Lung Manifestations of Rheumatological Diseases

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Financial Interest Disclosure
(over the past 24 months)
Sharon Dell

I have no conflict of interest relevant to this lecture

Objectives

1. Recognise the clinical presentations of pulmonary vasculitis in children

2. Understand the rationale behind the available treatment options for pulmonary vasculitis

3. Recognise the pulmonary presentations associated with connective tissue disease and inherited autoinflammatory disease

Why This is Important

- Pulmonologists may be the first consulted specialist
- Pulmonologists are often consulted by rheumatologists
- Lung disease can be severe, rapidly progressive and fatal
- Pulmonologists may be the primary driver of therapy (eg. isolated pulmonary capillaritis)

Systemic Inflammatory Diseases Most Often Encountered by Pediatric Pulmonologists

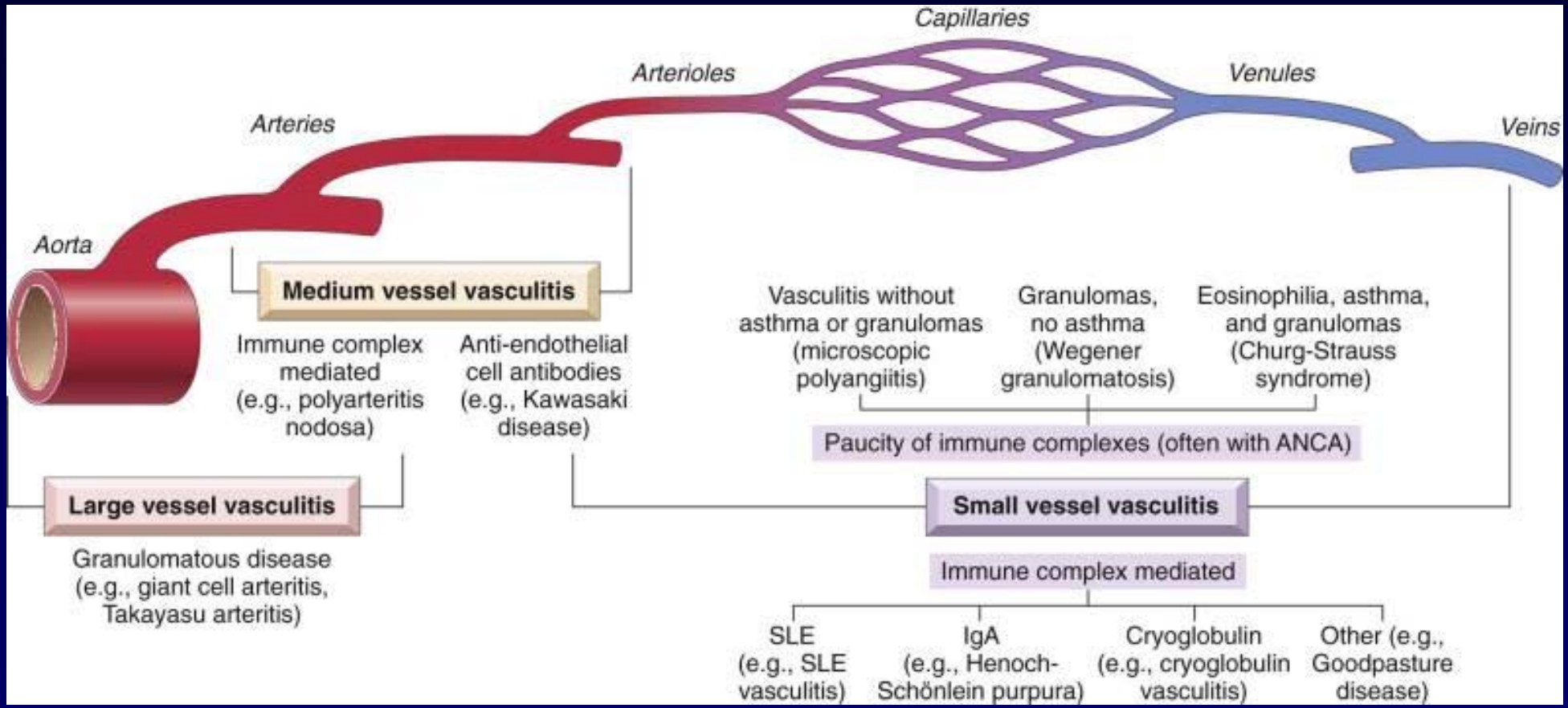
Rare but Serious Pulmonary Involvement is Common	Common but Serious Pulmonary Involvement is Rare
• Granulomatosis with Polyangiitis (GPA) and other vasculitides • Scleroderma	• Juvenile Idiopathic Arthritis (JIA) • Systemic Lupus Erythematosus

What is Vasculitis?

- Vasculitis = inflammation of blood vessels
- Pulmonary vasculitis= rare!
  - Usually a manifestation of a recognized systemic inflammatory disease

    OR
  - Isolated pulmonary vasculitis
- Always potentially fatal

Pulmonary Involvement in Systemic Vasculitides



Ann Rheum Dis. 2006;65(7): 936-41

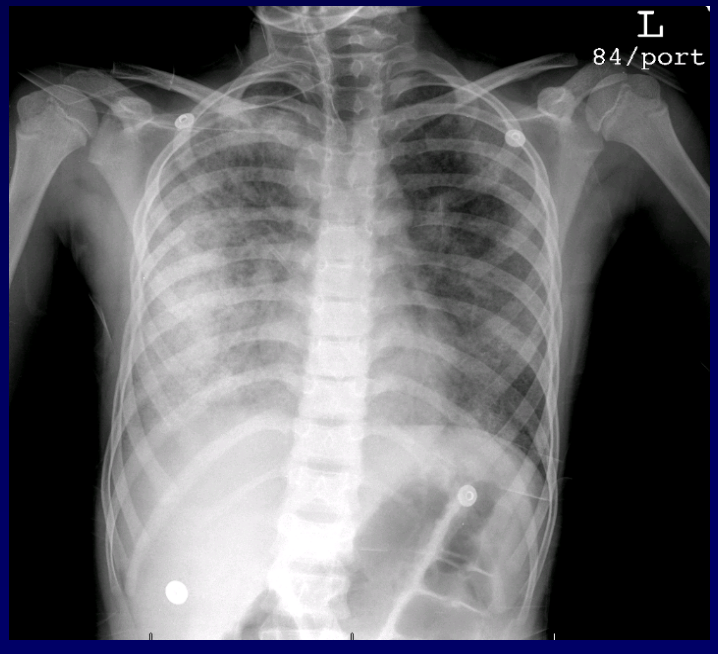
Kendig and Chernick's Disorders of the Resp Tract in Child. 2018; Chapt 57:822-847

