ANCA associated vasculitis

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AAV

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangitis (MPA)
- Renal limited vasculitis (pauci-immune GN)
- Eosinophlic granulomatosis with polyangitis (EGPA)
- Affecting Small –sized arteries

Introduction

- Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody–associated vasculitis.

- Characterized by a necrotizing vasculitis that can involve almost any organ.

- The diseases commonly affect the kidneys, lungs, upper respiratory tract, skin, eyes, and peripheral nerves.

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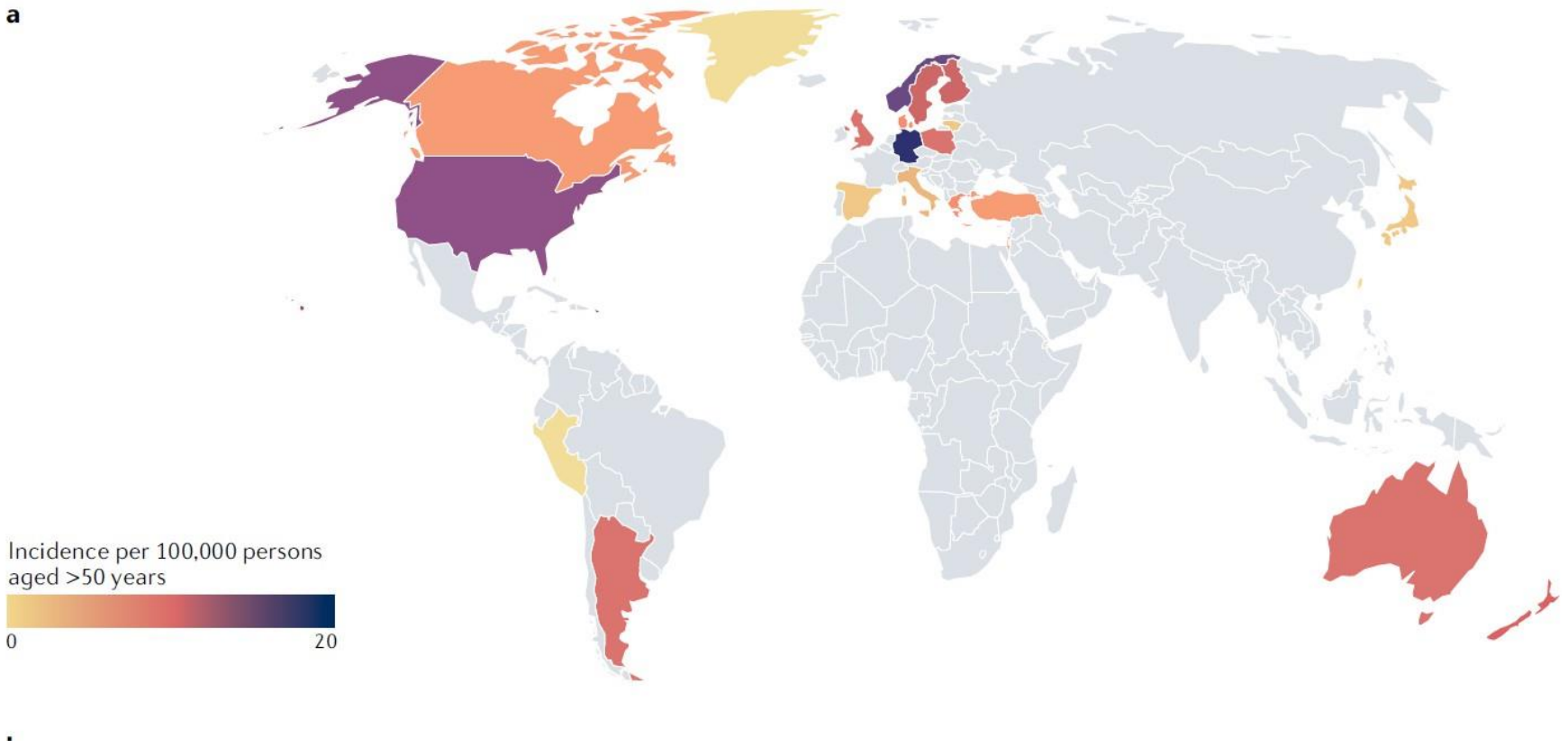
Epidemiology



