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Rare Kidney Disease
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ERKNet
Advanced Webinars on Rare Kidney Disorders

Date: 27 October 2020

Topic: Classification and Physiopathology of Vasculitis

Speaker: Rezan Topaloglu

Moderator: Francesco Emma

Plan

- Classification of Vasculitis
- Physiopathology of AAV
- Clinical features of AAV
- Physiopathology of IgAV
- Diagnostic criteria of IgAV

Classification of Vasculitis

CHAPEL HILL CONSENSUS CONFERENCE ON CLASSIFICATION OF SYSTEMIC VASCULITIS

- **Large vessel vasculitis**
  - Giant cell (temporal) arteritis
  - Takayasu's arteritis
- **Medium vessel vasculitis**
  - Polyarteritis nodosa
  - Kawasaki disease
- **Small vessel vasculitis**
  - Wegener's granulomatosis
  - Churg-Strauss syndrome
  - Microscopic polyangiitis
  - Henoch-Schönlein purpura
  - Essential cryoglobulinemic vasculitis
  - Cutaneous leukocytoclastic angiitis

CHCC Arthritis Rheum 1994,37: 187-192, 1994

EULAR/PRINTO/PRES CLASSIFICATION OF CHILDHOOD VASCULITIS

- **Predominantly large vessel vasculitis**
  - Takayasu's arteritis
- **Predominantly medium-sized vasculitis**
  - Childhood polyarteritis nodosa
  - Cutaneous polyarteritis
  - Kawasaki disease
- **Predominantly small vessel vasculitis**
  - GRANULOMATOUS
    - Wegener granulomatosis
    - Churg-Strauss syndrome
  - NON-GRANULOMATOUS
    - Microscopic polyangiitis
    - Henoch-Schönlein purpura
    - Isolated cutaneous leukocytoclastic vasculitis
    - Hypocomplementemic urticarial vasculitis
- **Other vasculitis**

ANKARA Classification EULAR, PRINTO PRES: Ann Rheum Dis. 2006,65 (7):936-941

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 (ChurgStrauss)(EGPA)
- **Immune complex SVV**
  - Anti–glomerular basement membrane (anti-GBM) disease
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Cryoglobulinemic vasculitis (CV)
  - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Variable vessel vasculitis (VVV)

- Behcet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)

- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease

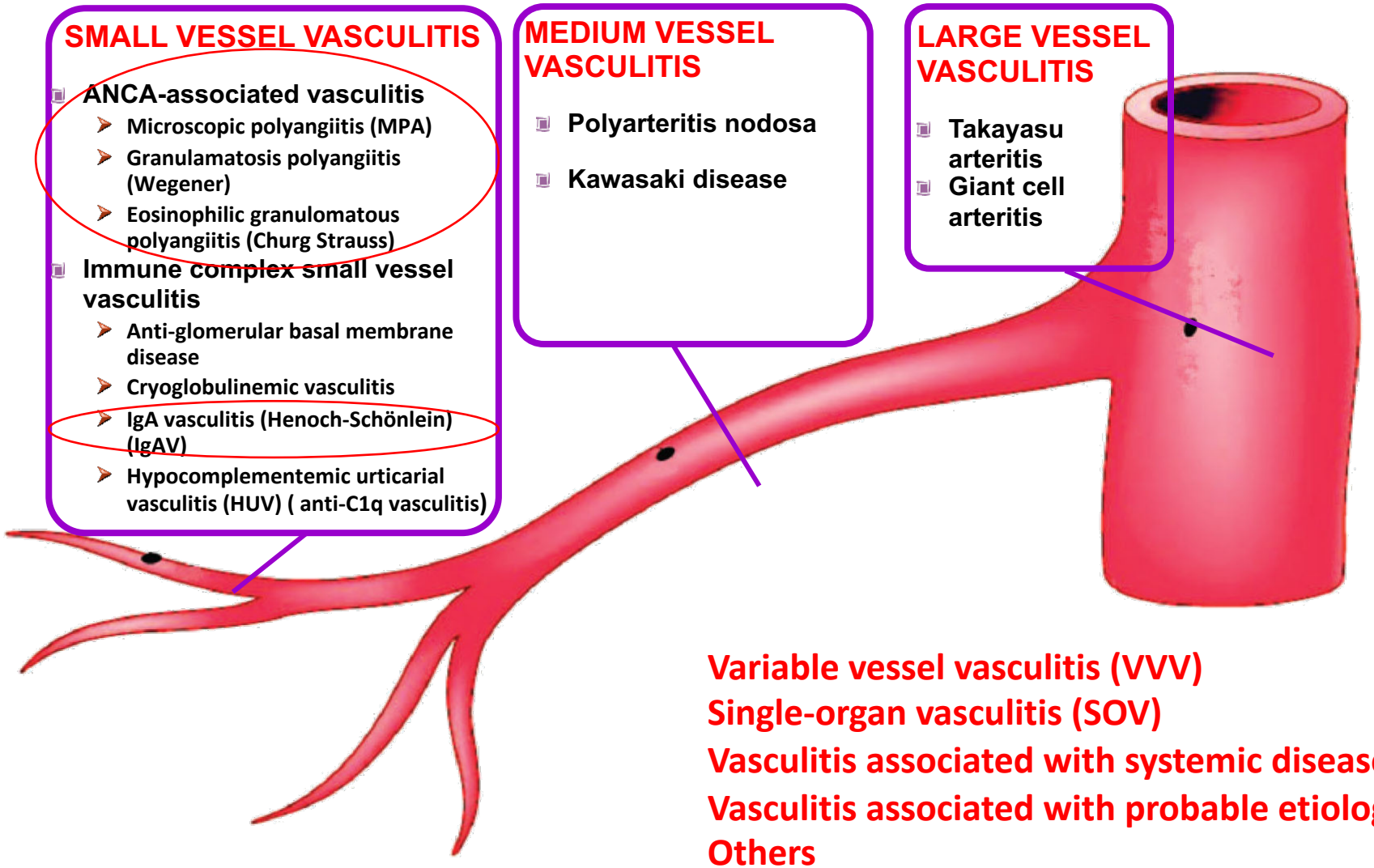
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

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

Arthritis Rheum 2013;65:1-11

Chapel Hill Consensus Conference 2012 Vasculitis Classification/Nomenclature



SMALL VESSEL VASCULITIS

- **ANCA-associated vasculitis**
  - Microscopic polyangiitis (MPA)
  - Granulamatosis polyangiitis (Wegener)
  - Eosinophilic granulomatous polyangiitis (Churg Strauss)
- **Immune complex small vessel vasculitis**
  - Anti-glomerular basal membrane disease
  - Cryoglobulinemic vasculitis
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

MEDIUM VESSEL VASCULITIS

- Polyarteritis nodosa
- Kawasaki disease

LARGE VESSEL VASCULITIS

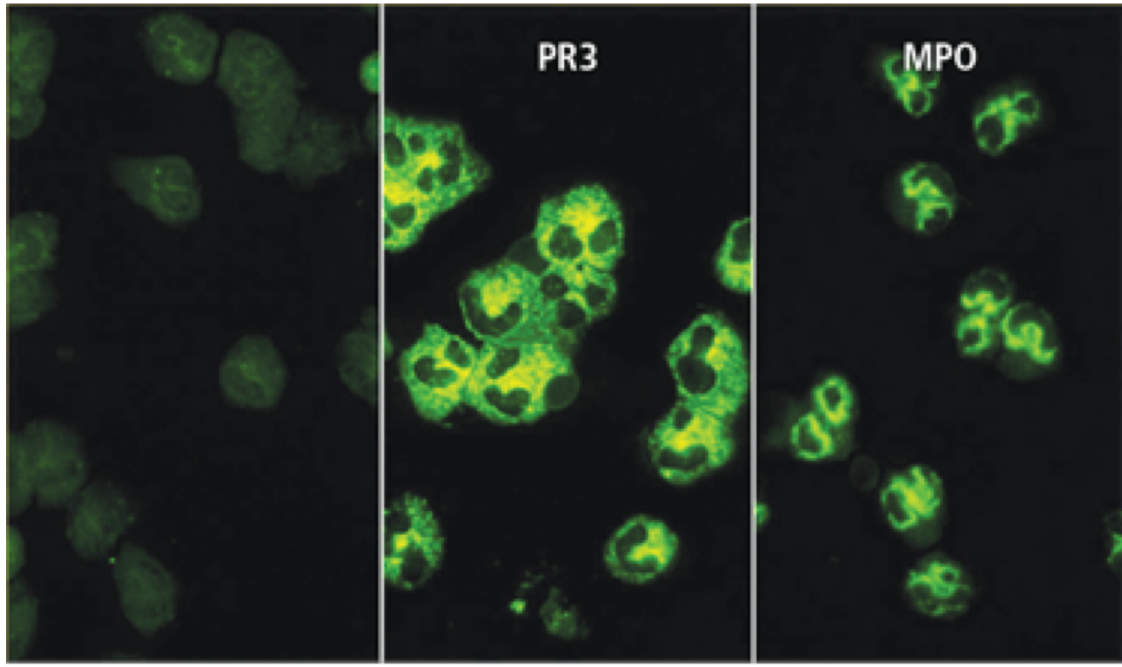
- Takayasu arteritis
- Giant cell arteritis

Variable vessel vasculitis (VVV)
Single-organ vasculitis (SOV)
Vasculitis associated with systemic disease
Vasculitis associated with probable etiology
Others

Arthritis Rheum 2013;65:1-11

ANCA-associated vasculitis

- Systemic vasculitis of small vessels
  - accompanied by the presence of **Anti- Neutrophil Cytoplasmic Antibodies (ANCAs)** in the serum
- Discovery of ANCAs in 1982
- ANCAs are antibodies directed against cytoplasmic antigens in the primary granules of neutrophils and lysosomes of monocytes
- The antigens responsible for these patterns
  - **Proteinase 3 (PR3) for c-ANCA**
  - **Myeloperoxidase (MPO) for p-ANCA**
- ANCAs - described based on their IF staining patterns
  - **Cytoplasmic (c-ANCA)**
  - **Perinuclear (p-ANCA)**



ANCA-associated vasculitis

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA)

Frequency of ANCA Positivity in Different Conditions

	PR3-ANCA (mostly cANCA)	MPO-ANCA (mostly pANCA)	Other
ANCA-Associated Vasculitis			
GPA	75%	20%	5% ANCA negative
MPA	30%	60%	10% ANCA negative
EGPA	5%	45%	50% ANCA negative
Renal-limited vasculitis	10%	80%	10% ANCA negative
Drug-induced vasculitis	10%	90%	Often high titer, dual positivity for MPO and PR3
Nonvasculitis Conditions			
Systemic lupus	2%	10%	10% atypical ANCA
Endocarditis	15%	5%	
Inflammatory bowel disease	Negative	Negative	Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%)
Primary sclerosing cholangitis	Negative	Negative	Atypical ANCA, various antigens: 60%-80%
Cystic fibrosis	Negative	Negative	Atypical ANCA pattern, directed against BPI (90%)

ANCA-Associated Vasculitis: Core Curriculum 2020, Am J Kidney Dis. 75(1): 124-137.