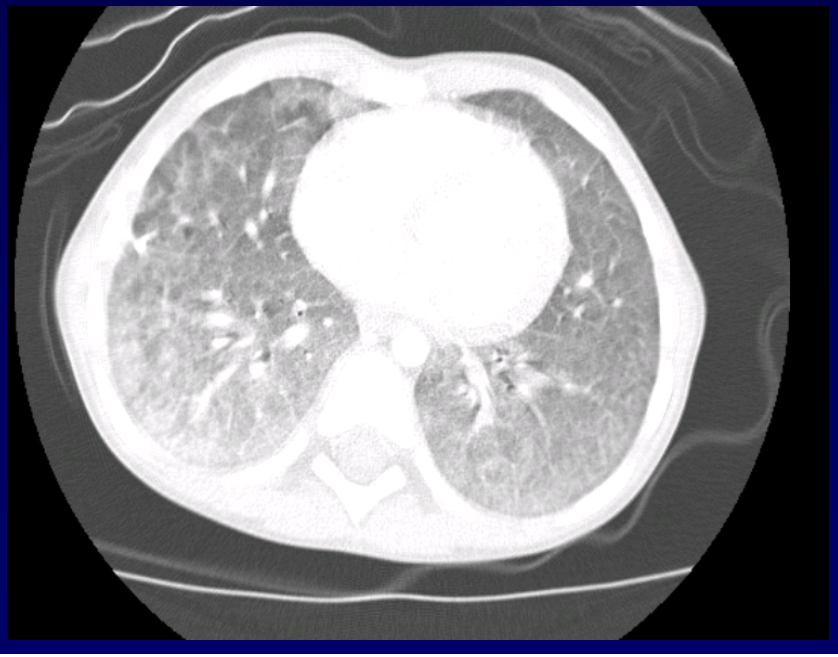
Clinical Presentations of Pulmonary Vasculitis

1. Diffuse Alveolar Hemorrhage (DAH)
2. Pulmonary Nodules or cavities
3. Tracheobronchial stenosis

Clinical Presentations of Pulmonary Vasculitis
1. Diffuse Alveolar Hemorrhage (DAH)

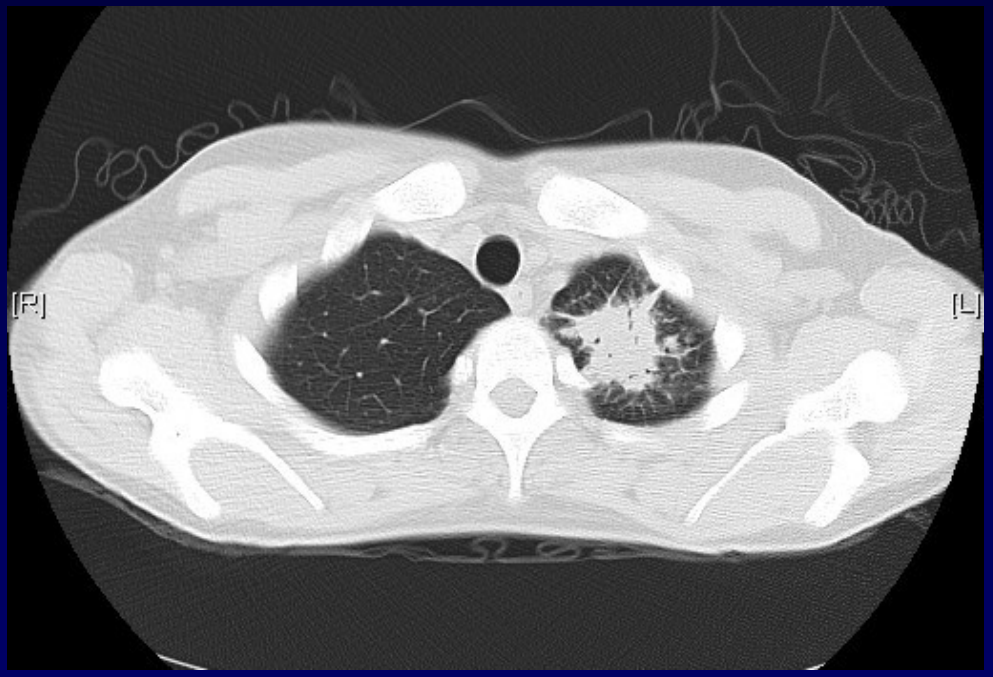
- Diffuse infiltrates, anemia, +/- hemoptysis
- Acute large volume hemorrhage: Hypoxia +/- respiratory failure
- Chronic insidious onset: Cough, dyspnea +/- fever

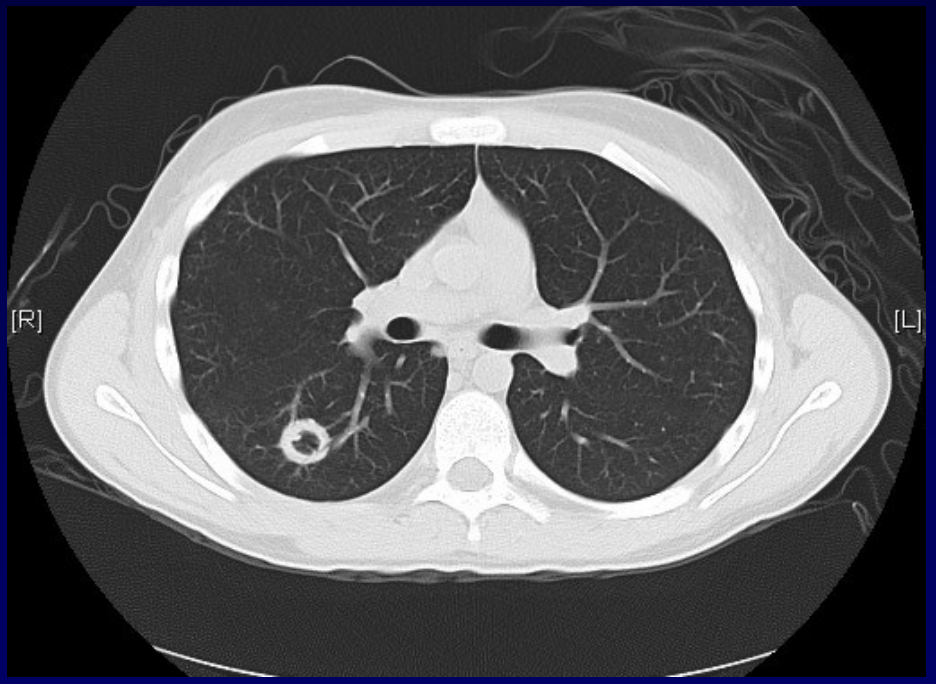




Clinical Presentations of Pulmonary Vasculitis
2. Pulmonary Nodules +/- cavities

Classic for GPA



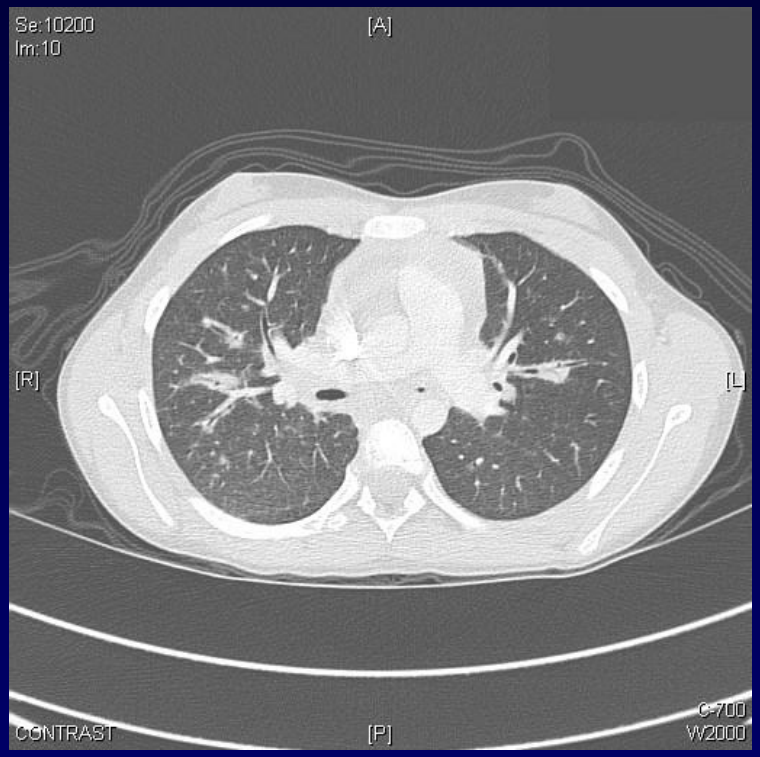


Images courtesy of Sharon Dell, University of Toronto, Canada.

