers M, Croonen AM, Dijkmans BA, et al. Renal findings in rheumatoid arthritis: clinical aspects of 132 necropsies. Ann Rheum Dis 1987; 46:658.
[47] Qarni MU, Kohan DE. Pauci-immune necrotizing glomerulonephritis complicating rheumatoid arthritis. Clin Nephrol 2000; 54:54
[48] Roccatello D, Fornasieri A, Giachino O, et al. Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. Am J Kidney Dis 2007; 49:69.
[49] D'Amico G, Colasanti G, Ferrario F, Sinico RA. Renal involvement in essential mixed cryoglobulinemia. Kidney Int 1989; 35:1004.
[50] Takekoshi Y, Tochimaru H, Nagata Y, Itami N. Immunopathogenetic mechanisms of hepatitis B virus-related glomerulopathy. Kidney Int Suppl 1991; 35:S34
[51] Li P, Wei RB, Tang L, et al. Clinical and pathological analysis of hepatitis B virus-related membranous nephropathy and idiopathic membranous nephropathy. Clin Nephrol 2012; 78:456.
[52] Qin W, Beck LH Jr, Zeng C, et al. Anti-phospholipase A2 receptor antibody in membranous nephropathy. J Am Soc Nephrol 2011; 22:1137.
[53] Lai KN, Li PK, Lui SF, et al. Membranous nephropathy related to hepatitis B virus in adults. N Engl J Med 1991; 324:1457.
[54] Lai KN, Lai FM. Clinical features and the natural course of hepatitis B virus-related glomerulopathy in adults. Kidney Int Suppl 1991; 35:S40.
[55] Lin CY. Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon. Kidney Int 1995; 47:225.
[56] Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. Medicine (Baltimore) 1995; 74:238.
[57] Matteson EL et al. Glucocorticoids for Management of Polymyalgia Rheumatica and Giant Cell Arteritis. Rheum Dis Clin North Am 2016; 42(1):75–90
[58] Tann OR, Tulloh RM, Hamilton MC. Takayasu's disease: a review. Cardiol 2008; 18(3):250–259
[59] Boubaker K et al. Renal injury in Takayasu's arteritis. Nephrol Ther 2014; 10(6):451–456
[60] Ribi C et al.Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010; 62(4):1186–1197
[61] Guillevin L et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. Arthritis Rheum 2003; 49(1):93–100
[62] Ishiguro H, Hashimoto T, Akata M, et al. Rituximab treatment for adult purpura nephritis with nephrotic syndrome. Intern Med 2013; 52:1079.
[63] Novack SN, Pearson CM (1971) Cyclophosphamide therapy in Wegener's granulomatosis. N Engl J Med 284:938–942
[64] Ferri C, Cacoub P, Mazzaro C, et al. Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: results of multicenter cohort study and review of the literature. Autoimmun Rev 2011; 11:48.

[65] Ntatsaki E, Mooney J, Scott DG, Watts RA. Systemic rheumatoid vasculitis in the era of modern immunosuppressive therapy. Rheumatology (Oxford) 2014; 53:145.
[66] Pisoni CN, Sanchez FJ, Karim Y, CuadradoMJ, D'Cruz DP, Abbs IC,et al.Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. J Rheumatol. 2005;32:1047–52.
[67] Ahn J, Lee HM, Lim JK, et al. Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. Aliment Pharmacol Ther 2016; 43:134.
[68] Sarrazin C, Isakov V, Svarovskaia ES, et al. Late Relapse Versus Hepatitis C Virus Reinfection in Patients With Sustained Virologic Response After Sofosbuvir-Based Therapies. Clin Infect Dis 2017; 64:44.