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Vasculitis Overview and Focus on Small Vessel Vasculitis

Elizabeth Kirchner DNP
Cleveland Clinic

Slide deck co-authored by Tiffany Clark, MSN, and
Betsy Kirchner, DNP, Cleveland Clinic

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Faculty Disclosures

- Betsy Kirchner, DNP
 - Advisor: Janssen
- Tiffany Clark, MSN, CNP
 - There are no relevant financial relationships to disclose.

Learning Objectives

- The learner will identify the major types of vasculitis and correctly associate them with the associated vessel type.
- Learners will be able to recognize red flags in patients with vasculitis that require a higher level of urgency in evaluation and treatment.
- Participants will demonstrate familiarity with recent treatment guidelines for AAV.

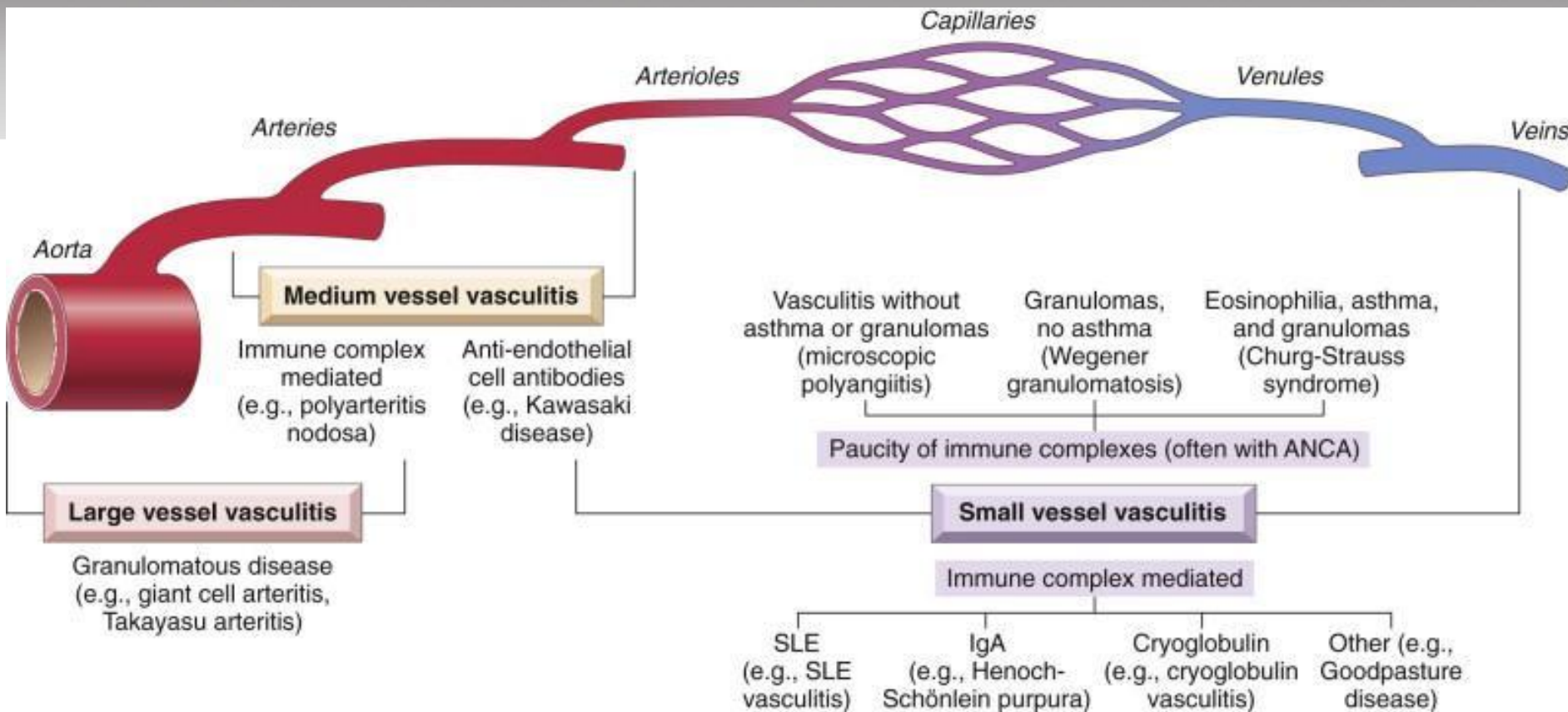
What is vasculitis?

