Vasculiti dei piccoli vasi e vasculiti ANCA – associati

23º corso di aggiornamento per medici di base

Diego Kyburz
Rheumatologie
Universitätsspital Basel

Case

36 yrs old female

History:

- Good health, no relevant diseases or operations

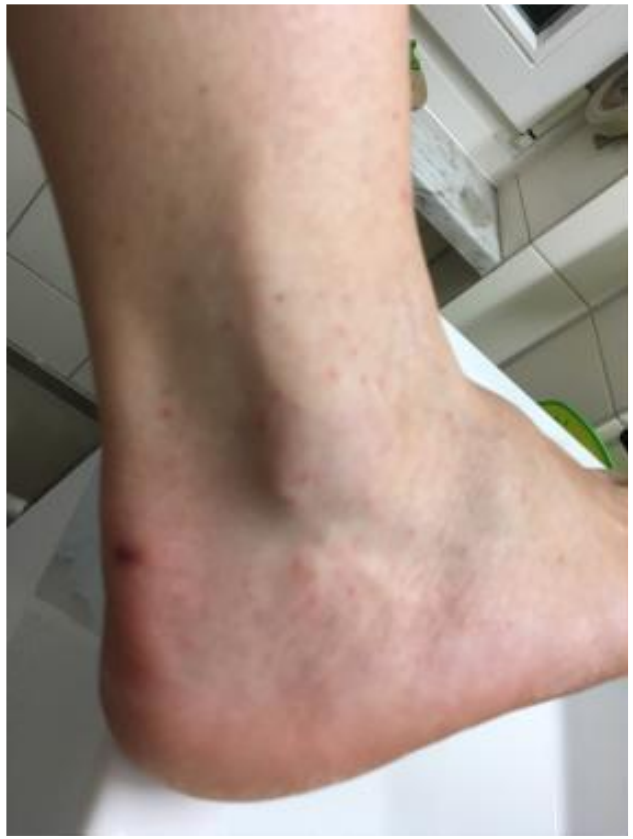
Presenting problem

- New skin rash and pain in the ankle
- Since 3 weeks sore throat
- Medication: NSAID

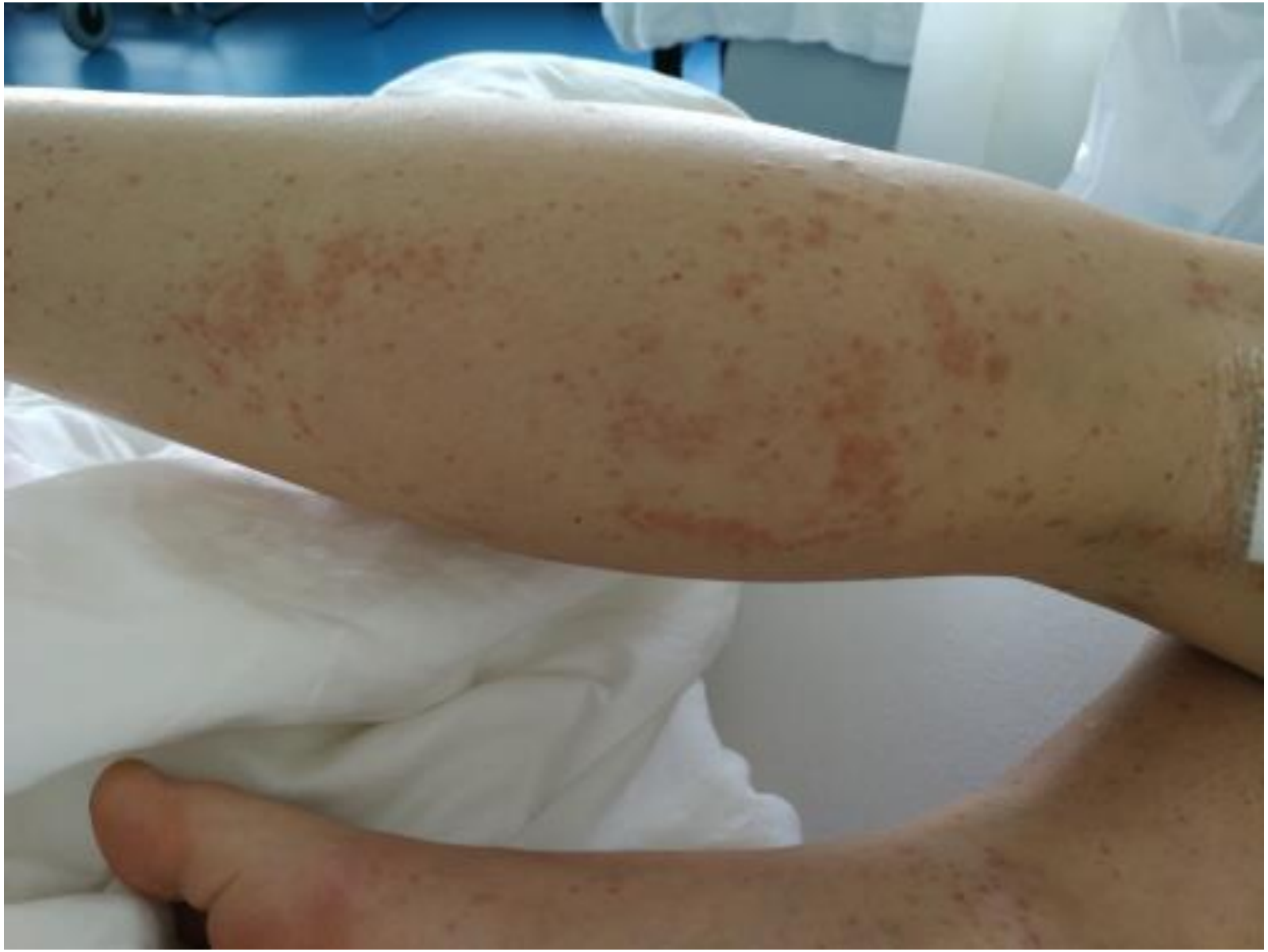
Case

Examination

- Afebrile, BP normal, normal cardiopulmonary auscultation
- inflamed throat, no pus
- Ankles bilaterally tender on palpation, no synovitis



Case



Case

8.59		Leukozyten	3.50 - 10.00	x10^9/l
3.75	-	Erythrozyten	4.20 - 5.40	x10^12/l
113	-	Hämoglobin	120 - 160	g/l
0.33	-	Hämatokrit	0.36 - 0.46	l/l
89		- MCV	79 - 95	fl
30.2		- MCH	27.0 - 33.2	pg
339		- MCHC	320 - 360	g/l
12.8		- EVB	11.5 - 14.5	%
0.3		- hypochrome Ec	<5.0	%
436		Thrombozyten	150 - 450	x10^9/l
9		- MTV	6-10	fl
		Retikulozyten		‰
		- absolut		x10^9/l
		- reife		%
		- unreife		%
		- CHr		pg
5.248		Neutroph.abs.(Seg+St	1.300 - 6.700	x10^9/l
2.208		Lymphozyten	0.900 - 3.300	x10^9/l
0.696	+	Monozyten	0.120 - 0.620	x10^9/l
0.155		Eosinophile	0 - 0.300	x10^9/l
0.069		Basophile	0 - 0.090	x10^9/l
0.215		LUC	0 - 0.310	x10^9/l
4174		Arbeitsplatz ID		
4		Blutsenkung	0 - 28	mm/1Std