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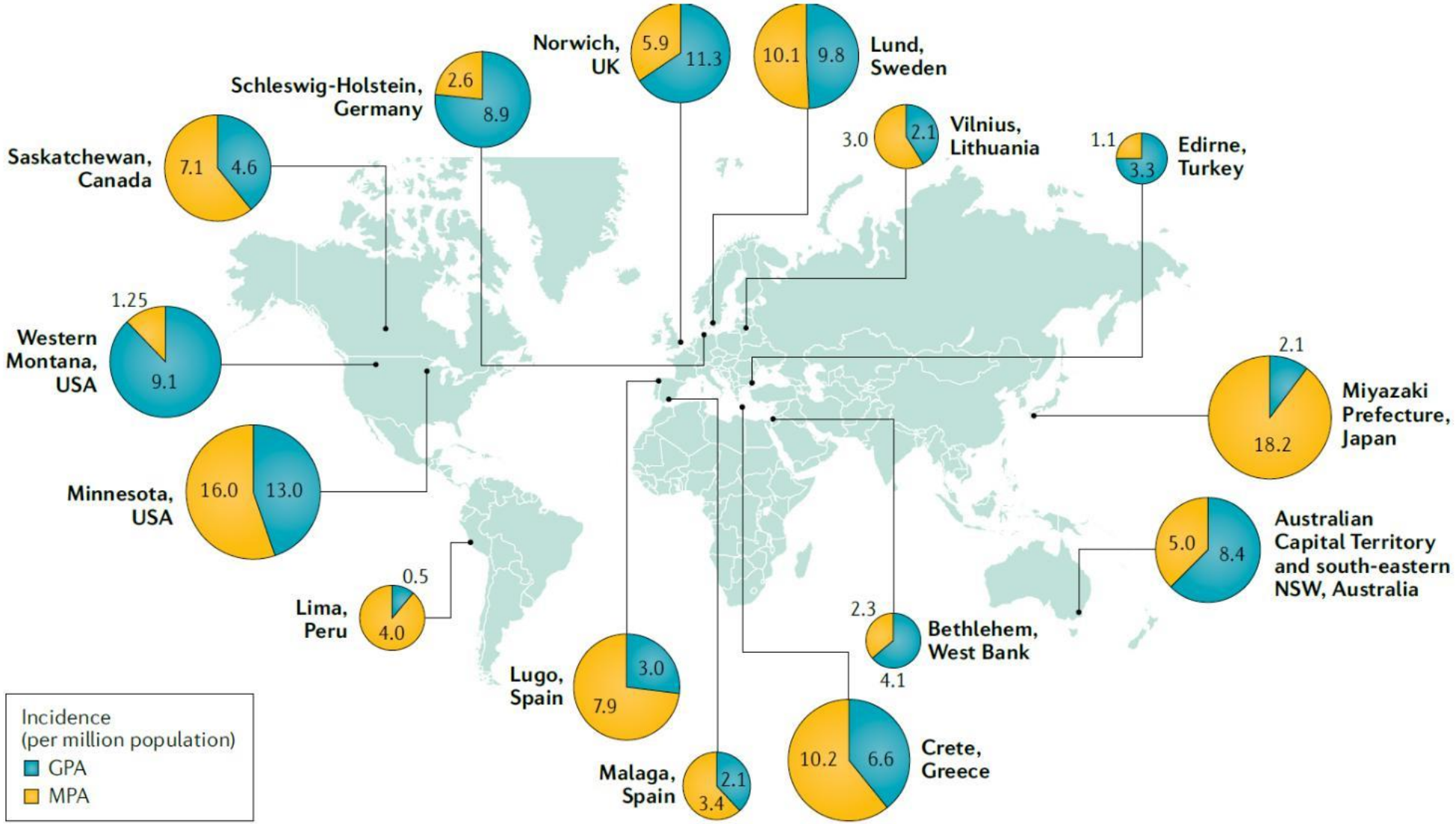
Norwich, UK
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Saskatchewan, Canada
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Edirne, Turkey
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Western Montana, USA
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Miyazaki Prefecture, Japan
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Minnesota, USA
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13.0
Australian Capital Territory and south-eastern NSW, Australia
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Lima, Peru
4.0
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Bethlehem, West Bank
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Lugo, Spain
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Crete, Greece
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Malaga, Spain
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Incidence (per million population)
GPA
MPA