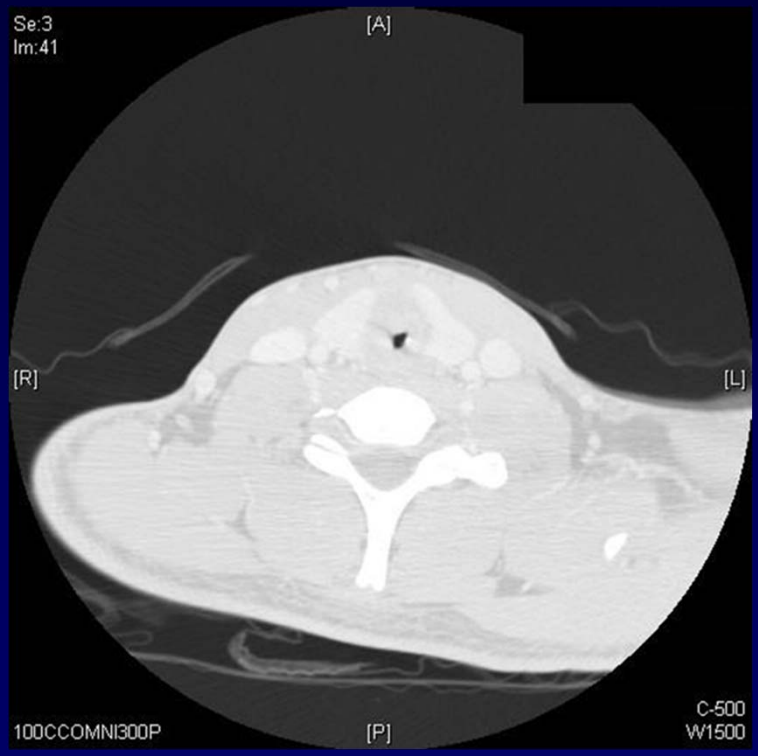
Pediatr Radiol. 2007; 37: 57-62

Clinical Presentations of Pulmonary Vasculitis

3. Tracheobronchial stenosis (specific for GPA)



Pinhole Bronchus



Tracheal Stenosis

Granulomatosis with Polyangiitis (GPA)
~Wegener's Disease

- Most common pediatric vasculitis
  (0.5 per 100,000 per year in U.S., predominantly teens)

- Presentation: constitutional symptoms, upper airway involvement (sinusitis, epistaxis, nasal septal perforation) +/- renal failure

+

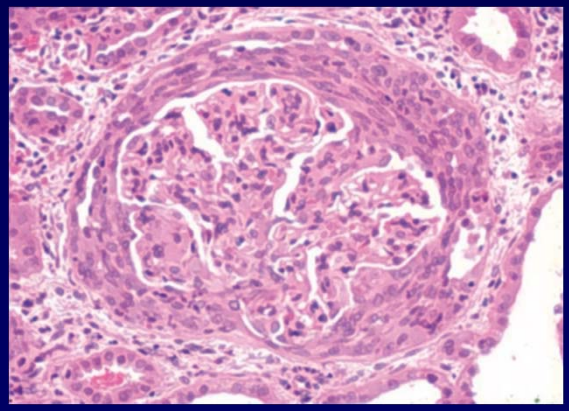
- Lower airway involvement in ~80% of cases:
  - Pulmonary nodules / cavities
  - Tracheobronchial stenosis
  - DAH

Saddle-Nose Deformity

Arthritis & Rheum. 2009; 60(11): 3413-24

Microscopic Polyangiitis (MPA)

- Rare systemic vasculitis (3-15 per million adults) and even more rare in children
- Typically presents with profound constitutional symptoms, joint involvement and renal involvement
  - Necrotizing crescenteric GN
  - Pauci-immune
- Lower airway involvement in ~30-60%
  - Classically DAH

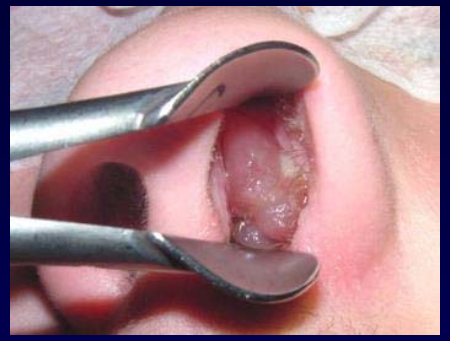


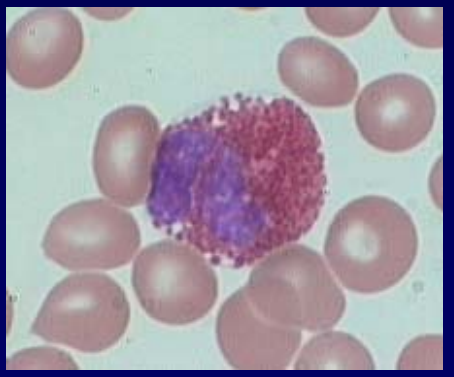
Ped Pulmonology. 2014; 49: 285-90

Pediatr Nephrol. 2006; 21(1): 46-53

Eosinophilic Granulomatosis with Polyangiitis (EGPA)
~Churg-Strauss

- Exceedingly rare in children (0.15-3 million adults)
- Prodromal phase of worsening asthma, chronic rhinosinusitis and nasal polyposis
- Constitutional symptoms; eosinophilia (>10%); cardiac disease more common in children
- Lower airway involvement in ~70-90% of cases:
  - Patchy migrating pulmonary infiltrates
  - Rarely DAH