- Group of disorders (~20)
- Inflammation (destructive) of blood vessels
- Both arteries and veins may be affected
- *Primarily caused by leukocyte migration and resultant damage*
- One of the true emergencies encountered in rheumatology

What Is Vasculitis?

Classification

- Large-vessel vasculitis
 - Aorta and the great vessels (subclavian, carotid)
 - Claudication, blindness, stroke
 - GCA, Takayasu's arteritis, Behcet's disease, Cogan's syndrome
- Medium-vessel vasculitis
 - Arteries with muscular wall
 - Mononeuritis multiplex (wrist/foot drop), mesenteric ischemia, cutaneous ulcers
 - PAN, Buerger's disease, CNS vasculitis, Kawasaki's disease, rheumatoid vasculitis
- Small-vessel vasculitis
 - Capillaries, arterioles, venules
 - Palpable purpura, glomerulonephritis, pulmonary hemorrhage
 - GPA, MPA, EGPA, cryoglobulinemic vasculitis, HSP



What Is Vasculitis?

Secondary Vasculitis Syndromes

- Drug-induced vasculitis
- Serum sickness
- Vasculitis associated with other primary diseases, infection, malignancy, rheumatic disease

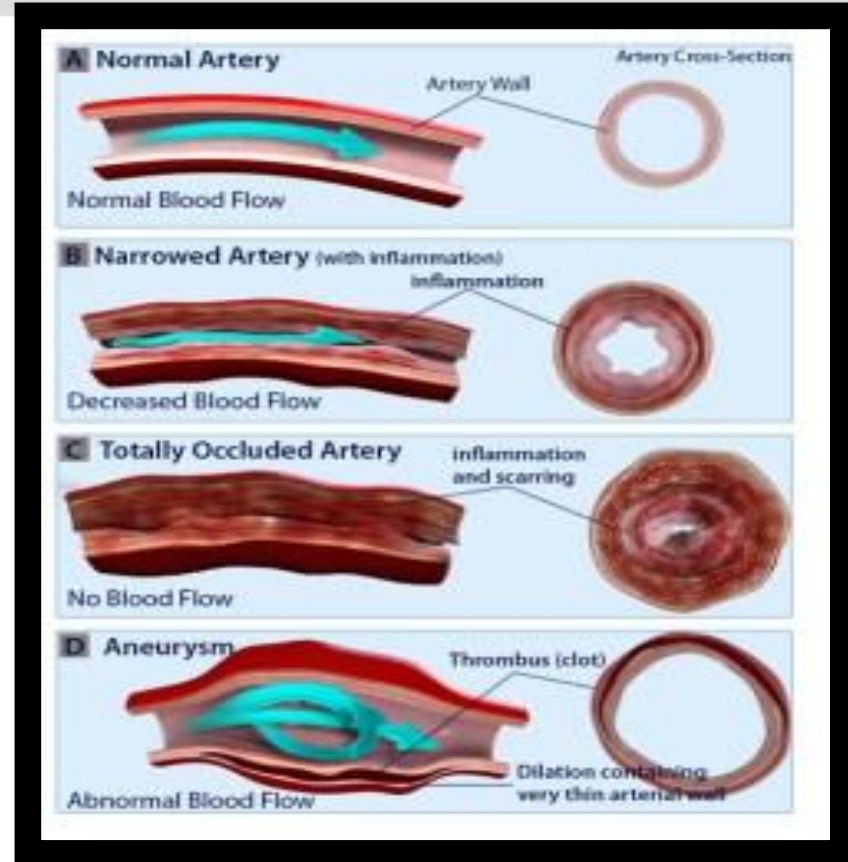
Vasculitis - General Principles

Definition

- Vasculitis = inflammation of the blood vessel.

Blood vessel damage

- 1. Compromise of vessel lumen >>> stenosis >>>> organ ischemia
- 2. Attenuation of vessel wall >>> aneurysm formation hemorrhage >>> rupture



What Does Vasculitis Look Like?

Common Clinical Manifestations

- **Systemic**
 - Fever, sweats, weight loss
- **Skin**
 - Palpable purpura
 - Rash
 - Ulcers
- **Neurologic**
 - Mononeuritis Multiplex
- **Musculoskeletal**
 - Arthralgia/arthritis
 - Muscle pain/ Claudication
 - Myositis
- **Respiratory**
 - Sinusitis/Epistaxis
 - Pulmonary infiltrates
- **Gastrointestinal**
 - Abdominal pain
 - Bloody stools
 - Hepatitis/pancreatitis/cholecystitis
- **Genitourinary**
 - Testicular pain
 - Urinary casts/hematuria
- **Renal**
 - Glomerulonephritis
 - Hypertension
- **Ocular**
 - Scleritis/Iritis
 - Retinal vasculitis

What Does Vasculitis Look Like?

