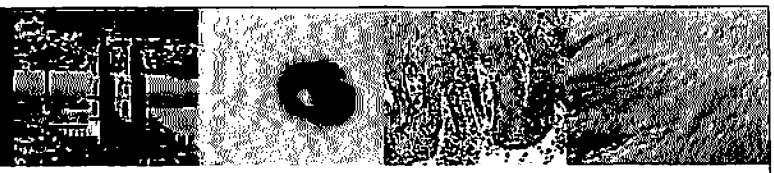

# Small vessel vasculitis – Handout

## DIAGNOSIS AND THERAPY

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## Primary Vasculitides

| | |
|---|---|
| Large vessel vasculitis (LVV) | Giant cell arteritis (GCA) |
| | Takayasu arteritis (TAK) |
| Medium-sized vessel vasculitis (MVV) | Polyarteritis nodosa (PAN) |
| | Kawasaki disease (KD) |
| Small vessel vasculitis (SVV) | **ANCA-associated vasculitis:**<br>- Granulomatosis with polyangiitis (GPA) = formerly Wegener's syndrome<br>- Eospinophilic granulomatosis with polyangiitis (EGPA) = formerly Churg-Strauss syndrome<br>- Microscopic polyangiitis (MPA)<br><br>**Immune complex vasculitis:**<br>- Anti–glomerular basement membrane (anti-GBM) disease<br>- Cryoglobulinemic vasculitis (CV)<br>- IgA vasculitis (IgAV) = Henoch-Schönlein purpura (HSP)<br>- Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis) |
| Variable vessel vasculitis (VVV) | - Behçet's disease (BD)<br>- Cogan's syndrome (CS) |
| Single-organ vasculitis (SOV) | - Cutaneous leukocytoclastic angiitis<br>- Cutaneous arteritis<br>- Primary central nervous system vasculitis<br>- Isolated aortitis<br>- Others |



Jennette JC et al. 2012. Arthritis Rheum 2013;65:1-11.

# Secondary Vasculitides

| | |
|---|---|
| Vasculitis associated with systemic disease | - Lupus vasculitis<br>- Rheumatoid vasculitis<br>- Sarcoid vasculitis<br>- Others |
| Vasculitis associated with probable etiology | - Hepatitis C virus–associated cryoglobulinemic vasculitis<br>- Hepatitis B virus–associated vasculitis<br>- Syphilis-associated aortitis<br>- Drug-associated immune complex vasculitis<br>- Drug-associated ANCA-associated vasculitis<br>- Cancer-associated vasculitis<br>- Others |

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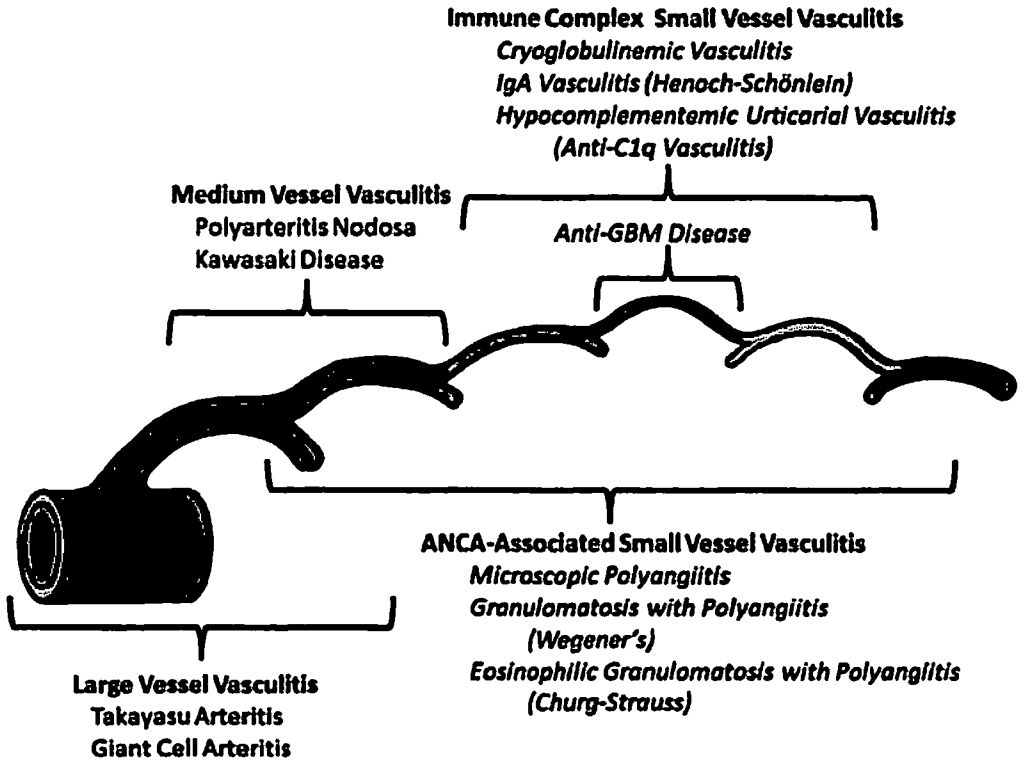
Jennette JC et al. 2012. Arthritis Rheum 2013;65:1-11.

# Classification according to vessel size (Chapel-Hill)

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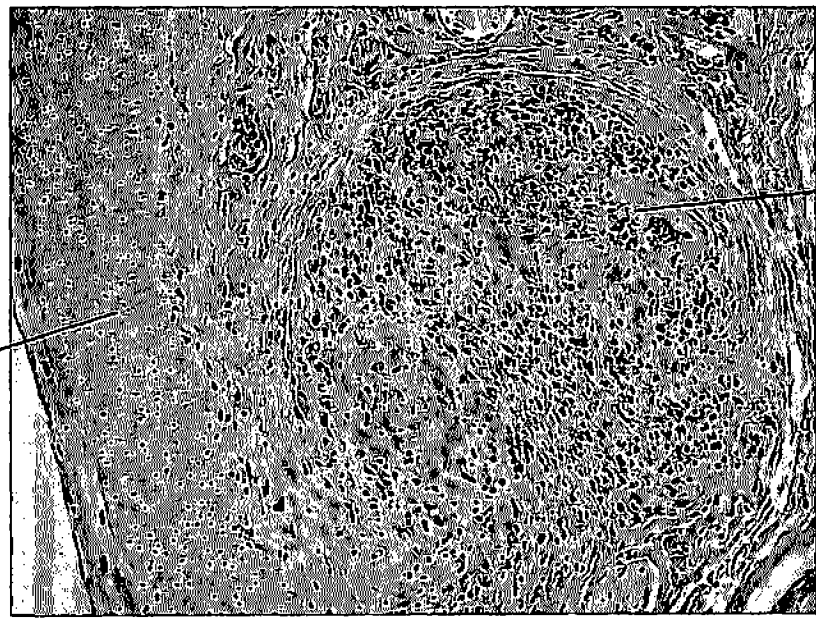
Jennette JC, et al. Clin Exp Nephrol 2013; 17: 603–606

# Always exclude small vessel (ANCA-associated) vasculitis

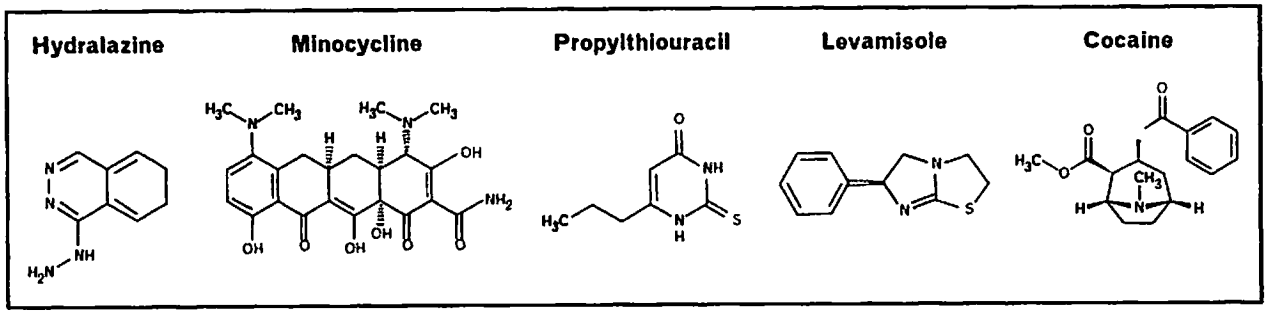
Temporal artery biopsy in a 54 year-old women with suspected giant cell arteriitis




courtesy of Pr Carlo Chizzolini, Immunology & Allergology - Geneva University Hospital

# Drug-induced ANCA-associated vasculitis

Several drugs are known to induce ANCA




Some are also implicated in drug-induced lupus

Possible pathomechanism:
Antigen hyperexpression through inhibition of DNA methylation
Probable HLA-association (B27 for levamisole-induced agranulocytosis)

## The cocaine-levamisole epidemic

**Levamisole**

Anthelminthic and immunomodulatory properties

Used in the 70ies and 80ies

Frequent adverse events: agranulocytosis, induced auto-immunity

Declared improper for human use (extensive veterinary use)


Since 2003 added to cocaine as adulterant

Additional psychotropic properties

Currently found in up to 80% of adulterated cocaine in US[1] and Europe[2]

2009: first cases of levamisole-induced vasculitis in cocaine users

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1. Buchanan et al. JAMA. 2011
2. Eiden et al. Clin Toxicol. 2015

## Typical features of levamisole-induced vasculitis

Clinical:

- general symptoms: fever, arthralgia, myalgia
- painful, purpuric skin lesions with necrosis
- erosive upper airway lesions
- pauci-immune glomerulonephritis (rare)

Retiform purpura

Lab:

- leukopenia (neutropenia)
- high-titer p-ANCA, directed to MPO, PR3 and human neutrophil elastase
- also ANA, anti-dsDNA and antiphospholipid antibodies

Histology:

- mixed pattern of vasculitis and thrombosis

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Pendergraft WF, et al. Curr Opin Rheumatol 2014, 26:42–49

## When to suspect systemic vasculitis

Look for vasculitis in case of involvement of one or more organs:

- skin: palpable purpura, erythema nodosum
- pulmonary: nodules and/or infiltrates, haemoptysia
- neurologic: peripheral neuropathy of acute or subacute onset
- GIT: persistent abdominal pain, intestinal blood loss
- renal: nephritic urine sediment, rapid progressive renal failure
- eye: episcleritis, scleritis, (uveitis)
- ENT: chronic rhinosinusitis, discharge, crusting
- CNS: new headache

+

- elevated acute phase reactants

and/or

- general symptoms: fever, weight loss, myalgia, arthralgia

## EGPA (Churg-Strauss) – Natural history

| | |
|---|---|
| **Prodromal phase** (age 30-40 years) | Inflammation of the airways<br>second and third decades of life<br>eosinophilic rhinosinusitis / asthma (atopy, Widal) |
| **Eosinophilic phase** | peripheral blood eosinophilia and eosinophilic infiltration of multiple organs (lung – 40%, GIT) |
| **Vasculitic phase** (age 40-50 years) | life-threatening systemic vasculitis<br>mediumand small vessels, major eosinophilia<br>vascular and extravascular granulomatosis<br>often preceded by non-specific constitutional signs (fever, weight loss, malaise, asthenia) |
| **CAVE:** | only 40% of patients have ANCA |

## EGPA – ACR classification criteria and main DD

**≥ 4/6 criteria: sensitivity of 85% and specificity of 99.7% for EGPA**

- asthma
- paranasal sinus abnormality
- more than 10% of eosinophils on the differential leukocyte count
- mononeuropathy (including multiplex) or polyneuropathy
- migratory or transient pulmonary opacities detected radiographically
- biopsy with blood vessel showing extravascular eosinophil infiltrate

