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# Urological manifestations and treatment of the primary systemic vasculitides

Peracha J *et al*. Urological manifestations of the systemic vasculitides

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# Abstract

The primary systemic vasculitides (PSV) are a group of rare inflammatory disorders affecting blood vessels of varying size and multiple organs. Urological manifestations of PSV are uncommon. Testicular vasculitis is the most commonly reported finding and is associated with Polyarteritis Nodosa (PAN), Henoch-Schönlein Purpura (HSP), anti-neutrophil cytoplasm antibody associated Vasculitides (AAV), Giant Cell Arteritis (GCA) and Kawasaki’s Disease. Prostatic vasculitis has been reported in association with GCA and AAV. Ureteric involvement has been noted in PAN, HSP and AAV. Other urogenital manifestations of PSV include genital ulceration and bladder dysfunction in Behçets Disease and haematuria which is commonly seen in many of the PSV. Finally, therapies used to treat the PSV, especially cyclophosphamide, are associated with urological side-effects including haemorrhagic cystitis and urothelial malignancy. The aim of this review is to examine how the urological system is involved in the PSV. Each PSV is examined in turn, with a brief clinical description of the disease followed by a description of the urological manifestations and management. Identification of urological manifestations of PSV is important as in many cases symptoms may improve with immunosuppressive therapy, avoiding the need for invasive surgery. Additionally, patients who present with isolated urogenital PSV are at higher risk of developing subsequent systemic vasculitis and will need to be followed up closely.

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# Key words: Urology; Vasculitis; Takayasu arteritis; Giant cell arteritis; Polyarteritis Nodosa; Kawasaki disease; Henoch-schonlein purpura; Anti-neutrophil cytoplasm antibody associated vasculitides; Granulomatosis with polyangiitis; Microscopic polyangiitis; Eosinophillic granulomatosis with polyangiitis; Behcets disease; Epididymo-orchitis; Prostatitis; Ureteric stenosis

# Core tip: Urogenital manifestations of primary systemic vasculitides are rare. Patients will usually have other systemic signs and symptoms to suggest an underlying vasculitic process. Inflammatory markers including erythrocyte sedimentation rate and C-reactive protein are often raised and specific auto-antibody testing may be useful in identifying the underlying diagnosis. If an underlying vasculitic process is suspected, early involvement of a specialist is essential. Symptoms usually improve with immunosuppressive therapy and may avoid the need for invasive surgery. Patients who present with isolated single-organ vasculitis of the urogenital tract will need to be followed up closely in case they subsequently develop systemic disease.

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# INTRODUCTION

The primary systemic vasculitides (PSV) are a group of rare inflammatory disorders affecting blood vessels of varying sizes and multiple organs. The PSV are classified according to the size of vessel they predominantly affect. Nomenclature and detailed definitions for each of the PSV were set out by the Chapel Hill Consensus Conference (CHCC) in 1994 and reviewed again in 2012[[1](#_ENREF_1)]. In this review each PSV is examined in turn, with a brief clinical description of the disease followed by a description of the urological manifestations and management (Table 1). It should however be borne in mind that the treatments for these diseases change and improve over time and management of these rare diseases should be undertaken in collaboration with a specialist with appropriate expertise.

# LARGE VESSEL VASCULITIDES

## *Takayasu arteritis*

Takayasu arteritis (TA) is a rare, systemic, large-vessel vasculitis of unknown aetiology. It is defined by the CHCC as “granulomatous inflammation of the aorta and its major branches”. TA occurs most commonly in Mexico, Japan and parts of Asia, predominantly in women of childbearing age. It is classified depending on the specific part of the aorta that is affected. Complications of disease include stroke, seizures, hypertension and retinopathy. Treatment is usually with immunosuppression to control inflammation but if vessels become fibrosed and stenotic, angioplasty +- stenting and bypass grafting may be necessary [[2](#_ENREF_2),[3](#_ENREF_3)].

 No specific urological manifestations of TA have been reported in the literature. There are a few isolated case reports of retroperitoneal fibrosis causing obstructive uropathy in association with TA. In the acute setting this was managed with ureteric stents and long-term improvement in symptoms was noted with immunosuppressive therapy[[4-6](#_ENREF_4)].

## *Giant cell arteritis*

Giant cell arteritis (GCA) is a large vessel vasculitis characterized by granulomatous inflammation predominantly affecting the thoracic aorta and its branches.

#### Epidemiology and clinical features: It is predominantly a disease of older people with the highest incidence in patients 70-80 years of age. The incidence of disease is also highest in patients of Northern European, North American or Scandinavian descent [[7](#_ENREF_7)].

Constitutional symptoms such as fever, fatigue and weight loss are common in GCA as are specific manifestations of the disease include headache, scalp tenderness, jaw claudication and visual disturbance. Approximately 20% of patients will manifest clinical signs of large vessel involvement, including aneurysmal and stenotic lesions of the abdominal aorta[[8](#_ENREF_8)].

#### Treatment and prognosis: The mainstay of treatment in GCA is with high dose corticosteroids to induce disease remission. Methotrexate may be used as adjunctive therapy, whilst TNF inhibitors and the IL-6 inhibitor, tocilizumab, may have a role in the treatment of relapsing and refractory disease[[9](#_ENREF_9),[10](#_ENREF_10)].

The most serious complication in patients with GCA is blindness secondary to ischaemic optic neuropathy, which develops in approximately 7%-14% of all patients. As a result, patients often receive prolonged courses of steroids, with an average duration of therapy of two years. Side effects from long-term steroid therapy, include hypertension, diabetes and osteoporosis [[11](#_ENREF_11)].

#### Urological manifestations: Urological manifestations of GCA are seldom reported. Epididymal involvement has been reported in a 66 year old male with a 3 mo history of generalised fatigue, right sided epididymal tenderness, raised inflammatory markers and a normochromic normocytic anaemia. Epididymal biopsy demonstrated chronic inflammatory cell infiltration and the presence of ‘giant cells’. The patient subsequently underwent a temporal artery biopsy, which confirmed the diagnosis of giant cell arteritis. This patient responded well to high dose corticosteroids[[12](#_ENREF_12)].