Diagnosis

- **Diagnosis of a systemic vasculitis is often a diagnosis of exclusion, based on recognition of the clinical syndrome**
 - e.g. EGPA: adult onset asthma x 2 years, followed by atypical pneumonias, followed by peripheral nerve involvement
- **Biopsy of involved organ is the most straightforward method of establishing a diagnosis**
 - Biopsy may be helpful to exclude infection/malignancy
- **Other tests may be suggestive, but not diagnostic**
 - Blood
 - ANCA
 - Urine
 - Imaging
 - Scope

What are ANCA's?

- Autoantibodies
- Anti-neutrophil cytoplasmic antibodies
 - Antibodies against myeloperoxidase (MPO-ANCA “p”) and Proteinase 3 (PR3-ANCA “c”)
- Not 100% specific or sensitive, but still can be very useful

pANCA disease association

- Primary vasculitis
MPA
EGPA
PAN
- Collagenosis
Felty's syndrome
SLE
Rheumatoid arthritis
Sjögren's syndrome
- Chronic inflammatory bowel disease
- Chronic liver disease
Primary sclerosing cholangitis

cANCA disease association

- *Primary vasculitis*
- *GPA*
- *MPA*
- *EGPA*

Atypical

- Primary sclerosing cholangitis
- Primary biliary cirrhosis
- Autoimmune hepatitis
- SLE
- RA

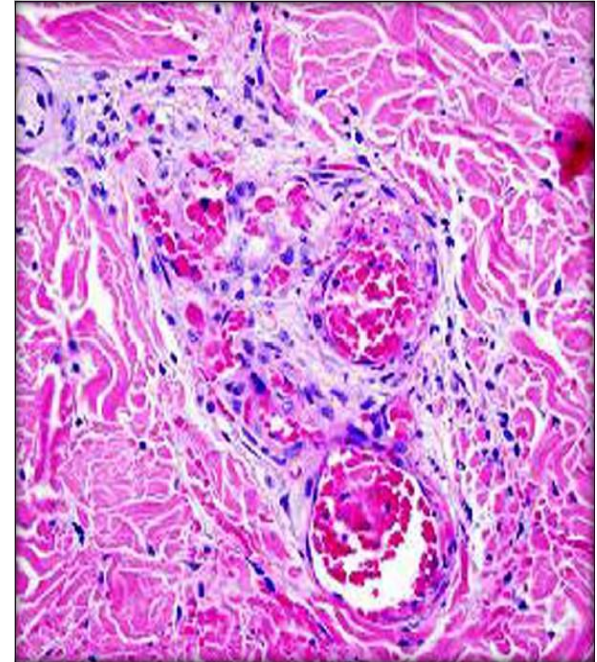
Small Vessel Vasculitis

How to approach

- Confirm diagnosis
- Good review of systems
- Laboratories studies

1. Confirm diagnosis

- Skin biopsy of skin lesions are less than 48 hours old – 4mm depth
- Leukocytoclastic vasculitis is neutrophilic infiltration, fibrinoid necrosis of the blood vessel wall and extravasation of red blood cells.
- DIF : to look for immune complex deposits (IgA + C3)