Main **DD** (hypereosinophilia with respiratory involvement):

- idiopathic hypereosinophilic syndrome (myeloproliferative, reactive)
- Aspirin-exacerbated airway disease
- other vasculitides (GPA in particular)
- chronic eosinophilic pneumonia (Carrington)
- Allergic bronchoalveolar aspergillosis

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## EGPA – Heart involvement (30% of cases)

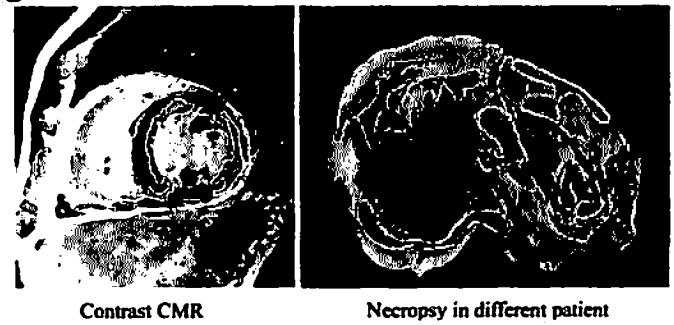
Poor prognostic factor (1st cause of disease-related mortality)

Troponin in context of hypereosinophilia:

- very sensitive for myocardial damage

Cardiac MRI

most sensitive imaging technique



Contrast CMR | Necropsy in different patient

Histology (n.b. endomyocardial biopsies not often of diagnostic value)

Interstitial inflammatory infiltrate with abundant eosinophils

Occasionally: vasculitis of coronary vessels, granulomas in epicardium

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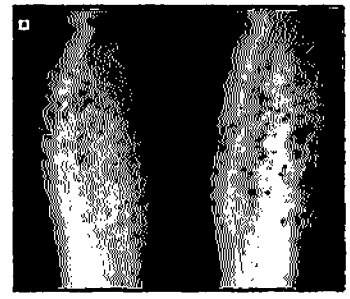
# EGPA – Skin involvement

## Frequent (>50% of cases), polymorphic

## Easy to biopsy, high diagnostic yield

Palpable purpura



Ulcer elbow

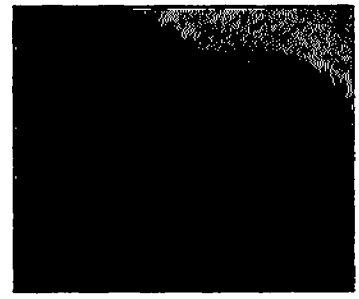


**Table 2.** Histologic findings in 102 biopsy samples from 66 patients with Churg-Strauss syndrome

| Type of biopsy | No. of samples | No. (%) with vasculitis | No. (%) with eosinophilic infiltrate |
|---|---|---|---|
| All biopsy samples | 102 | 40 (39) | 48 (47) |
| Skin | 32 | 19 (59) | 18 (56) |
| Neuromuscular (sural) | 23 | 17 (74) | 13 (57) |
| Muscle | 10 | 1 (10) | 1 (10) |
| Temporal artery | 5 | 1 (20) | 0 |
| Airways | 28 | 2 (7) | 16 (57) |
| Bronchi | 13 | 1 (8) | 6 (46) |
| Nasal cavity and paranasal sinuses | 13 | 0 | 9 (69) |
| Lung (open) | 2 | 1 (50) | 1 (50) |
| Other | 4 | 0 | 0 |
| Gastrointestinal | 3 | 0 | 0 |
| Accessory salivary glands | 1 | 0 | 0 |

Ribi C, et al. Arthritis Rheum 2008:58:586-94

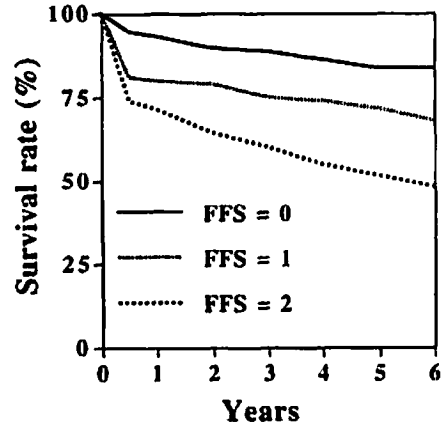
# The five-factor score – a tool to assess severity

## Five factors associated with poor survival in a French cohort (N=342)

## An FFS > 0 should prompt incisive immunosuppressive treatment

**Proteinuria > 1g/24h**
**Creatininemia > 133 µmol/L**
**Severe GI tract involvement**
**CNS involvement**
**Cardiomyopathy**

| FFS | Dead % | Alive % | Relative Risk | No. of Patients |
|---|---|---|---|---|
| 0 | 11.9 | 88.1 | 0.62 | 218 |
| 1 | 25.9 | 74.1 | 1.35 | 81 |
| 2 | 45.95 | 54.05 | 2.40 | 37 |
| Total | 64 | 272 | | 336 |




## Immunosuppressants should also be considered in mononeuritis with FFS = 0

Guillevin L, et al. Medicine (Baltimore) 1996;75:17–28
Samson M, et al. Autoimmun Rev 2014;13:945-53

# IgA-Immunocomplexvasculitis (Henoch-Schönlein purpura)

- **Definition**: "Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur." EULAR/PRINTO/PRES (children)
- **Epidemiology**: most common vasculitis in childhood (75% of patients), 3-26/100.000 children, 4-7 y/o, adults rare 0.1-1.8/100.000
- **Etiology and Pathogenesis**: IgA1 serum levels elevated due to increased production and clearance defect, aberrant IgA1 glycosylation, antigen exposure processed by mucosa-associated immune-system.
  - **Trigger**: genetically prone individuals e.g. HLA-DRB1, bacteria (group A beta-hemolytic streptococci 10-30%), virus, parasites, adults also malignancies (esp. lung cancer, IgA plasmocytoma, M. Hodgkin)

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# Diagnostic criteria HSP

| Criterion | Glossary | Sensitivity (%) | Specificity (%) | AUC (%) |
|---|---|---|---|---|
| Purpura (mandatory criterion) | Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, * not related to thrombocytopenia | 89 | 86 | 87.5 |
| 1. Abdominal pain | Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding | 61 | 64 | 62.2 |
| 2. Histopathology | Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit | 93 | 89 | 91.1 |
| 3. Arthritis or arthralgias | Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion<br>Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion | 78 | 42 | 59.9 |
| 4. Renal involvement | Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample<br>Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick | 33 | 70 | 51.4 |
| HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96) | Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria:<br>Abdominal pain<br>Histopathology<br>Arthritis or arthralgia<br>Renal involvement | 100 | 87 | 93.5 |

*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.
AUC, area under the curve; EULAR, European League Against Rheumatism; HSP, Henoch–Schönlein purpura; PRES, Paediatric Rheumatology European Society; PRINTO, Paediatric Rheumatology International Trials Organisation.

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Ozen S et al., Ann Rheum Dis. 2010 May;69(5):798-806.

# Organ involvement HSP

- Symptoms: **purpura, arthralgia, abdominal pain** (classic triad)
- **Skin**: purpura (pressure areas), adults maybe necrotic or hemorrhagic (1/3). Purpura appears in 75-90% within 4 weeks after begin of symptoms, nearly all within 3 months, commonly with arthritis and GIT involvement, rarely after renal involvement.
- **Joint**: arthralgia (2/3), esp. knees and ankles, arthritis very rare, myalgia possible
- **Gastrointestinal** (2/3): abdominal pain (100%, typical colicky) caused by ischemia and oedema, nausea and vomiting (14.4%), melena and/or rectorrhagia (12.9%), positive stool guaiac test (-> occult blood, 10.3%).
  - Severe complications: intussusception, infarction, perforation. Descending duodenum / terminal ileum frequently involved (endoscopy: diffuse mucosal redness, petechiae, hemorrhagic erosions ulcers. CT: bowel wall thickening with engorgement of mesenteric vessels)
- **Renal** (45-85%): Microscopic hematuria (most sensitive and earliest), proteinuria, sometimes nephrotic (10-20%), rarely macroscopic hematuria. Hypertension (1/3). Adults: renal failure at time of diagnosis 30%! Histologic classification by Pillebout with strong clinic-pathological correlation
- **Others**: very rare alveolar hemorrhage (0,8-5%, esp. adults and male children)53, myocarditis, orchitis, episcleritis, CNS/PNS (consciousness, convulsions, focal neurological deficiency, visual loss, verbal disability)



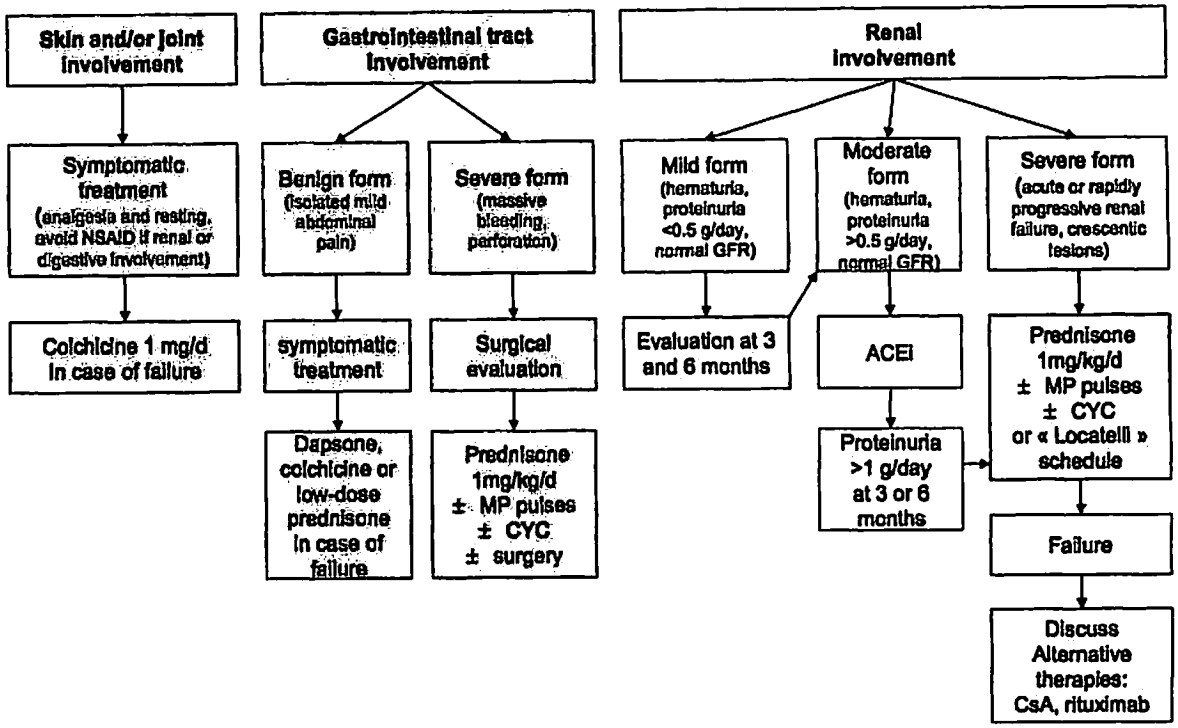
# Check-up HSP

- **Laboratory**: elevated inflammation parameters, complement normal to low, anemia, reactive thrombocytosis, serum IgA elevated (50% of cases)
  - Renal involvement: more severe in adults (creatinine, proteinuria, hematuria),
  - Gut involvement: LDH or lactate elevation
  - controversial: IgA-ANCA (mostly MPO-ANCA) or IgA-rheumatic factor
  - **With begin of symptoms urine test every week until cessation of symptoms, then every 3 months**

- **Imaging**: ultrasonography, CT, MRI, endoscopy for organ involvement, esp. gut, kidney

- **Biopsy**: discuss renal biopsy in case of acute renal failure related to rapidly progressive glomerulonephritis, nephrotic syndrome, diagnostic uncertainty, or in case of persistent proteinuria (>1 g/day) at 3–6 months despite ACE inhibitors

# Treatment HSP

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Audemard-Verger A et al., Autoimmun Rev. 2015 Jul;14(7):579-85.