- Incidence of GPA,
  - Europe < 0.5 /1.000.000 children (French series)
  - Canada 6,39 /1.000.000 children
- Incidence of MPA ve EGPA in children is unknown
- Heterogeneous diseases characterized by inflammation of the vessel wall
  - involve any system of the body
- Clinical presentation depends on
  - *size* of the affected blood vessel
  - *severity* of the disease
- Significant *morbidity* and *mortality*

Pediatr Nephrol 2016;DOI 10.1007/s00467-016-3490-6

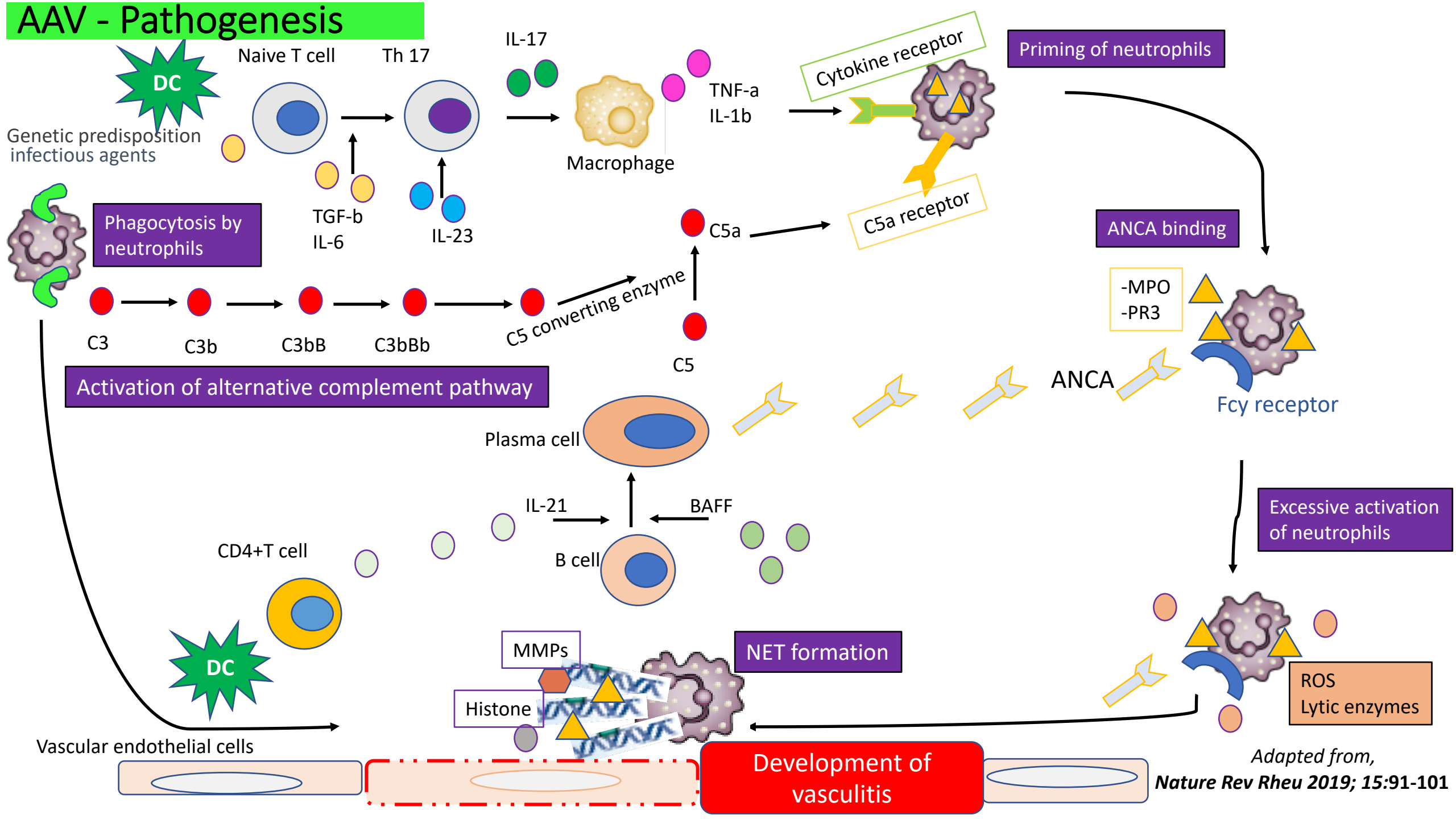
AAV - Pathogenesis

- **Genetic factors**
  - the strongest associations with AAV are major histocompatibility complex class II (MHC II) genes
  - GPA with PR3-ANCAs is most strongly associated with the *HLA-DP* region
  - MPA with MPO-ANCAs is highly associated with the *HLA- DQ* region
  - HLA genomic signature was associated with ANCA specificity (PR3 or MPO) rather than with the clinical manifestation (GPA or MPA)
  - Other genes
- **Enviromental factors**: infections, drugs, silica hydro carbon exposure

Gene	Associated disease	OR
HLA-DP	• GPA • PR3-AAV	• 5.39 • 7.03
HLA-DQ	• MPA • MPO-AAV	• 0.67 • 0.65
HLA-DR	• MPA • MPO-AAV	• 1.56 • 1.57
PTPN22	PR3-AAV	1.63
SERPINA1	• GPA • PR3-AAV	• 0.54 • 0.53
PRTN3	• GPA • PR3-AAV	• 0.78 • 0.73
SEMA6A	GPA	0.74

***Nature Rev Rheu 2019; 15:*91-101**

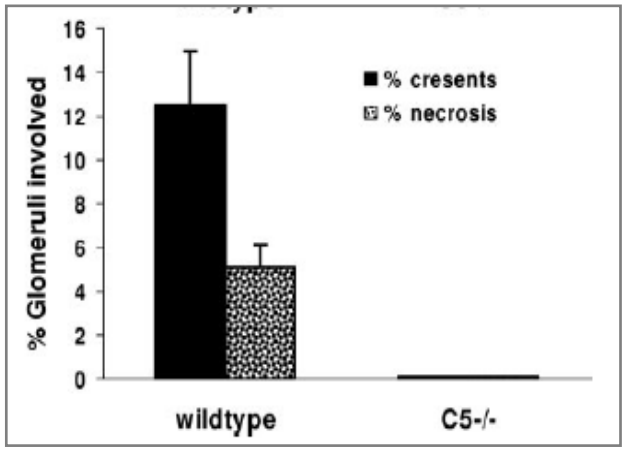
AAV - Pathogenesis

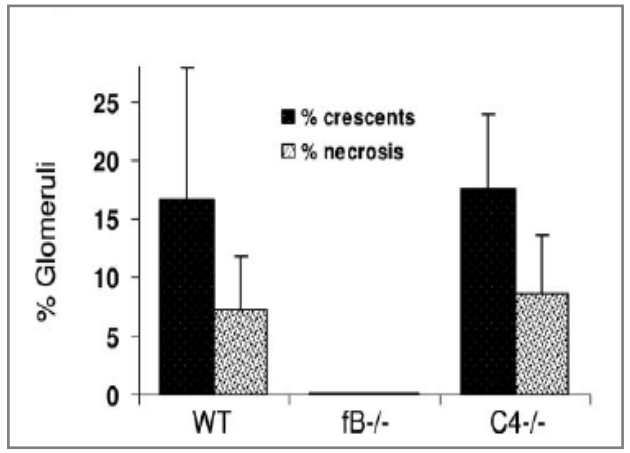


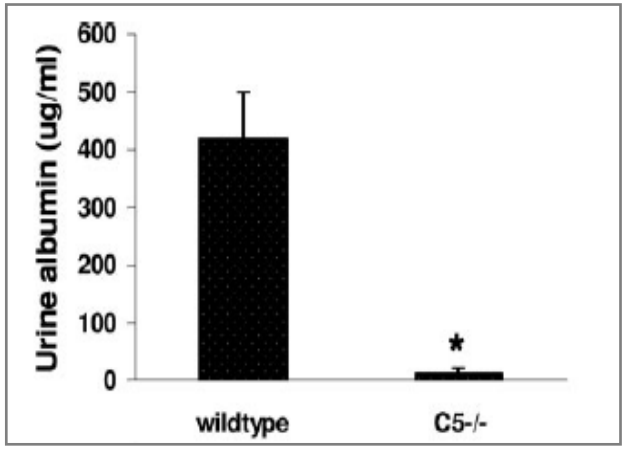
Adapted from,
***Nature Rev Rheu 2019; 15:*91-101**

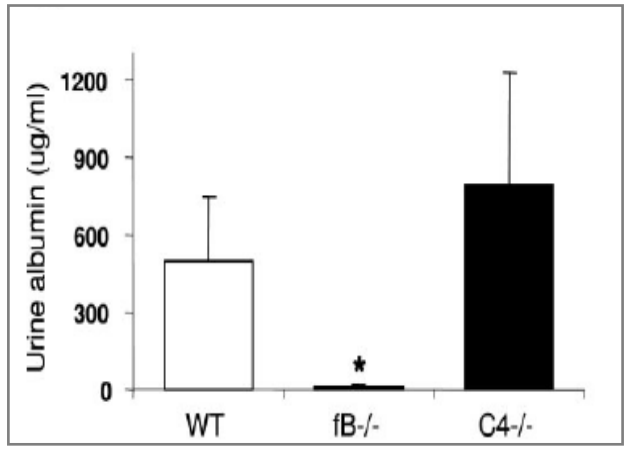
First evidence for the role of complement activation in AAV pathogenesis

- **Animal models**
  - **C5$^{-/-}$ knockout mice** did not develop glomerulonephritis and vasculitis after anti MPO IgG injection.
  - **Factor B$^{-/-}$ knockout mice** were also fully protected from disease
  - **Wild type** and **C4 -/- knockout mice** disease severity was similar
  - **Alternative pathway activation** thought to be critical in AAV pathogenesis