Testicular involvement has also been reported in a 76 years old male with weight loss, malaise and right testicular swelling. His ultrasound scan was suggestive of testicular malignancy and he underwent radical orchidectomy. The excised specimen showed a shrunken testis surrounded by dense, focally calcifed tissue, up to 7 mm thick with patchy intimal thickening of the spermatic cord and a chronic inflammatory cell infiltrate in the vessel walls. One arteriole showed a focus of destructive arteritis with the presence of giant cells[[13](#_ENREF_13)].

# MEDIUM VESSEL VASCULITIDES

## *Polyarteritis Nodosa*

Polyarteritis Nodosa (PAN) is a rare necrotising systemic vasculitis typically affecting medium and small sized arteries. Inflammation usually targets muscular arteries at bifurcations or branch points. The inflammatory lesions start at the vessel intima and may progress to involve the entire arterial wall, destroying the internal and external elastic lamina and resulting in fibrinoid necrosis. The weakened vessel walls are prone to aneurysm formation and subsequent rupture, haemorrhage and thrombosis. During the healing process medial and intimal proliferation may result in occlusion of vessels, leading to tissue ischaemia or infarction[[14](#_ENREF_14)].

Glomerulonephritis and pulmonary involvement are not usually a feature of PAN, as there is characteristic sparing of smaller blood vessels including arterioles, capillaries and venules[[1](#_ENREF_1)] .

PAN may be idiopathic or secondary to specific viral triggers, the most common of these being Hepatitis B viral (HBV) infection but rare associations with hepatitis C virus and HIV have been reported[[15](#_ENREF_15),[16](#_ENREF_16)]. Patients may display a wide variety of clinical presentations from limited single organ disease to widespread fulminant multi-organ failure.

#### Epidemiology: PAN is a rare disease. Accurate estimation of incidence and prevalence rates are difficult and largely dependent on the disease classification method used. Reported annual incidence of PAN in most developed countries is estimated between 2-9 cases/ million population/year[[17-19](#_ENREF_17)], with overall prevalence of the disease estimated at approximately 30 cases/ million population in France[[20](#_ENREF_20)]. PAN can affect patients of any age, ethnicity or gender but a peak in incidence has been consistently noted in the 5th and 6th decades of life. Males are also more commonly affected than females[[21](#_ENREF_21)].

Over the past 20 years PAN has become less common. This may be due to a reduction in the number of PAN cases secondary to HBV infection, falling from approximately one third of all cases to 7%-10% in more recent estimates[[22](#_ENREF_22)] which may be secondary to widespread HBV vaccination of high risk groups and screening of blood products[[23](#_ENREF_23)]. The reduction in PAN cases may also be due to re-classification of a number of other necrotising systemic vasculitides, which were previously grouped together as PAN, including MPA and cryoglobulinaemic vasculitis.

#### Clinical features: Patients typically present with systemic symptoms including malaise, weight loss and fever. The kidneys, skin, joints, muscles, nerves, and gastrointestinal tract are commonly involved (Table 2)[[21](#_ENREF_21)].

#### Classification and diagnosis: There is no specific serological test for PAN and a combined assessment of clinical, angiographic and biopsy findings are usually required for diagnosis. Angiographic evaluation is key to this process with conventional arteriography remaining a “gold standard” despite MRI and CT being increasingly used for this purpose. Typical findings are multiple small aneurysms (< 1 cm) which are most commonly seen in the distribution of the renal and mesenteric arteries, although these are not pathognomic for PAN[[24](#_ENREF_24)]. Biopsy findings include the presence of transmural non-granulomatous necrotising inflammation in medium sized arteries[[25](#_ENREF_25)]. Areas most likely to be biopsied are those easily accessible including, sural nerve, muscles and testes[[26](#_ENREF_26), [27](#_ENREF_27)].

Classification of PAN was published by the American College of rheumatology (ACR) in 1990[[28](#_ENREF_28)]. This classification lists the following typical signs and symptoms of PAN: (1) Livedo reticularis; (2) Testicular pain or tenderness; (3) Myalgia (excluding that of the shoulder hip and girdle) or weakness; (4) Mononeuropathy or polyneuropathy; (5) New onset rise in diastolic blood pressure > 90 mmHg; (6) Elevated levels of serum blood urea nitrogen (> 40 mg/dL or > 14.3 mmol/L) or creatinine (> 1.5 mg/dL or > 132 mmol/L); (7) Evidence of hepatitis B virus infection *via* serum antibody or antigen serology; (8) Characteristic arteriographic abnormalities not resulting from non-inflammatory disease processes; and (9) A biopsy of medium or small sized artery containing polymorphonuclear cells.

According to the ACR criteria, the presence of at least 3 of these features is required for classification of disease as PAN with 82% sensitivity and 87% specificity rate.

#### Treatment and prognosis: Previously, untreated PAN was fatal in weeks to months in approximately 50% of patients. The five year survival rate was as low as 13%. In 1996 the French Vasculitis Study Group (FVSG) analysed data from a prospective study of 346 patients with PAN and eosinophillic granulomatosis with polyangiitis (EGPA) and identified five factors that were associated with poor prognosis. These factors are: (1) Renal Involvement - Proteinuria > 1 g/24 h; (2) Renal Impairment-Serum creatinine > 1.5 mg/dL; (3) Gastrointestinal Involvement-Presence of bleeding, perforation, infarction or pancreatitis; (4) Neurological Involvement; and (5) Cardiac involvement–Presence of cardiomyopathy.

 These factors were adapted into a prognostic “Five Factor Score” (FFS) system. The presence of any one of these five factors is associated with poor prognosis and increased mortality[[29](#_ENREF_29)]. When the FFS is zero, the predicted mortality rate at 5 years is 11.9%. When the FFS is 1, the mortality rate is 25.9%, and when the FFS is 2 or more, the mortality rate is as high as 45.9%

Trials conducted by the FVSG suggest that corticosteroids alone are adequate first line therapy for patients with PAN with a FFS of zero although 40% may require additional immunosuppression[[30](#_ENREF_30)]. Patients with a FFS ≥ 1 should receive intermittent intravenous cyclophosphamide in addition to corticosteroids[[31](#_ENREF_31)]. For cases of HBV associated PAN, antiviral therapy, including vidarabine, lamivudine and interferon alpha 2-b, may be added to corticosteroid therapy, with or without plasma exchange[[32](#_ENREF_32),[33](#_ENREF_33)].