# Course and Prognosis

- generally benign and self-limited in children and more severe in adults (esp. renal, and joints), less frequent abdominal pain and fever.
- Children usually unique flare, relapses in adults about 20%, usually within the first 3 months.
- Early and acute lifethreatening: gastrointestinal perforation / bleeding, pulmonary involvement with intraalveolar hemorrhages.
- Long-term organ-threatening: renal (11% ESRD, 13% severe renal failure (eGFR <30 mL/min), 14% moderate renal insufficiency (eGFR <50 mL/min))
  - Poor renal prognosis: baseline renal function impairment, baseline proteinuria, >1 or 1.5 g/day, macroscopic hematuria, hypertension, and proteinuria ≥1 g/day during follow-up, biopsy degree of interstitial fibrosis, sclerotic glomeruli and fibrinoid necrosis
  - Recurrence of IgA vasculitis after renal transplantation: renal recurrence 35% and graft loss due to recurrence 11% 5 years after transplantation

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# Treatment principles in systemic vasculitis

Be certain of the diagnosis

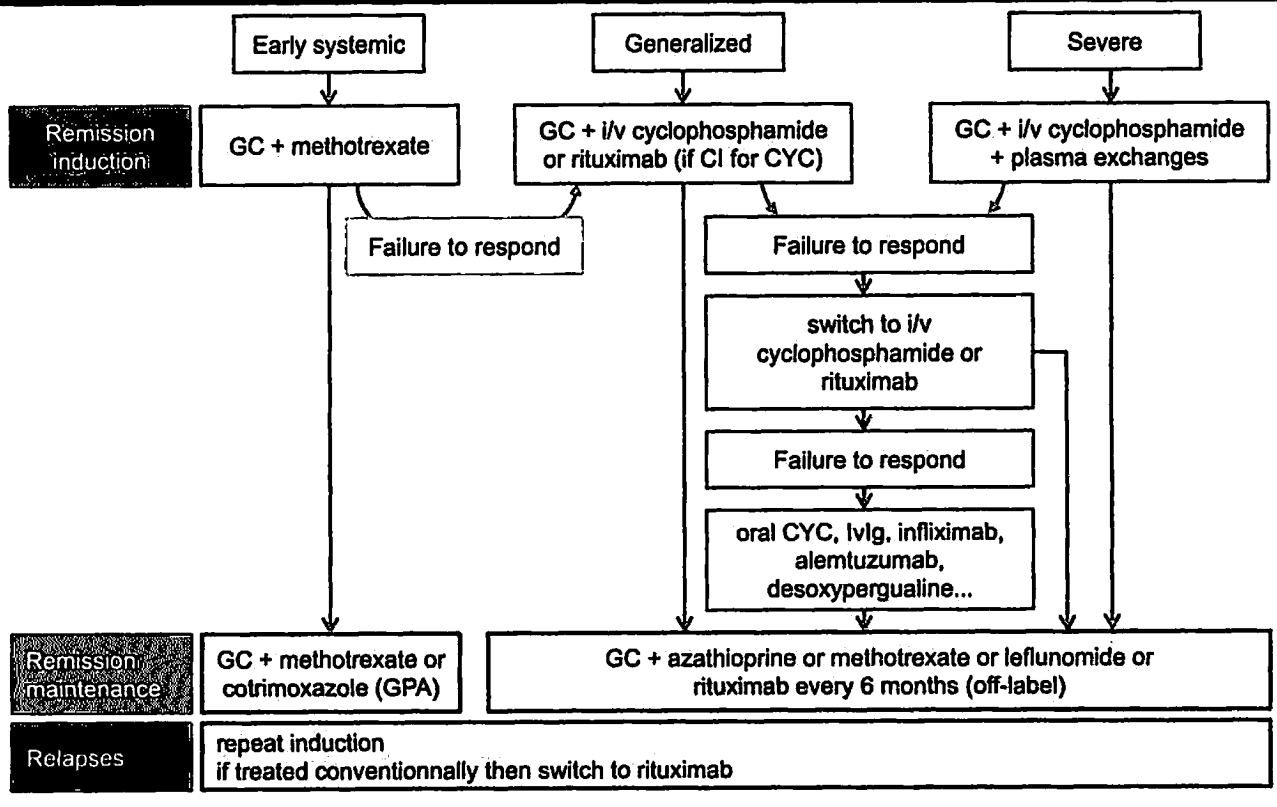
Assess disease extent/severity:

Do not confound damage with activity

Prevent relapses

Limit treatment-related toxicity

# General therapeutic approach in AASV




adapted from: Kallenberg CGM. Nat Rev Rheumatol 2014;10:484-93

## Disease- and treatment-related comorbidity in vasculitis

**3 major cause of mortality** in systemic small vessel vasculitis
- infections (20% of mortality after 1st year, 48% within 1st year)
- malignancies (22%)
- CV events (26%)

**Major risk factors for infection:**
- use of corticosteroids (high-dose but also low-dose for > 6 months)
- lymphopenia and neutropenia resulting from immunosuppressant

> cotrimoxazole and other prophylactic measures during induction

**Glucocorticosteroid-induced osteoporosis**

EGPA: often persistent respiratory disease after remission of vasculitis

> bone prophylaxis, steroid-sparing immuno-modulation

## Disease- and treatment-related comorbidity in vasculitis

**Venous thrombosis:**
- High incidence in AASV (particularly during active disease)

> prophylaxis in patients with other risk factors (eg mononeuritis...)

**Coronary hearth disease and cerebro-vascular complications:**
- 2 to 4-fold increased risk in AASV
- within 5 years from diagnosis, 14% of patients will suffer a CV event

> control of inflammation and traditional cardiovascular risk factors

**Malignancy:**
- increase of bladder cancer after treatment with cyclophosphamide
- increase in non-melanotic skin cancer

> CYC i/v and only for induction, mesna, dermatological controls

# Cutaneous cardinal symptoms and typical mainfestations from selected vasculitidies (rate cutaneous involvement in %)

**Immunkomplexvaskulitis (IgA-negative Immunkomplexvaskulitis) (100%)**
Palpable Purpura; hämorrhagische Maculae, seltener hämorrhagische Blasen, Nekrosen und Hautulzerationen

**IgA-Immunkomplexvaskulitis (Purpura Schönlein Henoch) (100%)**
Klinik analog Immunkomplexvaskulitis; neben Extremitäten auch Befall von Glutealregion und Kopfbereich typisch; bei Erwachsenen häufig Hautnekrosen
- **Merkmale/Assoziation:** Gelenk-, Nieren- und gastrointestinale Beteiligung; schwerwiegende Organkomplikationen hauptsächlich im Erwachsenenalter; vorausgehende Infektion oberer Atemwege häufig; gelegentlich Nachweis β-hämolysierende Streptokokken im Rachenabstrich

**Urtikariavaskulitis (100%)**
>24h bestehende, teilweise schmerzhafte, teilweis anuläre Urticae; Angioödeme
- **Merkmale/Assoziation:** bei hypokomplementämischer Urtikariavaskulitis Entwicklung eines SLE in ca. 1/3 der Fälle

**Akutes hämorrhagisches Ödem des Kindesalters (100%)**
Kokardenförmige oder anuläre, teils hämorrhagische Plaques; ausgeprägte lokale Ödeme; insbesondere Extremitäten und Gesicht betroffen
- **Merkmale/Assoziation:** Vaskulitis des Säuglings- und Kleinkindesalter; respiratorischer Infekt als potenzieller Auslöser

**Erythema elevatum diutinum (100%)**
Symmetrische, livid rötlich-bräunliche polsterartige Papeln oder Plaques über den Gelenkstreckseiten.
- **Merkmale/Assoziation:** potenziell zugrunde liegende Paraproteinämie (IgA > IgG)

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Nobbe S., DERMATOLOGIE PRAXIS 2014; Vol. 24, Nr. 4

# Cutaneous cardinal symptoms and typical mainfestations from selected vasculitidies (rate cutaneous involvement in %)

**Kryoglobulinvaskulitis (100%)**
Klinik analog Immunkomplexvaskulitis, Nekrosen und Ulzerationen aber häufiger; begleitend Livedo racemosa und Akrozyanose möglich; Symptome treten bei Abkühlung und insbesondere an den Akren auf
- **Merkmale/Assoziation:** Vaskulitis bei Kryoglobulinämie Typ II/III; häufig zugrunde liegende Hepatitis C-Infektion, seltener auch bei HIV, Kollagenosen, lymphoproliferativen Erkrankungen

**Mikroskopische Polyangiitis (40%)**
Klinik analog Immunkomplexvaskulitis; selten Ulzerationen; subunguale Kapillarblutungen
- **Merkmale/Assoziation:** begleitende nekrotisierende Glomerulonephritis und pulmonale Kapillaritis typisch; Nachweis von pANCA häufig

**Granulomatose mit Polyangiitis (Morbus Wegener) (40%)**
Mund- und Nasenschleimhautulzerationen; palpable Purpura; subkutane Knoten; Ulzera
- **Merkmale/Assoziation:** Befall von oberen Luftwegen, Lunge und Niere typisch; Nachweis von cANCA häufig

**Eosinophile Granulomatose mit Polyangiitis (Churg-Strauss-Syndrom) (50%)**
Palpable Purpura; papulonekrotische Läsionen an Kopf und Extremitäten, insbesondere über Ellenbogen; subkutane Knoten; Livedo racemosa; multiforme Erytheme
- **Merkmale/Assoziation:** allergische Rhinitis; Asthma bronchiale; Bluteosinophilie; Befall von Lunge, peripherem Nervensystem und Herz typisch; pANCA in ca. 50% der Fälle

**Panarteriitis nodosa (50%)/kutane PAN (100%)**
Livedo racemosa; subkutane Knoten, die ulzerieren können; periphere Gangrän; Raynaud-Syndrom
- **Merkmale/Assoziation:** multiple Organsysteme betroffen; Mononeuritis multiplex häufig; potenziell zugrunde liegende Hepatitis B/C-Infektion

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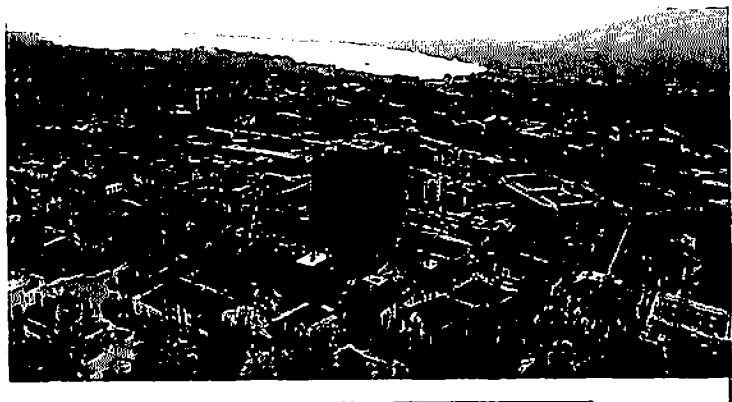

Thank you for your attention!

Questions ?