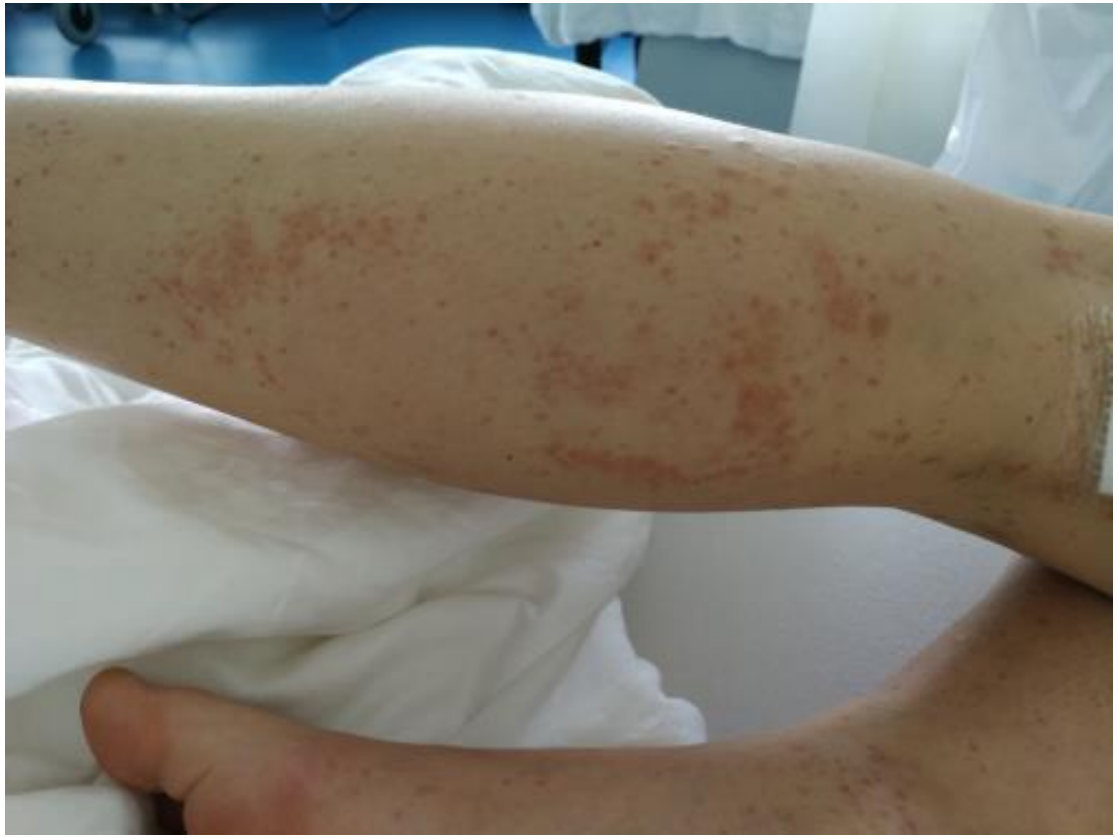
138		Natrium	135-145	mmol/l
3.8		Kalium	3.6-4.8	mmol/l
105		Chlorid	97-110	mmol/l
77		Kreatinin	42-80	µmol/l
86*		GFR geschätzt (CKD-EPI		ml/min/1.73
3.9		Harnstoff	2.6-6.7	mmol/l
10		Bilirubin	<15	µmol/l
12		ASAT	11-34	U/l
9		ALAT	8-41	U/l
10		GGT	6-40	U/l
54		alk. Phosphatase	35-105	U/l
2.09	-	Calcium	2.10-2.65	mmol/l
2.36*		Albumin korrig. Calcium	2.10-2.65	mmol/l
1.20		Phosphat	0.80-1.50	mmol/l
		Magnesium		mmol/l
154	-	Harnsäure	173-359	µmol/l
		Triglyzeride		mmol/l
		Cholesterin		mmol/l
		HDL-Cholesterin		mmol/l
		Chol./HDL-Chol.-Quotient		
		LDL-Chol.Friedewald		mmol/l
59	-	Total Protein	64-83	g/l
29	-	Albumin	35-52	g/l
30		Globuline	18-39	g/l
8.2		C-reakt.Protein	<10.0	mg/l
118	-	LDH	135-214	U/l
58		Creatinkinase	38-157	U/l
		Troponin T hs (ng/L)	<14	ng/L
24		Pankreas-Amylase	13-53	U/l
		Glucose Fluorid		mmol/l
		Glucose	3.8-6.1	mmol/l

Case

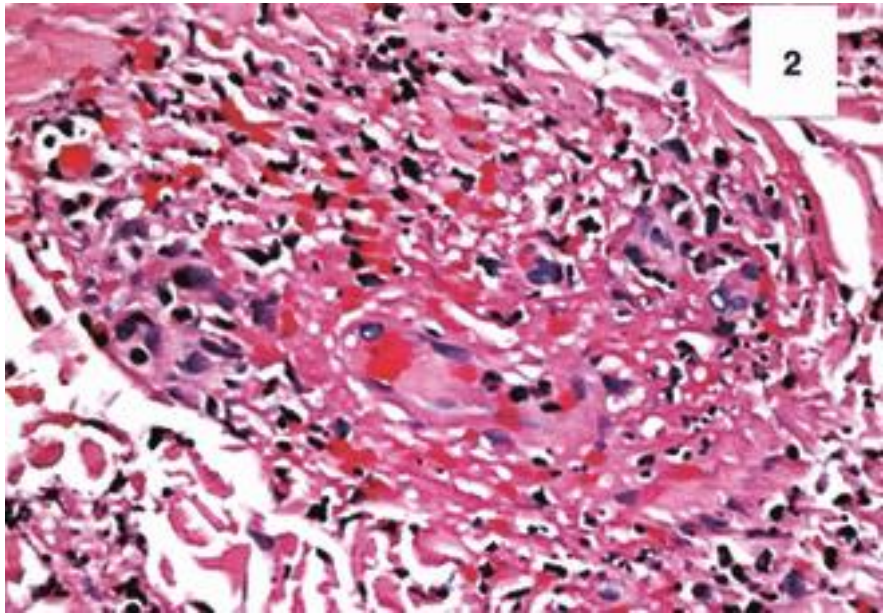
- Sore throat, arthralgia, petechial skin rash
- Next step?
- Throat swab: Strep A rapid test positive
  - Therapy with Amoxycillin

Case

- Dermatologic consult
  - Multiple partially confluent petechiae: Purpura



Skin punch biopsy:
leukocytoclastic vasculitis



J A Carlson, Histopathology 56(1), 2010

Leukocytoclastic vasculitis

- Small vessel vasculitis, broad differential diagnosis

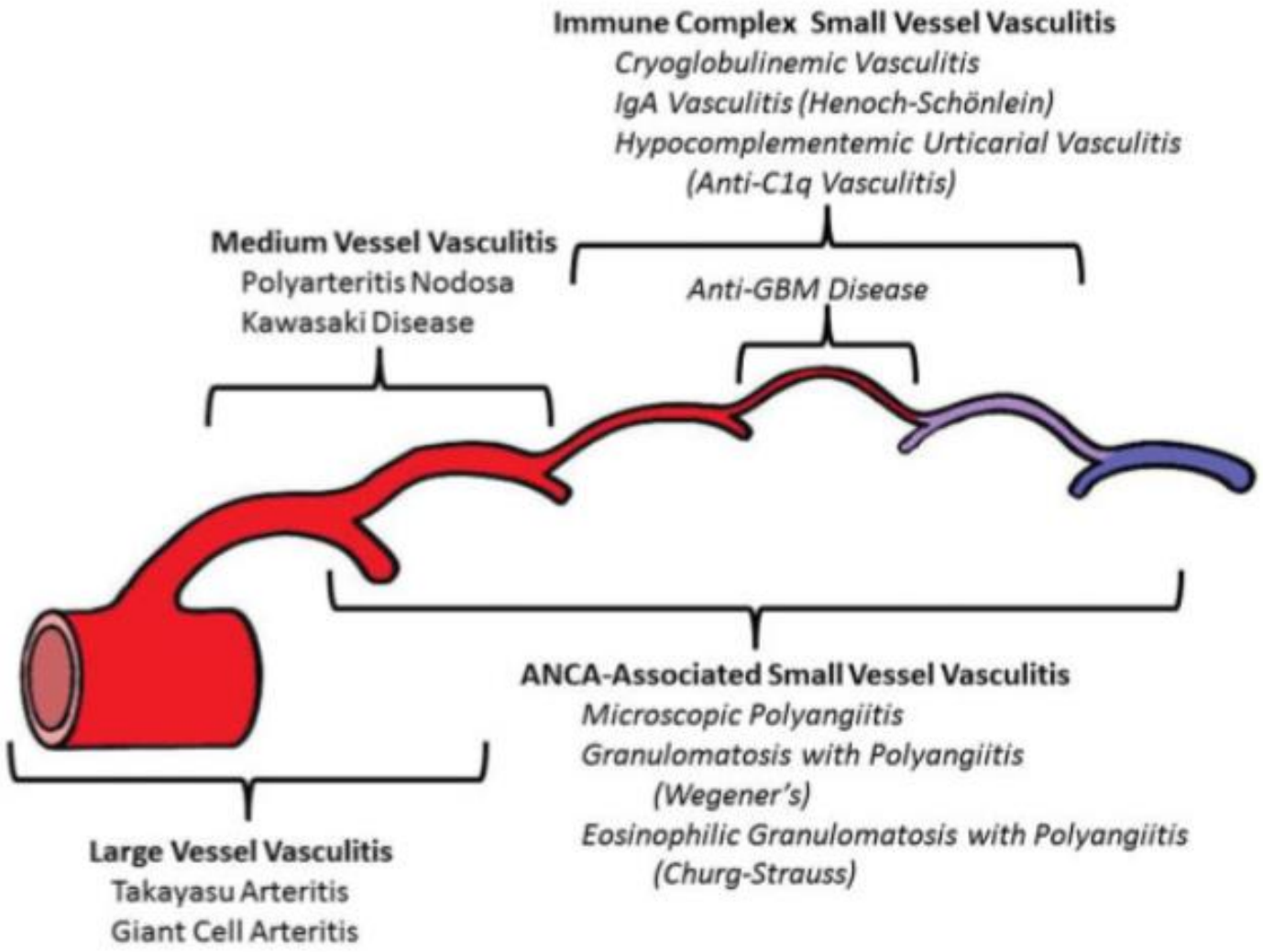
  - Cutaneous small vessel vasculitis (idiopathic in 50%)
  - IgA vasculitis (Henoch-Schönlein Purpura)
  - Infection: HCV, HBV, bacterial infection
  - Drug induced (allopurinol, penicillin, sulfonamides, quinolones, thiazides, propylthiouracil, hydralazine etc)
  - Systemic diseases: RA, SLE, Colitis ulcerosa, M. Crohn
  - Systemic vaskulitis: AAV