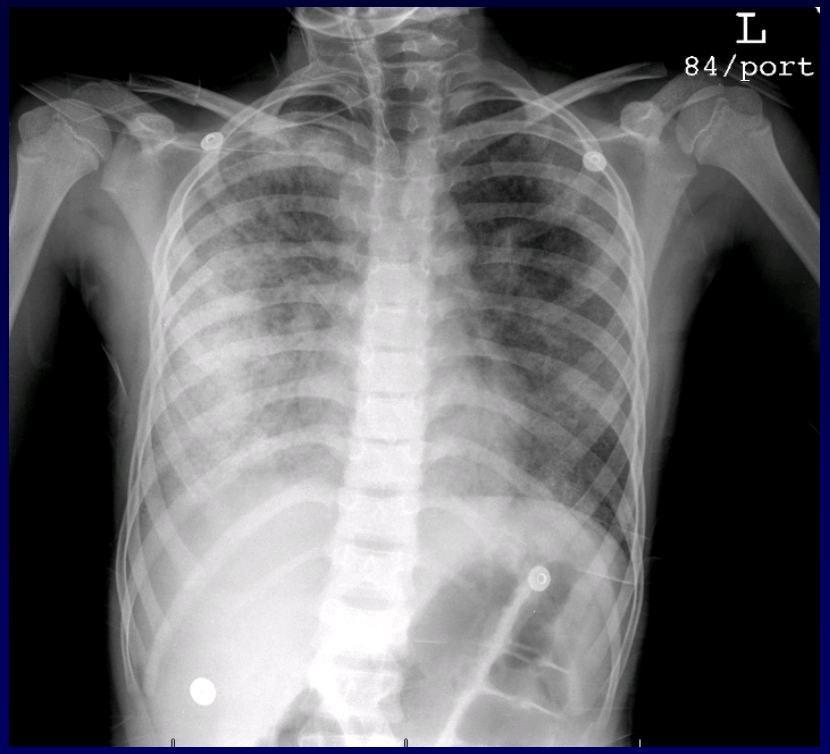
Ann Int Med. 2005;143: 632-8

Ped Pulm 2016;51:203-216

Pediatric Pulmonology 2018;53: 1640-1650

Isolated Pulmonary Capillaritis (IPC)

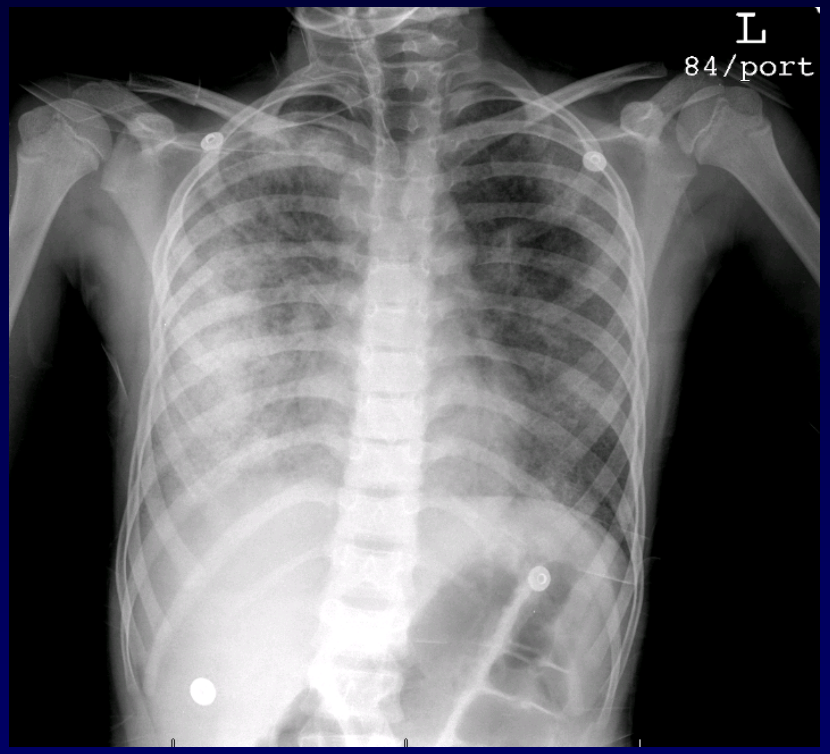
- Rare, but more common than EGPA
- Presents with isolated DAH
- +/- ANCA positivity (usually MPO)
- Frequent relapses and high mortality without treatment
- May develop extrapulmonary involvement with time



Am J Resp Crit Care Med. 1997; 155: 1101-09
J Pediatr. 2005; 146(3): 376-81

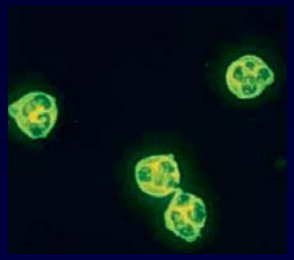
Isolated Pulmonary Capillaritis (IPC)

- Classified as “single organ vasculitis” in revised Chapel Hill Consensus Criteria*
- May be misclassified as idiopathic pulmonary hemosiderosis (IPH) in cases of bland, ANCA-negative pulmonary hemorrhage



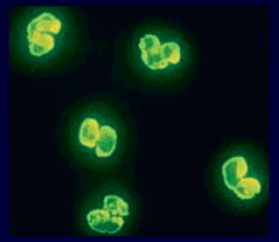
*Arthritis Rheum 2013; 65(1): 1-11

c-ANCA IF



Q1. Which of the following vasculitides is least likely to have positive ANCA serology?

p-ANCA IF



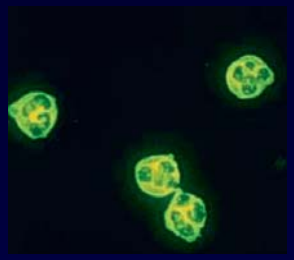
A. Eosinophilic granulomatosis with polyangiitis (EGPA, ~ Churg-Strauss)

B. Granulomatosis with polyangiitis (GPA, ~ Wegener's disease)

C. Isolated pulmonary capillaritis (IPC)

D. Microscopic polyangiitis (MPA)

c-ANCA IF



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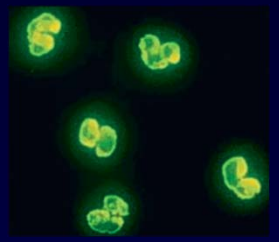