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**Table 1. The classification of vasculitides.**

| |
|---|
| Vasculitides included in the Chapel Hill nomenclature |
| Small-vessel vasculitis |
| Associated with ANCA |
| GPA |
| MPA |
| EGPA |
| HSP |
| Mixed essential cryoglobulinaemic vasculitis |
| Cutaneous leukocytoclastic angiitis |
| Medium-vessel vasculitis |
| Polyarteritis nodosa |
| Kawasaki disease |
| Large-vessel vasculitis |
| GCA |
| TA |
| Vasculitides not included in the Chapel Hill classification |
| Immune complex-mediated vasculitis |
| IgA nephropathy |
| Behçet's disease |
| Anti-GBM disease |
| Secondary vasculitis |
| Other autoimmune disease SLE |
| Rheumatoid arthritis |
| Polymyositis/dermatomyositis |
| Systemic sclerosis |
| Antiphospholipid syndrome |
| Inflammatory bowel disease |
| Drug induced |
| Paraneoplastic |
| Infection |

EGPA: Eosinophilic granulomatous polyangiitis; GBM: Glomerular basement membrane; GCA: Giant cell arteritis; GPA: Granulomatosis with polyangiitis; HSP: Henoch–Schönlein purpura; MPA: Microscopic polyangiitis; SLE: Systemic lupus erythematosus; TA: Takayasu arteritis.

defined as unexplained pulmonary infiltrates plus at least one of the following: haemoptysis (absent in one-third), increased carbon monoxide transfer factor on lung function tests, > 2 g/dl drop in haemoglobin (Hb) or anaemia without alternative causes, or bronchoscopic evidence of haemorrhage.

AH secondary to a vasculitic process is characterised by a capillaritis, unlike the 'bland' haemorrhage seen in ARDS and coagulopathy. Capillaritis classically affects the lungs in conjunction with the kidneys (glomerulonephritis) giving rise to the pulmonary–renal syndrome. After AAV, other causes include SLE, anti-glomerular basement membrane (GBM) disease and mixed essential cryoglobulinaemia (Table 3).

## 2. Assessment strategy of the patient with pulmonary vasculitis

### 2.1 Clinical evaluation

The assessment of a patient with suspected pulmonary vasculitis starts with a systematic history and physical examination, looking for clinical evidence of vasculitis, detection of its secondary causes or exclusion of vasculitis mimics. Other important aspects to consider in the management of pulmonary and general vasculitis are determination of the extent and severity of disease, and identification of co-morbidities.

### 2.2 Laboratory investigations

Serological analysis is paramount in the differential diagnosis of small-vessel vasculitides and can also be helpful to monitor disease activity or damage. Useful diagnostic tests include full blood count, renal and liver function, inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein), ANCA, anti-GBM antibodies, complement levels and cryoglobulins, screening for other connective tissue diseases (anti-nuclear and extractable nuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide, hepatitis serology and anti-phospholipid antibodies). There are no specific serological tests for medium, large and non-ANCA small-vessel vasculitides.

During the 1980s, anti-ANCAs were found to be associated with the pauci-immune small-vessel vasculitides, GPA, MPA and EGPA. Three ANCA subtypes have been detected: cytoplasmic staining (c-ANCA), peri-nuclear (p-ANCA) and atypical ANCA, using indirect immunofluorescence (IIF) which is a useful screening test with high sensitivity but lower specificity. IIF should be used in combination with enzyme-linked immunoassays (ELISA), which are more specific but less sensitive. c-ANCA is usually directed against proteinase-3 (in the azurophilic granules of neutrophils and monocytes), common in GPA, with 85 – 90% sensitivity and 95% specificity for generalised active disease [17-19], which may be sufficient for diagnosis in a relevant clinical context without the need for biopsy. ANCA is positive in many patients with limited vasculitis [20,21] However, vasculitis that is in remission is associated with lower ANCA positivity (22%) [10,22]. False-positive c-ANCAs are rare but have been detected in some infections and non-vasculitic autoimmune diseases [23].

p-ANCA is usually directed against myeloperoxidase (MPO) (also detected in azurophilic granules), although p-ANCA is less sensitive (50 – 75% in generalised active MPA, 30 – 50% in EGPA) and specific compared with the higher sensitivity and specificity of c-ANCA/PR3 for GPA [24]. p-ANCA may be directed against other antigens (elastase, lactoferrin, cathepsin, azurocidin, lysozyme and bacterial-permeability increasing protein) in some infections and other autoimmune inflammatory diseases, such as rheumatoid arthritis and ulcerative colitis [23].

A negative ANCA does not exclude pauci-immune small-vessel vasculitis, as seronegative forms may exist. ANCA is also insufficient for prediction of vasculitis relapse, which is still a clinical diagnosis [25,26] but still useful for monitoring when treatment withdrawal is contemplated, as persistently positive ANCA, its reappearance [27,20,28,29] and, in particular, a rise in ANCA level are associated with higher risk of relapse [30].

### 2.3 Lung function tests

Lung function tests are non-invasive and easy to perform, provided patients are not critically ill. The flattening of

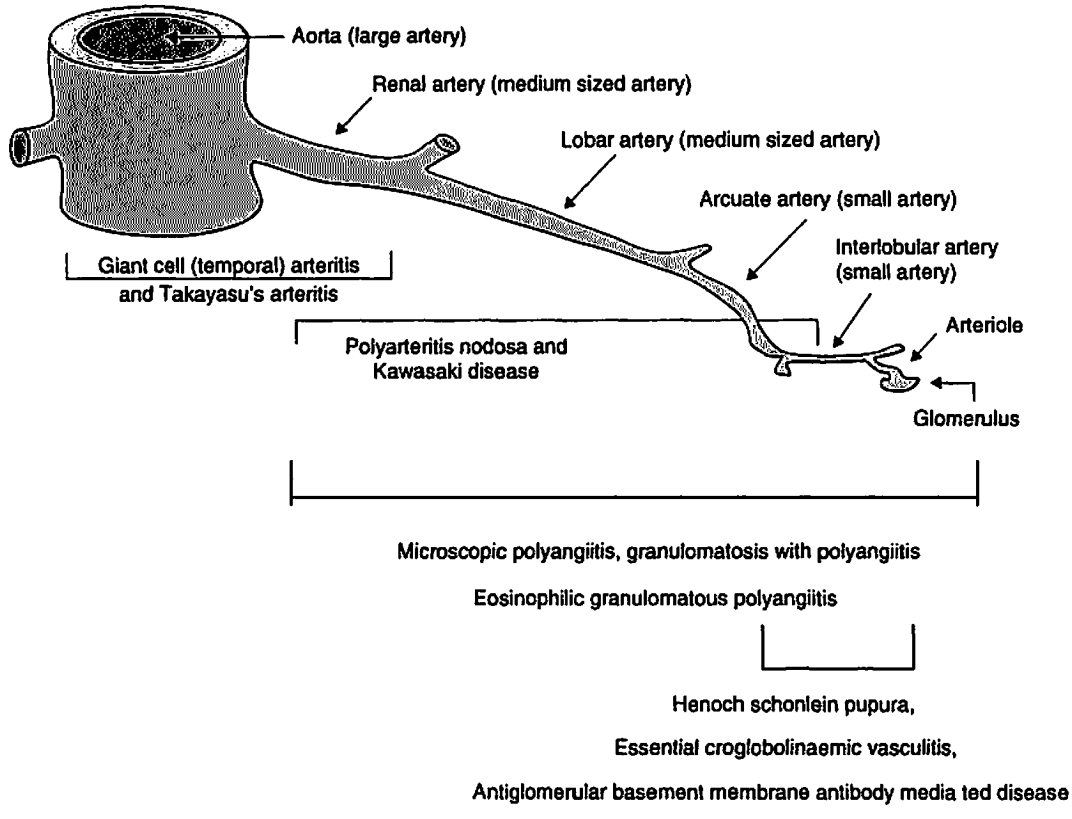



**Figure 1. Classification of vasculitides according to blood vessel size.**



inspiratory and expiratory flow-volume traces can be used to assess the extent of stenoses (trachea and main bronchi), both as diagnostic tools and to delineate therapeutic response.

Spirometric analysis may reveal reduced forced expiratory volume in one second and maximal expiratory flow, suggestive of obstructive defects, especially in GPA [31] or/and reductions in lung volumes and diffusing capacity for carbon monoxide indicative of restrictive defects and pulmonary parenchymal involvement. Increased (> 100%) diffusion capacity for carbon monoxide (KCO) should raise suspicion of AH.

## 2.4 Imaging modalities

### *2.4.1 Imaging*

Imaging can help establish the diagnosis of pulmonary vasculitis and quantify the extent of organ involvement. The threshold for imaging should be lowered in the presence of laboratory abnormalities suggestive of vasculitis, respiratory symptoms and signs.

It can also be useful to image other organs known to be frequently affected by vasculitis (e.g., sinuses) or associated with high morbidity and mortality (e.g., kidneys, heart).

Plain chest radiographs are often abnormal in the context of pulmonary vasculitis but lack sensitivity and specificity. High-resolution, thin-section computed tomography (CT) scans or multidetector row CT (MDCT) angiography are valuable tools for differential diagnosis of pulmonary vasculitides, MDCT allowing three-dimensional reconstruction, faster and improved visualisation of blood vessels and contrast material enhancement of adjacent organ parenchyma, prompting need for other imaging modalities or clinical tests, guiding therapy during follow-up and obviating need for invasive angiography [32]. MDCT angiography is also useful in large-vessel vasculitis for delineating late enhancement suggestive of pulmonary arterial wall thickening that can progress to stenosis or obstruction, resulting in pulmonary hypertension, oligaemia, localised infarction or arterial aneurysms and subsequent pulmonary haemorrhage.

Both AH and non-haemorrhagic small-vessel pulmonary vasculitis can give rise to inflammatory infiltrates manifested as localised or diffuse ground-glass opacification or air-space consolidation (typically peripheral in EGPA) on imaging and sometimes long-term sequelae such as inter- or intralobular interstitial thickening.

Magnetic resonance imaging (MRI) is another valuable tool for the diagnosis of pulmonary vasculitides. Increased signal intensity on T1-weighted MR views and drastically reduced signal intensity on T2-weighted images [33] is suggestive of haemosiderin deposition in AH.

**Table 2. Pulmonary manifestations of vasculitides.**

| Type of vasculitis | Pulmonary nodules | Tracheobronchial stenosis | Alveolar infiltrates | Pulmonary-renal syndrome | Pulmonary artery aneurysms | Pulmonary hypertension |
|---|---|---|---|---|---|---|
| GPA | Common | Common | Common haemorrhagic | 50 - 75% | No | No |
| MPA | No | No | Up to 40%, commonly diffuse haemorrhage | 75 - 100% | No | No |
| EGPA | Rare | No | Common (rarely haemorrhagic | 25% | No | No |
| HSP | No | No | Present (rarely haemorrhagic) | Rare | | |
| PAN | No | No | Very rare, diffuse haemorrhage associated with hepatitis B | No | No | No |
| GCA | Very rare | No | Rare, focal haemorrhage | No | Very rare | Rare |
| TA | No | No | Rare (< 10%), focal haemorrhage | No | Yes, post-stenosis | Up to 60% |
| Behçet's disease | No | No | Focal haemorrhage in 50% of patients with aneurysms | No | Up to 5% | Very rare |
| Mixed connective tissue disease | No | No | Rarely diffuse haemorrhage | No | No | Up to 45% |
| SLE | No | No | 2% diffuse haemorrhage, 60% mortality | Up to 60% in advanced disease | No | Up to 43% |
| Systemic sclerosis | No | No | Rare diffuse haemorrhage | No | No | 10 - 60% |
| Rheumatoid arthritis | Yes | No | Very rare, diffuse haemorrhage | No | No | Rare |

Definitions: Rare: present in < 10% of cases; Common: present in > 50% of cases.