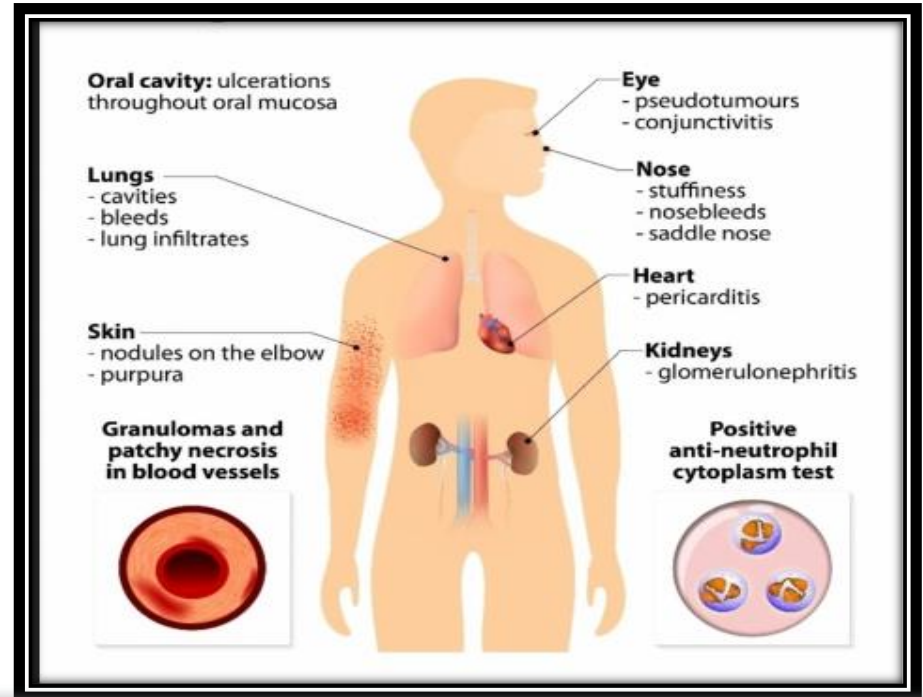
Small Vessel Vasculitis

2. Good history/review of systems

Medications/ infections / malignancy/ illicit drugs

Limited cutaneous vasculitis vs systemic vasculitis

- Constitutional symptoms
- Nasosinus
- Ocular
- Respiratory
- Cardiovascular
- Musculoskeletal
- Nervous system
- Urinary



Small Vessel Vasculitis

3. Laboratory studies

- No standard protocol but should be guided by the clinical signs and clinical manifestations.

A must:

- CBC, CMP, Urinalysis.

Additional testing:

- ANA by IFA, c3, c4, ANCA, RF, CCP abs, DM- PM panel, cryoglobulins
- Hepatitis C, B, HIV
- CT chest/sinus, CTA, arteriogram, EMG, MRI brain and orbits.
- Biopsies : Kidney, sinus, lung, nerve.

GPA: Nasal Exam

- Critical element
- Nasal speculum required
- Tilt head back, gently exam inner mucosa of nares
- Nasal: crusting, blood (epistaxis), “cobblestone appearance/granular/friable”, nasal septal perforation (trans lumination of light), saddle nose appearance (late, ? mimic) , nasal ulcers, nasal chondritis
- Oral: ulcerative stomatitis, hyperplastic gingivitis, ulcerations