Disease	Incidence * [7]	ANCA-Positivity	PR3-ANCA	MPO-ANCA	Predominant Organ Involvement	Rate of Renal Involvement [77]	RPGN [77]
GPA	1.9–13	~90%	~75%	~20%	Nose and sinuses, lungs, kidneys, joints, eyes	~70%	~50%
EGPA	0.8–4	~40%	<10%	30–40%	Lungs, upper airways, peripheral nerves, heart, skin	~25%	<15%
MPA	1.5–16	~90%	~25%	~60%	Kidneys	>90%	~65%

* per million person-years. Abbreviations: AAV: ANCA-associated vasculitis. ANCA: Antineutrophil cytoplasmic antibody. PR3: leukocyte proteinase 3. MPO: myeloperoxidase. RPGN: rapidly progressive glomerulonephritis. GPA: granulomatosis with polyangiitis. EGPA: eosinophilic granulomatosis with polyangiitis. MPA: microscopic polyangiitis.

AAV is an uncommon disease with an incidence of about 20 per million population per year in Europe and North America. There is a **slight male preponderance**. Incidence increases with age, with a peak in the **60- to 70-year** age range.

prevalence

- Granulomatosis with polyangitis (GPA):
- prevalence 2.3 to 146.0 cases per million persons
- Incidence of 0.4 to 11.9 cases per million person-years .
- Microscopic polyangitis (MPA)
- Prevalence 9.0 to 94.0 cases per million persons
- Incidence of 0.5 to 24.0 cases per million person-years .

- A global study reported that MPO-ANCA was much more common in Japanese, Chinese, and Southern European individuals than in Northern European individuals.

- In the same study, ophthalmological and ear, nose and throat involvement was less common in Japanese and Chinese patients with AAV than in Northern European patients with AAV.

- In a multi-ethnic series from Chapel Hill in the USA, **GPA was less common in African American** individuals than in those with European ancestry

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2012 International Chapel Hill Consensus Conference (CHCC 2012) classification

- **Large vessels**
  - **Takayasu arteritis**
- **Medium vessels**
  - **Polyarteritis nodosa**
  - **Kawasaki dis**
- **Small vessels**
  - **Microscopic polyangitis, Granulomatosis with polyangiitis,**
  - **Eosinophilic Granulomatosis with polyangiitis**
- **Any vessels**
  - **Infectious vasculitis**
  - Vasculitis associated with other diseases

Small-vessel vasculitis (SVV)

- Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
  - ◇ Microscopic polyangiitis (MPA)
  - ◇ Granulomatosis with polyangiitis (Wegener) (GPA)
  - ◇ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Immune complex SVV
  - ◇ Anti–glomerular basement membrane (anti-GBM) disease
  - ◇ Cryoglobulinemic vasculitis (CV)
  - ◇ Immunoglobulin A (IgA) vasculitis (Henoch-Schönlein) (IgAV)
  - ◇ Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Medium-vessel vasculitis (MVV)