EGPA: Eosinophilic granulomatous polyangiitis; GCA: Giant cell arteritis; GPA: Granulomatosis with polyangiitis; HSP: Henoch-Schönlein purpura; MPA: Microscopic polyangiitis; PAN: Polyarteritis nodosa; SLE: Systemic lupus erythematosus; TA: Takayasu arteritis.

**Table 3. Vasculitic causes of diffuse AH.**

| |
|---|
| Primary, ANCA-associated small-vessel vasculitis (80%) |
| GPA |
| MPA |
| EGPA |
| Other small-vessel vasculitides |
| Mixed essential cryoglobulinaemia |
| Anti-GBM disease |
| Primary immune complex-mediated vasculitis |
| HSP |
| Secondary vasculitis |
| Other autoimmune diseases |
| SLE |
| Rheumatoid arthritis |
| Polymyositis/dermatomyositis |
| Antiphospholipid antibody syndrome |
| Mixed connective tissue disease (e.g., systemic sclerosis) |
| Behçet's disease |
| Drug induced |
| Cancer |
| Lung or bone marrow transplantation |
| Infection |

AH: Alveolar haemorrhage; ANCA: Anti-neutrophil cytoplasmic antibody; EGPA: Eosinophilic granulomatous polyangiitis; GBM: Glomerular basement membrane; GPA: Granulomatosis with polyangiitis; HSP: Henoch–Schönlein purpura; MPA: Microscopic polyangiitis; SLE: Systemic lupus erythematosus.



CT with endoscopic views ('virtual bronchoscopy') is a useful tool for guiding and complementing invasive bronchoscopy [34], although it is unlikely to replace the former and does not allow biopsy to establish tissue diagnosis.

CT may reveal typical morphologic patterns of the various vasculitides and is valuable for assessing focal parenchymal or vascular abnormalities but of limited use with regards to diffuse AH, when it cannot differentiate the underlying type of vasculitis. Imaging is usually not sufficient on its own as a diagnostic tool and should be correlated with clinical and serological features.

18-Fluorodeoxyglucose positron emission tomography (FDG-PET) is a promising but still exploratory tool for visualisation of vascular inflammation diagnosis (reflected by increased FDG uptake) and monitoring of vasculitis activity, used for large-vessel vasculitis, with few studies in ANCA vasculitides [35] and none assessing the effect of immunosuppression.

### 2.5 Invasive studies and biopsy

Histological evidence of vasculitis is frequently although not invariably needed to establish a diagnosis of vasculitis. The biopsy site is selected according to organ involvement, accessibility, risk and likelihood of diagnostic yield. A negative result does not exclude the diagnosis as inflammation is sometimes patchy and sampling may have been undertaken from an unaffected area.

Bronchoscopy evaluates airway disease reflected by epithelial erythema, ulceration and stenoses. Bronchoalveolar lavage with progressively more blood-stained returns indicates AH. These techniques also permit bronchoscopic biopsy and microbiological evaluation of the lower respiratory tract. Transbronchial biopsies can reveal a small-vessel vasculitis but lack sensitivity, they help in the exclusion of malignancy and infection. Infection is an important differential diagnosis at presentation and relapse, but is also a frequent complication of immunosuppression. Open (surgical) lung biopsy is a high yield diagnostic procedure, with vasculitis detected in 94% of GPA biopsies, parenchymal necrosis in 84%, giant cells in 79%, microabscesses in 69% and granulomas in 59% [36]. However, it requires general anaesthesia, carrying a higher risk of complication (especially in the presence of AH) and is currently performed less commonly compared with more accessible sites (e.g., skin, sinuses) or kidney. Furthermore, a video-assisted thoracoscopic approach is used nowadays, with lower risk of complications and discomfort. With the availability of ANCA testing, open lung biopsy is now rarely required in vasculitis.

Histology can be more easily obtained from other sites, such as affected skin, nose and paranasal sinuses, nerves or kidneys [37].

Renal biopsy is undertaken in the presence of an abnormal urinary sediment with or without acutely impaired renal function and has a high diagnostic yield. A segmental, necrotising glomerulonephritis is suggestive of vasculitis, with a lack of immune deposits on immunofluorescence further pointing towards an ANCA-associated, small-vessel vasculitis, while linear immunoglobulin G (IgG) deposits are typical of anti-GBM disease. IgA deposits are detected in Henoch–Schönlein purpura (HSP) and heterogeneous, clustered IgG in SLE. Crygobulinaemia gives rise to a membranoproliferative glomerulonephritis.

Renal biopsy is unlikely to be helpful for diagnosing Behçet's disease, giant cell arteritis (GCA) or Takayasu arteritis (TA) that usually spare the kidneys.

A biopsy requires a concerted multidisciplinary approach involving the physician, pathologist and surgeon, as parts of the sample need to be processed for immunofluorescence, with formalin fixation or placed in saline for cultures.

## 3. Vasculitis types

### 3.1 Small-vessel vasculitides

This group accounts for most cases of pulmonary vasculitis.

#### *3.1.1 ANCA-associated vasculitis*

The AAV syndromes are grouped together in view of some common clinical features, histological findings of small-vessel inflammation, a similar response to immunosuppressive treatment and frequent ANCA positivity. The incidence of ANCA vasculitis is 15 – 20/million/year, with a prevalence rate of 90 – 300/million [38] in adults. It is less common in children.

#### 3.1.1.1 GPA (previously known as Wegener's granulomatosis)

GPA is the most common AAV subgroup, presenting more commonly in Caucasian men in the fifth decade with positive proteinase-3 ANCA, necrotising granulomata, upper and lower respiratory tract disease and pauci-immune glomerulonephritis. However, 60% of Chinese patients with GPA were found to be MPO-ANCA positive [39]. Other common GPA manifestations include the skin (45 – 60%), eyes (25 – 50%), peripheral nervous system (10 – 30%), musculoskeletal system (30 – 70%), heart (5 – 15%) and non-specific constitutional symptoms such as fatigue, malaise, anorexia, fever or weight loss. GPA has a broad range of respiratory manifestations and the upper and lower respiratory tract is the most frequently involved system in GPA, affecting 75 – 95% of patients.

Upper airway involvement features epistaxis, rhinitis, sinusitis, nasal deformities, otitis, tinnitus, hearing loss, laryngeal disease and subglottic or tracheal stenosis. Symptoms suggestive of pulmonary disease include shortness of breath, haemoptysis, cough, chest pain, wheezing, hoarseness, stridor.

The majority of GPA patients have abnormal chest radiographs, although no single pattern is pathognomonic of GPA. The most common radiological feature (90%) consists of nodules (granulomata) (**Figure 2**): usually bilateral, in an arteriolo-centric distribution, with surrounding opacity in 15% ('halo sign') [40] increasing in number and size as disease progresses, with the largest diameter reported as 10 cm [41]. Half of the nodules eventually cavitate due to necrosis, usually if > 2 cm in diameter [42] and can be detected more accurately by CT rather than plain X-ray. Approximately half of the nodules resolve with therapy, 40% decrease in size and 10% are unaffected [40]. It is essential to exclude other underlying causes for nodules, such as malignancy or infection (especially tuberculosis).

Other common radiological lesions, detected in 50% of the patients, include interstitial, alveolar or mixed infiltrates with diverse patterns of distribution [43]. The diffuse air-space consolidation or ground-glass opacities typically sparing the lung apices represents pulmonary haemorrhage (from injury to the alveolar microcirculation and pauci-immune capillaritis) which is most common in AAV, accounting for 80% of the causes of the pulmonary–renal syndrome [44]. Severe AH accounts for a minority of AAV patients and, if treated promptly with immunosuppression and not requiring mechanical ventilation, the prognosis is relatively good with no overall increase in mortality.

The tracheobronchial tree can be involved in up to 50% of patients with GPA [41], and this is more prevalent in patients younger than 30 years [45] and women [46] but is seldom the initial or the only feature of the disease. Tracheobronchial disease may present with subtle, insidious symptoms initially misdiagnosed as asthma or other airway diseases. The most common manifestations are tracheobronchitis, bronchial, subglottic or tracheal stenosis (15%) [41], which may sometimes become sufficiently severe to require tracheostomy. The stenosis most frequently affects the main bronchi followed by trachea then smaller bronchi is usually localised and can cause distal atelectasis.

The degree of stenosis is most accurately assessed by spiral CT, using thin sections and three-dimensional reconstructions [43]. Less common pulmonary manifestations of GPA include bronchiolitis obliterans organising pneumonia [47], bronchiectasis (10 – 20%) [40], pleural effusions in up to a quarter of cases, mediastinal lymphadenopathy (20% of patients) and, rarely, pleural, bronchial or interlobular septal thickening or pneumothorax [42,43]. CT is not highly predictive of vasculitis activity but helps assess response to treatment.

#### 3.1.1.2 Microscopic polyangiitis

Microscopic polyangiitis (MPA) is a pauci-immune necrotising vasculitis (incidence 1:100,000) without granulomata, involving mainly arterioles, venules and capillaries.

MPA is the predominant type of ANCA vasculitis in older age groups and Japanese/Chinese populations [48] and is usually preceded by a prodromal period of non-specific constitutional symptoms such as malaise, poor appetite, weight loss, fever and night sweats, aches and pains. It typically presents with rapidly progressive or already advanced glomerulonephritis (> 90% of cases) [49] and is the most common cause of pulmonary–renal syndrome, with associated pulmonary haemorrhage [50]. Like GPA, MPA can also affect a variety of other organ systems (especially peripheral nervous system, skin, heart, gastrointestinal tract or eyes), and rarely, the ear, nose and throat (ENT).

The majority of patients with MPA are MPO-ANCA positive, up to 40% may have PR3-ANCA and 10% are ANCA negative. The ANCA negative group require diagnostic confirmation by tissue biopsy, this may be difficult in the absence of renal involvement. Earlier studies have often amalgamated MPA with PAN under the now obsolete term of 'microscopic polyarteritis', however, since the mid-90s they have been described as distinct vasculitides.

Respiratory involvement is less common than in GPA, in up to a third of patients, usually in the form of AH (**Figure 3**), which is often severe and is the most common cause of mortality [51]. Imaging may be normal or showing patchy, bilateral, usually lower zone pulmonary infiltrates suggestive of AH in up to 25% of patients.

The imaging abnormalities associated with a single episode of acute haemorrhage usually takes 10 – 14 days to resolve, slower than pulmonary oedema, which it can mimic.