#### Urological manifestations: Urogenital manifestations are reported more commonly in patients with PAN secondary to HBV infection than in patients with primary PAN[[34](#_ENREF_34)]. Autopsy data from patients with PAN confirms testicular involvement in 38%-86% of cases. Of these patients only 18% will manifest any clinical signs and symptoms[[35](#_ENREF_35)]. Testicular involvement may be part of a spectrum of systemic involvement or in rare cases it may be an isolated presentation of the disease. It is not unusual to see unilateral testicular involvement as part of a spectrum of systemic disease. Symptoms of testicular involvement are hugely variable, ranging from completely asymptomatic to severe pain, swelling, erythema and/or a local mass, with one isolated case report of asynchronous bilateral complete testicular necrosis in association with PAN[[36](#_ENREF_36)]. This clinical picture often leads to a misdiagnosis of acute orchitis, torsion or neoplasm. As laboratory data and radiological findings are often non-specific in these cases, histological analysis of biopsy specimens remains the mainstay of diagnosis. Testicular biopsies in PAN commonly reveal transmural necrotising arteritis with focal infarcts and haemorrhagic lesions, vasculitis of testicular and epididymal arteries is commonly noted[[36-45](#_ENREF_36)].

Corticosteroid therapy, with or without cyclophosphamide in refractory cases, has good outcomes for testicular symptoms in PAN. Length of therapy and dosage will vary in each individual case[[37](#_ENREF_37),[38](#_ENREF_38),[46](#_ENREF_46)]. Current consensus is that orchidectomy is the treatment of choice in cases of isolated single-organ testicular PAN. In many of these cases exclusion of a testicular neoplasm is difficult on the basis of clinical findings and the safest option is to remove the testicle. Close follow up and monitoring of these patients is also essential to rule out subsequent development of systemic PAN, although analysis of case reports show that this has rarely been reported[[39](#_ENREF_39)].

There are a number of case reports describing ureteral strictures in polyarteritis nodosa[[47-55](#_ENREF_47)]. The finding of imprints on the ureteral wall or a nodular appearance of the ureter, simulating a string of pearls, on an excretory urogram, are suggested to be pathognomonic for this disorder[[51](#_ENREF_51)]. In the majority of these cases resolution of the stricture was achieved with systemic therapy for PAN but in isolated cases, resection of the stenosed ureteric segment became necessary[[49](#_ENREF_49)].

There is a single case report of a patient with hepatitis B-associated PAN presenting with bilateral hydronephrosis in the absence of an obstructive lesion. It was presumed that vasculitis-related myopathy or neuropathy of the ureter was the most likely cause of this finding. The patient was treated with high-dose steroids, cyclophosphamide, and plasmapheresis with successful resolution of the hydronephrosis and resolution of acute kidney injury[[56](#_ENREF_56)].

Kidneys are commonly affected in PAN. Luminal narrowing of inflamed renal arteries leads to glomerular ischemia but not inflammation or necrosis. Urinalysis in PAN, when abnormal, tends to show shows sub-nephrotic range proteinuria and microscopic hematuria. Red blood cell casts (indicative of a glomerular focus of inflammation) are usually absent. In patients with red blood cell casts, alternative diagnoses should be considered, including anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis or systemic lupus erythematosus.

Aneurysm formation of renal arteries in PAN may lead to life-threatening spontaneous peri-renal haemorrhage (SPH). In a meta-analysis of 165 cases of SPH, PAN was the reported cause in 12% of patients and is the most likely cause in patients with bilateral SPH[[57](#_ENREF_57)]. The typical clinical presentation is of a patient with loin pain and a peri-renal mass, in combination with hypotension and a significant fall in haemoglobin. Rapid recognition of this condition and emergency resuscitation is essential. CT angiogram is the imaging modality of choice and endovascular management, such as percutaneous transcatheter embolisation is used with increased frequency to deal with ruptured visceral artery aneurysms associated with PAN[[58](#_ENREF_58)]. In some cases the haemorrhage resolved with conservative therapy and observation but in other cases surgical evacuation of the haematoma or partial/complete nephrectomy was necessary[[57](#_ENREF_57)].

## KAWASAKI DISEASE

Kawasaki disease (KD) or “Mucocutaneous Lymph Node Syndrome” is an acute medium-vessel vasculitis syndrome of early childhood.

#### Epidemiology and clinical features: KD is one of the commonest vasculitides in early childhood, with the majority of cases occurring in patients less than 5 years of age and a peak in incidence occurring at approximately 30 mo of age. There is significant geographical variation in the incidence of KD with the majority of cases occurring in East Asia[[59](#_ENREF_59)].

Diagnosis of KD is confirmed by the presence of fever for > 5 d and four of the following American Heart Association diagnostic criteria, listed below[[60](#_ENREF_60)]: (1) Bilateral conjunctival injection; (2) Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue; (3) Polymorphous rash; (4) Changes of the extremities: peripheral oedema, peripheral erythema, periungual desquamation; and (5) Cervical adenopathy.

KD is a self-limiting disease, lasting for an average of 10-12 d without treatment. However coronary artery aneurysms develop in 20%-25% of cases with significant morbidity and mortality if untreated[[59](#_ENREF_59)].

#### Urological manifestations: Urogenital involvement in KD is extremely rare, described in two isolated case reports. A six year old boy presented with typical symptoms of KD and it was incidentally noted that he had pain and swelling of his left testicle, in keeping with epidiymo-orchitis. The inflammation settled over the next few weeks with symptomatic treatment only and at six weeks follow up there were no persisting abnormalities. A second case report describes a seven year old boy with a one week history of cough, neck pain and swelling, fever and vague abdominal pain. He was diagnosed with KD and subsequently developed left sided pelvi-ureteric junction obstruction. Initially he was treated conservatively but due to worsening hydronephrosis, a nephrostomy was inserted and immunoglobulin therapy initiated. Subsequent scans confirmed an inflammatory stricture at the level of the left pelvi-ureteric junction. The stricture was surgically excised and a left sided dismembered pyeloplasty was performed. The patient subsequently recovered normal function of the left kidney and pelvi-calyceal system. The excised section of ureter showed findings in keeping with vasculitis[[61](#_ENREF_61),[62](#_ENREF_62)].