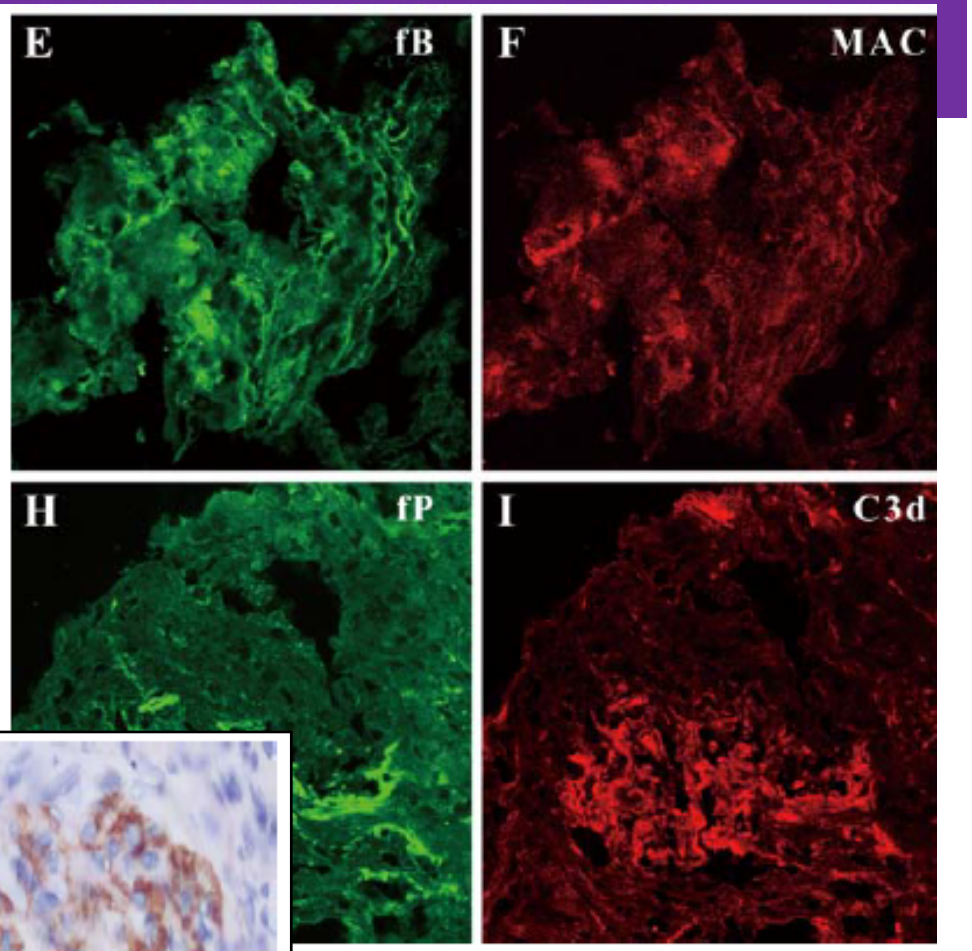


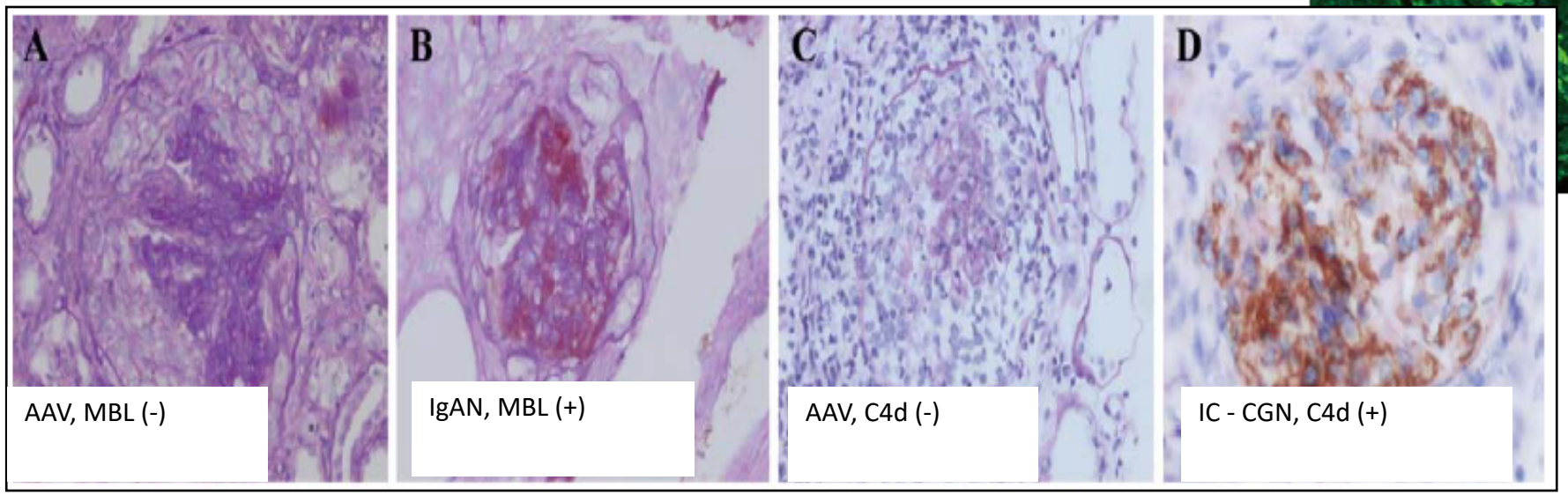


Xiao et al., *Am J Pathol*. 2007;170(1):52-64.

AAV and Complement

- Patients with MPO-ANCA glomerulonephritis
- Factor B, MAC, Factor P and C3d (+)
  - **Absence of MBL** and **C4d**
  - **An indication of alternative pathway activation**





Xing, G. Q. *et al. J. Clin. Immunol.* **29**, 282–291 (2009).

- The histological hallmark of AAV → *necrotizing vasculitis and glomerulonephritis*
  - without apparent deposition of immune complexes (pauci- immune glomerulonephritis)
- TNF-primed neutrophils were exposed to ANCAs → induction of NETs → neutrophil elastase → the ANCAs disappeared after owing to their digestion
- These findings suggest that NETs contribute to the disappearance of immunoglobulins from AAV lesions.

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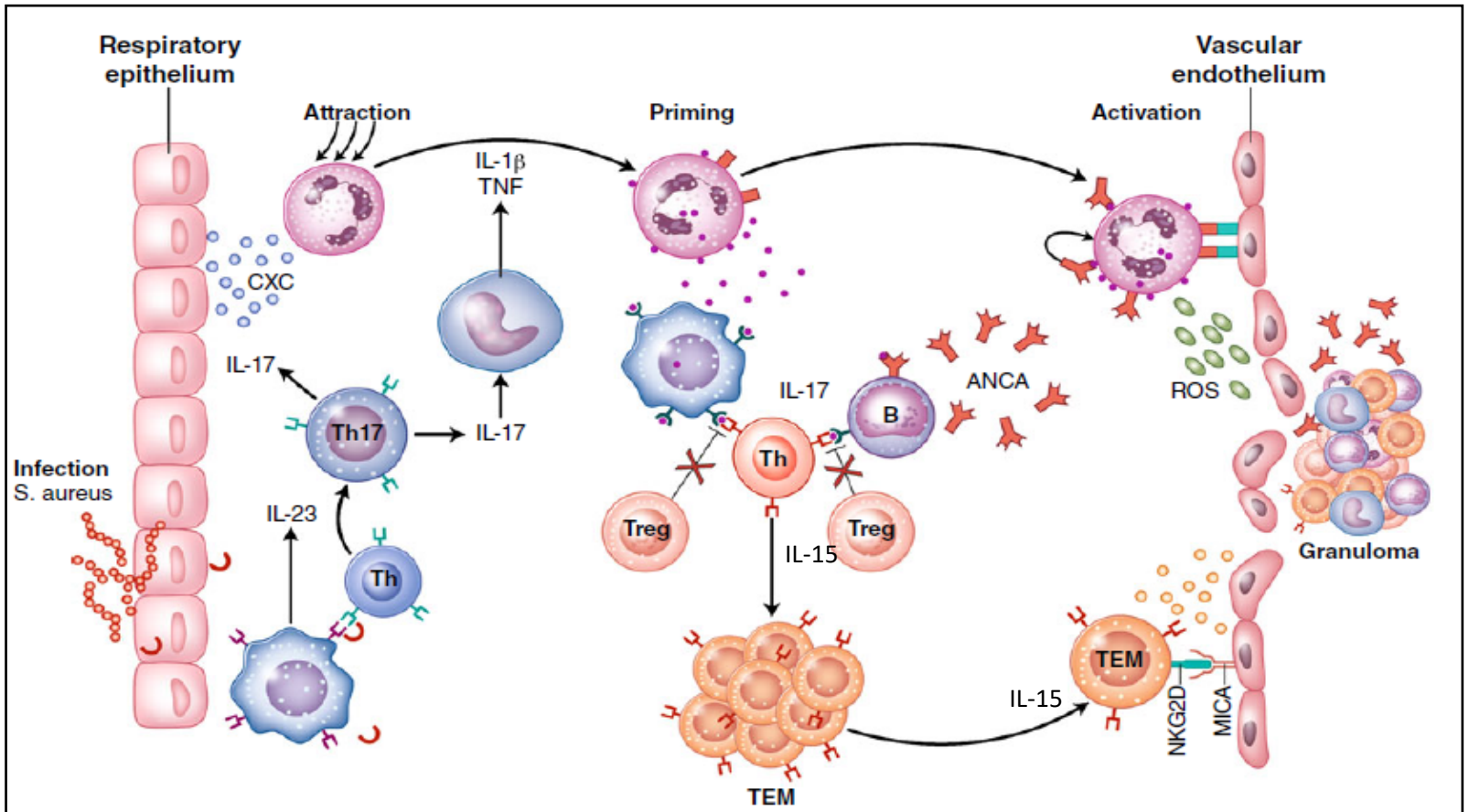
***Nature Rev Rheu 2019; 15:*91-101**

Granulomatosis with polyangiitis (GPA)

- Neutrophil priming and ANCA- mediated excessive activation of neutrophils occur in both GPA and MPA.
- Necrotizing granulomas in the respiratory tract and PR3-ANCA production are characteristics of GPA.