Case

- ANA, ANCA, RF negative
- No signs of renal involvement
- Probably:
  immune complex mediated vasculitis associated with streptococcal infection

- Protracted course with persisting purpura and arthralgia
  - Steroid pulse 20mg/d with rapid response and resolution of symptoms

Classification of vasculitis: Chapel Hill 2012



Jennette et al, Arthritis Rheum 2014

Nomenclature

Table 2. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

- **Large vessel vasculitis (LVV)**
  - Takayasu arteritis (TAK)
  - Giant cell arteritis (GCA)
- **Medium vessel vasculitis (MVV)**
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- **Small vessel vasculitis (SVV)**
  - Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
    - Microscopic polyangiitis (MPA)
    - Granulomatosis with polyangiitis (Wegener's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Anti–glomerular basement membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- **Single-organ vasculitis (SOV)**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- **Vasculitis associated with systemic disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- **Vasculitis associated with probable etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Jennette et al, Arthritis Rheum 2013

Types of vasculitis

- Primary Vasculitis
  - Systemic
  - Localised
- Secondary Vasculitis
  - Connective tissue diseases (Lupus, Sjögren..), RA, sarcoidosis
  - M. crohn, ulcerative colitis
  - Paraneoplastic
  - Infectious (HBV, HCV, HIV…)
  - Drug induced

Nomenclature

Category	Disease Name	Typical Vessel Type	Key Antibody Association	Main Clinical Features	Notes / Associations
Immune complex–mediated	**IgA vasculitis (Henoch–Schönlein purpura)**	Capillaries, venules	IgA immune complex deposition	Palpable purpura (legs), arthralgia, abdominal pain, renal involvement	Often follows infection (esp. upper respiratory)
Immune complex–mediated	**Cryoglobulinemic vasculitis**	Capillaries, venules	Mixed cryoglobulins (IgM + IgG complexes)	Palpable purpura, arthralgia, peripheral neuropathy, glomerulonephritis	Associated with Hepatitis C, autoimmune disease
Immune complex–mediated	**Anti–GBM disease** (Goodpasture's)	Capillaries (especially in lungs & kidneys)	Anti–GBM antibodies	Pulmonary hemorrhage + rapidly progressive glomerulonephritis	Linear IgG on immunofluorescence
Immune complex–mediated	**Hypersensitivity (leukocytoclastic) vasculitis**	Postcapillary venules	None specific (immune complexes)	Palpable purpura, often drug-induced	Commonly triggered by drugs, infections, or autoimmune disease

Nomenclature

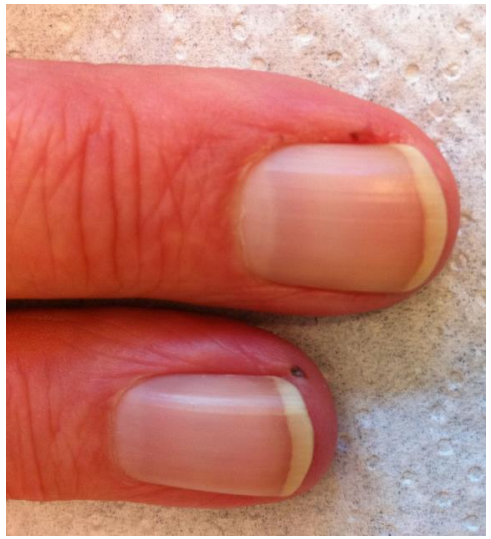
Category	Disease Name	Typical Vessel Type	Key Antibody Association	Main Clinical Features	Notes / Associations
ANCA-associated	**Granulomatosis with polyangiitis (GPA)** (formerly Wegener's)	Small arteries, arterioles, venules, capillaries	c-ANCA (PR3-ANCA)	Upper/lower respiratory tract involvement, sinusitis, pulmonary nodules, hematuria, glomerulonephritis	Granulomatous inflammation in respiratory tract
ANCA-associated	**Microscopic polyangiitis (MPA)**	Capillaries, venules, arterioles	p-ANCA (MPO-ANCA)	Pulmonary capillaritis, rapidly progressive glomerulonephritis, skin purpura	No granulomas (unlike GPA)
ANCA-associated	**Eosinophilic granulomatosis with polyangiitis (EGPA)** (formerly Churg–Strauss)	Small arteries, venules	p-ANCA (MPO-ANCA) in ~40%	Asthma, eosinophilia, sinusitis, neuropathy, skin purpura	Granulomatous + eosinophil-rich inflammation

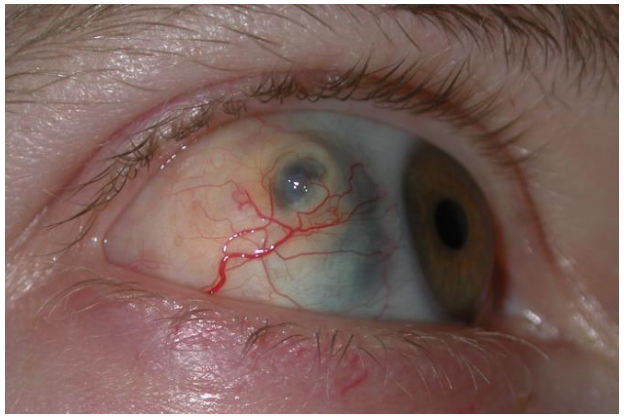
Clinical presentation

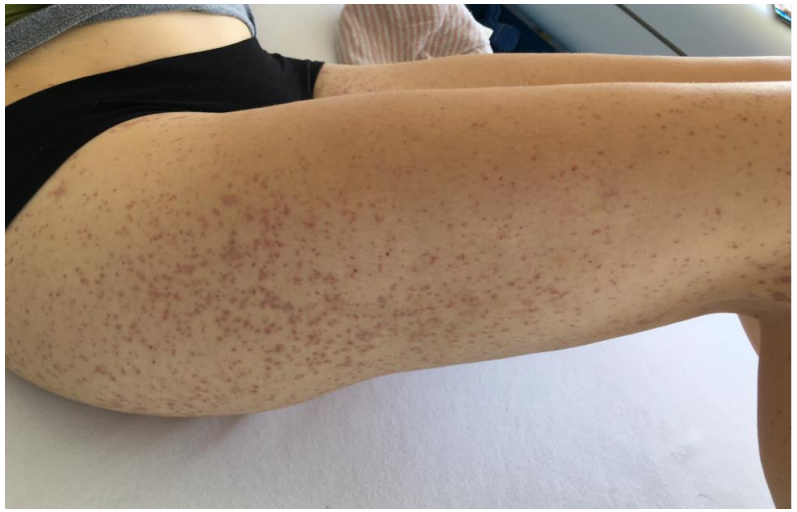
- General symptoms (especially with systemic vasculitis)
  - Fever
  - Fatigue
  - Weight loss
  - Arthralgia

Clinical findings with small vessel vasculitis

- Purpura, splinter hemorrhage, ulcers, urticaria (cutaneous vasculitis)
- Cough, dyspnea, hemoptysis (GPA, MPA)
- Rhinitis with bloody crusts (GPA)
- Leg edema (glomerulonephritis) (GPA, MPA, cryoglobulinemic, IgA vasculitis)
- Red eye: episcleritis/scleritis (GPA)
- Arthritis (all forms of systemic vasculitis)
- Paresis (neuritis) (GPA, EGPA, cryoglobulinemic)