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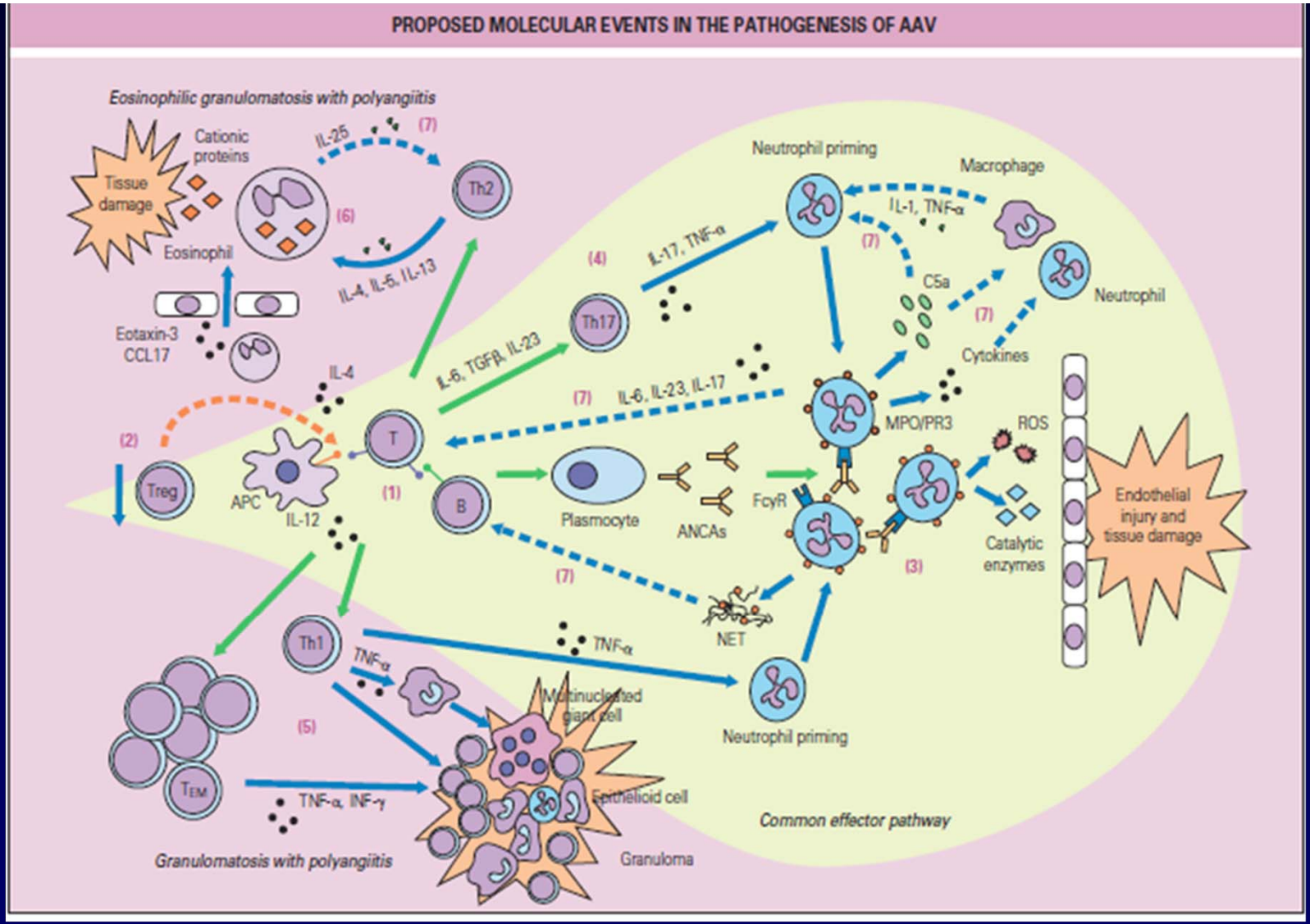


ANCA Vasculitis Hochberg Chapter 157

Comparison of Small Vessel Vasculitides

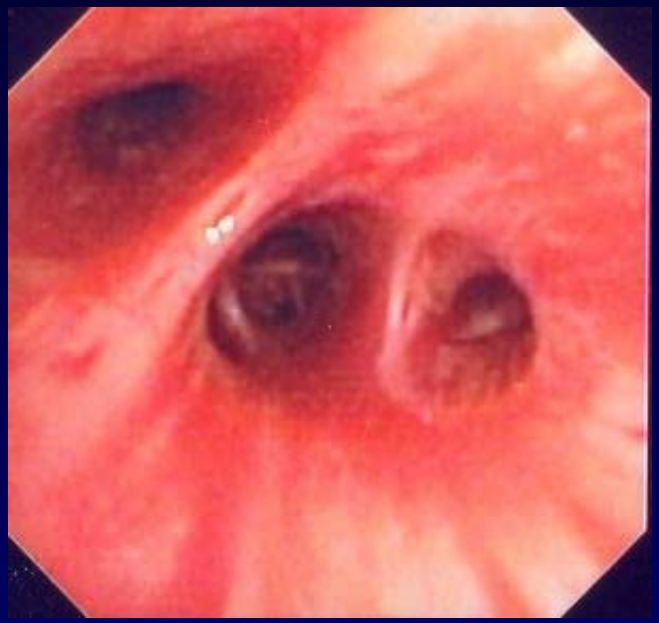
	GPA	MPA	EGPA	IPC
Pulmonary involvement	>80%	~30-60%	70-90%	100%
Typical pulmonary presentation	Nodules +/- cavities Airway stenosis DAH	DAH	Asthma Patchy infiltrates Rarely DAH	DAH
ANCA IF positive	90-95%	70%	0-40% child 40-50% adult	0-?
ANCA pattern	c-ANCA/ anti-PR3	p-ANCA/ anti-MPO	p-ANCA/ anti-MPO	? p-ANCA/ anti-MPO?

Modified from Ann Am Thorac Soc 2016: 13(6); 955-966.

Initial Workup of Pulmonary Vasculitis

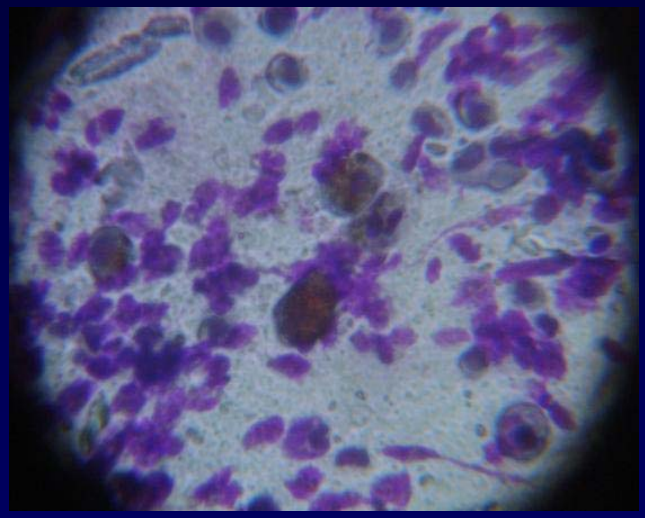
- Laboratory investigations
  - CBC, coagulation profile, inflammatory biomarkers, renal studies
  - Autoantibody panel (ANCA, ANA, RF)
- Imaging
  - High resolution CT chest
  - Consider CT sinuses if clinical suspicion of sinus disease or GPA
  - Echocardiogram: r/o myocardial disease & pulmonary hypertension
- Bronchoscopy
  - To identify diffuse alveolar hemorrhage and large airway lesions
  - To rule out infection
- Tissue biopsy (eg. kidney, skin, nose, lung, bronchial lesions)