Curr Rheumatol Rep (2010) 12:399–405

*Nature Rev Rheu 2019; 15:*91-101

Granulomatosis with Polyangitis

ACR criteria (1990)	Ankara 2008 criteria
≥2 of the following:	***At least three of the six:***
• Abnormal urinary sediment • Abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates) • Oral ulcers or nasal discharge • Granulomatous inflammation on biopsy	• Histopathology (granulomatous inflammation) • Upper airway involvement • Laryngo-tracheo-bronchial stenosis • Pulmonary involvement • Chest x-ray or CT → nodules, cavities or fixed infiltrates • ANCA positivity • Renal involvement

- ANCA-positivity was included
- CT findings were included to define pulmonary abnormalities
- More definitive items were added for upper and lower airway involvement

GPA

Frequent involvement	%	Symptoms	Signs
Constitutional symptoms	88	Fever, anorexia, weight loss	
Era, nose, throat	80	Recurrent epistaxis Sinusitis, oral ulceration	Nasal septum perforation Saddle-nose deformity Conductive hearing loss Subglottik stenosis (%50)
Pulmonary	80	Dyspneoa Cronic cough, hoarseness Stridor Haemoytysis	Diffuse pulmonary infiltrates Nodules and cavitating lesions Glanulomata Pulmonary haemorrhage
Renal	75.4	Oliguria	Oliguria Akut kidney injury (GFR<60$_{ml/min/1.73m2}$) Nephrotic range proteinuria Chronic glomerulary lesions Renal impairment-RRT

Pediatr Nephrol. 2017 Jan 6. doi: 10.1007/s00467-016-3559-2

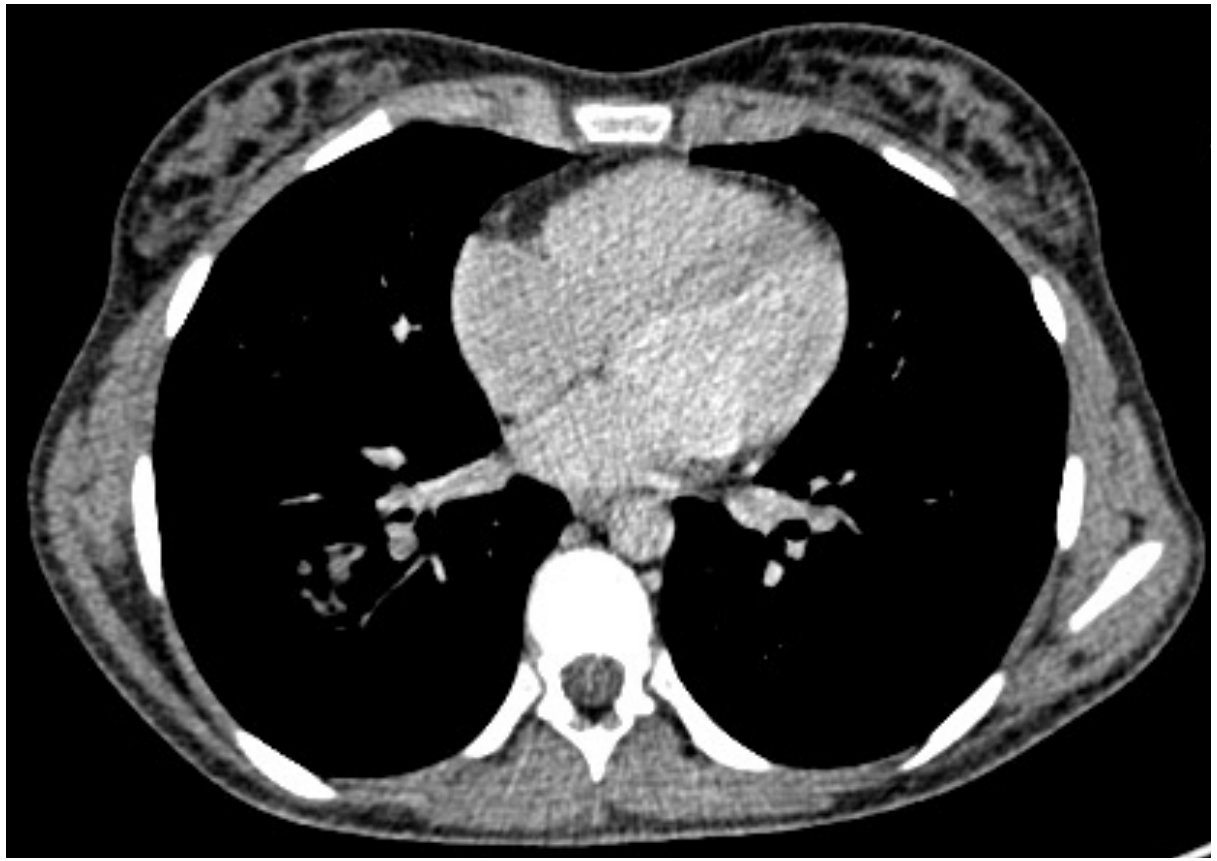
GPA

Rare involvement	%	Symptoms	Signs
Musculosceletal	57	Arthralgia and myalgia(%64)	Arthritis (%20-32)
Gastrointestinal	42	Non-specific abdominal pain, Chronic nausea	
Eye	37	Red eye	Proptosis episcleritis Uveitis
Skin	35		Palpabl purpura Petechiae Nodule
CNS	25	Headache Dizziness	Mononeuritis Epileptic seizure Upper motor neurone signs
CVS	5		Deep vein thrombosis

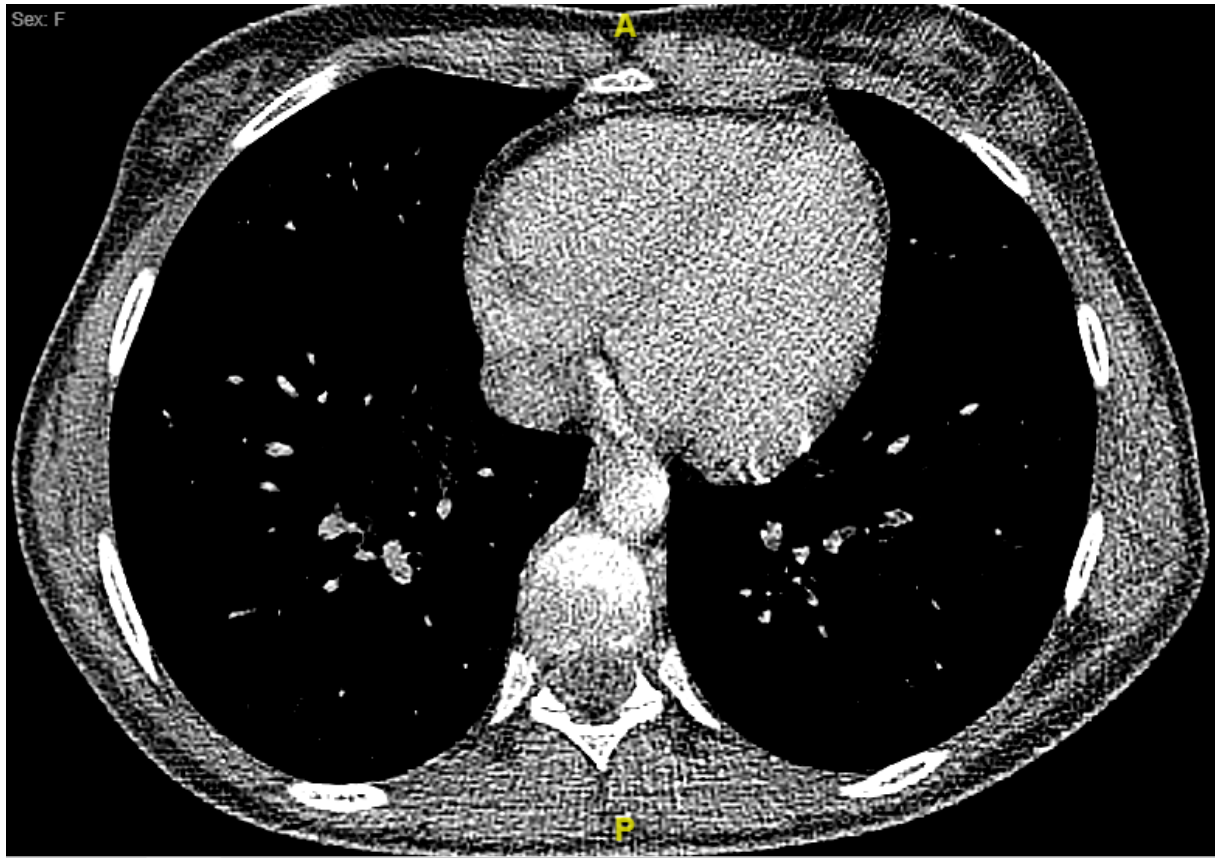
Pediatr Nephrol. 2017 Jan 6. doi: 10.1007/s00467-016-3559-2