History

- Characteristic symptoms
- Associated diseases
  - Infections: HBV, HCV, other viral, bacterial infections
  - Systemic rheumatic disease (SLE, RA etc)

- Drugs
  - Penicillin, sulfonamides, phenytoin, hydralazine, prophylthiouracil, minocyclin…

  - Cocain: Levamisol-induced vasculitis, ANCA positive

Exams

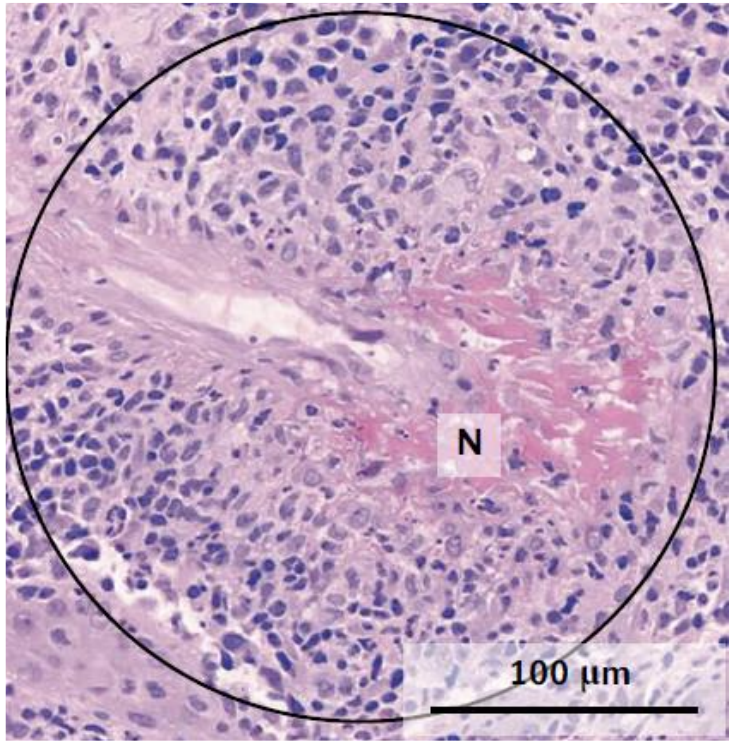
- Physical examination: skin changes, internistic and neurologic exam)
- Lab tests
  - Routine lab (blood cells, chemistry, urine with protein analysis and sediment)
  - Immunoserology: rheumatoid factor, ANA, ANCA, complement, cryoglobulins
  - Infection serologies: HBV, HCV

- Imaging according to presentation

Diagnosis

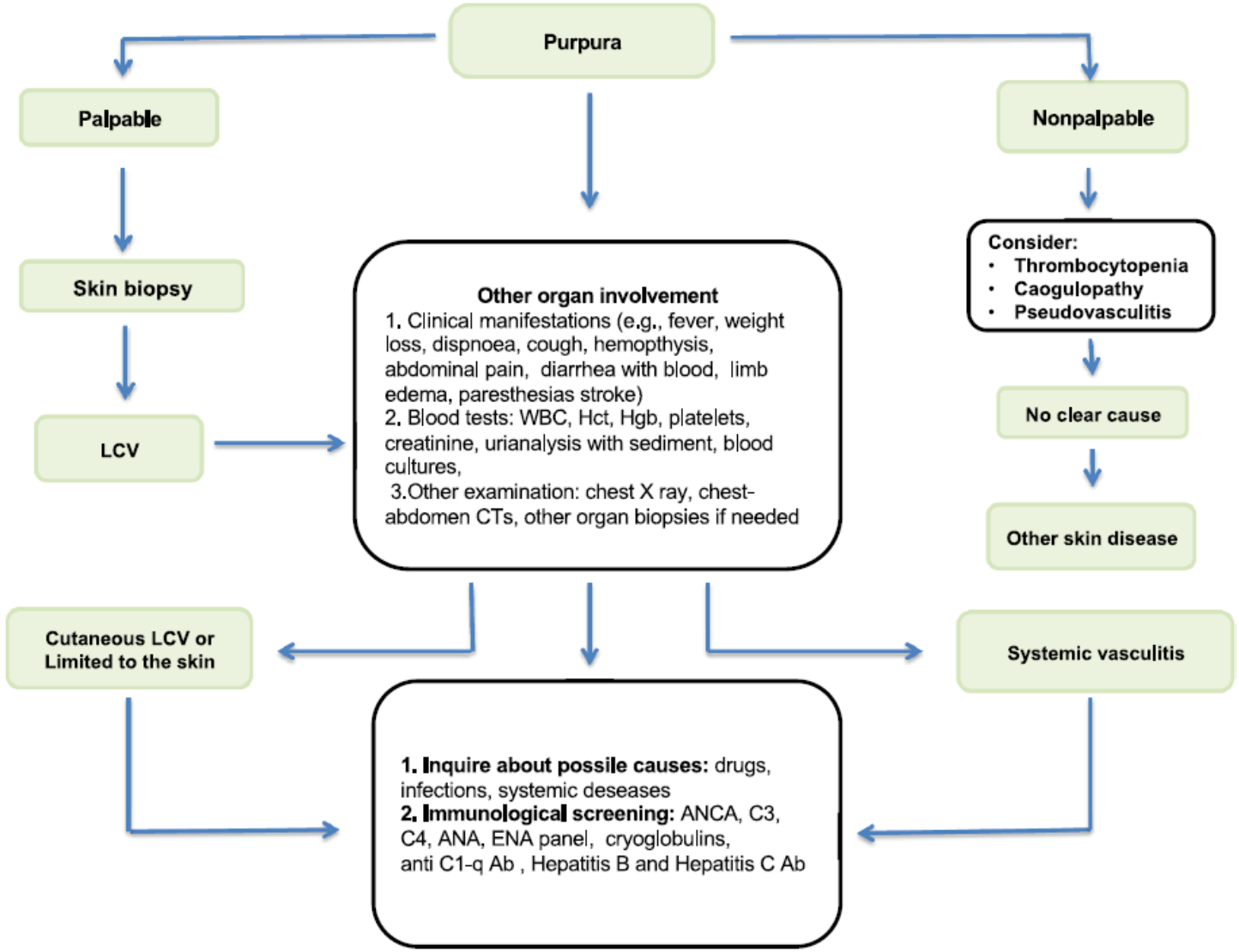
- Typical pattern of a specific vasculitis?

- Confirmation with tissue biopsy
  - Skin biopsy
  - Kidney biopsy
  - Nerve biopsy
  - ….



Kitching et al, Nat Rev Dis Prim 2020

Diagnosis algorhythm for pupura



De Horatius, Postgraduate Med 2023, 135, sup1

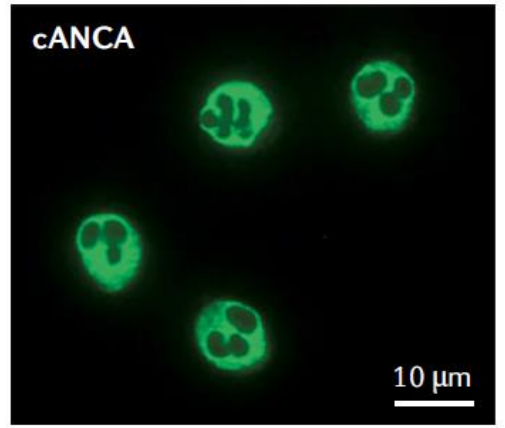
Universitätsspital Basel

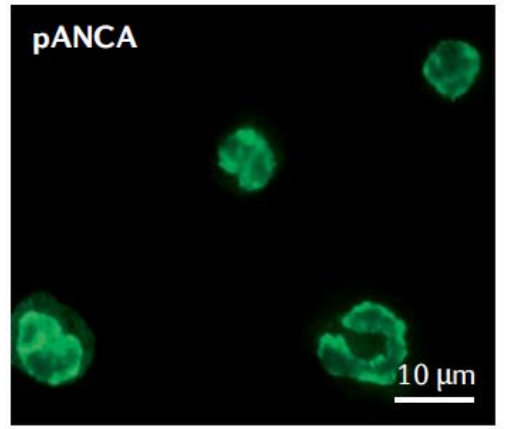
ANCA-associated vasculitis

- Heterogeneous group of small vessel vasculitis
  - Granulomatosis with polyangiitis (GPA, formerly Wegener): Incidence 0.4-12/10^6 ptyr
  - Microscopic polyangiitis (MPA): Incidence 0.5-23/10^6
  - Eosinophilic granulomatosis with polyangiitis (EGPA, form. Churg-Strauss): 0.5-2.3/10^6 ptyr
- Characterised by presence of ANCA