Bronchoscopy in DAH



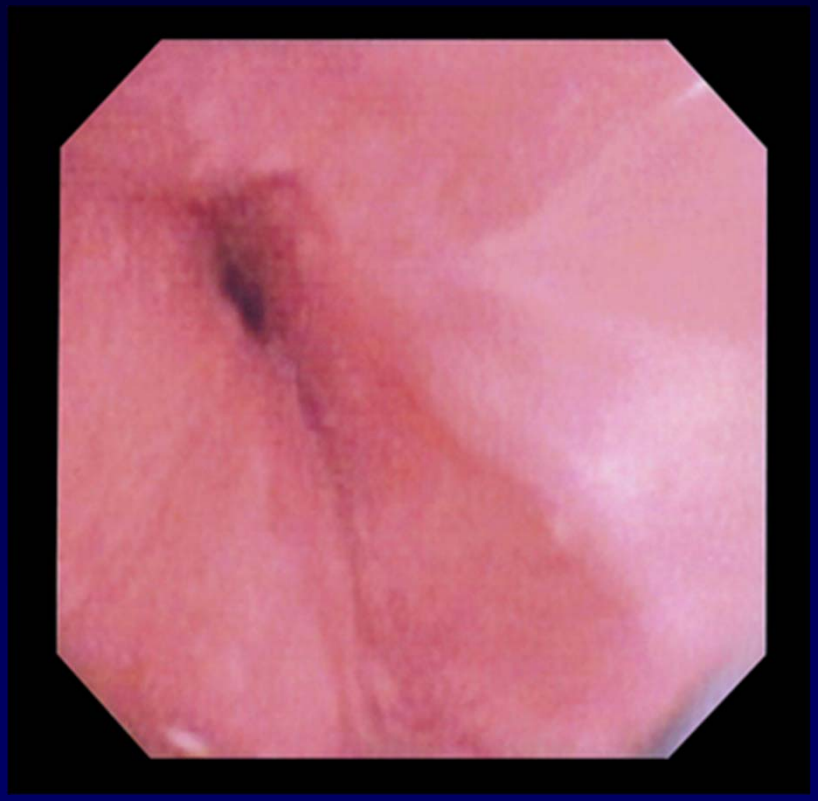
Fresh blood in airways vs clean airways

Bloody lavage return despite clean appearing airways

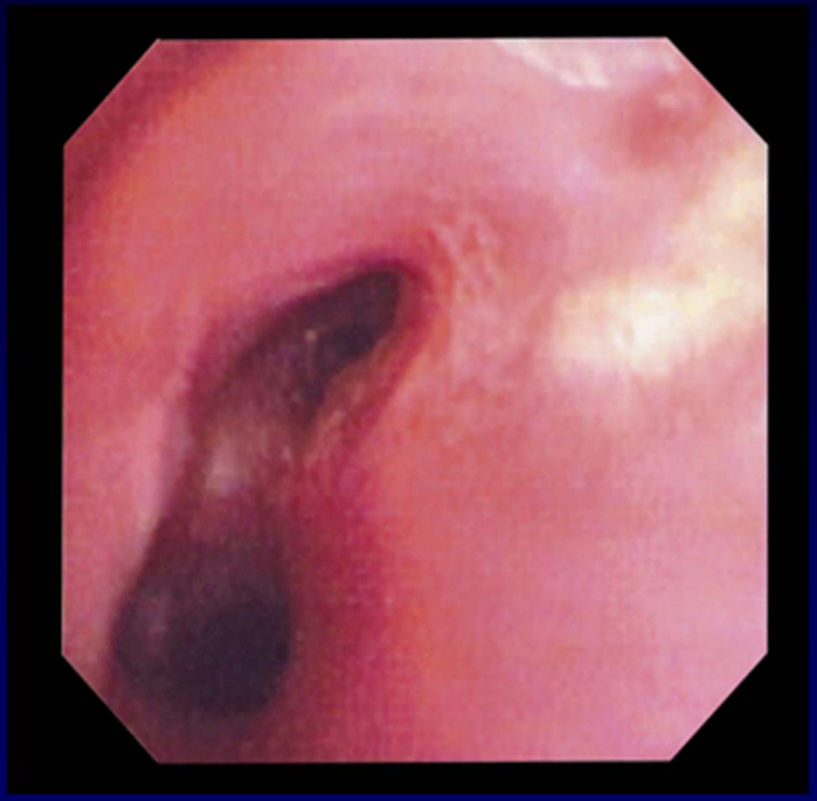


Hemosideron-ladin Macrophages in BALF

Bronchoscopy in GPA with Airway Stenosis

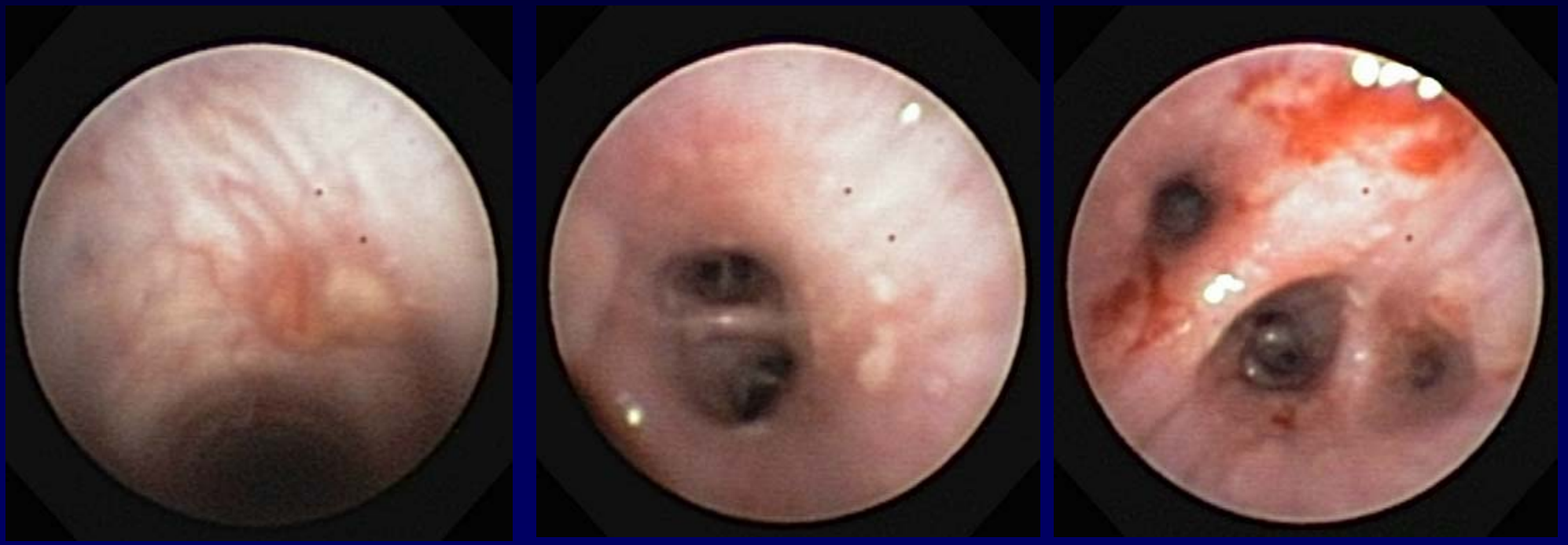


Pinhole LMB



RMB stenosis & ulceration

Bronchoscopy in active EGPA



Images courtesy of Sharon Dell, University of Toronto, Canada
J Bronchol Intervent Pulm. 2012;19(1): 81-2

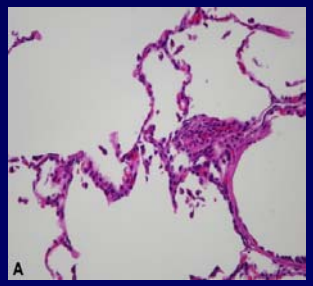
Lung Biopsy in Pulmonary Vasculitis

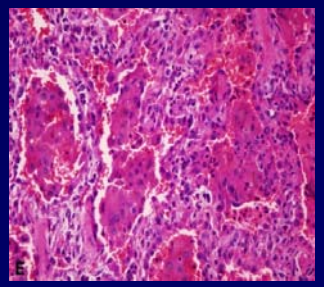
- Pathology
  - Transthoracic lung biopsy is gold standard for diagnosis
  - Can be difficult to interpret
    - Pre-op steroid administration
    - Patchy disease
    - Subtle findings (esp. in IPC)