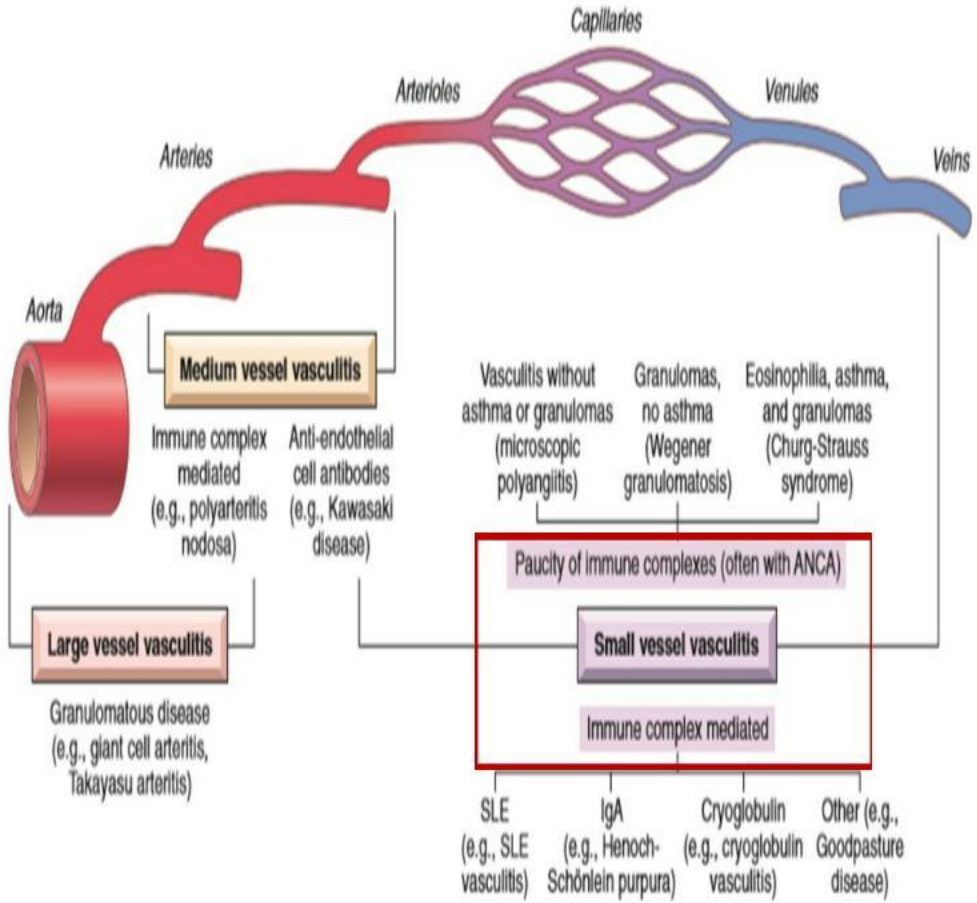
- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Large-vessel vasculitis

- Takayasu arteritis (TA)
- Giant cell arteritis (GCA)

Variable vessel vasculitis (VVV)

- Behçet disease (BD)
- Cogan syndrome (CS)



2020 American College of Rheumatology/European League Against Rheumatism

Clinical Criteria	Nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect /perforation	+3
	Cartilaginous involvement (cartilage inflammation of the ear or nose, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
	Conductive or sensorineural hearing loss	+1
Diagnostic Testing Criteria	cANCA or anti-PR3 ANCA positive	+5
	Pulmonary nodules, mass, or cavitation on chest imaging	+2
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
	Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
	Pauci-immune glomerulonephritis on biopsy	+1
	pANCA or anti-MPO ANCA positive	-1
	Serum eosinophil count ≥ 1 ($x10^9$/L)	-4

Sum scores for 10 items, if present. A score of ≥ 5 is needed for classification of granulomatosis with polyangiitis.

ANCA-use in diagnosis

c ANCA/PR3

- **Very specific for GPA**
- **Sensitive for diffuse disease**
- **Increasing recognition of false positives**
- **Less specific at very low titer**

P ANCA /MPO

Usually associated with MPA in > 50-75%, also 15% GPA

Renal limited vasculitis ANCA + 75 -80 % having MPO/ANCA

- **Other associations: Infections,IBD, EGPA, drug induced**
- **False positives (by IIF) if ANA present**

IIF MORE sensitive

ELISA MORE specific

ANCA-Negative Pauci-Immune Vasculitis

- **A subgroup (10%) of patients with clinical features and pathology consistent with AAV remain ANCA negative**

- **Failure of assay???**
- Masked by circulating fragments of enzymatically degraded ceruloplasmin, which may be elevated in patients with active disease

- **ANCA-negative patients are more likely to have renal-limited disease or less severe systemic disease.**

ANCA- use in management

- **Often (not always) correlates with disease activity**
- **Increasing titer predictive of flare in SOME (not all) cohorts reported**

DO NOT TREAT ISOLATED RISES IN ANCA TITER

LAB TEST

- ESR ,CRP
- ANA
- Anti-GBM
- C3 ,C4
- Cryoglobulin
- HBV ,HCV , HIV
- LFT
- Tuberculosis screen

Microscopic Polyangiitis (MPA)

- **Necrotizing small-medium vessel vasculitis**
- **Pulmonary and renal involvement most common**
- **Association with ANCA**
  - **perinuclear pattern (pANCA)**
  - **Anti-myeloperoxidase (MPO) specificity by ELISA (80-85% MPO positive)**