HACETTEPE UNIVERSITY

EGU-3 HRCT



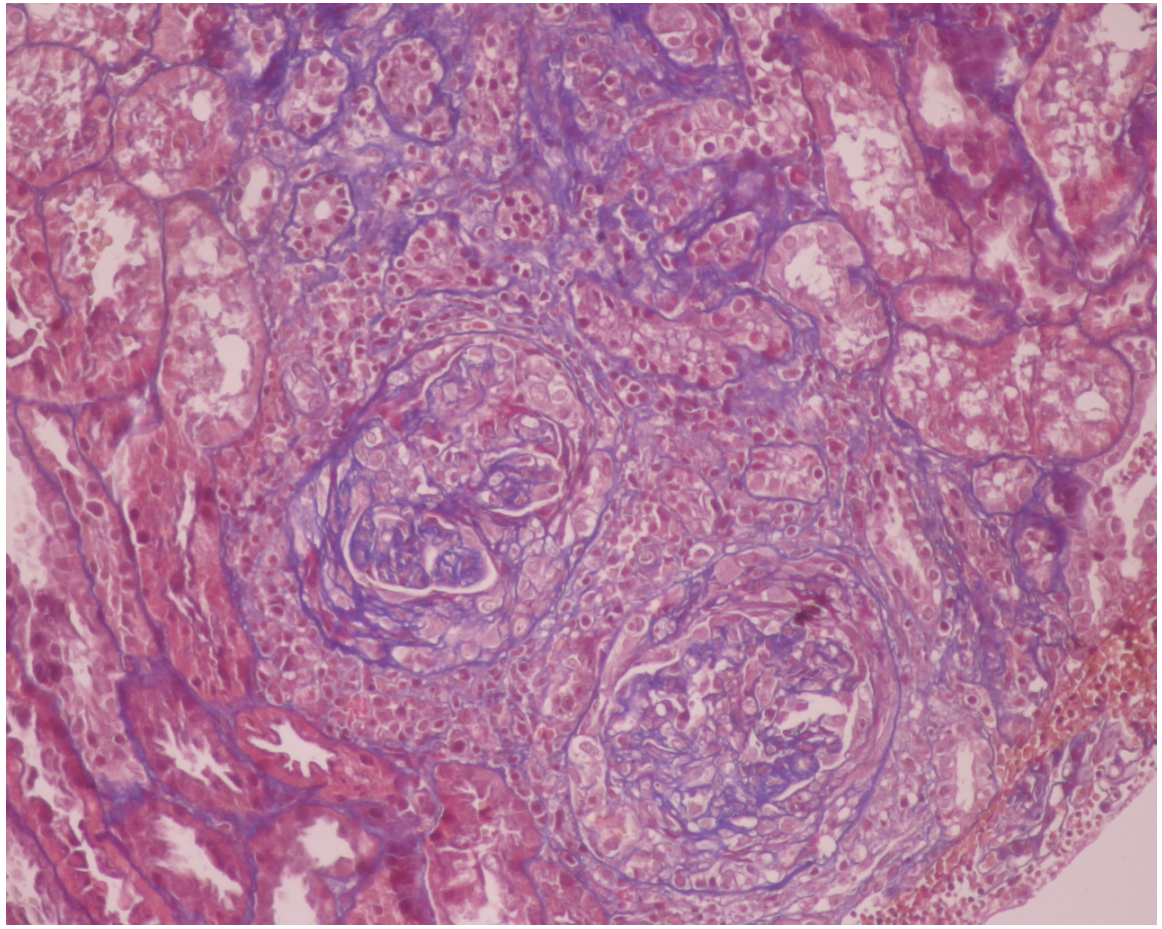
Peribronchial thickening



Nodules in both lungs

Renal involvement

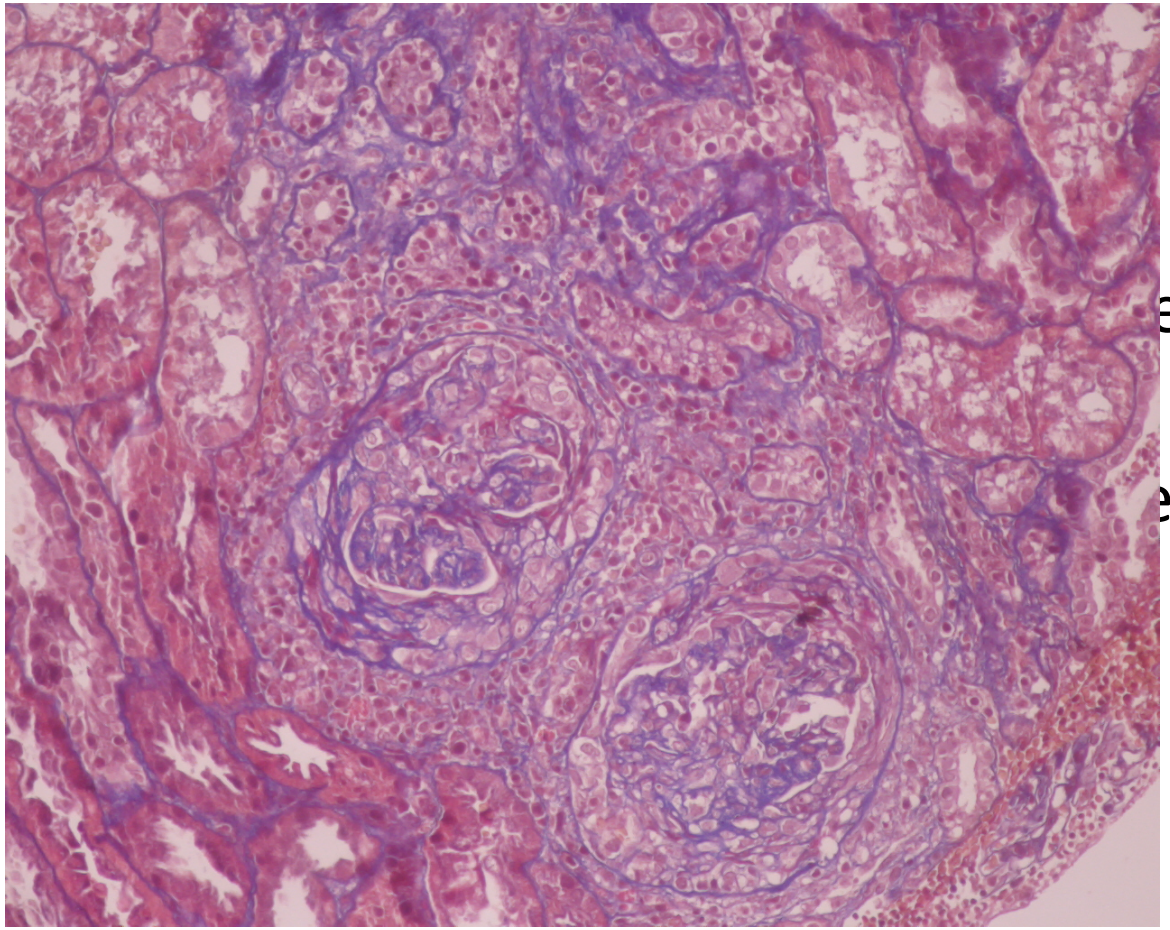
- Necrotising pauci immune glomerulonephritis is present in 70-80% of the patients
- Most patients (75%) have ANCA directed against proteinase 3
- MPO ANCA 20%
- 5% ANCA negative
- GPA in children (n=28)
  - Proteinuria, 18
  - Hematuria, 15
  - HT, 5
  - AKI, 14
- Some patient require dialysis at diagnosis

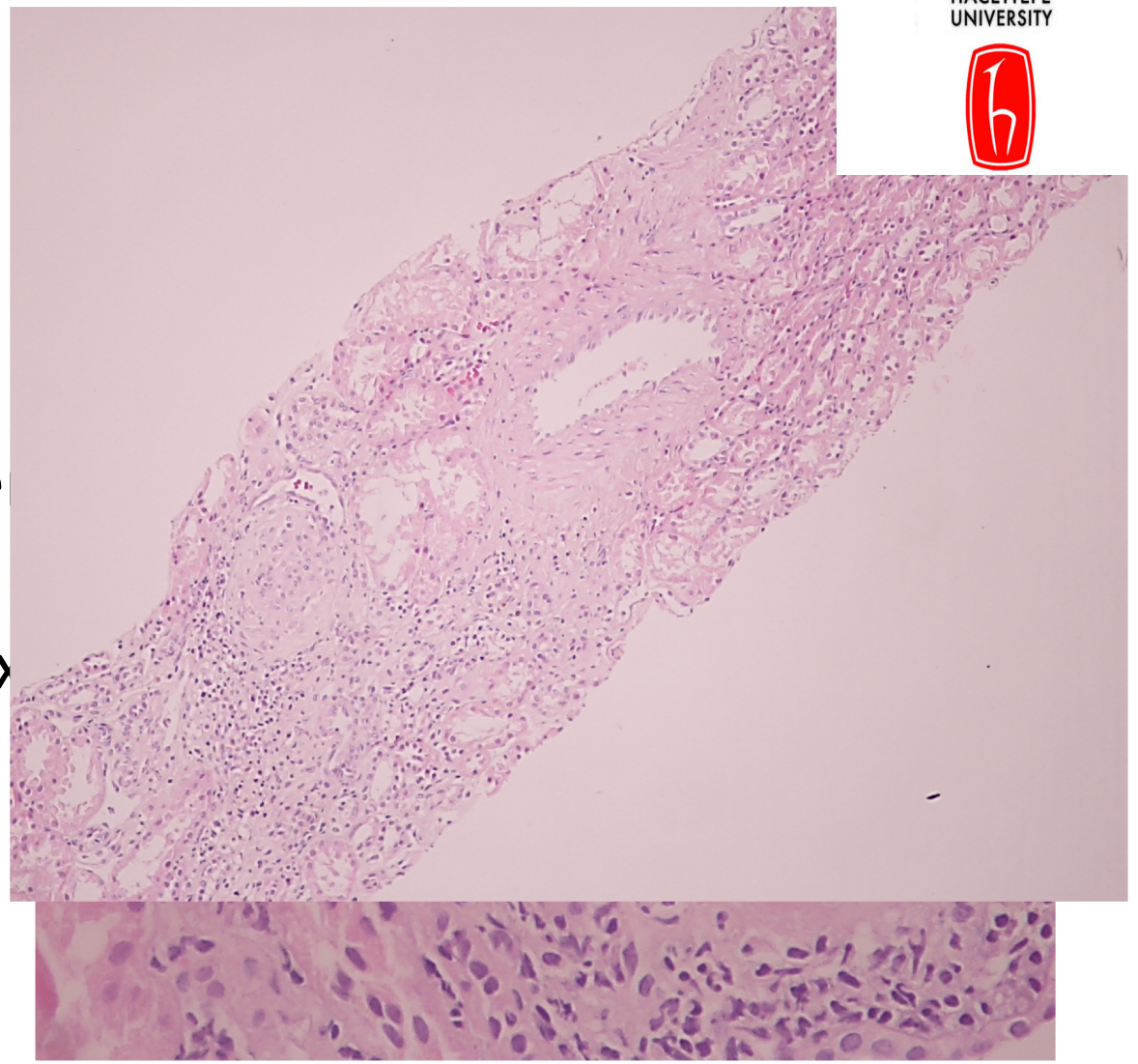


Nephrol Dial Transplant 2015; 30: 104-12

J. Nephrol 2018; 31: 197-208

EGU-4 Renal Biopsy





Pauci -immune, crescentic and segmental necrotizing glomerulonephritis, consistent with ***Wegener Granulomatosis***

Microscopic polyangitis (MPA)