Isolated Diffuse Alveolar Hemorrhage

Idiopathic Pulmonary Capillaritis (IPC)

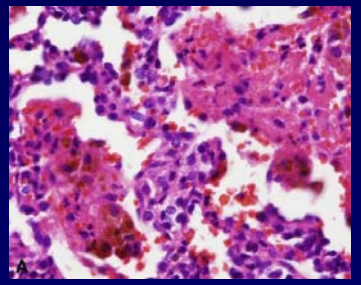
- Pauci-immune
- +/- Mild fibrosis
- +/- AEC2 hyperplasia
- Neutrophil infiltrate & fibrinoid necrosis of capillary walls

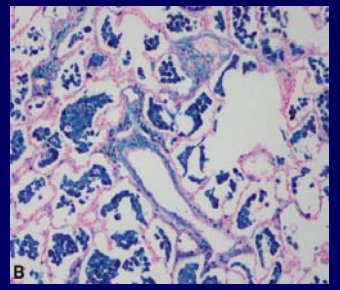




Idiopathic Pulmonary Hemosiderosis (IPH)

- Pauci-immune
- +/- Mild fibrosis
- +/- AEC2 hyperplasia
- Bland alveolar hemorrhage





Images courtesy of Sharon Dell, University of Toronto, Canada

AJRCCM. 1997; 155: 1101-9. *J Pediatr.* 2005; 146(3): 376-81

Systemic Vasculitis Treatment Options

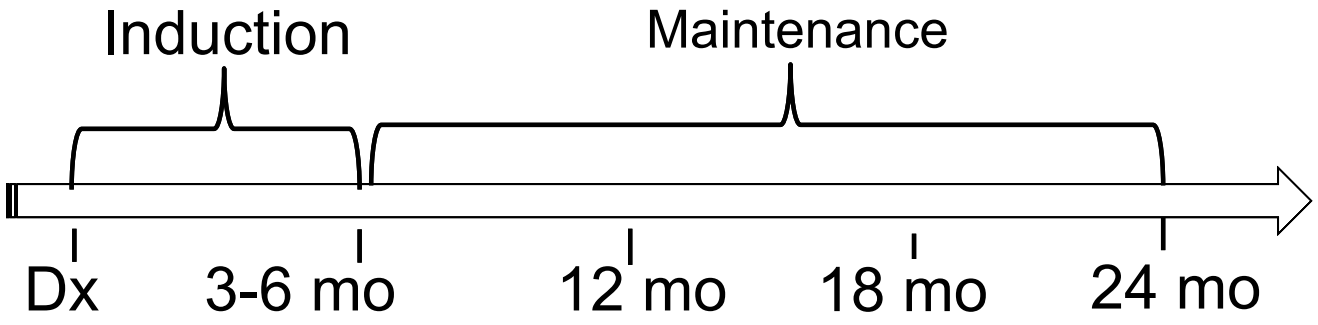
- Rapidly fatal if untreated
  - GPA 1 year mortality 80%
- No RCTs in pediatric vasculitis; treatment options extrapolated from adult RCTs
- Modern treatment divided into “induction” and “maintenance” phases

Ann Int Med. 1983; **98**: 76-85
Am J Resp Crit Care Med. 2012; 186(3): 216-24
Kendig & Chernick’s Dis of Resp Tract in Children. 2018; Chapter 57

Therapy for Generalized Active AAVs

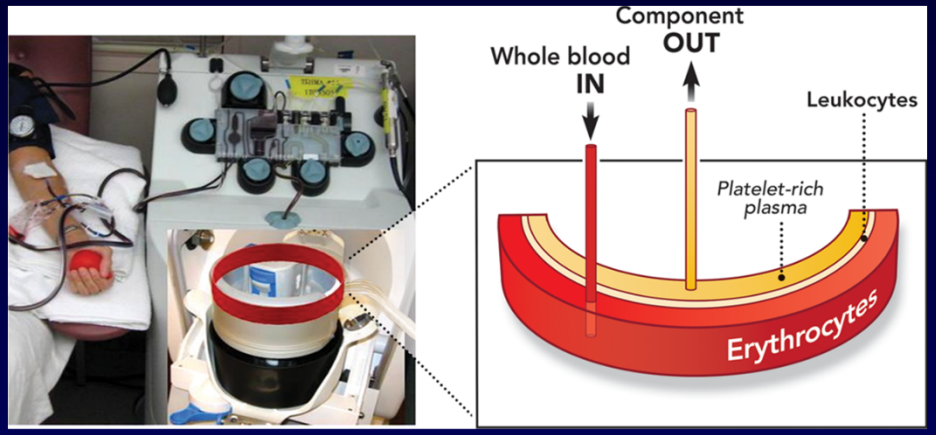
Steroid + Cyclophosphamide
Or
Steroid + Rituximab

Low dose Prednisone + Azathioprine
Or
Rituximab



NEJM 2010;**363**:221+ 211; *Ann Rheum Dis* 2015**;47**:1178-82
NEJM 2014;371:1771

Plasmapheresis for Induction of Remission



- **MEPEX trial** showed reduced end stage renal disease when combined with high dose steroids*
- Ongoing **PEXIVAS trial** to determine role in AAV
  - clinicaltrials.gov NCT#00987389
- Currently used for severe acute renal failure and DAH not responding to immunosuppressive therapy

Image: Anesthesiology. 2013; 118(3): 722-8

*J Am Soc Nephrol 2007;18:2180–8

Maintenance Therapy

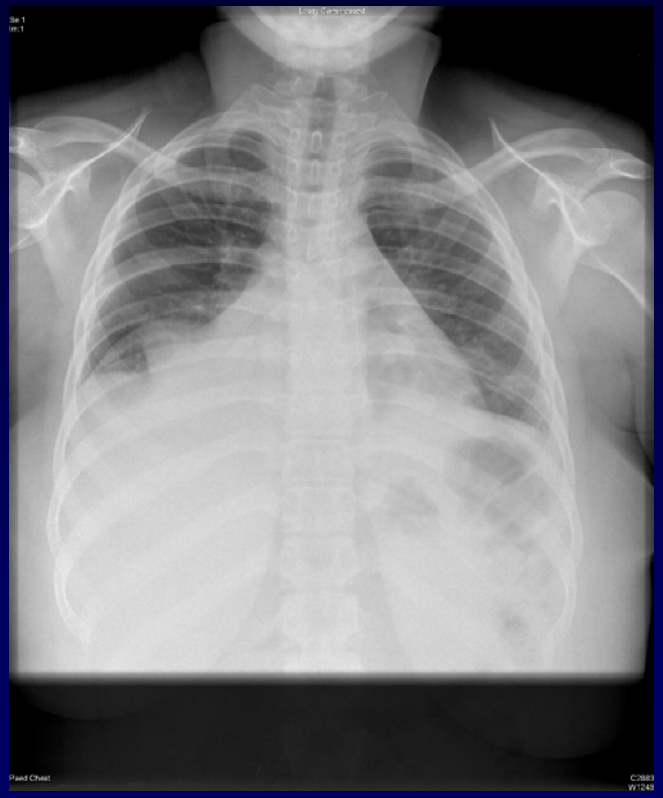
- Necessary due to high relapse rates after cessation of therapy: 30-70% at 24-36 mo (highest for GPA and lowest for MPA)
- Minimum 18-24 months duration
- Role for continuing maintenance therapy indefinitely in select cases
- IPC misclassified as IPH and not treated with induction & maintenance is likely to be poorly controlled (expert opinion)