#### Management: As KD is a self-limiting illness, the aim of therapy is to limit cardiovascular morbidity and mortality. Patients are treated with aspirin and intravenous immunoglobulin, as the addition of intravenous immunoglobulin has been shown to reduce the incidence of coronary artery complications compared with aspirin alone[[63](#_ENREF_63)].

# SMALL VESSEL VASCULITIS

## *ANCA AAV*

AAV are multisystem necrotising small vessel vasculitides of unknown cause. Included in this group are: (1) Granulomatosis with polyangiitis (GPA) (formerly Wegener’s granulomatosis); (2) Microscopic polyangiitis (MPA); and (3) Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome).

The AAV are a group of rare disorders, with varying estimates of incidence and prevalence worldwide. In the United Kingdom reported incidence is estimated at 10.3/million population/year (GPA), 8.9/million (MPA) and 3.7/million (EGPA)[[17](#_ENREF_17)]. There is a peak in incidence in the 7th and 8th decades of life[[64](#_ENREF_64)].

#### Clinical features and diagnosis: Constitutional symptoms such as fever, malaise, anorexia, myalgia and weight loss are common in AAV.

#### *Granulomatosis with polyangiitis*

In GPA, necrotising granulomatous inflammation most commonly affects the upper and lower respiratory tract and kidneys. Upper respiratory tract symptoms include rhinorrhoea, epistaxis, sinusitis, otitis media, collapse of the nasal bridge, and tracheal stenosis. Lung involvement in GPA usually presents with cough, haemoptysis, and dyspnoea and can progress to life-threatening pulmonary haemorrhage. Rapidly progressive crescentic glomerulonephritis is also common. GPA may also affect the eyes; the bowel, causing ischemia and haemorrhage; the heart, causing myocardial ischemia, and the peripheral nervous system, causing mononeuritis multiplex[[65](#_ENREF_65),[66](#_ENREF_66)].

#### *MPA*

MPA is clinically very similar to GPA, except there is no granuloma formation and upper respiratory tract involvement is rare. Renal involvement is very common, and pulmonary haemorrhage can also occur[[66](#_ENREF_66)].

**EGPA**

EGPA, is characterized by eosinophilia, asthma, and necrotizing vasculitis. Vasculitis can affect the skin, peripheral nerves, muscles, and the intestine. Renal involvement is usually mild, and severe renal failure is uncommon[[67](#_ENREF_67)].

**Diagnostic tests**

The diagnosis of ANCA-associated vasculitis is made using a combination of clinical findings, biopsies from relevant involved organs (typically kidney, nasal mucosa, or occasionally lung) and the presence of ANCA autoantibodies. ANCA autoantibodies may be directed against the neutrophil enzymes proteinase-3 (PR3) and/or myeloperoxidase (MPO). These specific ANCAs can be detected by enzyme-linked-immunosorbent assays (ELISA). Initial screening for detection of ANCA antibodies is by indirect immunofluorescence (IIF), prior to antigen specific ELISAs. ANCA detected by IIF are described as having a cytoplasmic (cANCA) or perinuclear (pANCA) pattern. cANCA found by IIF usually corresponds to anti-PR3 on ELISA and pANCA to anti-MPO. cANCA is seen in 81% of GPA patients and less commonly in MPA and EGPA. pANCA are detected in 65% of patients with MPA and less commonly in GPA and EGPA. In patients with clinical symptoms suggestive of these diseases, a combination of cANCA and positive PR3 ELISA has a positive predictive value (PPV) for GPA of nearly 100% but a sensitivity of only 69%. pANCA and MPO positive ELISA has a PPV of 47.5% for MPA and a specificity of 99.5%[[68](#_ENREF_68)].

#### Treatment and prognosis: Although previously almost universally fatal the current five-year survival is approximately 80%. Early morbidity and mortality are mainly due to side effects of immunosuppressive therapy[[69](#_ENREF_69)].

Treatment consists of two phases. Remission induction (3-6 mo) followed by maintenance of remission (at least 18 mo) to prevent disease relapse. Corticosteroids and cyclophosphamide are most commonly used to induce remission although there may be a role for methotrexate in more limited disease and rituximab in refractory cases and patients with a contraindication to cyclophosphamide. In order to minimise cyclophosphamide toxicity, patients are usually changed to azathioprine or a suitable alternative for maintenance therapy[[70-72](#_ENREF_70)].

#### Urological manifestations: Renal involvement is common in GPA and MPA. In studies from the National Institute of Health in the United States, glomerulonephritis (GN) was present in 18% of patients at the time of presentation and subsequently developed in 77% to 85% of patients, usually within the first two years of disease onset. Patients with active GN and AKI will have haematuria and glomerular red cell casts. Cases of intermittent asymptomatic haematuria in association with normal renal function have also been reported.

Lower urogenital tract involvement in AAV is not commonly reported. Of the reported cases, the majority are in association with GPA.

Approximately 2.3%-7.4% of GPA patients will suffer from urogenital manifestations of the disease. The prostate is the most commonly involved organ but the ureters, testes, epididymis, seminal vesicles and penis may also be affected.

Prostatis secondary to GPA may present with dysuria, haematuria or bladder outflow tract obstruction and urinary retention. A combination of histopathological and serological tests are usually necessary to confirm the diagnosis. Resolution of symptoms is successfully achieved in most patients with medical therapy alone[[65](#_ENREF_65),[73-87](#_ENREF_73)].

In a study of 72 male patients with testicular vasculitis, GPA was the second most common diagnosis, after PAN. Approximately 17% of all cases of isolated testicular vasculitis were due to GPA. As with other forms of testicular vasculitis, patients may present with testicular pain, erythema, swelling or a localised mass. Ultrasound imaging may demonstrate multiple hypo-echoic areas and impaired blood flow. Diagnosis is usually confirmed with serological testing for ANCA autoantibodies and testicular biopsy, demonstrating granulomatous necrotising inflammation. Therapy with corticosteroids and immunosuppressants is reported to result in rapid resolution of symptoms[[88-94](#_ENREF_88)].

Ureteric stenosis has also been reported in patients with GPA. Ureteric stents may be required in the short-term to relieve acute obstructive uropathy. Systemic therapy with immunosuppressants is usually successful in treating the inflammatory ureteric lesions but surgical intervention may become necessary[[78](#_ENREF_78),[95-98](#_ENREF_95)].