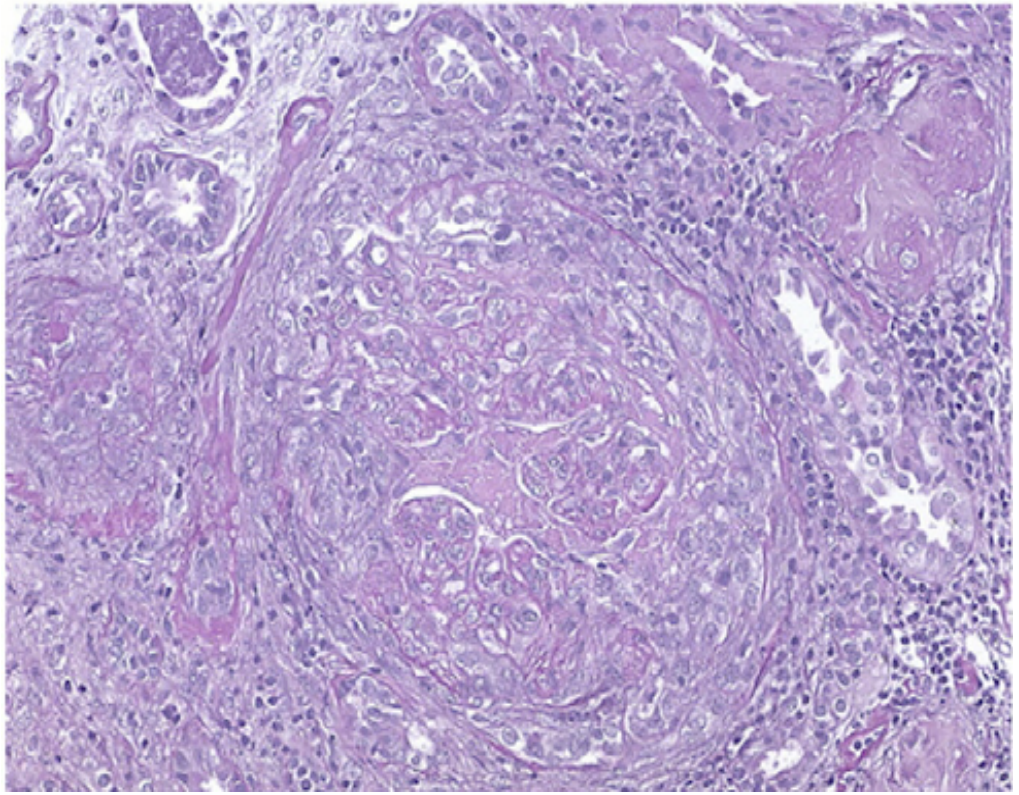
- MPA is considered the prototypic AAV because the pathways involved in its pathogenesis are actually shared by all types of AAV
- Necrotising vasculitis with few or no immune deposits affecting small vessels
- a diagnostic criteria for MPA in children is not available

MPA

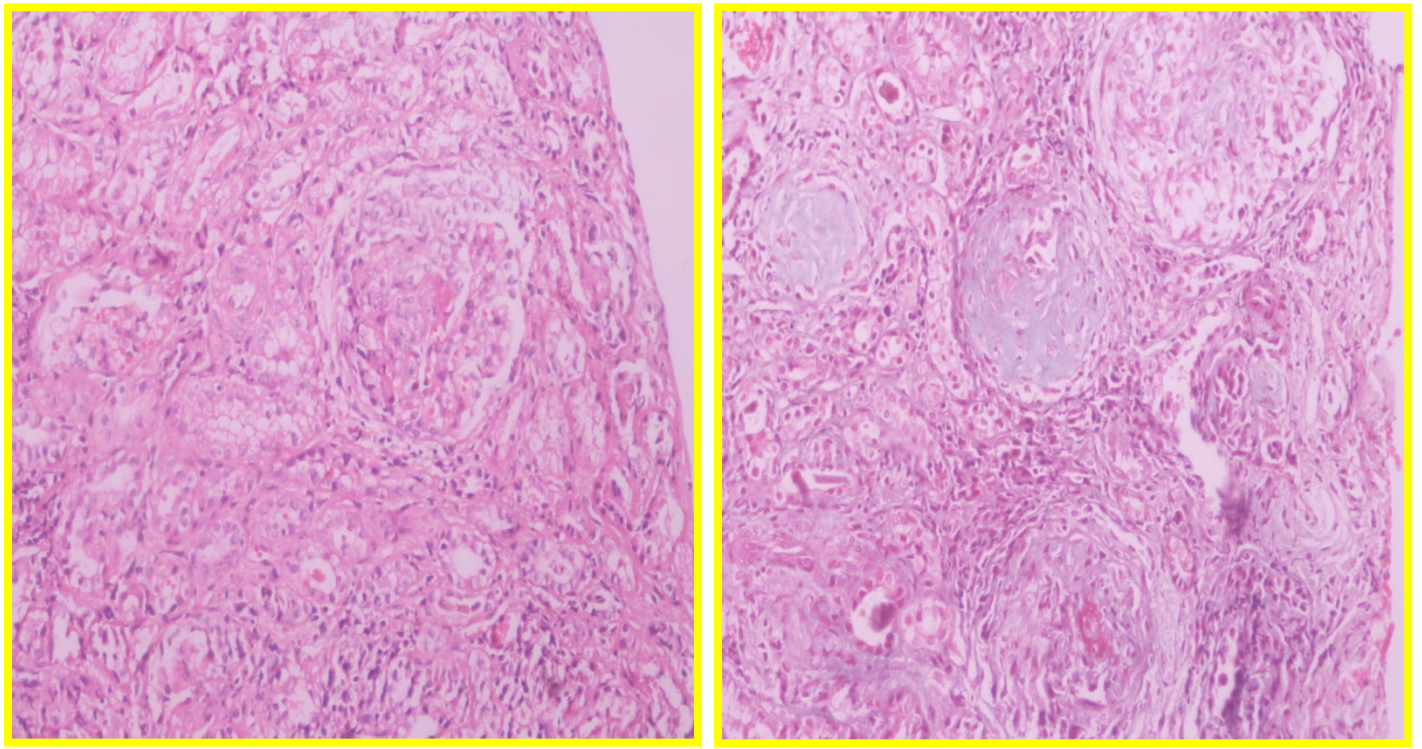
- Female predominance as high as 6:1
- Patients are significantly younger than GPA patients 11 vs 14
- Onset is insidious and associated constitutional symptoms in almost all patients
- Purpuric rash is common
- CNS involvement 21-86%
- Peripheral neuropathy
- Pulmonary symptoms 44% but less severe than GPA
- Renal involvement is 75-100%

MPA

- Kidney involvement
  - almost 100% of the adult patients
  - 75-90% in children
  - Necrotising and crescentic pauci-immune GN
- MPO ANCA is positive
  - 75-80% of adult patients
  - similar in children
- PR3 ANCA could be positive in 15-20%



ST-3 Renal Biopsy



Circumferential fibrous – IF negative necrotizing crescentic GN

Microscopic polyangiitis

Clinical and histopathological prognostic factors affecting the renal outcomes in childhood ANCA-associated vasculitis

Pediatr Nephrol (2019) 34: 847

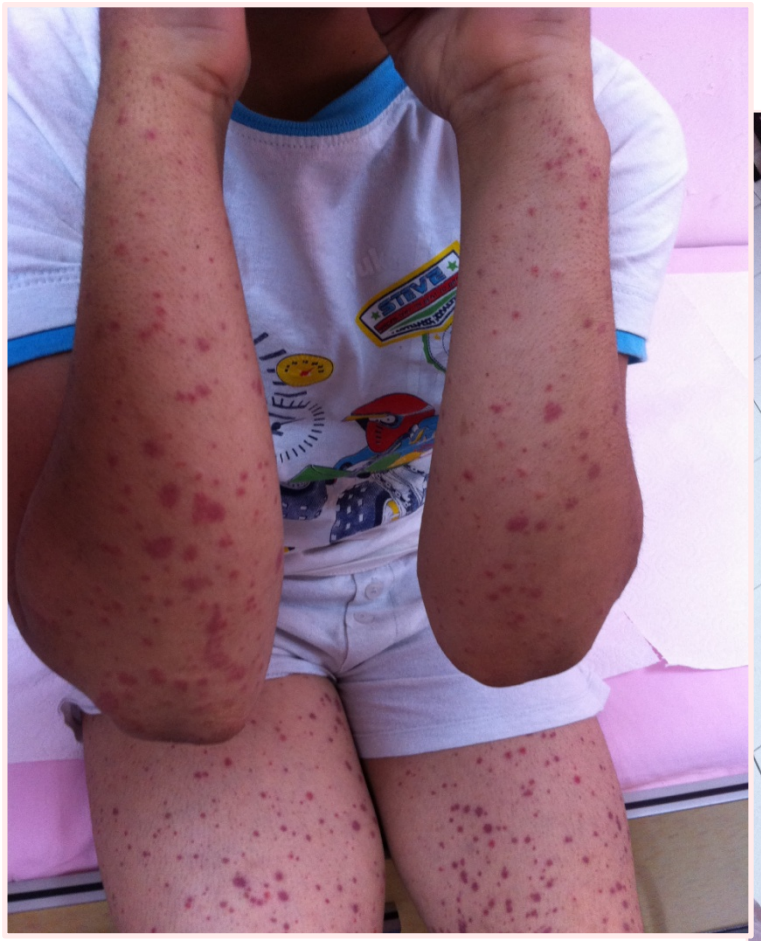
Gül Özçelik[1] · Hafize Emine Sönmez[2] · Sezgin Şahin[3] · Ayşim Özağarı[4] · Meral Torun Bayram[5] · Rümeysa Yasemin Çiçek[6] · Evrim Kargın Çakıcı[7] · Elif Çomak[8] · Kenan Barut[3] · Nihal Şahin[9] · Sevcan Bakkaloğlu[10] · İbrahim Gökçe[11] · Ali Düzova[12] · Yelda Bilginer[2] · Ceyhun Açarı[13] · Engin Melek[14] · Beltinge Demirdoğlu Kılıç[15] · Semanur Özdel[16] · Amra Adroviç[3] · Özgür Kasapçopur[3] · Erbil Ünsal[13] · Harika Alpay[11] · Diclehan Orhan[17] · Rezan Topaloğlu[12] · Ruhan Düşünsel[9] · Seza Özen[2,18]