ANCA

- Immunofluorescence
  - C-ANCA, P-ANCA
- ELISA
  - Proteinase 3 (PR3)
  - Myeloperoxidase (MPO)





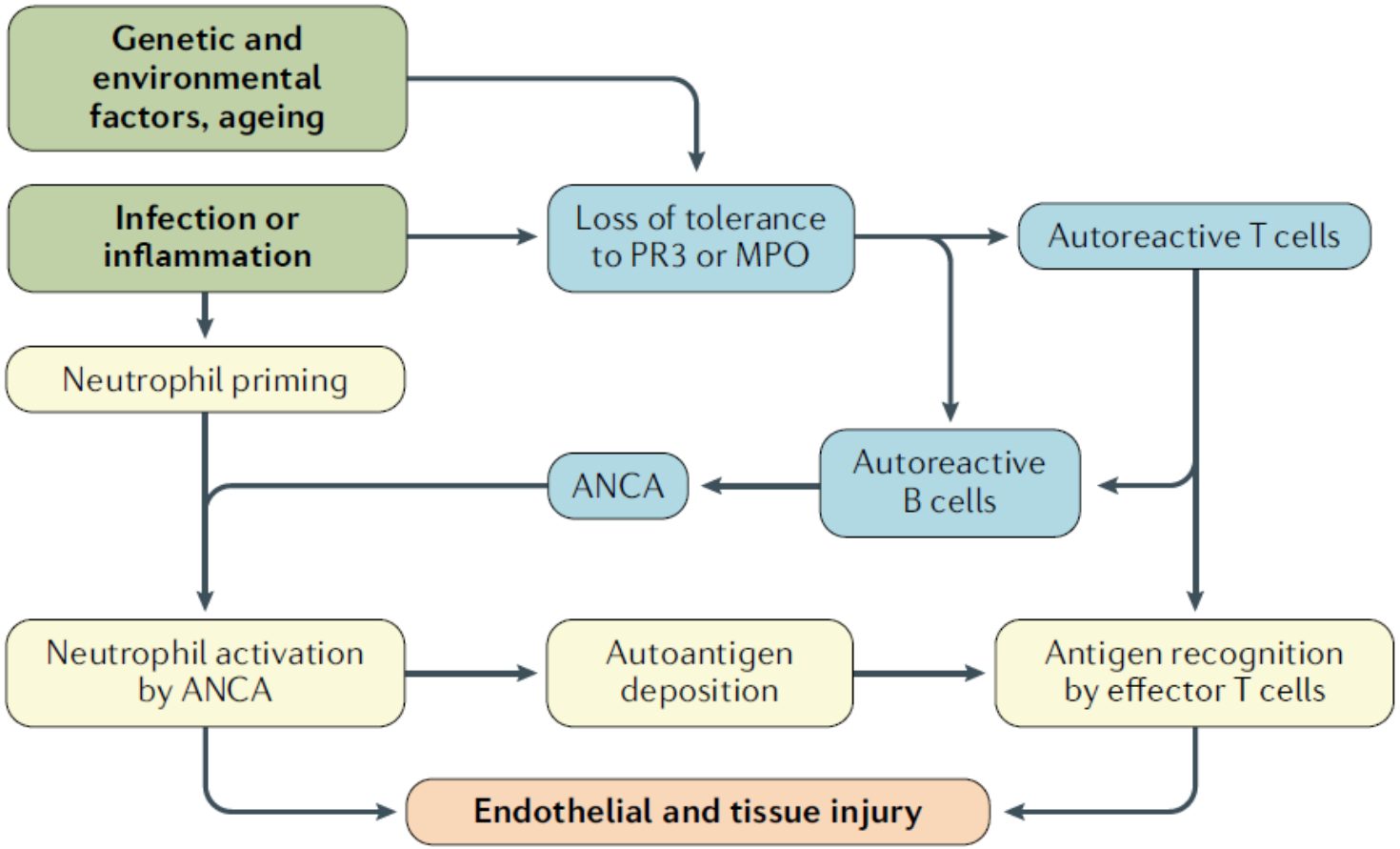
- cANCA and PR3 highly specific for GPA
- pANCA and MPO in 60-85% of MPA
- pANCA without MPO: nonspecific (also found in RA, SLE, IBD)