Chronic clinical or subclinical AH may give rise to interstitial haemosiderin deposition and subsequent reticulonodular opacities or pulmonary fibrosis [52] that can precede or follow the diagnosis of vasculitis and is a poor prognostic factor. Histological analysis reveals small-vessel, necrotising vasculitis with a mixture of inflammatory cells [53], differentiating itself

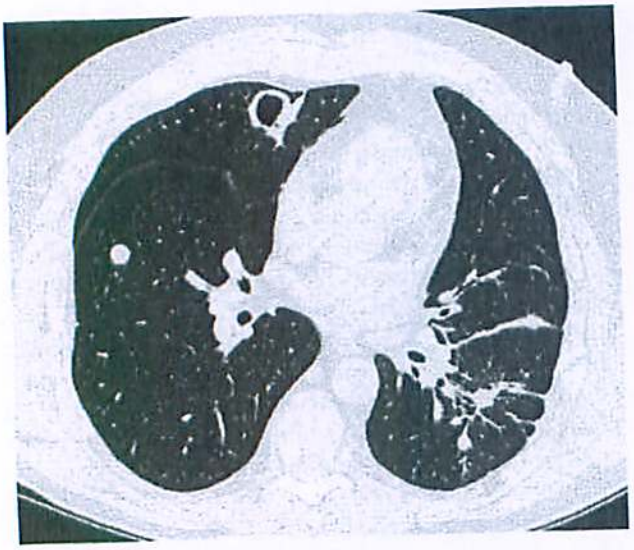


**Figure 2. Right upper lobe pulmonary nodule with cavitations in granulomatosis with polyangiitis (courtesy of Dr. Claire Cousins, consultant radiologist).**

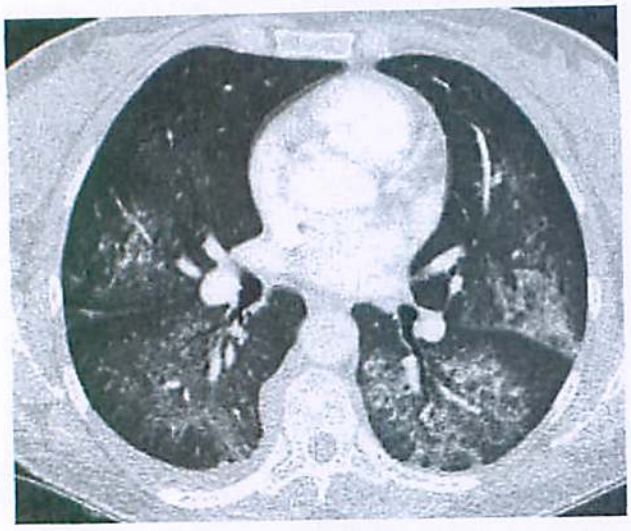


**Figure 3. Diffuse ground-glass opacity (alveolar haemorrhage) in MPA (courtesy of Dr. Claire Cousins, consultant radiologist).**

from other AAVs by the absence of granulomas, giant cells or marked eosinophilia.

*3.1.1.3 EGPA (previously known as Churg–Strauss angiitis)*

EGPA is less common than the other small-vessel vasculitides (prevalence 11 – 14 per million), typically defined by a succession of three phases that may respond differently to treatment: a prodrome of asthma, rhinitis and sinusitis, followed by a markedly eosinophilic phase, and finally a vasculitic phase. EGPA is almost invariably preceded by steroid-dependent asthma by an average of 7 – 8 years [54], and two disease subtypes have been noted: one ANCA positive (40 – 74% of all EGPA patients, usually MPO) with renal involvement (less common than in AAV), and the other ANCA negative with severe eosinophilia, pulmonary and cardiac disease [55]. While nasal polyps, sinusitis and rhinitis are frequent in EGPA, they are rarely deforming, unlike in GPA. Cutaneous vasculitis and mononeuritis multiplex also occur in the majority of patients. Cardiac involvement (usually coronary arteritis or myocardial disease) occurs in as many as 62% of patients [56], and is responsible for the majority of EGPA-related deaths [57-59].

The lung is the most commonly affected organ in EGPA. Chest X-rays and especially high-resolution CT (HRCT) demonstrate abnormalities in the vast majority (90%) of EGPA patients, usually patchy, peripheral, fleeting bilateral ground-glass opacities with or without consolidation and sometimes features of severe asthma (hyperinflation, air-trapping or bronchial wall thickening), as well as 'tree in bud' pattern of centrilobular granulomata (less common than in GPA), lymphadenopathy or AH (uncommon), interlobular septal thickening or pleural effusions (30 – 50% of cases) [60] which may be secondary to cardiac involvement.

Eosinophilia (> 25%) in the bronchoalveolar lavage can support the diagnosis. In view of the non-specific nature of the other tests, tissue diagnosis may be necessary and histopathologic findings of EGPA include a necrotising small- to medium-vessel vasculitis, eosinophilic alveolar infiltrate, extra-vascular necrotising granulomata and giant cells [61]. Vasculitic changes may be absent and differential diagnoses that need to be considered include steroid-dependent asthma, hypereosinophilic syndrome, eosinophilic pneumonia, aspergillosis or parasitic infections. Transbronchial biopsies do not usually yield sufficient information to secure a diagnosis of EGPA [62].

Any persistent steroid-dependent asthma (30 – 40% of patients) and sinusitis associated with EGPA must be meticulously treated, with focused topical glucocorticoids, bronchodilators or nasal saline douching, while avoiding potential allergic triggers [63]. While glucocorticoids target all manifestations of EGPA, cytotoxic agents are more effective for treating the vasculitic (rather than eosinophilic) components which may also be unmasked after glucocorticoid reduction made possible by leukotriene antagonists or anti-IgE monoclonal antibodies used to treat presumed asthma [64,65].

*3.1.2 Henoch–Schönlein purpura*

HSP is the most common small-vessel vasculitis in paediatric patients (incidence 20:100,000), albeit with the lowest frequency of pulmonary involvement. HSP is less serious in children (boys twice as commonly affected) than in adults. This syndrome typically presents with purpura in the lower limbs, arthritis (80%), nephritis (40%), abdominal pain (60%) and gastrointestinal bleeding. Transient, asymptomatic abnormalities of imaging and pulmonary function tests (e.g., reduced transfer factor for carbon monoxide) have been

reported [66,67], however, interstitial pneumonitis and pulmonary haemorrhage (secondary to breakage of the alveolar-capillary membranes by circulating immune-complexes) usually present later, are uncommon and more frequent in adults. By contrast, AH is a rare (3%) [68] but serious occurrence in HSP, with mixed outcomes. Its aetiology and pathophysiology are unclear, but preceding upper respiratory tract infections and IgA play a role, with higher circulating levels of IgA and associated immune complexes deposition in vessel walls and renal mesangium.

#### 3.1.3 *Mixed essential cryoglobulinaemia*

Cryoglobulins are circulating immunoglobulins that reversibly precipitate below body temperature to cause large immune complexes deposition on small and, occasionally, medium blood vessels, resulting in systemic vasculitis in 50% of patients. The skin, joints, kidneys and peripheral nerves can be affected. Complement (especially the C4 component) levels may be low, with positive rheumatoid, however cryocrit often does not correlate reliably with vasculitis activity. Pulmonary vasculitis is rare (approximately 2 – 3%) [69], and presents as severe diffuse AH and associated with high (60%) mortality.

#### 3.1.4 *Isolated pauci-immune pulmonary capillaritis*

Isolated pauci-immune pulmonary capillaritis (IPPC) is a small-vessel vasculitis limited to the lung, without clinical or serologic evidence of accompanying systemic disease. A study of 29 cases of biopsy-confirmed pulmonary capillaritis concluded IPPC was the commonest cause of diffuse AH [70] and associated with a favourable prognosis.

### 3.2 Medium-vessel vasculitis

Polyarteritis nodosa is a necrotising medium-vessel vasculitis that is twice as common in men and tends to involve the renal and visceral arteries, resulting in stenosis and aneurysms, respectively. Coronary aneurysms and pericarditis also occur, pleural effusion and pulmonary infiltrates have been reported.

### 3.3 Large-vessel vasculitis

#### 3.3.1 *Takayasu arteritis*

TA is a rare, progressive large-vessel vasculitis (annual incidence 0.12 – 0.26 per 100,000) [71] that affects the aorta, its proximal branches, less commonly the pulmonary trunk [72] and usually spares the cranial arteries. Most (90%) cases occur in young women [73], with non-specific symptoms, along with diminished or absent pulses and bilateral blood pressure discrepancies. As many as 50% of the patients may have pulmonary vascular involvement, rarely severe, often subclinical and incidentally detected on lung perfusion scans, FDG-PET or angiography [74].

Pulmonary vasculitis in TA may present as pulmonary hypertension (in 50%), pulmonary artery stenoses (Figure 4) or occlusions, compensating systemic-to-pulmonary artery collaterals or post-stenotic aneurysms that may rupture and cause severe focal haemorrhage [75-77]. Diffuse AH due to capillaritis is very rare [78]. Pulmonary oedema and coronary arteritis are other relatively frequent thoracic features of TA. Lung parenchymal abnormalities are uncommon and feature areas of hypoperfusion on HRCT in 44% of patients with pulmonary arteritis [79]. The chest X-ray is often unremarkable or shows non-specific expansion of the ascending aorta and aortic arch. Clinical symptoms and laboratory results are also non-specific, therefore, the diagnosis relies heavily on three-dimensional imaging.

CT is usually abnormal and intravenous contrast is needed to reveal high attenuation of the vessel wall (usually the thoracic aorta or brachiocephalic artery) and features of active arterial inflammation such as delayed enhancement of mural thickening (1 – 4 mm) and an inner hypoattenuating rim [72]. Calcification and lack of enhancement post-contrast are suggestive of chronic inactive arteritis. Central stenoses or occlusions show as chronic arterial wall ischaemia on CT angiography, with a patchy mosaic pattern [72]. The descending aorta is the most common site of stenosis, while aneurysms usually affect the ascending aorta. Pulmonary hypertension is strongly predicted by CT angiography showing a diameter of main pulmonary artery greater than 28 mm or than the width of the ascending aorta.

The diagnosis of TA is established in the majority using a combination of clinical and multiplanar CT features. MRI can also be particularly useful for delineating the vascular tree if spiral CT is not available and, importantly, avoids radiation in these mainly young female patients. Imaging modalities may not be able to distinguish between stenosis and recanalisation. FDG-PET is a novel imaging modality for early diagnosis of TA [80] and guiding response to therapy, although the associated radiation exposure must be considered carefully.

Histology reveals granulomatous changes of the adventitia and media with subsequent degeneration, fibrosis, intimal hyperplasia, lymphocytic and giant cell infiltrate.

TA needs to be distinguished from arteriosclerosis or syphilitic aortitis.

#### 3.3.2 *Giant cell arteritis*

This is the most common large-vessel vasculitis, with similar histology to TA and some overlapping features, although it tends to affect patients older than 50 years of age (prevalence > 200 per 100,000 people), and has a predilection for the thoracic aorta, cranial and extra-cranial subclavian, axillary, carotid arteries and their main branches (e.g., ophthalmic). It usually presents with headache, jaw claudication, scalp tenderness, visual impairment or constitutional symptoms and may pursue a more aggressive course than TA. The aorta is affected in 15% of patients and related complications range from dissection, aneurysm, rupture, regurgitation to heart failure. Pulmonary complications are exceedingly rare and include pulmonary artery stenosis, nodules, interstitial lung disease [81], pleural effusions, aneurysms [82] that may

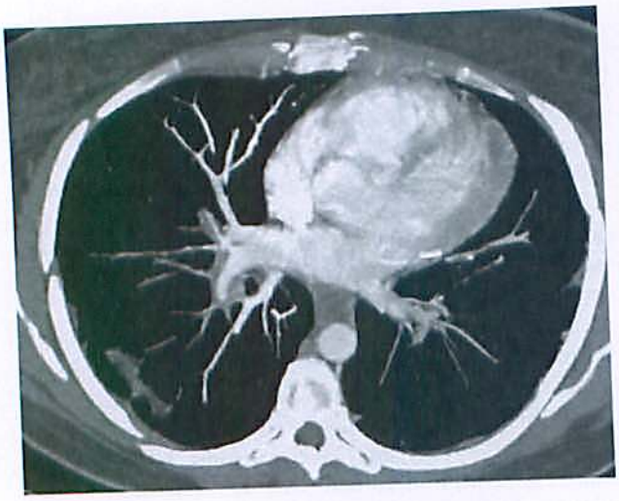


**Figure 4. Takayasu arteritis: right pulmonary artery stenosis (courtesy of Dr. Claire Cousins, consultant radiologist).**

rupture and result in alveolar haemorrhage. The main histological and CT findings resemble those in TA. Interpretation of PET scans in GCA can be more difficult than in TA, as concomitant arteriosclerosis in an older patient group also causes increased FDG uptake [83].