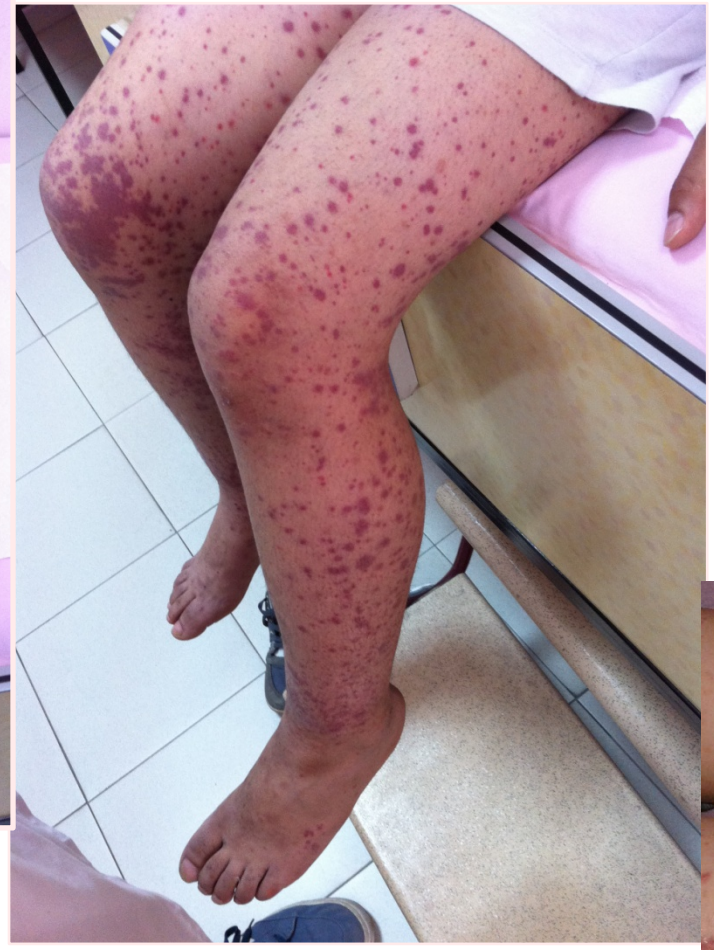
Comparison of clinical and laboratory findings of AAV subgroups

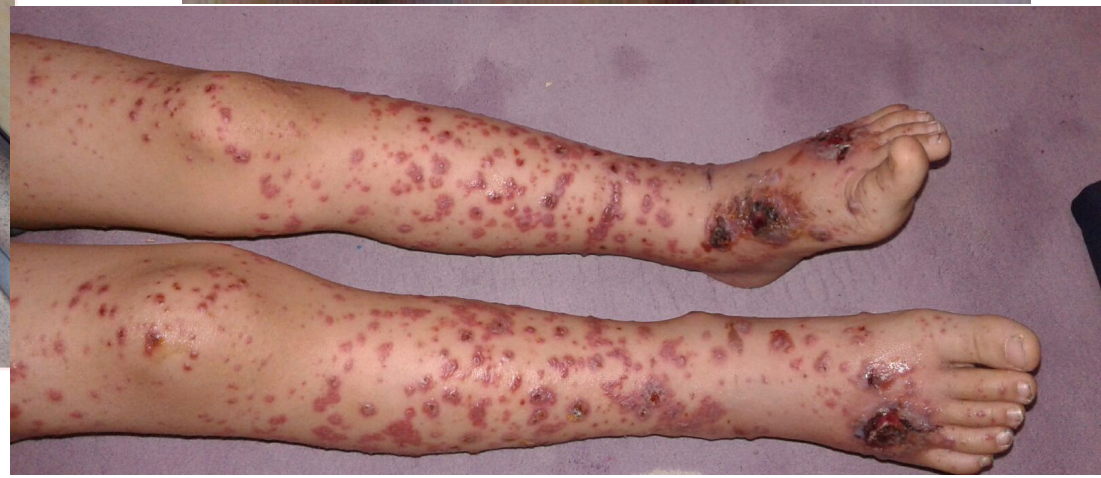
	MPA (n = 8)	GPA (n = 26)
Gender (F/M)	7/1	20/6
Age at diagnosis, mean ± SD	14.1 ± 3.7	13.1 ± 3.3
ETN involvement, n (%)	0 (0)	19 (73.1)
Skin findings, n (%)	4 (50)	11 (42.3)
Pulmonary involvement, n (%)	3 (37.5)	10 (38.5)
GIS involvement, n (%)	4 (50)	5 (19.2)
Neurologic involvement, n (%)	1 (12.5)	1 (3.8)
Musculoskeletal involvement, n (%)	4 (50)	14 (53.8)
Ocular involvement, n (%)	0 (0)	6 (23.1)
PR3-ANCA positivity, n (%)	1 (12.5)	16 (61.5)
MPO-ANCA positivity, n (%)	5 (62.5)	7 (26.9)
Renal involvement, n (%)	8 (100)	20 (76.9)
Proteinuria, n (%)	7 (87.5)	17 (65.4)
Hematuria, n (%)	7 (87.5)	21 (80.8)
GFR, ml/min/1.73 m2, mean ± SD	32.6 ± 42.4	87.6 ± 56.2
Decline in GFR > %25, n (%)	4 (50)	7 (26.9)
ESRD, n (%)	3 (37.5)	7 (26.9)
Relapse, n (%)	0 (0)	4 (15.4)

- There is clinical overlap in clinical features of GPA and MPA
- It has been suggested AAV should be classified according to ANCA specificity
- CHCC 2012 advocated for adding a prefix to the clinical phenotype (PR3-ANCA GPA or MPO-ANCA MPA)
- Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) is collecting data (>6000 patients from 136 centers in 32 countries)

IgA Vasculitis (HSP)







IgA vasculitis - HSP

- The most common cause of small vessel vasculitis in childhood
  - 13.5 - 20.4 cases per 100,000
  - most common in 4–6 year-old children

- CHCC- 2012
  - affects small vessels with IgA1-dominant immune deposits
    - typically involves the skin, gut, glomeruli and associated with arthralgia and/or arthritis

Piram M.,Curr Opin Rheumatol 2013;25(2):171e8.
Gardner-Medwin JM, Lancet 2002;360(9341):1197e202.

EULAR/PRINTO/PRES criteria for HSP

Criterion		Frequency (%)
Palpable purpura (mandatory) +	- Symmetric purpura, mainly over extremities following gravity - Exclude thrombocytopenia!	100
Abdominal pain	- Colic-like, postprandial - Nausea, gastrointestinal bleeding - Intussusception, infarction, perforation	50-60
Histopathology	- Immune complex vasculitis - Proliferative glomerulonephritis (IgA deposition)	-
Kidney involvement	- Proteinuria >0.3 g/24 h or - Albumin/creatinine ratio >30 mmol/mg - Micro-hematuria - Arterial hypertension - Nephritic or nephrotic syndrome	20-50
Joint involvement	- Arthritis, mostly ankles and/or knees	70

1 of 4

Ankara 2008. Part II: final classification criteria. Ann Rheum Dis. (2010) 69:798–806.
SChildhood Vasculitis. 2019 Front. Pediatr. 6:421

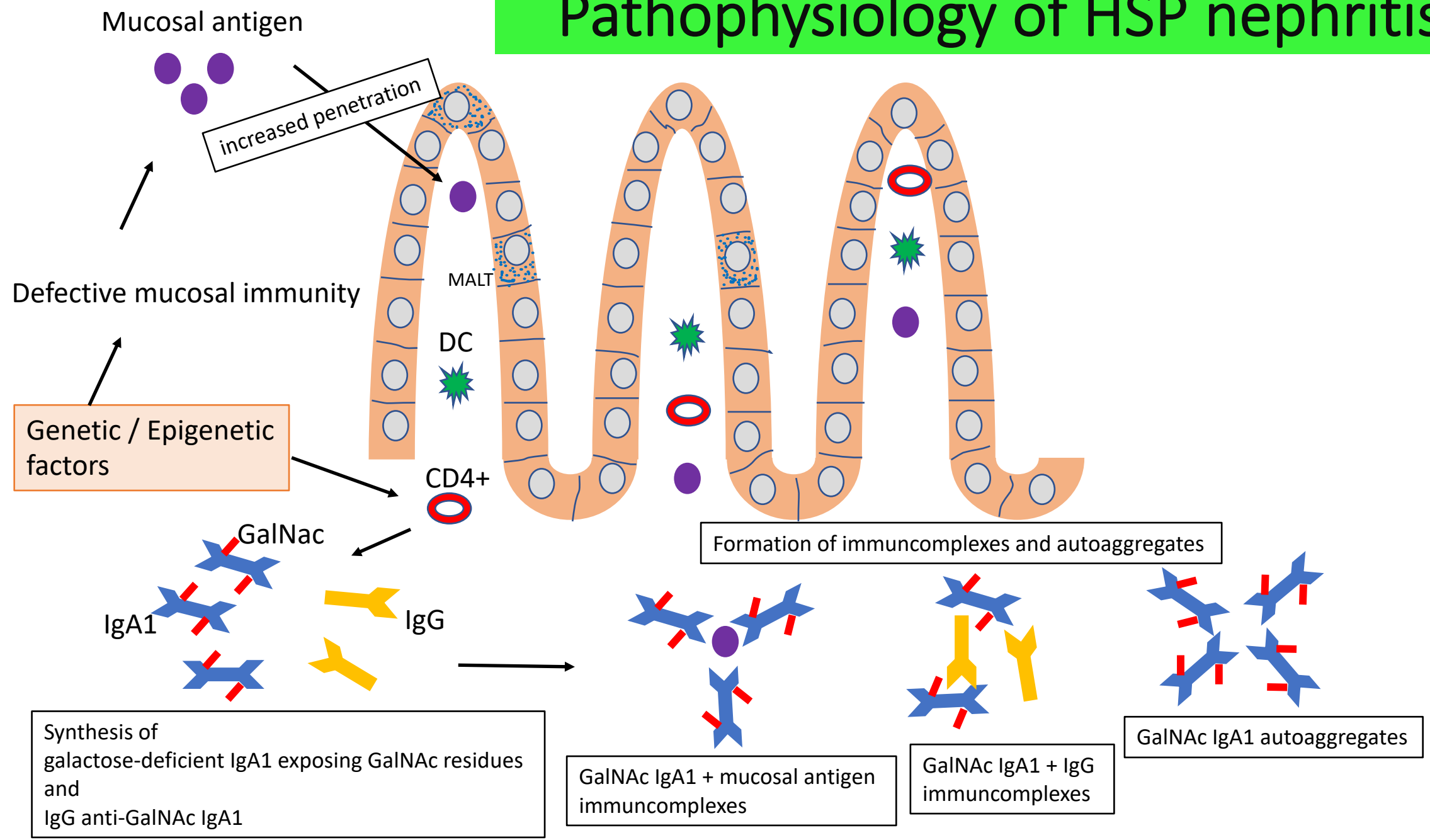
Genetic Predisposition in IgAV

Genetic susceptibility	Genetic protection
HLA-B*15	HLA-B*7
HLA-B*35	HLA-B*40
HLA-B*4102	HLA-B*49
HLA-B*52	HLA-B*50
HLA-A*2	HLA-A*1
HLA-A*11	HLADRB1*3
HLA-A*26	HLADRB1*7
HLA-DRB1*0103	Agtrs699M235T
HLA-DRB1*11	MEFV
HLA-DQA1*0301	PONI
HSPA21267GG	
IL1815187238-137G	
MCP1-2518TT	
MCP1-2518T	
TGF beta rs1800469-509TT	
Agt	
ACE	
C1GALT1rs	
NOS2A	
eNOS	
PONI192QQ	
MEFV	