- ANCA partially correlate with disease activity

Kitching et al, Nat Rev Dis Prim 2020

ANCA associated vasculitis

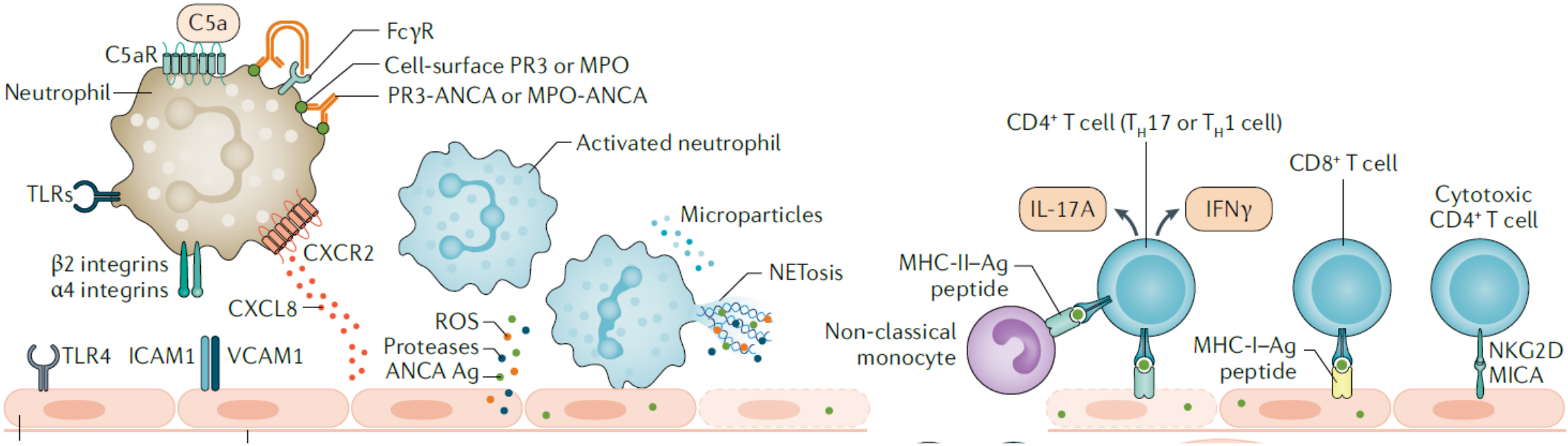
- Pathogenesis



Kitching et al, Nat Rev Dis Prim 2020

ANCA associated vasculitis

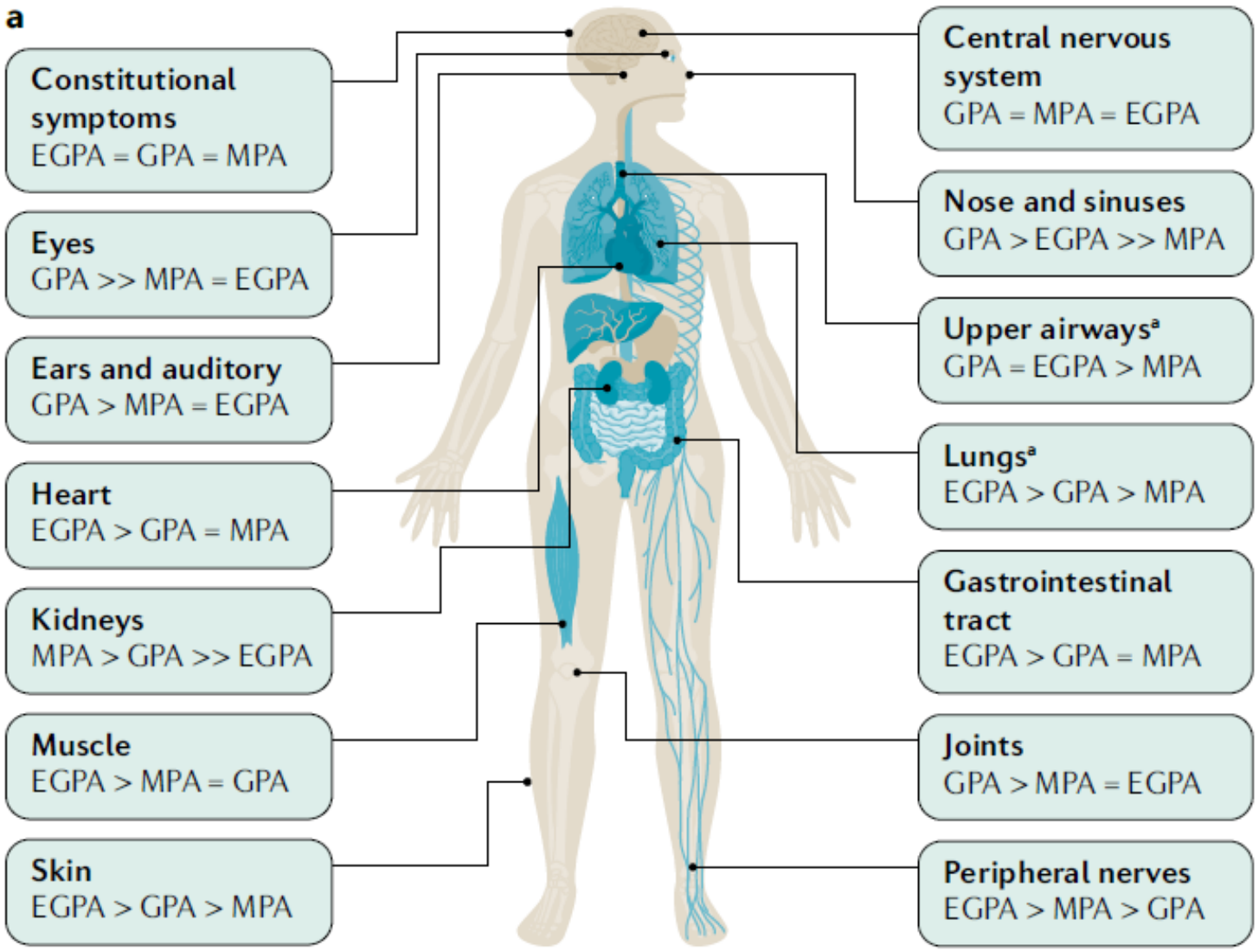
- Pathogenesis: vascular injury



Kitching et al, Nat Rev Dis Prim 2020

ANCA associated vasculitis

- Multiorgan manifestations

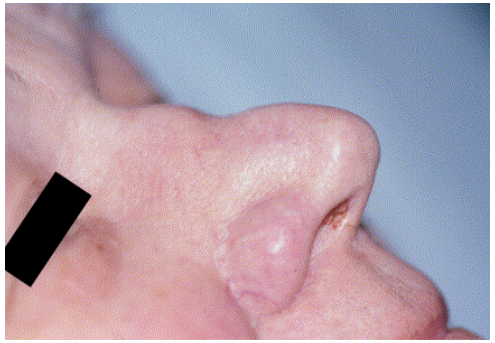


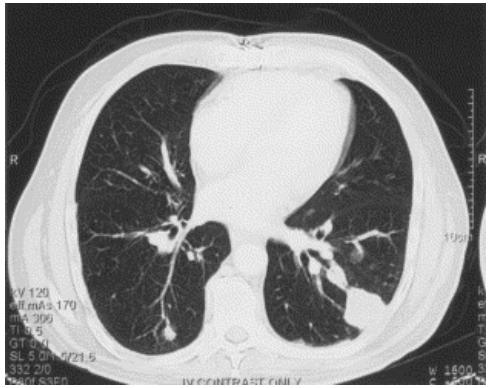
Kitching et al, Nat Rev Dis Prim 2020

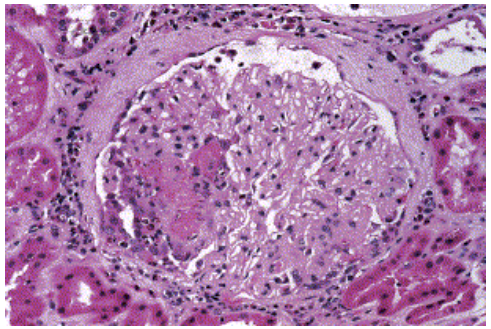
Granulomatosis with polyangitis (GPA)

- F/M 1:1, mean age 70, rarely before 50 yrs old
- Clinical presentation:
  - Upper respiratory tract: sinusitis, ulcerative rhinitis, saddle nose
  - Pulmonary: granulomas, hemorrhage
  - Glomerulonephritis (80% during course of disease)
  - Neurologic: mononeuritis multiplex, CNS-vasculitis
  - Ophalmologic: retroorbital pseudotumour
  - Purpura
  - Arthralgia/-itis

- cANCA in 90% pos.



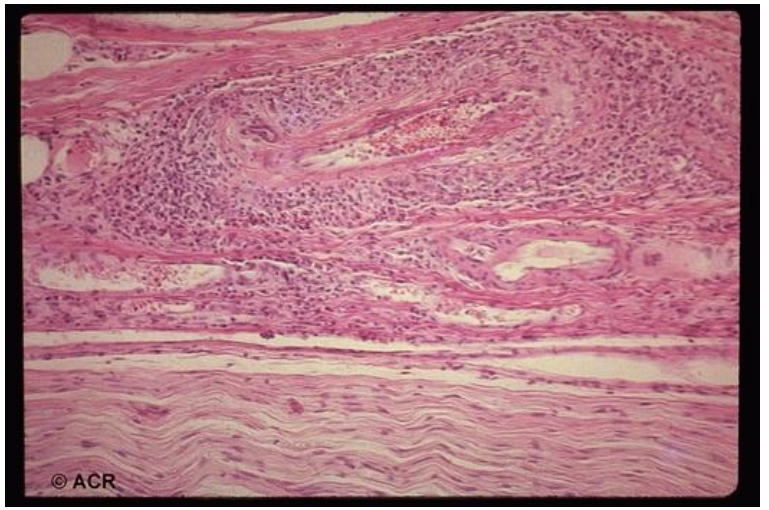




GPA histology

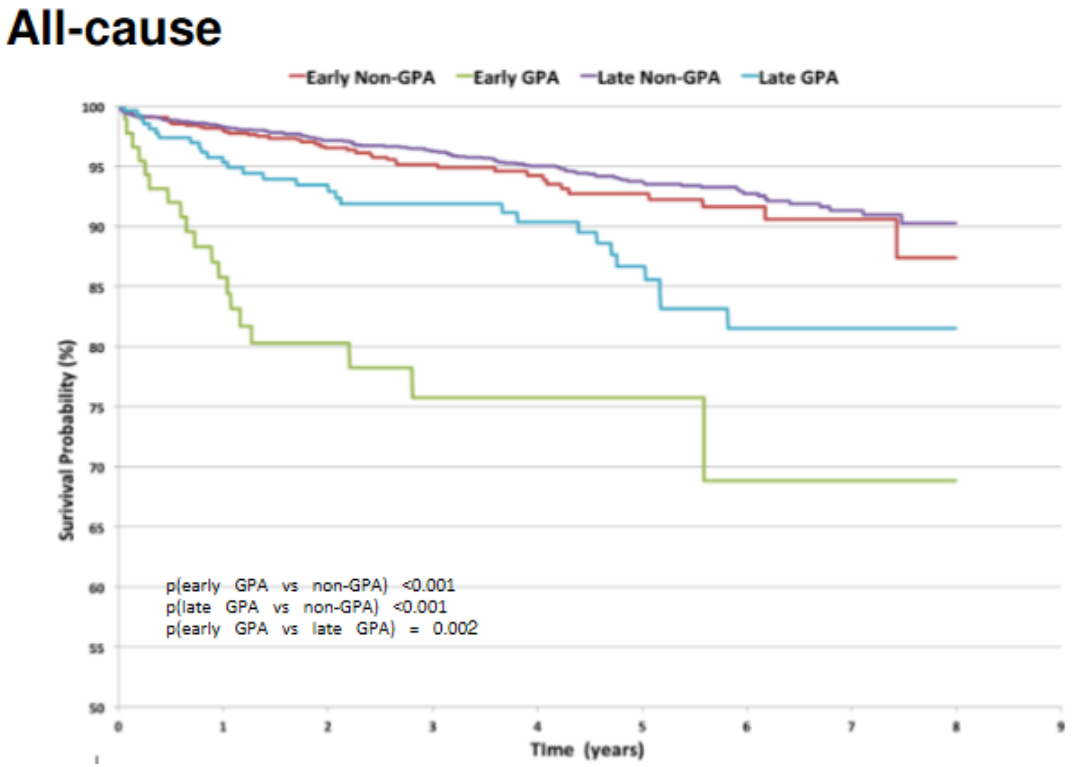
- Vasculitis with necrosis
- Granulomatous inflammation