There are a few case reports describing aggressive penile ulceration, which may become necrotic, in association with GPA. It is a rare, but important differential diagnosis, for penile lesions in the elderly population[[78](#_ENREF_78),[99-104](#_ENREF_99)]. There are also a few case reports describing aggressive necrotising urethritis in both male and female elderly patients. This form of destructive urethritis may mimic invasive urethral carcinoma, but may respond well to immunosuppression[[102](#_ENREF_102),[105](#_ENREF_105),[106](#_ENREF_106)].

Rarely patients with GPA present with large granulomas of the kidney and bladder or “pseudotumours”. Radiologically these lesions mimic malignant tumours but immunosuppressive therapy usually results in a rapid reduction in the size of these masses[[78](#_ENREF_78),[93](#_ENREF_93),[107](#_ENREF_107),[108](#_ENREF_108)].

There are two isolated case reports of prostatic involvement with MPA. In both cases 79 years old males who presented with fever, malaise, weight loss and a cough. One had interstitial pneumonitis and the other a small mass in the left lower lobe of the lung. In both urinalysis revealed non-visible haematuria and serum prostate specific antigen (PSA) was elevated. In the first prostate biopsy demonstrated fibrinoid degeneration with vasculitic changes involving the arterioles. In the second prostate biopsy revealed changes consistent with vasculitis. Both had detectable serum MPO-ANCA. Both patients responded well to corticosteroids and cyclophosphamide[[109](#_ENREF_109),[110](#_ENREF_110)].

Prostatic involvement is also reported in EGPA. In one a 74 years old male, who had previously been treated for asthma, underwent transurethral resection of the prostate. Post-operatively he developed pyrexia and eosinophilia. The biopsy specimens showed eosinophillic prostatitis in keeping with EGPA. The patient’s symptoms responded to oral prednisolone[[111](#_ENREF_111)].

Ureteric obstruction secondary to calcification and stenosis has been reported in a 19 years old male with multiple bowel perforations due to EGPA. Initially nephrostomies were inserted and subsequent ureteroscopy revealed multiple ureteral stones and dystrophic calcification within the ureteric walls. The obstruction was managed with repeated ureteroscopy and ureteric stent insertion with preservation of renal function[[112](#_ENREF_112)].

A 33 years old male with known EGPA presented ulceration of the mid-penile urethra. Biopsy showed chronic inflammation with infiltration of eosinophils as well as granulomas, giant cells and histiocytes and a thick walled blood vessel. This was occluded and infiltrated with inflammatory cells indicating active vasculitis. The patient responded well to intermittent intravenous cyclophosphamide with corticosteroids [[113](#_ENREF_113)].

## [HENOCH–SCHÖNLEIN](https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CC4QFjAA&url=http%3A%2F%2Fen.wikipedia.org%2Fwiki%2FHenoch%25E2%2580%2593Sch%25C3%25B6nlein_purpura&ei=Ax8hU_H3CYWk0QWioYHYCg&usg=AFQjCNExZ0OMrJ74_0R8uuiVq7rWjdDx_Q&sig2=fKSXeT5k8XFOWzd6fht35w&bvm=bv.62922401,d.d2k)PURPURA

Henoch Schonlein Purpura (HSP), also known as IgA vasculitis, anaphylactoid purpura and purpura rheumatica, is a systemic inflammatory disorder of small vessels characterised by IgA immune complex deposition and leukocytoclastic vasculitis. Skin, joints, bowel and kidneys are the most commonly affected organs.

#### Epidemiology

HSP is the commonest form of systemic vasculitis in childhood. Seventy five percent of all HSP cases involve children aged 2-11. The incidence of HSP in children < 17 has been variously reported between 10-20 per 100000 population per year, with a peak in incidence between 5-7 years of age[[114-116](#_ENREF_114)]. Exact incidence of adult HSP is not known but it is relatively rare and known to follow a more severe course, with a higher incidence of renal impairment and end-stage renal disease[[117](#_ENREF_117),118].

#### Clinical features and classification

Clinical Features of HSP typically include prodromal symptoms including headache, fever and anorexia. The hallmark of disease is the presence of a palpable purpuric rash in the absence of thrombocytopaenia or coagulopathy. This rash is typically found on the lower limbs and buttocks and less commonly on the upper limbs. This rash is present in almost all cases of HSP and is the presenting feature in over half of all patients[[119](#_ENREF_119)]. The rash may be accompanied by arthralgia, especially of the knees and ankles, in up to 80% of cases [[119](#_ENREF_119),[120](#_ENREF_120)].

Gastrointestinal manifestations of the disease are common, including colicky abdominal pain and vomiting, diarrhoea, GI bleeding, intussusception, infarction, strictures, perforation, fistula formation, gall bladder hydrops and acute appendicitis[[121](#_ENREF_121)].

Renal disease occurs in approximately half of all patients. Haematuria and significant proteinuria are common and renal biopsy may demonstrate a diffuse or focal segmental mesangioproliferative pattern of glomerulonephritis. HSP nephritis may lead to progressive chronic kidney disease. Approximately 1%-5% of patients will develop end stage renal failure[[120](#_ENREF_120),[122](#_ENREF_122)].

#### Urological manifestations of HSP

A wide variety of urogenital manifestations of HSP have been reported in the literature. This includes: (1) Haematuria (visible and non-visible); (2) Unilateral or bilateral ureteritis with associated stenosis and hydronephrosis[[123](#_ENREF_123)]; (3) Bladder wall hematoma[[124](#_ENREF_124)]; (4) Haemorrhagic Cystitis[[125](#_ENREF_125)]; (5) Painful swelling of the scrotum and penis[[126](#_ENREF_126),[127](#_ENREF_127)]; (6) Epididymo-orchitis or orchitis[[128-133](#_ENREF_128)]; (7) Priapism[[134](#_ENREF_134)]; and (8) Thrombosis of the spermatic veins[[135](#_ENREF_135)].

Many of the above complications are rare and have only been described in isolated case reports.

Haematuria is a common feature of the disease. A prospective study of 250 patients noted that 85% of patients had non-visible haematuria at the time of presentation and a further 10% had visible haematuria[[118](#_ENREF_118)].