## 3.4 Other vasculitides

### 3.4.1 *Behçet's disease*

Behçet's disease is a rare multisystem autoinflammatory disease that can affect blood vessels of any size (veins more frequently than arteries) and is defined by uveitis, oral and genital ulcers, but may also affect the gastrointestinal and central nervous system. It occurs more commonly in Oriental populations ('Silk Road' route) and men. The pulmonary vessels are affected in a quarter of patients and other respiratory manifestations occur in 5%. The most frequent thoracic complications of Behçet's disease are pulmonary thromboembolism and superior vena cava stenosis or thrombosis (giving rise to mediastinal widening on imaging), areas of oligaemia or atelectasis [84]. Behçet's disease is the most common cause of pulmonary artery aneurysms (Figure 5) [85] and a study of over 2000 patients with Behçet's disease reported a 1% prevalence. Pulmonary aneurysms are usually multiple and bilateral, mainly involving the lower lobes or main pulmonary arteries. A high index of suspicion is needed as associated haemoptysis could be mistakenly attributed to thromboembolism and inappropriate anticoagulation may prove fatal.

If untreated, pulmonary aneurysms may rupture, resulting in focal pulmonary haemorrhage and death in a third of patients within 2 years [78,84]. By contrast, three-quarters of those receiving immunosuppressive treatment resolve completely. Sometimes, pulmonary aneurysms may thrombose and subsequently either regress or give rise to infarction [84].

Pulmonary aneurysms show as perihilar opacities on plain chest radiographs and are best assessed in more detail by CT angiography [86], although they may evolve rapidly therefore size (up to 7 cm) cannot be used to predict risk of rupture; perianeurysmal air-space consolidation or ground-glass opacification are suggestive of imminent rupture [87].

Areas of pulmonary infarction or consolidation have the appearance of wedge-shaped consolidation on imaging. Conventional angiography is not advisable for Behçet's disease as it carries a risk of venous thrombosis or aneurysm formation.

### 3.4.2 *Anti-GBM disease*

Anti-GBM disease is a rare condition with an incidence of 1 per million per year, more common in young adults and males, usually presenting as a pulmonary–renal syndrome (in 60 – 80% of cases) characterised by glomerulonephritis, diffuse AH and linear IgG deposits with anti-GBM antibodies. AH in anti-GBM disease is associated with cigarette smoking. Isolated pulmonary involvement is unusual; chest imaging may reveal diffuse or patchy ground-glass opacities or areas of consolidation, usually sparing the apices and costophrenic angles [88].

### 3.4.3 *Pulmonary capillaritis associated with collagen vascular disease*

Collagen vascular diseases, such as rheumatoid arthritis, scleroderma and polymyositis (anti-synthetase syndrome) are only seldom associated with vasculitic lung involvement. Immune complex-mediated pulmonary vasculitis of varying severity is more frequent in SLE, accounting for up to a quarter of its pulmonary complications and usually co-exists with other organ involvement.

The SLE pulmonary vasculitic manifestations range from haemorrhage secondary to capillaritis to arteriolitis with subsequent centrilobular small nodules or tree-in-bud vascular opacities on CT [89], sometimes contributing to development of pulmonary hypertension affecting 0.5 – 14% of SLE patients.

### 3.4.4 *Vasculitis occurring in the context of other lung diseases*

Chronic infections such as endocarditis [90] or bronchiectasis [91] can induce a secondary vasculitis associated with ANCA (usually atypical, e.g., bactericidal permeability increasing protein BPI-ANCA, and, out of the classical ANCA subtypes, MPO-ANCA positive more frequently than PR3-ANCA). It is essential to identify vasculitis secondary to infection as immunosuppressive treatment is relatively contraindicated.

### 3.4.5 *Drug-induced vasculitis*

Multiple drugs such as hydralazine, leukotriene antagonists, prophylthiouracil [92], phenytoin, transretinoic acid [93] or cocaine have been associated usually with MPO-ANCA positive pulmonary vasculitis, with concurrent diffuse

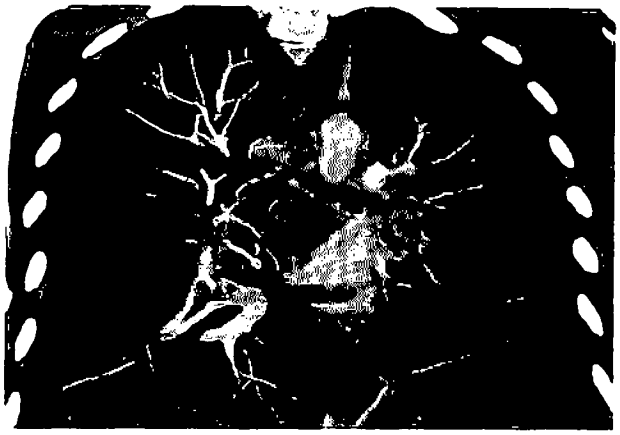


**Figure 5. Pulmonary artery aneurysms with thrombosis in BehÓet's disease (courtesy of Dr. Claire Cousins, consultant radiologist).**

AH [94]. However, c-ANCA positive pulmonary vasculitis mimicking GPA has also been reported, secondary to levamisole or other substances contaminating cocaine stocks [95] or sulphasalazine [96]. Thoracic CT scans cannot specifically diagnose drug-induced pulmonary vasculitis and may also show centrilobular small lung nodules as well as late fibrosis.

## 4. Therapeutic approach to pulmonary vasculitides

Since their introduction in the 1970s, glucocorticoids and cyclophosphamide have changed outcomes in vasculitis from invariably fatal to 90% remission at 6 months, albeit with treatment-related toxicity, 25% mortality at 5 years, suboptimal disease control (20%) and 50% relapse by 5 years. The purpose of induction therapy is to achieve prompt remission of vasculitis and that of maintenance treatment is to lower the risk of relapse.

The intensity of treatment should be decided according to the severity of pulmonary and extrapulmonary involvement and the latest evidence-based recommendations. Severe pulmonary vasculitis requires ventilatory and critical care support, with cautious management of any co-existent sepsis (Table 4). The optimal treatment of secondary vasculitides is not fully clear, but mainly supportive, addressing the underlying cause. Stopping the suspected drug frequently reverses the AAV and AH secondary to drugs or stem cell transplant may benefit from immunosuppression [97].

The best evidence of therapeutic strategies stems from randomised controlled trials in ANCA vasculitides, with only sparse reports in the other conditions. No previous systematic studies have focused specifically on the treatment of pulmonary vasculitides and their management follows that of vasculitis in general, according to disease severity, which has been divided in five subgroups by the European Vasculitis Study Group:

Category 1: localised disease (e.g., limited ENT involvement)

Category 2: early, systemic disease (active vasculitis with constitutional symptoms but no threatened vital organ function)

Category 3: generalised disease (threatened organ function, e.g., glomerulonephritis)

Category 4: severe/life-threatening disease (vital organ failure, e.g., respiratory or renal)

Category 5: refractory disease (not responsive to conventional therapy)

Pulmonary vasculitis may 'fall' into category 2, 3, 4 or 5 according to its severity.

### 4.1 Induction therapy for pulmonary vasculitis

#### *4.1.1 Treatment of mild pulmonary vasculitis without functional impairment (category 2)*

Therapeutic regimens including cyclophosphamide are most commonly used for early systemic AAV but less toxic alternatives such as methotrexate [21] and rituximab [98,99] may have similar efficacy in this patient subgroup.

Evidence is sparse for other pulmonary vasculitides, although case reports found asymptomatic AH secondary to GCA to be steroid-responsive [100].

#### *4.1.2 Treatment of moderate pulmonary vasculitis with functional impairment but not requiring mechanical ventilation (category 3)*

Glucocorticoids with cyclophosphamide (or rituximab) are recommended for pulmonary ANCA vasculitides in this category [98,101]. A subgroup with AH from the RAVE trial (28% of patients) responded equally well to cyclophosphamide or rituximab [99]. Pulsed intravenous cyclophosphamide was shown to have similar efficacy to oral cyclophosphamide but with less leucopaenia and overall immunosuppressive burden.

Pulmonary capillaritis of any severity in the context of anti-GBM disease usually co-exists with glomerulonephritis and is typically treated with a combination of prednisolone, plasmapheresis and cyclophosphamide induction titrated according to disease activity and anti-GBM antibody levels [102].

AH secondary to HSP has sometimes been found to resolve with prednisolone monotherapy [66], or combined with cyclophosphamide [103] or cyclosporin, while other studies reported fatalities despite treatment with prednisolone [104]. No studies of pulmonary HSP involvement and plasma exchange were detected in the literature. PAN is treated in a similar fashion to AAV [105].

For cryoglobulinaemic manifestations threatening vital organ function, a combination of plasmapheresis, glucocorticoids and cyclophosphamide is usually recommended, with reports of rituximab or infliximab as other emerging efficacious therapies [106,107]. Cryoglobulinaemia associated with hepatitis C is treated with corticosteroids and anti-viral agents and cyclophosphamide is avoided.

**Table 4. Aspects to address in the treatment with pulmonary vasculitis (applicable to all types).**

| |
|---|
| Control of vasculitis |
| Intravenous glucocorticoids, cyclophosphamide or rituximab |
| Plasma exchange |
| Detection and treatment of 'refractory' vasculitis |
| Rituximab, intravenous immunoglobulin |
| Monitoring of vasculitis activity |
| Clinical symptoms (including extrapulmonary) |
| ESR, C-reactive protein and ANCA |
| Lung function tests |
| Imaging |
| Supportive measures |
| Maintenance of euvolaemia |
| Treatment of anaemia (Hb > 10 g/dl) |
| Correction of coagulopathy |
| Ventilation (non-invasive if possible) with minimal pressure support |
| Diagnosis and treatment of infection |
| Blood and sputum cultures |
| Bronchoscopy and BAL culture |
| Prophylactic antimicrobial therapy |
| Minimisation of glucocorticoids and immunosuppression |
| Detection of concomitant conditions that may mimic vasculitis |
| Infection, ARDS, fibrosis |

ANCA: Anti-neutrophil cytoplasmic antibody; ARDS: Acute respiratory distress syndrome; ESR: Erythrocyte sedimentation rate; Hb: Haemoglobin.

#### *4.1.3 Treatment of severe pulmonary vasculitis requiring respiratory support (category 4)*

Cylophosphamide combined with intravenous glucocorticoids are effective for severe pulmonary AAV, albeit with a need for heightened awareness of potential for subsequent sepsis with atypical presentations. Antifungal and antibiotic prophylaxis against *Pneumocystis jirovecii* is recommended for all patients, regardless of the need for ventilatory support. After reports of efficacy in pulmonary anti-GBM disease [108], adjunctive plasma exchange has also been used for AH due to AAV with conflicting reports from heterogeneous uncontrolled studies [109,110] and awaiting to be systematically assessed in the ongoing PEXIVAS trial.

The mechanism of plasma exchange is unclear and involves removal of ANCA, various chemokines or coagulation factors; the latter ought to be replaced in the case of active AH. Plasma exchange also has the potential to remove therapeutic agents, therefore, intravenous immunosuppressives should be administered after a PLEX session. A few cases of life-threatening AH have been treated effectively with intrapulmonary recombinant factor VII [111] or extracorporeal membrane oxygenation [112].

High flow oxygen is frequently needed but may, in theory, increase activation of neutrophils and oxidative damage. Respiratory failure secondary to pulmonary vasculitis requires assisted ventilation and its non-invasive form is particularly valuable for reducing the need for intubation. Co-existent fluid overload secondary to renal vasculitis may exacerbate the respiratory status and sometimes requires haemodialysis or haemofiltration.