Microscopic polyangiitis (MPA)

Constitutional manifestations:

- Fever (55%)
- Malaise, fatigue, flulike syndrome
- Myalgia (48%)
- Weight loss (72%)

Renal manifestations:

more than 80% of patients and on a spectrum from asymptomatic hematuria to necrotizing crescentic GN causing end-stage kidney disease. (Risk of RRT 10%)

Other manifestations :

Skin - Rash (50%), Arthralgias (10-50%)

Pulmonary - Hemoptysis (11%), dyspnea, cough

Cardiovascular – Chest pain, symptoms of heart failure

Gastrointestinal (GI) - GI bleeding, abdominal pain

Neurologic - mononeuritis multiplex (57%); CNS- (seizures) (11%

MPA

- Most patients (55 to 65 percent) are positive for MPO-ANCA.
- The kidneys and skin are very commonly affected
- ENT involvement is less frequent in MPA than in GPA.
- Tissue biopsy

  necrotizing vasculitis

  pauci-immune necrotizing glomerulonephritis is common.
- In contrast with GPA, granulomatous inflammation is generally **absent.**

GPA (symptoms and signs)

- typically present with of small-vessel vasculitis involving the ear, nose, and throat (ENT)
- airways and lungs; kidneys; skin; eyes; and/or peripheral nervous system.
- Most patients (65 to 75 percent) are positive for PR3-ANCA.
- Tissue biopsy typically shows evidence of necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting small-to-medium vessels;
- pauci-immune necrotizing glomerulonephritis is common.

- They are younger at disease onset and more likely to be women

Serotype versus Clinical Syndrome

- ANCA antigen specificity is more closely associated with disease phenotype/prognosis than the clinical syndrome
- PR3-ANCA
  - Granulomatous inflammation
  - More extensive extrarenal involvement
  - Higher relapse rate
- MPO-ANCA
  - Renal-limited disease
  - More kidney scarring
  - Carries an overall worse renal prognosis

- **kidney presentations**
- **MPO-ANCA**-associated vasculitis affecting the kidney can have a **slowly progressive phenotype** characterised by **extensive sclerosis** at diagnosis.
- **Rapidly progressive renal decline** is more typical of **PR3-ANCA**-associated vasculitis.(RPGN)
- **More patients with MPO-ANCA-associated** vasculitis **reach end stage** kidney disease or already have advanced kidney damage at presentation.

- **Substantial overlap exists** between the **PR3-ANCA** and **MPO-ANCA** disease subsets.

- **Usual interstitial pneumonia** is a pulmonary finding that almost always occurs in association with **MPO-ANCA-associated vasculitis**

- **Cavitary pulmonary nodules** **are largely exclusive** to patients with **PR3-ANCA-associated vasculitis.**

Some patients with GPA or MPA present with vasculitis limited to a single organ, such as the kidneys, ENT tract or lungs, which may represent the early stages of AAV.

However, in MPO- ANCA+ patients with MPA, isolated renal disease or isolated pulmonary fibrosis is not infrequent.

✓ A minority of MPO- ANCA+ patients with MPA also have anti- glomerular basement membrane antibodies and exhibit a hybrid disease phenotype.

(Dual-Positive ANCA and Anti-GBM Disease)

Moreover, individuals with systemic lupus erythematosus or systemic sclerosis can be MPO- ANCA+ and develop some features of AAV, especially the vasculitic pattern of glomerulonephritis.

- Specific drugs induce ANCA formation; these include **propylthiouracil**, **allopurinol**, **D-penicillamine**, **hydralazine**, and **levamisole** (which may be a contaminant of cocaine).
- Patients with drug-induced ANCA may develop lesions that are indistinguishable from those of MPA, GPA, or EGPA.