GPA- Nasal Exam



https://en.wikipedia.org/wiki/Granulomatosis_with_polyangiitis

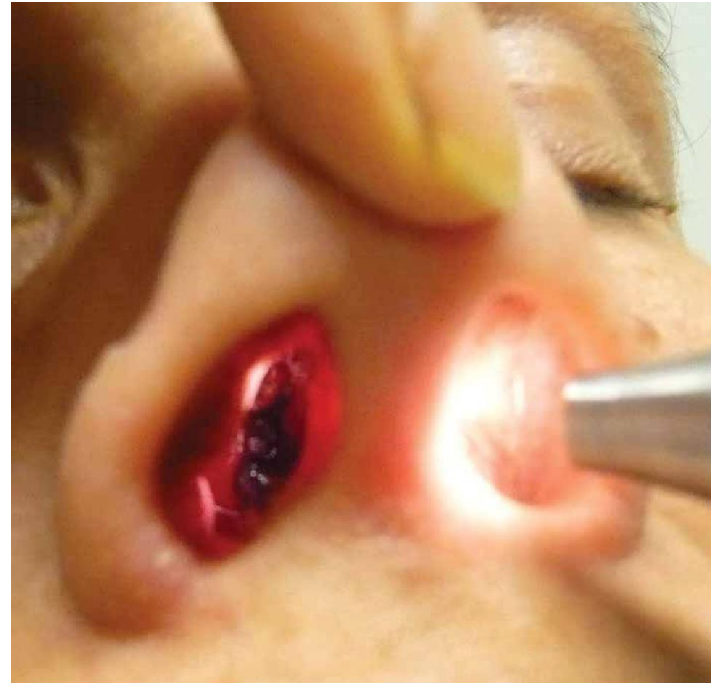


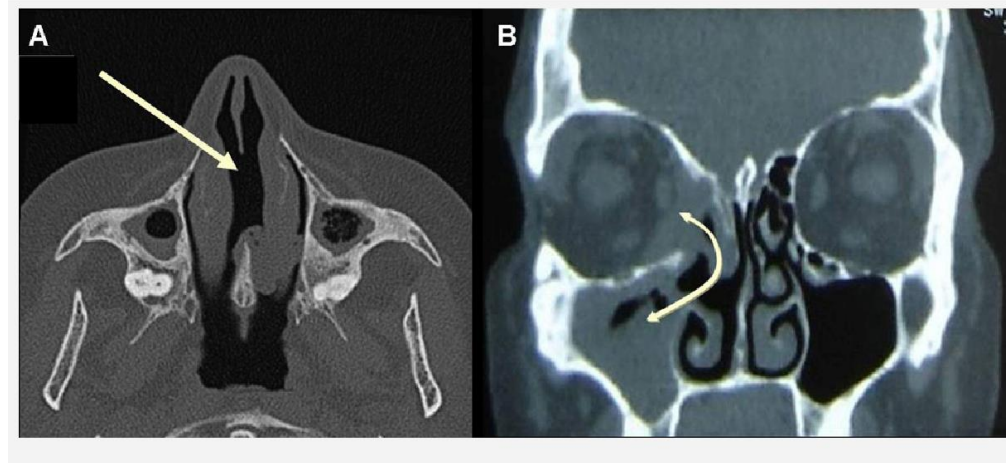
Figure 3. Nasal septum perforation in a patient with polyangiitis (GPA).

<https://www.semanticscholar.org/paper/Updates-in-ANCA-associated-vasculitis.-Pagnoux/c47def732ecb8a99a303d5eaaff6f6a5f23fee73/figure>

GPA: Sinus exam

Sinus

- Thick fluid filled sinus cavities
- Recurrent “sinus” infections
- Dullness to percussion of sinuses



GPA : Orbital Exam

- Conjunctivitis, Scleritis, Episcleritis
- Nasal-Lacrimal gland obstruction- ? Tearing
- Orbital pseudo tumor- check ocular motions, ?
Double vision (diplopia), loss of vision, color changes, * proptosis of eye
 - Strangulation of optic nerve
 - Entrapment of extra ocular muscles

GPA: Orbital

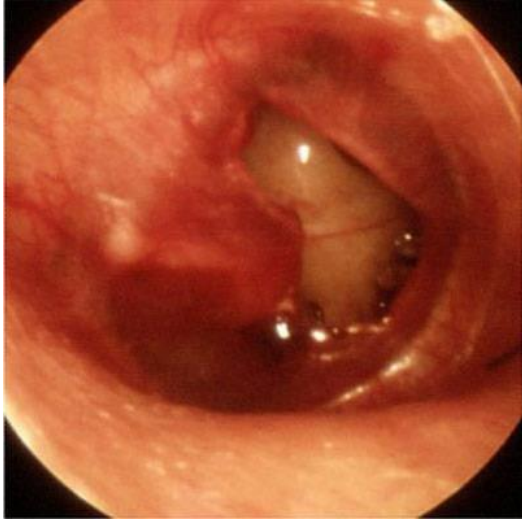


<https://www.merckmanuals.com/professional/musculoskeletal-and-connective-tissue-disorders/vasculitis/granulomatosis-with-polyangiitis-gpa>

GPA: Ear

- Must use ear speculum
- “recurrent ear infections”
- Visual inside ear- Fluid filled (serous or suppurative otitis media), red, draining, TM perforation, ? chondritis of ear
- Inner ear changes: hearing loss (sensorineural deafness- hearing test required), vertigo

GPA: Ear



GPA/MPA: Pulmonary Exam

- Stethoscope
- Wheezing, crackles, diminished lung sounds
 - Infiltrates, nodules, hemorrhage
- Stridor over the tracheal air way (SG stenosis)
- Percussion: dullness to percussion?
- Cough, SOB, **hemoptysis**

GPA/MPA: Skin

- Leukocytoclastic vasculitis, splinter hemorrhages, nodules (EN), Livedo reticularis, urtical rashes, gangrene, palpable purpura



<https://www.consultant360.com/articles/artralgias-painful-erythematous-nodules-lower-legs>