Scrotal and testicular involvement are the commonest lower urogenital tract manifestations of HSP and are reported in approximately 13% of cases. Clinical findings include pain, tenderness, and swelling of the involved testicle and/or scrotum. Occasionally, testicular symptoms may precede the development of a rash and may be the first presentation of disease[[136](#_ENREF_136)]. There is only one confirmed case of testicular torsion in HSP[[137](#_ENREF_137)].

#### Diagnosis

Diagnosis of HSP in childhood is primarily clinical. In adults a skin or renal biopsy may be performed. Serum IgA is raised in 50% of cases and autoantibodies that are present in other forms of vasculitis are usually absent[[122](#_ENREF_122)]. Radiology, especially ultrasound evaluation, may be useful for identifying GI complications of disease including bowel wall thickening, intussusception and haematomas[[138](#_ENREF_138)]. Similarly ultrasound examination of the scrotum and testicle is useful to assess for suspected epididymo-orchitis. Additionally Doppler flow studies and technetium Tc99m radionuclide scanning can aid in ruling out testicular torsion. In cases of torsion, these studies demonstrate decreased blood flow to the testicle, in contrast to the normal or increased flow seen in HSP[[136](#_ENREF_136)].

#### Treatment and outcomes

HSP is typically an acute and self-limiting illness, usually lasting less than four weeks. Short-term morbidity is dependent on the presence and severity of gastrointestinal involvement and long-term prognosis is dependent on the extent and chronicity of renal involvement[[121](#_ENREF_121)]. There is no form of therapy that has been found to shorten the duration of HSP and the focus of therapy therefore remains supportive, ensuring adequate hydration and analgaesia. There is no convincing evidence at present to suggest that corticosteroid therapy will reduce the risk of developing serious renal or gastrointestinal complications of the disease or that it will significantly shorten the duration of illness. Use of corticosteroids may however be considered in cases of persistent nephritic syndrome, with significant crescent formation or alternatively in patients with severe abdominal pain, GI haemorrhage, significant soft tissue or scrotal oedema or neurological involvement[[139-142](#_ENREF_139)]. In severe and resistant cases of HSP, additional immunosuppressive agents and plasmapharesis may be considered[[143-145](#_ENREF_143)].

Testicular and epididymal disease in HSP is usually self-limiting and resolves in a matter of days with conservative management. Corticosteroid therapy may be indicated in patients with severe testicular pain and swelling which is slow to improve or in cases accompanied by severe systemic symptoms[[146](#_ENREF_146)]. In the isolated case report of a patient with spermatic vein thrombosis, treatment with low molecular weight heparin was required[[135](#_ENREF_135)]. Anecdotal evidence in those patients presenting with ureteritis and associated stenotic lesions suggest that some cases are self-limiting and in other cases complete resolution was noted with a course of corticosteroids. In a few cases though, residual stenotic lesions and subsequent urinary tract obstruction necessitated surgical intervention[[136](#_ENREF_136)].

## ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

Anti-glomerular basement membrane (Anti-GBM) disease (Goodpasture’s Syndrome) is a rare condition with an incidence of 1-2/million population/year. In this condition antibodies are generated against the alpha-3 chain of type IV collagen, found in the glomerular basement membrane. Haematuria in association with rapidly progressive glomerulonephritis and pulmonary haemorrhage are common features of this condition. No other urological manifestations of anti-GBM disease have been reported in the literature [[147](#_ENREF_147)].

## *Cryoglobulinaemic vasculitis*

Cryoglobulins are immunoglobulins that precipitate in the cold and dissolve on rewarming. There are three main types of cryoglobulins: (1) Type I - a monoclonal antibody that is most commonly associated with lymphoma, Waldenström’s macroglobulinemia, and multiple myeloma. Because type I cryoglobulins do not easily activate complement, patients with type I are usually asymptomatic until the level of cryoglobulinemia is sufficiently high to cause hyperviscosity syndrome; (2) Type II - A mixture of both monoclonal and polyclonal cryoglobulins commonly associated with hepatitis C virus (HCV); and (3) Type III- Rheumatoid factor is polyclonal in type III and is usually associated with rheumatic disease and chronic infections especially HCV.

## Type II and III cryoglobulinemia frequently presents as vasculitis, most commonly with recurrent lower extremity purpura, glomerulonephritis, and peripheral neuropathy. Glomerulonephritis with non-visible haematuria appears to be the only reported urological manifestation of Cryoglobulinaemic vasculitis (CV)[[148](#_ENREF_148),[149](#_ENREF_149)].

## Hypocomplementaemic urticarial Vasculitis (anti-C1q vasculitis)

Hypocomplementaemic urticarial Vasculitis (HUV) is a rare form of vasculitis characterised by urticarial lesions, biopsy evidence of small vessel vasculitis and hypocomplementaemia. There may also be other systemic findings including arthralgia or arthritis, mild glomerulonephritis, uveitis or episcleritis and recurrent abdominal pain. It is estimated that approximately 50% of all HUV patients will have renal involvement. Although this is usually mild, haematuria and proteinuria are commonly noted[[150](#_ENREF_150)].

# VARIABLE VESSEL VASCULITIS

## *Behçets disease*

Behçets disease (BD) is a variable vessel vasculitis of unknown aetiology. BD is a multi-system chronic relapsing and remitting condition characterised by a triad of[[151](#_ENREF_151)]: (1) Recurrent oral apthous ulcers; (2) Genital ulcers; and (3) Uveitis.

#### Epidemiology: There is a peak incidence in the 3-5th decades of life. The exact aetiology and pathogenesis of BD remains unknown, although carriers of HLA B5/ HLA B51 are at increased risk of developing BD[[152](#_ENREF_152)].

#### Clinical features and classification: Clinical manifestations of BD include recurrent aphthous ulcers of the oral mucosa, skin lesions, genital ulceration, ocular inflammatory lesions, arthritis, epididymitis, intestinal ulcers, vascular lesions, neuropsychiatric symptoms and a positive pathergy test (the forearm is pricked with a small, sterile needle - occurrence of a small red bump or pustule at the site of needle insertion constitutes a positive test). There is no one diagnostic test for BD and therefore diagnosis is usually clinical. A number of classifications have been published to aid in diagnosis including the ‘International Study Group Criteria’, published in 1990, which is one of the most widely used and accepted (Table 3)[[153](#_ENREF_153)].