Table 1 | **Comparison of the three syndromic presentations of AAV**

Feature	GPA	MPA	Eosinophilic GPA
Incidence	0.4–11.9 cases per 1 million person-years	0.5–24.0 cases per 1 million person-years	0.5–2.3 cases per 1 million person-years
Prevalence	2.3–146.0 cases per 1 million persons	9.0–94.0 cases per 1 million persons	2.0–22.3 cases per 1 million persons
Typical age of onset (years)	45–65	55–75	38–54
Male: female ratio	1:1	1:1	1:1
2012 revised CHCC definition[145]	Necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract; necrotizing vasculitis affecting predominantly small-to-medium vessels (such as capillaries, venules, arterioles, arteries and veins); necrotizing glomerulonephritis is common	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (such as capillaries, venules or arterioles); necrotizing arteritis involving small and medium arteries may be present; necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs; granulomatous inflammation is absent	Eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract; necrotizing vasculitis predominantly affecting small-to-medium vessels; associated with asthma and eosinophilia; ANCA$^+$ is more frequent when glomerulonephritis is present
Frequency of ANCA	PR3-ANCA$^+$: 65–75% MPO-ANCA$^+$: 20–30% ANCA$^-$: 5%	PR3-ANCA$^+$: 20–30% MPO-ANCA$^+$: 55–65% ANCA$^-$: 5–10%	PR3-ANCA$^+$: <5% MPO-ANCA$^+$: 30–40% ANCA$^-$: 55–65%
Key innate immune cell	Neutrophil	Neutrophil	Eosinophil
Relapse rate	Higher than MPA (or MPO-AAV)	Lower than GPA (or PR3-AAV)	Relapse is frequent

RPGN: 80-100%

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CHCC, Chapel Hill Consensus Conference; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, leukocyte proteinase 3.

Table 2. Comparison of Clinical Features by ANCA Specificity

	PR3-ANCA	MPO-ANCA
Demographics	50-70 y	60-80 y (mean, 10 y older than PR3-ANCA)
Geography	Northern Europe, North America	Southern Europe, Asia
Genetic risk alleles	*HLA-DP, PRTN3, SERPINA1*	*HLA-DQ*
Pathology	Necrotizing vasculitis, granulomatous inflammation	Necrotizing vasculitis, no granulomatous inflammation
Renal	More acute presentation	More common, more chronic injury on biopsy, may have a slow indolent course, more likely renal limited, isolated interstitial kidney disease (rare), usually MPO-ANCA
Respiratory involvement	More common; nodules, cavitation, and central airway disease more specific to PR3	Less common; may be chronic lung fibrosis, peripheral reticulation, honeycombing and usual interstitial pneumonia more specific to MPO
Upper airway disease	More common, destructive lesions (nasal perforation, saddle nose)	Rare
Outcomes	More likely to have resistant disease	Worse long-term survival (more chronic injury)
Relapse rate	Higher	Lower
Treatment	May respond better to rituximab than cyclophosphamide	Similar response to rituximab and cyclophosphamide

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

These classification criteria should be applied when a diagnosis of small or medium vessel vasculitis has been made, to classify a patient as having microscopic polyangiitis. Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria.

Clinical	Nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect /perforation	-3
Diagnostic Tests	pANCA or anti-MPO ANCA positive	+6
	Fibrosis or interstitial lung disease on chest imaging	+3
	Pauci-immune glomerulonephritis on biopsy	+3
	cANCA or anti-PR3 ANCA positive	-1
	Serum eosinophil count ≥ 1 ($x10^9$/L)	-4

Sum scores for 6 items. A score of ≥ 5 is needed for classification of MPA

ANCA: anti-neutrophil cytoplasmic antibody; cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; pANCA: perinuclear anti-neutrophil cytoplasmic antibody; PR3: proteinase 3

Tissue biopsy

- Skin
- Kidney
- Lung (rare)
- Nasal (un helpful)