The few cases of severe AH secondary to mixed essential cryoglobulinaemia [69] reported high mortality in the majority, despite intensive immunosuppressive and PLEX therapy.

### 4.2 Refractory pulmonary vasculitis

Refractory pulmonary vasculitis carries a higher risk of mortality [113] and is important to distinguish from respiratory distress syndrome, pulmonary fibrosis or sepsis. Bronchoscopy is important for detection of microbial colonisation, which may exacerbate the persistent vasculitis. Any escalation of glucocorticoids and cyclophosphamide in this setting needs to be weighed against the increased infective risk and this balance can be difficult to achieve. Intravenous immunoglobulin is safer and may be effective to spare the use of other immunosuppressives but cost and availability limit its use [114]. Further plasma exchange probably also permits reduced glucocorticoid dosing.

Rituximab, a B-cell depleting anti-CD20 monoclonal antibody may be safer than cyclophosphamide and more effective against relapsing or refractory ANCA vasculitis [98,99]. The studies comparing the various treatments for refractory vasculitis have so far not focused specifically on pulmonary disease. Other therapies for refractory AAV include anti-TNF agents, for example, infliximab [115], or deoxyspergualin [116], alemtuzumab, a lymphocyte depleting anti-CD52 monoclonal antibody [117] and anti-thymocyte globulin.

### 4.3 Maintenance of remission

Maintenance immunosuppressive agents such as azathioprine or methotrexate are milder than induction therapy and usually instituted after 3 – 6 months, when vasculitis remission is achieved [118]. Mycophenolate mofetil was found to be associated with higher relapse rates than azathioprine maintenance [119]. The role of maintenance glucocorticoids is not clear-cut: a meta-analysis of seven randomised controlled studies and three observational studies reported that long-term low-dose glucocorticoids (up to 7.5 mg) were associated with fewer relapse rates but no differences in mortality [120].

Risk factors for relapse include GPA, respiratory tract vasculitis +/- nasal colonisation with *Staphylococcus aureus* [10], persistently positive ANCA, withdrawal of immunosuppressives and lack of renal involvement [121]. The optimal duration of maintenance therapy is unclear and regular follow-up is important, as relapse can occur after many years from the initial diagnosis.

### 4.4 Long-term monitoring

Ongoing monitoring is key to detect future relapses of pulmonary vasculitis and comprises clinical assessment, blood tests and imaging studies. Sometimes it can be challenging to distinguish between disease activity (graded by the Birmingham Vasculitis Activity Score) and damage or other pathology, in

order to select appropriate therapy. Drug-toxicity and infection remain major causes of morbidity, often more problematic than the vasculitis itself and accounting for up to a quarter of deaths [122]. Pulmonary vasculitis may impair ciliary motility, thus increasing vulnerability to infection which is a potential trigger of further vasculitis. Microbial colonisation may require prolonged antibiotics, especially co-trimoxazole that has a role in both infection prophylaxis and reduction of vasculitis relapses [123].

Venous thromboembolism is an important differential diagnosis to pulmonary vasculitis and a previously underrecognised manifestation of vasculitis which is correlated with disease activity and degree of inflammation. Reports in more recent years [124] found a similar risk of thromboembolism in GPA to that of patients with previous such events. The rates of thromboembolic events in other vasculitides remains unclear, nevertheless physicians should regard patients with vasculitis as higher risk [125].

### 4.5 Interventional management of tracheobronchial disease in GPA

A multidisciplinary approach with therapeutic immunology, microbiology, ENT surgery and respiratory medicine is required to manage this complication of GPA.

Interventional procedures are undertaken for symptomatic airway lesions not controlled by medical therapy and each case should be assessed individually as there is no consensus regarding the optimal type of intervention. Improvements in luminal diameter can be achieved by laser ablation [126] cryotherapy, balloon (Fogarty catheter) [127] or mechanical subglottic dilatation (by Maloney bougie), laryngotracheoplasty, surgical resection and reanastomosis [128]. Restenosis rates are improved by local steroid injection/inhalation or mitomycin. Although such direct therapies should usually be combined with efficient control of microbial infection and systemic immunosuppressive therapy to reduce inflammation, although tracheobronchial scarring and stenosis can be present in the absence of vasculitis activity [129].

Tracheal or bronchial stents are complicated by an exuberant epithelial reaction leading to secondary stenosis and should be avoided when possible, especially if the vasculitis is active.

Critical airway stenosis refractory to medical and dilatational treatment can be relieved by tracheostomy and up to 50% of patients may require multiple interventional procedures for restenosis [129].

## 5. Conclusion

Considerable progress has been achieved recently in the diagnosis and management of the challenging pulmonary vasculitides, with higher resolution non-invasive imaging modalities and less toxic therapies, although there is still room for improvement with regards to development of more specific laboratory immunological tests and tailored therapeutic strategies.

## 6. Expert opinion

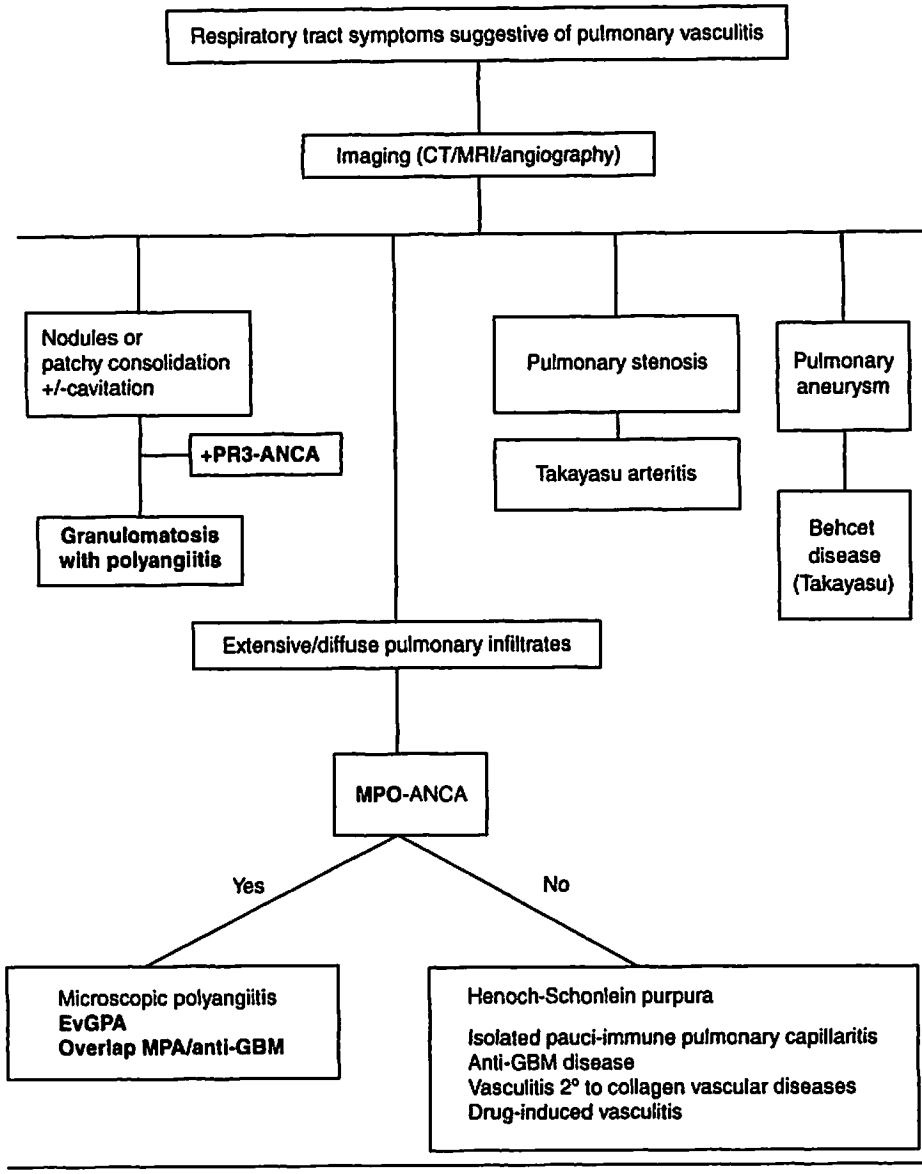
The diagnoses of the pulmonary vasculitis syndromes are challenging in view of their uncommon prevalence, often vague, non-specific presentation overlapping with features of connective tissue diseases, cancer and infection. Correct and timely diagnosis is important to optimise patient outcomes and avoid inappropriate immunosuppressive treatment. When interpreting an abnormal chest imaging or respiratory symptoms, other manifestations such as arthralgia, rash, sinusitis, uveitis or peripheral neuropathy ought to raise suspicion of underlying vasculitis. Blood tests often reveal mainly non-specifically elevated inflammatory markers, although ANCA and anti-GBM antibodies are more specific and usually suggestive of pauci-immune small-vessel vasculitides and anti-GBM disease, respectively. Findings on thoracic imaging can be variable and not diagnostic of a particular vasculitis type. Unexplained alveolar infiltrates can be caused by more than one type of vasculitis and should raise the possibility of AH, especially with concomitant renal impairment. The underlying cause of the AH cannot be deduced from its appearance on imaging.

Small-vessel vasculitides are the most common causes of pulmonary vasculitis. Unexplained pulmonary nodules or cavities are typical of GPA. Characteristic features of EGPA include patchy ground-glass opacities or consolidation with co-existing asthma, eosinophilia and peripheral neuropathy, rash or perinuclear ANCA. Clinical evidence of ischaemia or arterial wall thickening on imaging are suggestive of large-vessel vasculitis, while pulmonary artery aneurysms with our without orogenital ulcerations and uveitis raise the suspicion of Behçet's disease. The more selective technologies of immunoadsorption and lymphocytapheresis have the potential to offer future targeted removal of pathogenic factors thus reducing toxicity. The best evidence base comparing therapeutic regimens stems from randomised controlled trials of ANCA vasculitis, however, none focus on pulmonary vasculitic manifestations in particular. Future systematic studies are needed to compare the different diagnostic modalities and treatments in pulmonary vasculitides affecting blood vessels of various sizes.

The diagnosis-making process is facilitated by an algorithmic-like, pattern recognition approach (Table 5) that narrows the differential diagnosis and corroborates clinical, radiologic and histologic features, as a single test is usually not pathognomonic in isolation.

Following the recent genome-wide association study, its characterisation of CD8 T-cell genetic signatures predictive of relapse [130] and MHC associations in vasculitides, genetic tests have the potential to become increasingly important biomarkers for diagnosing patient groups with higher risk for developing pulmonary vasculitis and future relapses. Identification of individual genetic characteristics predictive of vasculitis risk and pulmonary involvement, refinement of more selective therapeutic strategies including monoclonal

**Table 5. Algorithm for differential diagnosis of pulmonary vasculitides.**




antibodies with specific mechanism of action (such as rituximab) and immunoadsorption/lymphocytapheresis will also provide a more tailored future approach in the management of vasculitic disorders.

Novel techniques for imaging vascular inflammation such as 'virtual', non-invasive angiography (using CT or MR technology), high-resolution ultrasound and FDG-PET are likely to be used more widely for assessing pulmonary and general vasculitis activity, as well as disease response in order to guide therapy, especially in the vasculitides lacking specific laboratory diagnostic tests such as ANCA or anti-GBM antibodies.

The greatest challenges are the overlapping, often unclear multisystem manifestations of vasculitides and their relative rarity which explains the paucity of large controlled studies in the past and necessitates coordinated efforts from international collaborative research networks in order to obtain sufficient statistical power in future systematic, global-scale studies.

## Declaration of interest

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