GPA/MPA: Joints- Muscles

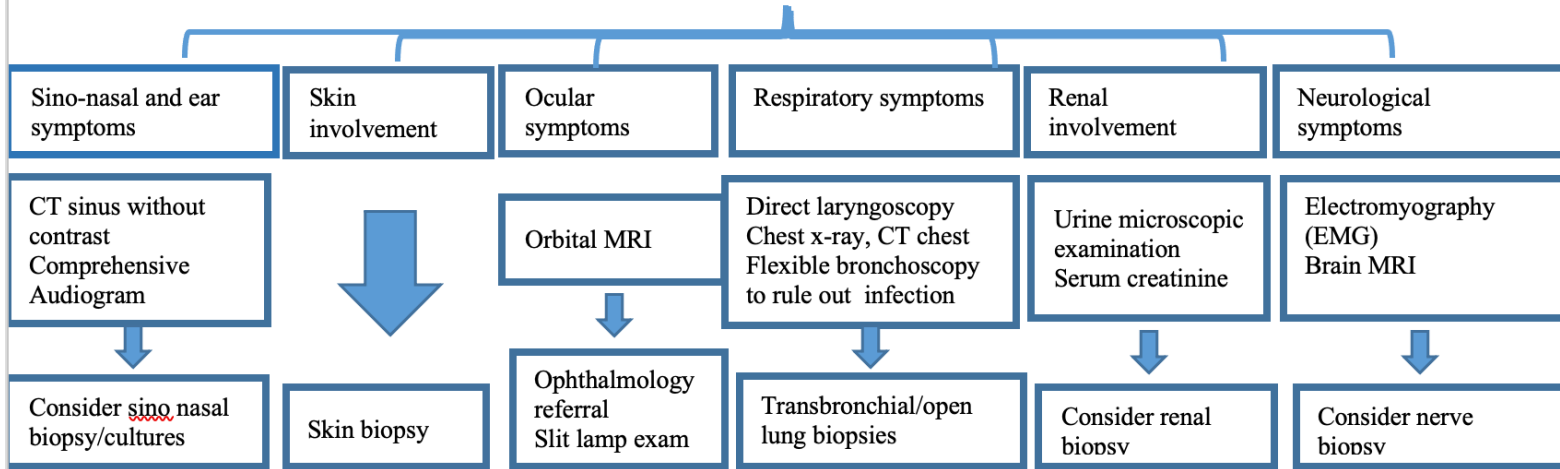
- Second most reported symptoms
- Inflamed swollen joints, may be migratory.
- Weakness- strength exam – denote upper and lower muscle groups, ? Myositis
- May mimic RA features- has been reported in up to 2/3 of patients

GPA/MPA: Neurological Exam

- Mononeuritis multiplex
- Sensory and motor exam upper and lower.
 - Foot drop
- Tuning fork vibrations
- GPA urgent issues, once nerves are inflamed and damage – may be permanent. Significant source of chronic damage
- CNS: mass-like lesions, rare- diabetes insipidus, meningitis

Figure 2: Diagnostic approach in GPA and MPA

General investigations
CBC, CRP, ESR, serum creatinine, urinalysis
ANCA testing with MPO and PR3
Chest x-ray and CT chest
Consider toxicology, hepatitis, and tuberculosis tests