In the kidneys

The characteristic lesion in AAV is

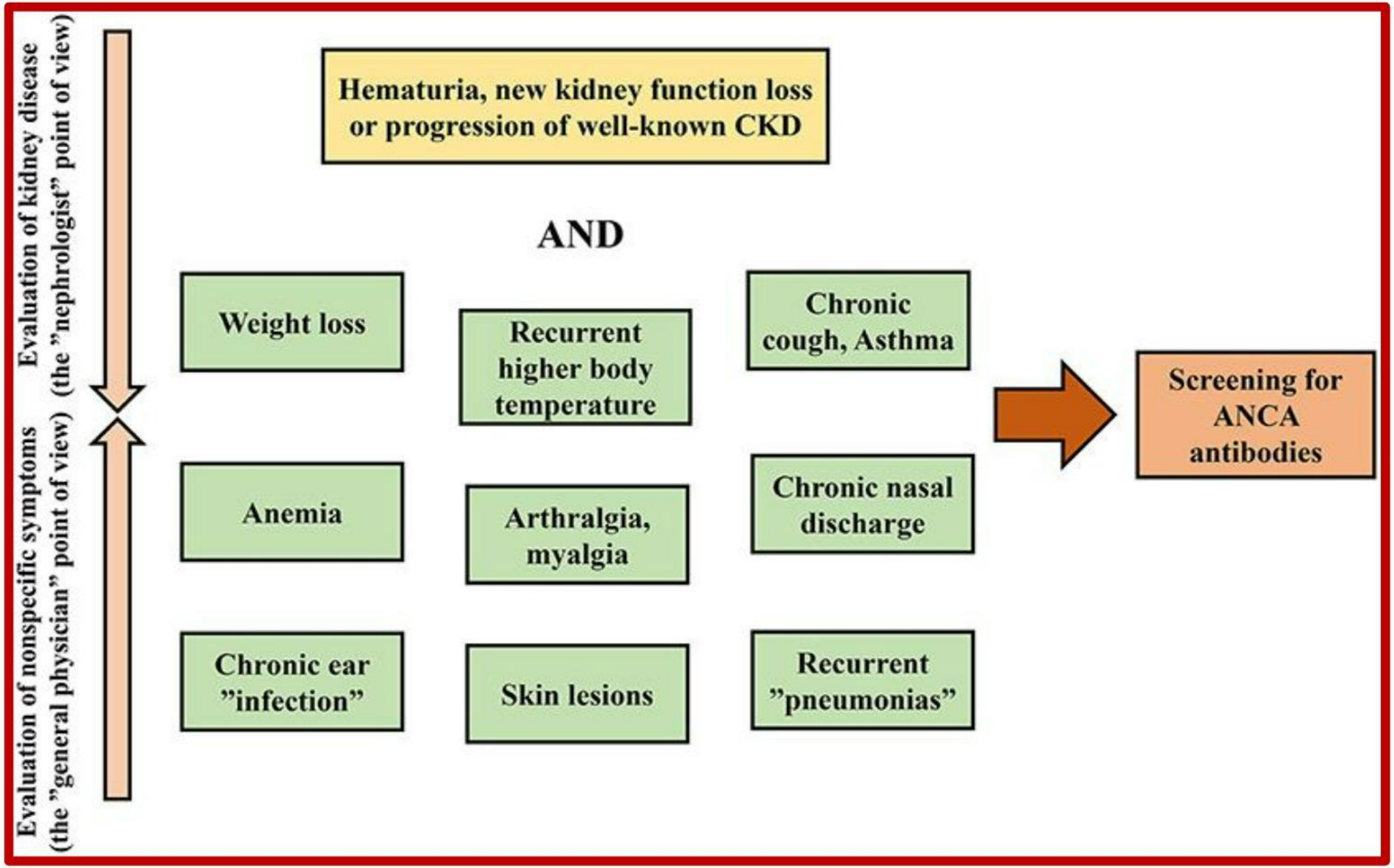
Segmental necrosis of glomerular capillary loops, with little or no deposition of immunoglobulin

or complement, termed

pauci -immune focal necrotizing and crescentic GN

Table 2. Classification of ANCA-associated glomerulonephritis *.

Class	Criteria
Focal	≥50% of glomeruli are normal
Crescentic	≥50% of glomeruli have cellular crescents
Sclerotic	≥50% of glomeruli are globally sclerosed
Mixed	Not fulfilling any of the above criteria


Evaluation of kidney disease (the "nephrologist" point of view)
Evaluation of nonspecific symptoms (the "general physician" point of view)
Hematuria, new kidney function loss or progression of well-known CKD
AND
Weight loss
Recurrent higher body temperature
Chronic cough, Asthma
Anemia
Arthralgia, myalgia
Chronic nasal discharge
Chronic ear "infection"
Skin lesions
Recurrent "pneumonias"
Screening for ANCA antibodies

- AAV is multisystem disease with varied clinical manifestations which are sometimes non- specific
- AAV can remain undiagnosed for months or years until think about it and request ANCA testing
- Role of renal biopsy

Early treatment is advised and should be initiated as soon as a diagnosis is probable