- The HLA region is the principal genetic factor related with IgAV.
- a solid relation with HLA class II alleles, especially HLA-DRB1 alleles, HLA class I alleles also appear to impact on the disposition of this disease.
- IgAV was intensely related with HLA-DRB1 in the European populations, mostly due to HLA-DR1*0103

Oni L, Front Pediatr. 2019;7:257
Ralli et al., EXCLI Journal 2020;19:817-854

Pathophysiology of HSP nephritis



Davin, J.-C. & Coppo, R. *Nat. Rev. Nephrol*. 10, 563–573 (2014)

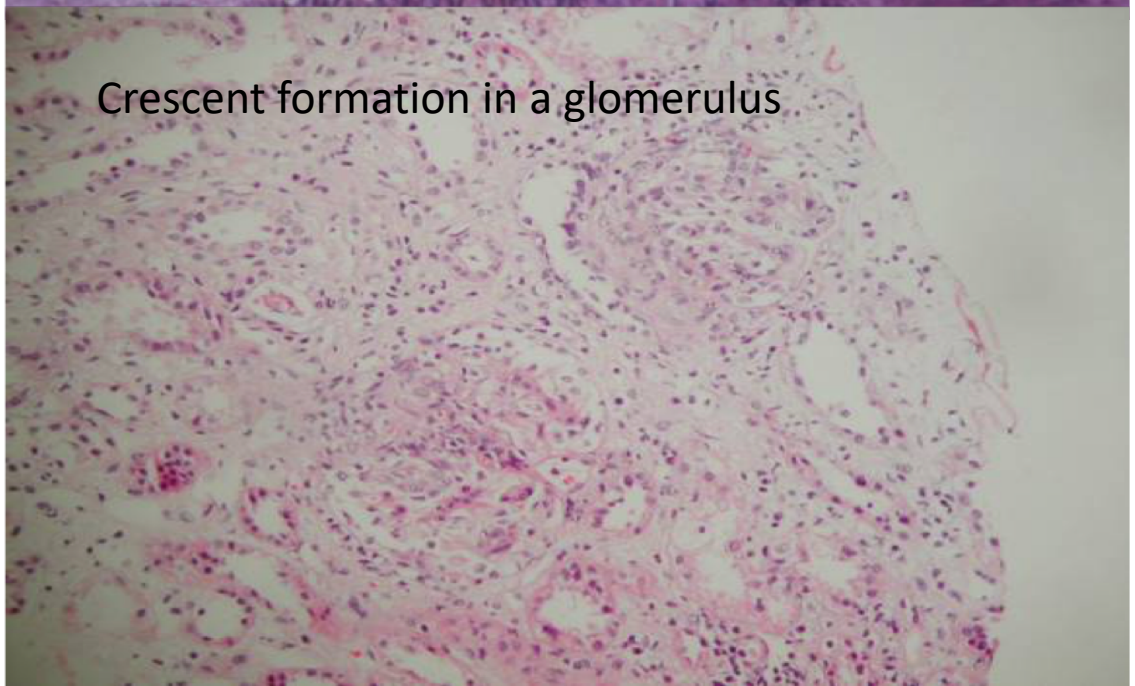
Mechanisms of renal injury in HSP nephritis

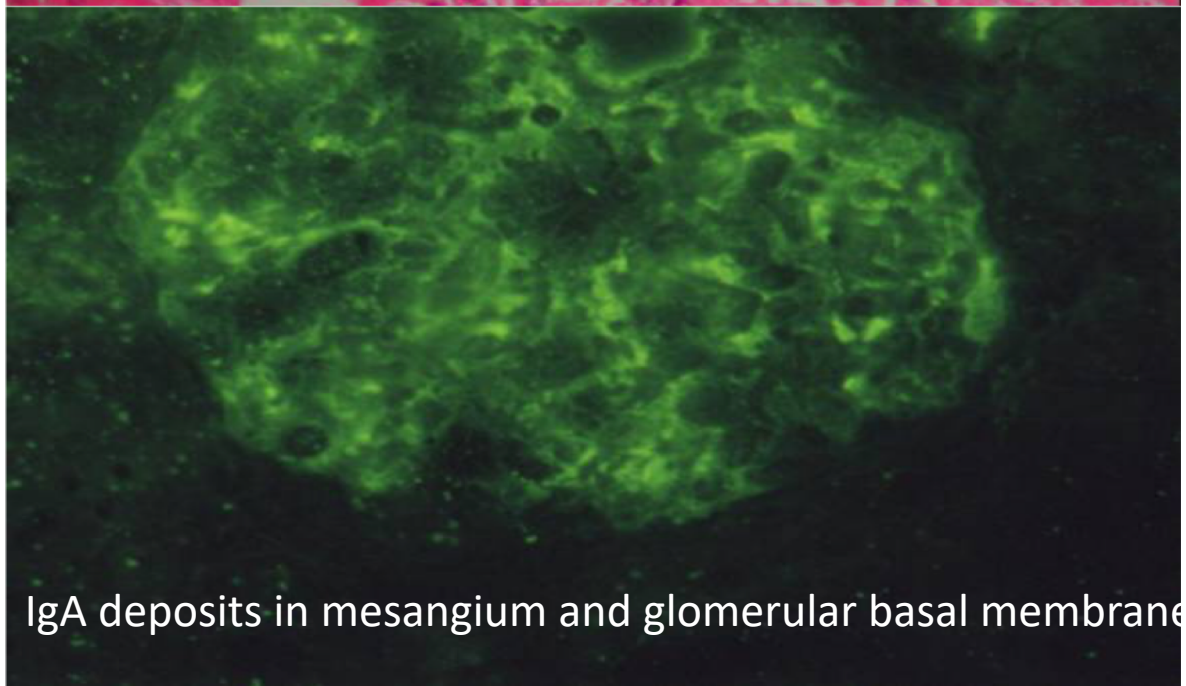
- Gd-IgA1 immunocomplex in the mesengial areas activates
- Mesengial cells
    - Proliferation of macrophages, lymphocytes
    - Production of inflammatory and profibrogenic cytokines and chemokines
- Complement pathway (alternate and lectin)
- Gd-IgA1 immunocomplex activates neutrophils via IgAFc receptor (CD89)
- Endothelial cell dysfunction
    - Fujieda et al., (1998)
        - High IgA antiendothelial cell antibody titers, elevated thrombomodulin levels
    - Kawasaki et al., (2004)
        - Higher serum E-selectin concentrations

Kawasaki et al., Fukushima J Med Sci. 2013;59(1):15-26.


Leukocytoclastic vasculitis in upper dermis


Segmental proliferation in mesangial area of a glomerulus


Crescent formation in a glomerulus


IgA deposits in mesangium and glomerular basal membrane

Different histological classifications for HSPN
ISKDC

ISKDC grade	Description
Grade I	Minimal alterations
Grade II	Mesangial proliferation
Grade III	Proliferation or sclerosis with < 50% crescents ((a) focal or (b) diffuse)
Grade IV	Mesangial proliferation or sclerosis with 50–75%, crescents ((a) focal or (b) diffuse)
Grade V	Mesangial proliferation or sclerosis with > 75% crescents ((a) focal or (b) diffuse)
Grade VI	Membranoproliferative like glomerulonephritis

- still the most frequently used for histological analysis of HSPN
- This classification is largely based on the **crescents**
- reflects active inflammation, in the same time neglecting vascular and tubulointerstitial changes
- the proportion of sclerotic glomeruli and interstitial fibrosis correlates better with the long-term outcome
  - leading to the idea that the Oxford classification, used in IgA nephropathy, could be used in predicting the progression of renal disease in HSPN

Haas M. Heptinstall's Pathology of the Kidney. Philadelphia: Lippincott, Williams & Wilkins; 2007. p. 423–86.
Jelusic et al. Pediatric Rheumatology (2019) 17:10

Different histological classifications for HSPN Oxford

Histological variable	Description
Mesangial hypercellularity	M_0 < 50% of glomeruli showing mesangial hypercellularity M_1 > 50% of glomeruli showing mesangial hypercellularity
Endocapillary hypercellularity	E_0 absent E_1 present
Segmental glomerulosclerosis/adhesion	S_0 absent S_1 present presence or absence of podocyte hypertrophy/tip lesions in biopsies with S1
Tubular atrophy/interstitial fibrosis	T0 ≤ 25% of the cortical area affected by tubular atrophy or interstitial fibrosis T1 26–50% of the cortical area affected by tubular atrophy or interstitial fibrosis T2 > 50% of the cortical area affected by tubular atrophy or interstitial fibrosis
Cellular/fibrocellular crescents	C0 absent C1 present in at least one glomerulus C2 present in > 25% of glomeruli

- 2009 – First version → MEST
- 2016 – Revised version → MEST-C

- the working group does not recommend the use of MEST-C score in HSPN since cases of patients with this condition were not included in the validation cohort

Trimarchi H et al. Kidney Int. 2017;91:1014–21.
Jelusic et al. Pediatric Rheumatology (2019) 17:10

Prognosis

- Overall the outcome is excellent. In the vast majority of children symptoms resolves in the first months
- Relapses can occur
- There is an accepted risk life long renal involvement
- Progression to some degree CKD reported in 5-45% of children but ESKD 1-5%

Summary

- AAV systemic vasculitis is small vessel vasculitis
- ANCAs are antibodies directed against cytoplasmic antigens in the primary granules of neutrophils and lysosomes of monocytes
- Neutrophil priming and subsequent inflamatory substance and netosis play key role in the pathogenesis of AAVs
- Renal involvement drives the prognosis of AAV
- There overlap in clinical features of GPA and MPA
- It has been suggested AAV should be classified according to ANCA specificity
- IgAV is the most common small vessel vasculitis seen in children
- Pathogenesis is IC driven vasculitis
- Renal involvement varies from 20-50% of the patients
- Progression to some degree CKD reported in 5-45% of children but ESKD 1-5%

Next Webinars

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **03 Nov 2020**

Speaker: **Marina Vivarelli**

Topic: **Steroid Resistant Nephrotic Syndrome: update from the IPNA Guideline Part 1: Diagnosis, definition, initial evaluation**

IPNA Clinical Practice Webinars

Date: **12 Nov 2020**

Speaker: **Agnes Trautmannn**

Topic**: Steroid Resistant Nephrotic Syndrome: update from the IPNA Guideline Part 2: Therapeutic managment**

ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **24 Nov 2020**

Speaker: **Roman Ulrich Müller**

Topic**: Management of autosomal dominant polycystic kidney diseases – state of the art**

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