#### Urological manifestations: A number of Urological manifestations of BD have been reported in the literature. The most common of these is genital ulceration. Genital ulceration in males is most commonly noted in the scrotal area but lesions may also be found on the shaft of the penis or in the peri-anal region. In women the labia are commonly affected, although vaginal and cervical ulcers can also occur[[154](#_ENREF_154)]. Genital lesions are usually deeper and last longer than oral ulcers, they are also much more likely to cause significant scarring after they heal. A prospective study of 100 BD patients in Turkey (70 males and 30 females) reported genital ulceration in 89% of those enrolled[[155](#_ENREF_155)]. In a separate survey of 2031 patients in Japan, genital lesions were present in 76% of the males and 83.8% of the females[[156](#_ENREF_156)].

In a prospective study from Turkey of 100 BD patients, 6% of males had experienced episodes of epididymitis and a further 3% of males were found to have had episodes of sterile urethritis with discharge[[155](#_ENREF_155)].

 Bladder involvement is uncommon in BD and is mainly limited to vasculitis of bladder wall and neuropathic bladder symptoms[[157](#_ENREF_157)]. Direct involvement of blood vessels in the bladder wall may result in localised ischemia, which can progress, to mucosal necrosis and bladder ulceration, nodules or recurrent cystitis. This process is likely to be responsible for the haematuria, storage symptoms and urge incontinence that patients with bladder involvement in BD report[[157](#_ENREF_157)]. There is also an isolated report of vesico-vaginal fistula as a result of posterior extension of the necrotic process in BD[[158](#_ENREF_158)].

Approximately 5%-10% of BD patients have neurological disease involvement and of these patients approximately 5% report voiding symptoms[[159](#_ENREF_159)]. Bladder symptoms secondary to neurological involvement in BD may vary considerably depending on the level of brain and spinal cord involvement. Detrusor areflexia, hyperreflexia and detrusor sphincter dysynergia have all been reported[[160](#_ENREF_160)]. In severe cases there may be complete urinary retention, incontinence and hydronephrosis, necessitating surgical intervention. Augmentation ileocystoplasty in these patients has been shown to have good clinical outcomes[[157](#_ENREF_157)]. Despite pathergy being a well-known phenomena in BD patients, cystoscopy, bladder biopsy, and even ileocystoplasty or radical cystoprostatectomy have been performed in this group without complication[[157](#_ENREF_157)].

#### Management and prognosis: Management of patients with BD will depend largely on the specific organs affected by disease and the severity of organ involvement. In 2008 the European League Against Rheumatism (EULAR) published consensus guidelines on management of BD.

For mild oral and genital ulcerations, the current recommendation is for localised application of topical steroids or sucralfate solution, as a first-line therapy. Colchicine has been widely used in more severe cases of BD but the evidence suggests that additional benefit may only be gained in females with genital ulcers and patients with erythema nodosum[[161](#_ENREF_161),[162](#_ENREF_162)]. For severe mucocutaneous lesions, systemic corticosteroids, azathioprine, interferon-alfa and TNF-alpha antagonists may be considered[[163](#_ENREF_163)].

The management of bladder involvement in BD needs to be tailored to each individual bearing in mind their specific symptoms and findings on cystoscopy and urodynamic testing. This may include intermittent self-catheterisation for patients suffering from urinary retention and anti-cholinergics for patients suffering from urge incontinence or surgical intervention in more severe cases[[164](#_ENREF_164)].

## *Cogans syndrome*

Cogans syndrome (CS) is a rare variable vessel vasculitis of young adults characterised by interstitial keratitis, vestibuloauditory dysfunction and other features including aortitis. There are no reported urogenital manifestations of CS[[165](#_ENREF_165)].

## TREATMENT RELATED UROLOGICAL ADVERSE EFFECTS

An important consideration for urologists is the use of potent immunosuppressive therapies for vasculitis and potential urological complications that may arise as a result of this.

The most well-known urological complication of immunosuppressive therapy is the association of cyclophosphamide with haemorrhagic cystitis and bladder cancer. The active metabolite of cyclophosphamide, acrolein, is excreted in urine and is toxic to urothelium. In a study of 145 GPA patients treated with daily oral cyclophosphamide in the United States, 73 patients (50%) experienced episodes of non-glomerular haematuria +/- dysuria. Sixty of these patients went on to have cystoscopic examination and cyclophosphamide-induced bladder injury was confirmed in 42 cases[[166](#_ENREF_166)].

In the same study seven patients treated with oral cyclophosphamide for GPA subsequently developed transitional cell carcinoma of the bladder. All seven of these patients had previous episodes of non-glomerular haematuria and six of the patients had received a total cumulative cyclophosphamide dose exceeding 100 g, with the cumulative duration of cyclophosphamide therapy exceeding 2.7 years. On the basis of these findings the incidence of bladder cancer after the first exposure to cyclophosphamide was estimated at 5% at 10 years and 16% at 15 years. A series of 12 case reports of bladder cancer in association with cyclophosphamide, found that the disease phenotype in these patients was very aggressive, with all tumours grade 3 or 4 at the time of presentation[[167](#_ENREF_167)].

Risk of developing bladder cancer appears to be related to cumulative dose and/or length of therapy received[[168](#_ENREF_168)] Risk of cyclophosphamide associated bladder toxicity can be reduced *via* a number of measures: (1) Co-administration of sodium 2-mercaptoethanesulfonate (Mesna) inactivates acrolein in urine, protecting the bladder from its toxic effects. Some controversy exists with regards to the effectiveness of mesna therapy and at present ‘The American Society of Clinical Oncology’ does not recommend the use of mesna in patients receiving cyclophosphamide except when high doses are used (*e.g.*, 50 mg/kg or 2 g/m2). The EULAR however continue to recommend its use[[169](#_ENREF_169),[170](#_ENREF_170)]; (2) Good hydration; (3) Treatment in the early morning to avoid overnight bladder accumulation of acrolein; and (4) Intermittent pulsed intravenous cyclophosphamide therapy rather than daily oral dosing-This has been shown to decrease the total cyclophosphamide dose received by up to half[[171](#_ENREF_171)]. Consequently intermittent pulsed intravenous cyclophosphamide use is associated with a decreased incidence of drug-induced cystitis[[172](#_ENREF_172)].