- Skin biopsy nonspecific
- Biopsy upper respiratory tract rarely diagnostic (nasal, sinus)
- Transbronchial biopsy in 25%, open lung biopsy in >50% diagnostic
- Kidney biopsy: focal, segmental GN
- Nerve biopsy (sural nerve)



GPA prognosis

- Untreated high mortality (80% within 1 yr)
- with treatment survival >80% over 5 yrs



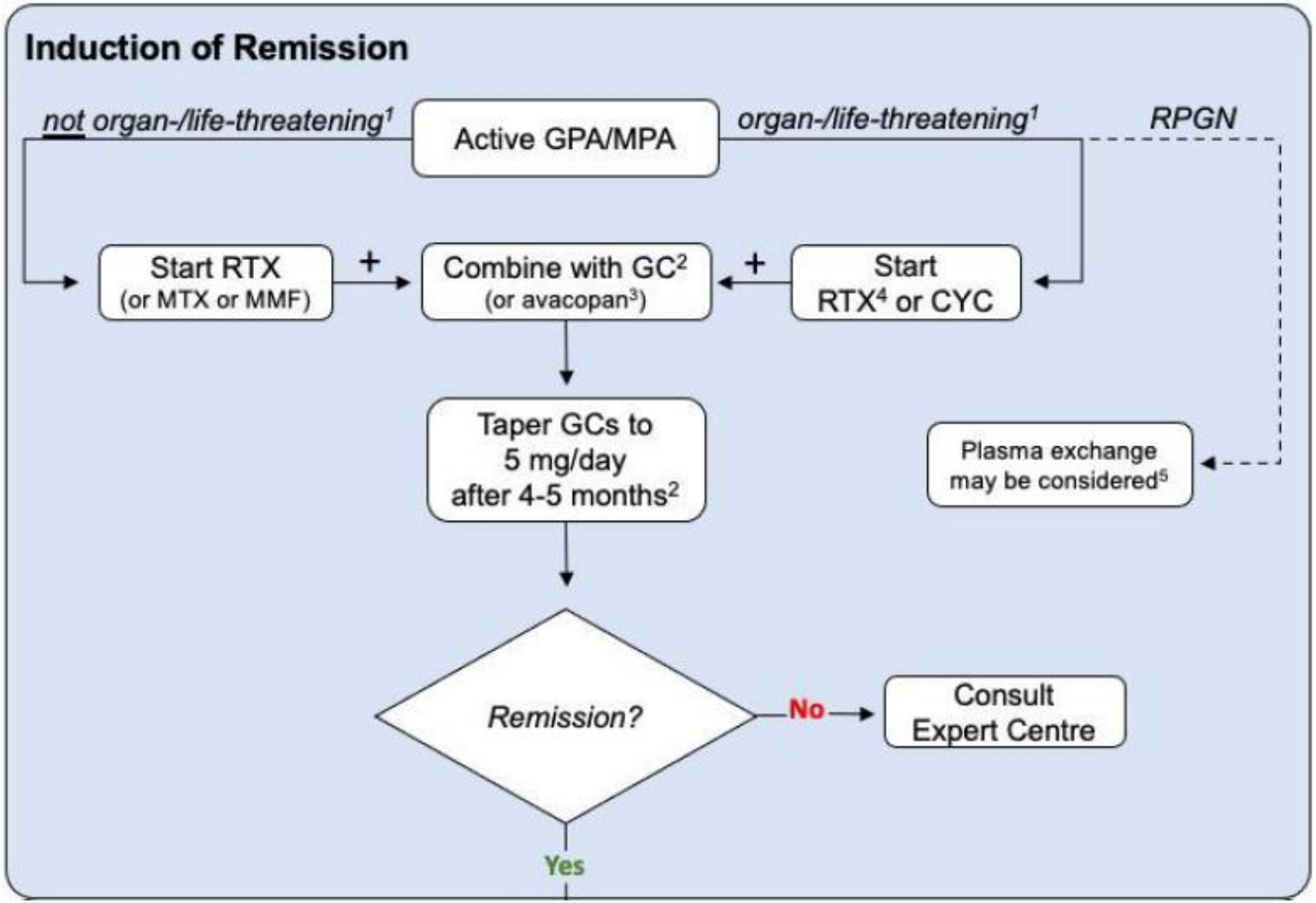
Early: 1997-2004
Late: 2005-2012

Tan et al, Arthritis Care Res 2018

AAV therapy

- Induction therapy
  - 3-6 months: Induction of remission
- Maintenance therapy
  - 6-24 months
- Long term follow up
  - Indefinite
  - Retreatment in case of relapse

AAV therapy



Hellmich et al, Ann Rheum Dis 2022

Universitätsspital Basel

AAV therapy

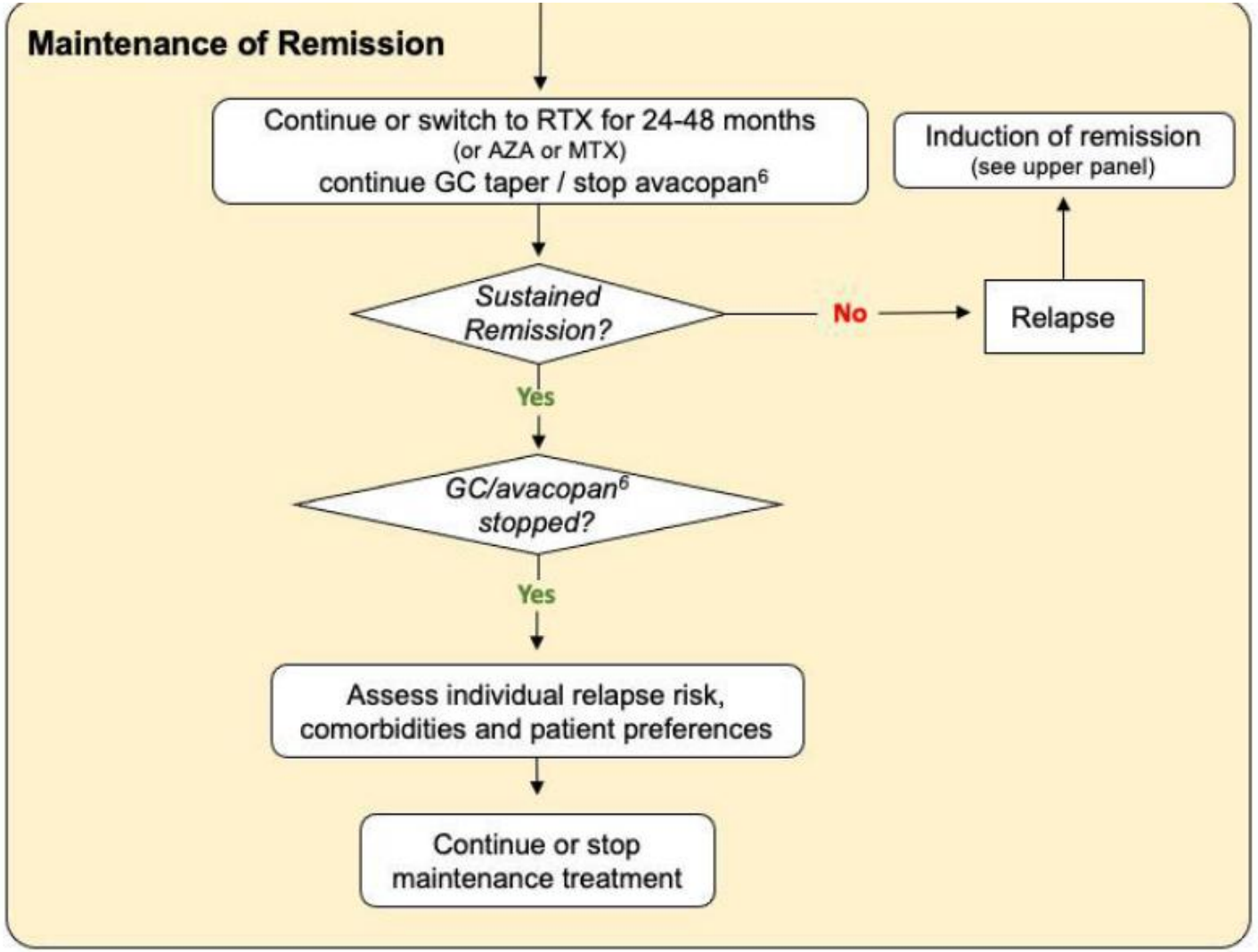
- Therapy dependent on the severity of the disease

Table 2 Examples of organ/life-threatening and not organ/life-threatening manifestations in patients with AAV

Examples of potentially organ/life-threatening manifestations*	Examples of manifestations that are not ultimately organ/life-threatening*
Glomerulonephritis	Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
Pulmonary haemorrhage	Skin involvement without ulceration
Meningeal involvement	Myositis (skeletal muscle only)
Central nervous system involvement	Non-cavitating pulmonary nodules
Retro-orbital disease	Episcleritis
Cardiac involvement	
Mesenteric involvement	
Mononeuritis multiplex	

*These are just examples of typical disease manifestations and many other manifestations of AAV exist. Assessment of severity in the individual patient may differ (eg, scleritis can become organ threatening under certain circumstances).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis.