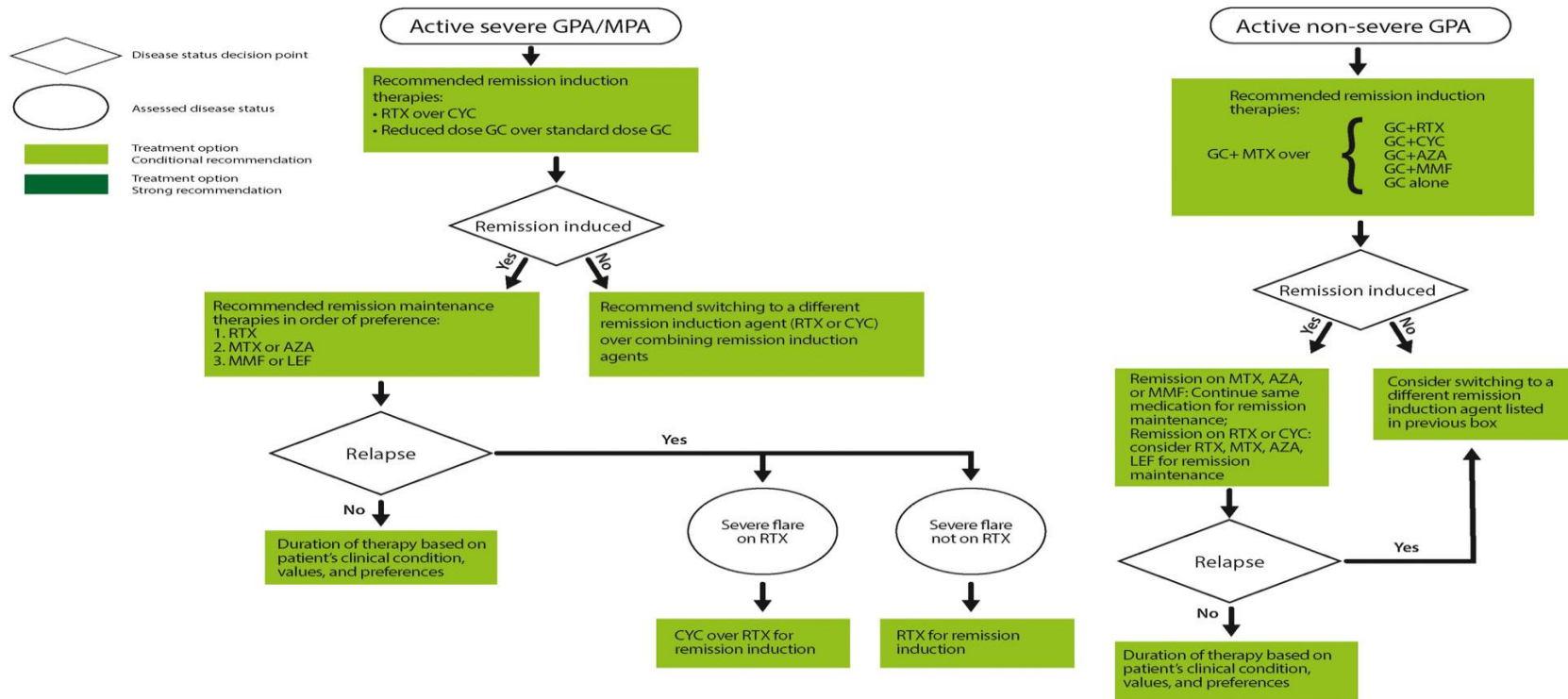


2021 American College of Rheumatology/Vasculitis Foundation Guidelines

Term	Definition
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GPA, MPA, or EGPA and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to GPA, MPA, or EGPA, on or off immunosuppressive therapy

2021 ACR/Vasculitis Foundation Guidelines for the Management of ANCA-associated Vasculitis

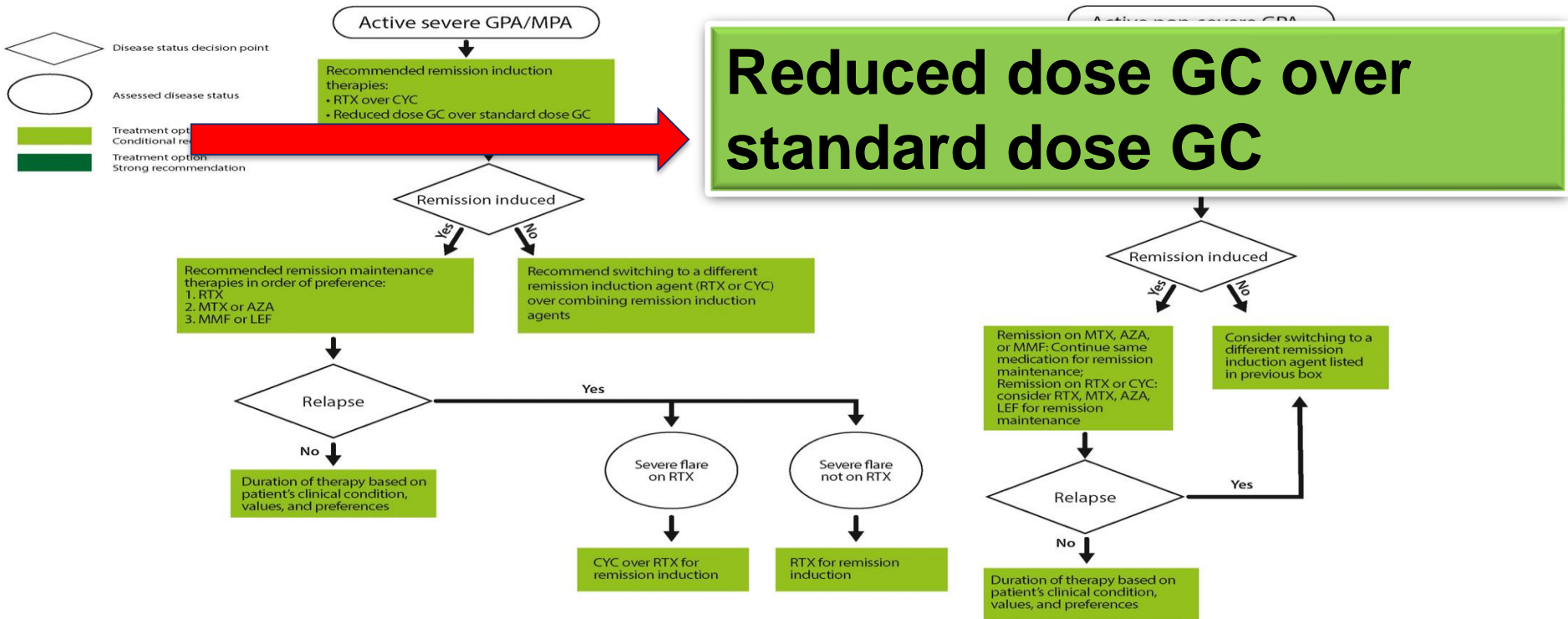
Key recommendations for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)



AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, LEF = leflunomide, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

Treatment Recommendations for GPA/MPA

Key recommendations for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)



AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, LEF = leflunomide, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

Treatment Recommendations for GPA/MPA

Disease	Recommendations
Induction: Active severe disease	<ul style="list-style-type: none"> • Recommend rituximab over cyclophosphamide • Reduced-dose glucocorticoid (GC) regimen over standard-dose GCs • Recommend against plasma exchange for active glomerulonephritis (GN) or alveolar hemorrhage
Induction: Active nonsevere dis.	<ul style="list-style-type: none"> • Methotrexate over cyclophosphamide or rituximab • Methotrexate with GCs over GCs alone • Methotrexate with GCs over azathioprine and GCs, or mycophenolate mofetil and GCs, or trimethoprim/sulfamethoxazole and GCs
Remission maintenance	<ul style="list-style-type: none"> • Recommend rituximab over methotrexate or azathioprine • Scheduled rituximab re-dosing over using ANCA titers or CD19+ B cell counts to guide re-dosing • Methotrexate or azathioprine over mycophenolate mofetil, leflunomide, or trimethoprim/sulfamethoxazole • Methotrexate and GC over trimethoprim/sulfamethoxazole and GC • Immunoglobulin supplementation for hypogammaglobulinemia and recurrent severe infections • Recommend against adding trimethoprim/sulfamethoxazole to other therapies
Relapsed disease	<ul style="list-style-type: none"> • Recommend rituximab over cyclophosphamide • Recommend cyclophosphamide over continuing rituximab if relapse occurs while receiving rituximab
Refractory disease	<ul style="list-style-type: none"> • Rituximab for cyclophosphamide refractory disease and cyclophosphamide for rituximab refractory disease over combining both therapies • Recommend adding IV immunoglobulin to current therapy

2022 EULAR Recommendations for Management of AAV (all forms)

- Testing
 - Primary method of diagnostic testing: Ag-specific assay (as opposed to indirect immunofluorescence) for both PR3 and MPO ANCA.
- Treatment (induction)
 - RTX (not MTX) should be 1st-line agent for non-organ- and non-life-threatening AAV
- Treatment (relapse)
 - RTX is the preferred agent for treatment of organ- or life-threatening AAV

2022 EULAR Recommendations for Management of AAV (GPA/MPA)

- Faster prednisone taper during induction
- No PLEX for alveolar hemorrhage
 - Can consider PLEX for sCr > 300 mmol/L
- Avacopan in combination with RTX or CYC for induction of remission (to reduce GC exposure)
- RTX: 1st-line tx for maintenance of remission
 - MTX and AZA are alternatives
 - Continue tx for at least 24–48 months for pts with new-onset disease
 - Longer for pts with relapsing disease (or risks)

2022 EULAR Recommendations for Management of AAV (EGPA)

- Mepolizumab indicated for induction of remission and for maintenance of remission in patients with relapsing or refractory EGPA without organ- or life-threatening disease.

Know your urgent findings

- AAV can progress rapidly
- AAV may lead to urgent life-threatening manifestations quickly
- AAV can be associated with severe chronic irreversible damage and severely impact quality of life

References

- *Inflammatory Disease of Blood vessels* (G. Hoffman, C. Weyand). 2002 Marcel Dekker, Inc.
- Philip Seo, MD, MHS, Johns Hopkins Vasculitis Center, Compassionate Allowances Outreach Hearing on Autoimmune Diseases, 16 March 2011
- Geordie Lawry MD, UC IRVINE, October 2015
- <https://www.the-rheumatologist.org/article/clinical-guidance-recommendation-updates-for-vasculitis-axspa-more/2/>

- *Thank you to Dr. Kinanah Yaseen*