A bladder cancer surveillance program is also suggested for patients that have received cyclophosphamide therapy. It is recommended that urinalysis is obtained from these patients on a six monthly basis to screen for haematuria. This should be repeated within one week if haematuria is detected. Patients with confirmed non-glomerular haematuria should then undergo cystoscopy to exclude bladder cancer. For patients with cystoscopic evidence of bladder damage, the procedure should be repeated every 6 to 12 mo[[166](#_ENREF_166)].

Cyclophosphamide is also teratogenic and causes gonadal toxicity. In females this may lead to irregularity of the menstrual cycle and reduced ovarian function. In males, alkylating drug therapy may reduce sperm count and testicular endocrine dysfunction[[173](#_ENREF_173)]. A study of men with BD showed significant infertility after cyclophosphamide therapy with oligospermia or azoospermia occurring in 13 of 17 men treated with cyclophosphamide but in none of the 10 men treated with colchicine alone or in the four control patients who did not receive any treatment[[174](#_ENREF_174)]. A separate study looking at the effect of colchicine alone on sperm production, in 62 male patients with BD, found evidence of oligonecrospermia in 37% of patients and azoospermia in 3% of patients[[175](#_ENREF_175)].

Patients may have the option of cryopreservation of sperm and ova prior to commencing cyclophosphamide therapy. The induction of gonadal quiescence during therapy with alkylating agents may minimize the risk of testicular and ovarian failure. Studies looking at the use of a gonadotropin-releasing hormone agonist (GnRH-a) such as [leuprolide](http://www.uptodate.com/contents/leuprolide-drug-information?source=see_link) to achieve gonadal quiescence in women are ongoing and results remain inconclusive[[176](#_ENREF_176),[177](#_ENREF_177)]. In male patients, studies are looking into adjuvant testosterone therapy to induce gonadal quiescence. Again the results remain inconclusive[[178](#_ENREF_178)].

In both male and female patients where preservation of fertility is a consideration the patient's management should be discussed early on with local fertility services and consideration given to minimising or avoiding the use of alkylating agents.

**CONCLUSION**

The PSV are a heterogeneous group of rare disorders with many varying features and presentations, which may affect urological organs. PAN, HSP, BD and GPA are the PSV that have the most commonly reported urological manifestations. Testes, prostate and ureters are the most commonly involved urological organs. Identification of vasculitic disease in the urogenital tract is important as not only may this be the first presentation of systemic disease but also management with immunosuppressive therapy may allow rapid resolution of symptoms and avoid the need for invasive surgical management.

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Table 1 Summary of the urogenital manifestations of the primary systemic vasculitides, defined according to the Chapel Hill Consensus Criteria

|  |  |
| --- | --- |
| Primary sytemic vasculitides | Urogenital manifestations |
| Large vessel | **Takayasu arteritis** **Giant cell arteritis** | Obstructive uropathy secondary to retroperitoneal fibrosisEpididymo-orchitis |
| Medium vessel | **Polyarteritis Nodosa****Kawasaki’s disease**  | Orchitis, ureteric stricture, haematuria, glomerulonephritis, spontaneous peri-renal haemorrhageOrchitis, ureteric stricture |
| Small vessel | **Antineutrophil cytoplasmic antibody associated vasculitis** **Microscopic polyangiitis****Granulomatosis with polyangiitis (Wegener’s)****Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)****Immune complex small vessel vasculitis****Anti-glomerular basement membrane disease****Cryoglobulinaemic vasculitis****IgA vasculitis (Henoch-Schonlein)****Hypocomplementaemic urticarial Vasculitis (anti-C1q vasculitis)** | Glomerulonephritis, prostatitisGlomerulonephritis, prostatitis, orchitis, ureteric stenosis, penile ulceration, necrotizing urethritis, large renal and bladder granulomas (‘psuedotumors’)Glomerulonephritis, prostatitis, ureteric stricture, urethral ulcerationGlomerulonephritis, haematuriaGlomerulonephritis, haematuriaGlomerulonephritis, haematuria, epididymo-orchitis, ureteric strictures, bladder wall hematoma, haemorrhagic cystitis, penile and scrotal pain and swelling, priapism, spermatic vein thrombosisGlomerulonephritis, haematuria |
| Variable vessel | **Behçets disease** **Cogan’s syndrome** | Genital ulceration, epididymitis, sterile urethritis, bladder wall ulceration, cystitis, vesico-vaginal fistula, neuropathic bladdernil |

Table 2 Main clinical manifestations of patients with polyarteritis nodosa[7,14]

|  |  |  |
| --- | --- | --- |
| Manifestation | Specific problems | Frequency  |
| Systemic symptoms | Fever, malaise, weight loss, myalgias arthralgias | 80% |
| Neuropathy | Mononeuritis multiplex, polyneuropathy | 75% |
| Arthralgias and/or myalgias | Articular and/or diffuse extremity pain | 60% |
| Cutaneous | Livedo reticularis, purpura, ulcers | 50% |
| Renal disease | Elevated creatinine, haematuria, proteinuria | 50% |
| Gastrointestinal symptoms | Abdominal pain, nausea/vomiting, diarrhoea rectal bleeding, ulceration, peritonitis | 40% |
| Hypertension | New onset | 35% |
| Central nervous system disease | Stroke, confusion | 20% |
| Orchitis | Testicular pain, swelling | 20% |
| Cardiac involvement | Cardiomyopathy, pericarditis, palpitations, myocardial infarction | 10% |
| Peripheral vascular disease | Claudication, ischaemia, necrosis | 10% |
| Ophthalmological | Exudates, vasculitis | 10% |

Table 3 International Study Group Criteria for Behçets disease[[153](#_ENREF_153)]

|  |  |  |
| --- | --- | --- |
|  | *Required criteria* |  |
|  | Recurrent oral ulceration (obligatory) | Minor aphthous, major aphthous, or herpetiform ulceration (observed by physician or patient); recurring at least 3 times in a 12 mo period |
|  | ***Plus 2 of*** |  |
|  | Recurrent genital ulceration | Aphthous ulceration or scarring (observed by physician or patient)  |
|  | Eye lesions | Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist |
|  | Skin lesions | Erythema nodosum (observed by physician or patient), pseudofolliculitis, or papulopustular lesions; or acneiform nodules (observed by physician) in post-adolescent patients not on corticosteroid treatment |
|  | Positive Pathergy test | Read by physician at 24-48 h |