AAV therapy



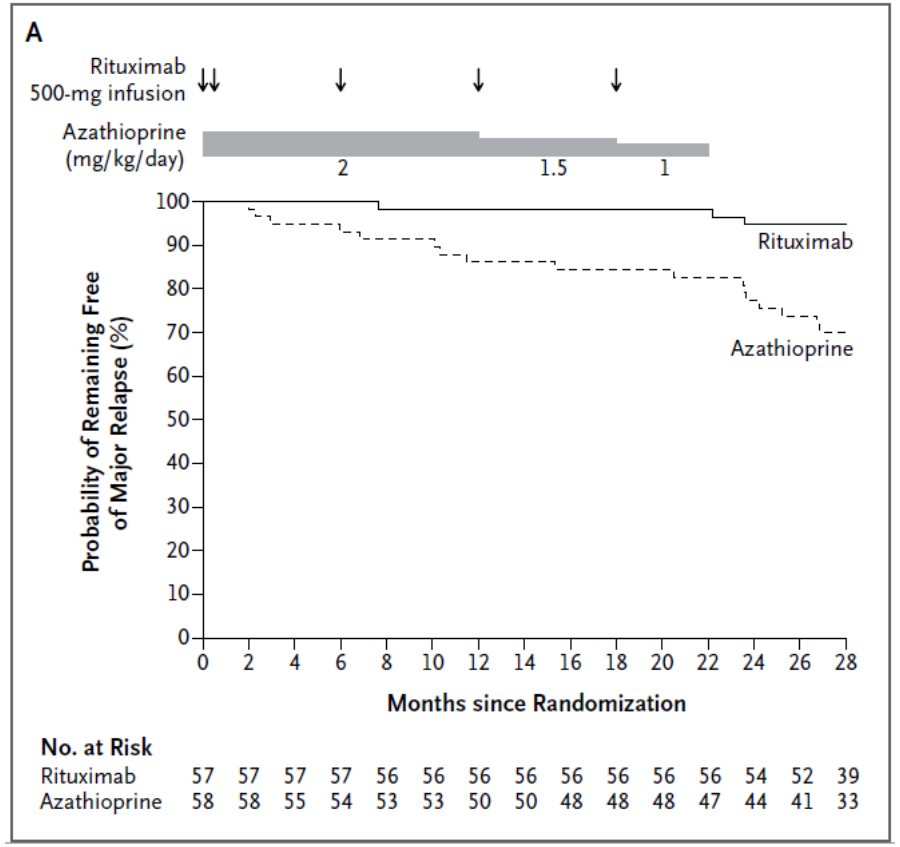
Hellmich et al, Ann Rheum Dis 2022

Universitätsspital Basel

AAV therapy

Maintenance therapy in GPA

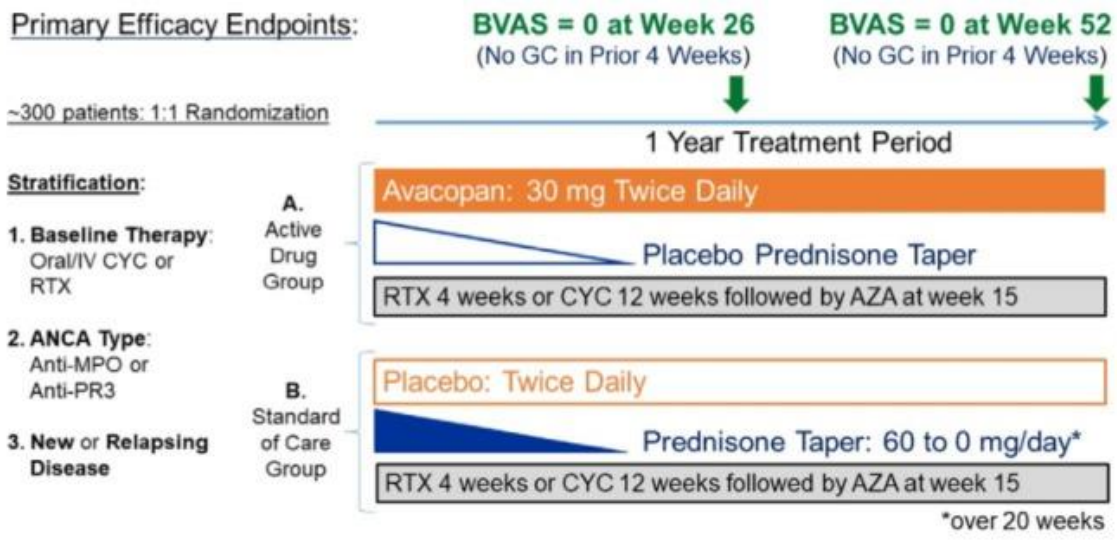
- RCT (MAINRITSAN): GPA in remission, randomised to Azathioprine vs Rituximab
- Outcome relapse rate

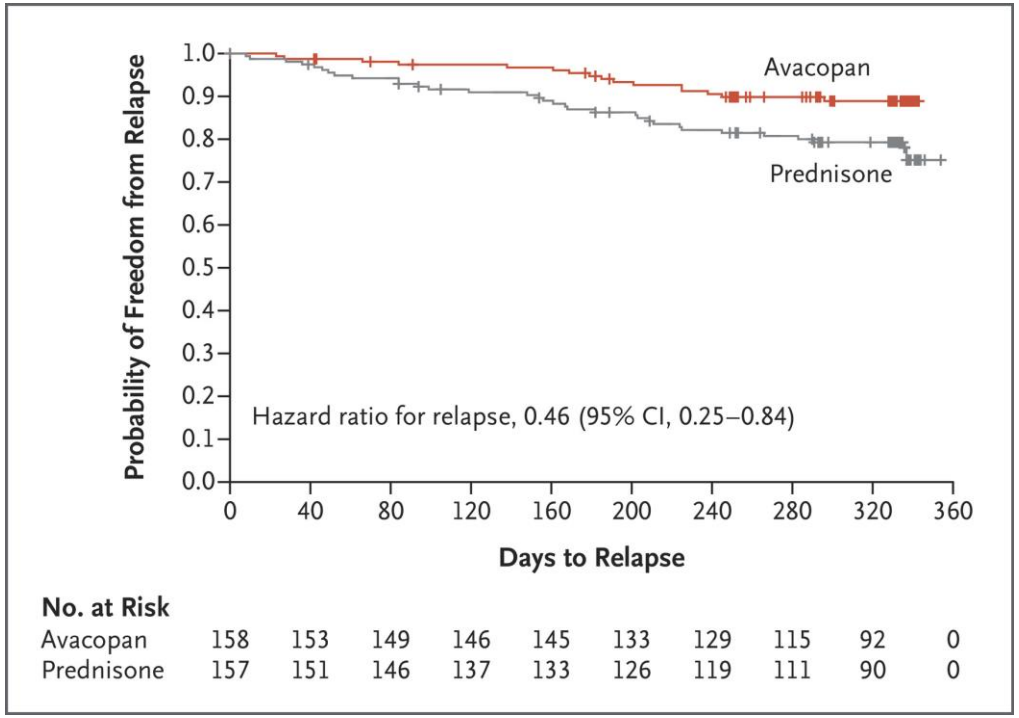


Guillevin et al, N Engl J Med 2014

AAV therapy

- Glucocorticoid therapy
  - Initially high dose therapy
  - If contraindications: Avacopan (C5aR antagonist)





Jayne et al, N Engl J Med 2021

Summary

- Small vessel vasculitis can be primary of secondary as part of a systemic disease
- Look for characteristic clinical findings
  - Lab testing: specific auto-Ab (ANCA, ANA, RF)
- Diagnosis of vasculitis confirmed by biopsy
- Primary cutaneous small vessel vasculitis with good prognosis
- ANCA associated vasculitis can be life-threatening
  - referral to hospital
  - Intensive therapy needed

Diego Kyburz, 2025

Universitätsspital Basel

Grazie per l’attenzione