1. NEJM. 2003; 349: 36-44 *2. NEJM.* 2008; 359: 2790–803
3. JAMA. 2010;304:2381–8 *4. NEJM.* 2014;371(19):1771-80

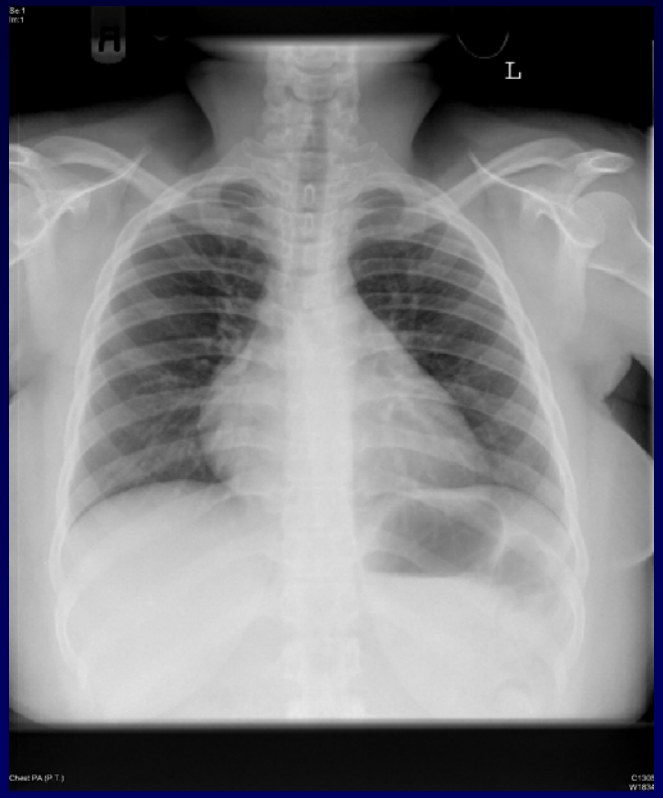
Systemic Lupus Erythematosis

- ANA, anti-dsDNA positive
- Multi-organ: kidney, skin, brain, MS
- Pleural effusion (serositis) most common pulmonary manifestation
- Reported Lung involvement: Infection, pleural effusions, acute lupus-related pneumonitis, ILD, bronchiolitis obliterans, pulmonary hemorrhage, pulmonary hypertension, shrinking lung, thrombosis

Systemic Lupus Erythematosus



At disease presentation

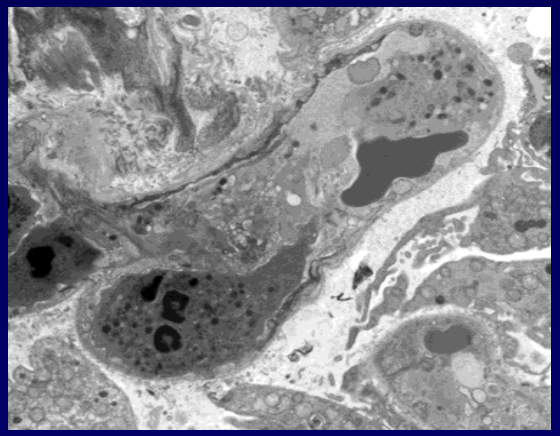


Post therapy

Thrombosis: Lupus & Vasculitis

- Antiphospholipid antibodies ↑ risk for thrombosis

- Thrombosis also associated with:
  - Adult ANCA-AV (6-30%)*
  - GPA in children (16%)**
  - Pediatric case report of IPC***



Thrombosis Journal 2015; 13:15
**Arthritis Rheum. 2007;57(5):837-44.
****Annals Am Thorac Soc* 2017; 14 (3): 470-3

Q 2. Non-specific interstitial pneumonitis (NSIP) pathology is most likely to be associated with which of the following?

A. Eosinophilic Granulomatosis with Polyangiitis
B. Juvenile Idiopathic Arthritis
C. Sarcoidosis
D. Scleroderma
E. Surfactant Protein B Deficiency

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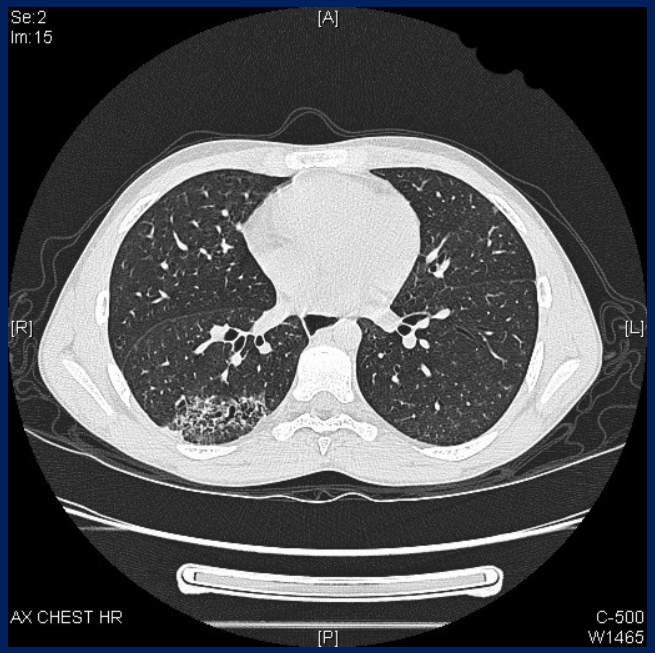
ILD in Pediatric Rheumatology

Teens

Scleroderma



Rarely JIA, JDM, MCTD, overlap

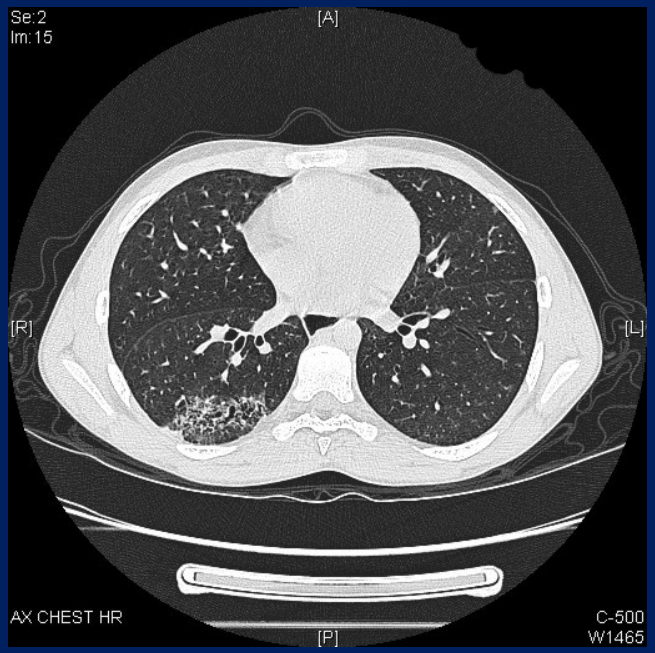
Infants-Toddlers

SickKids

ILD in Pediatric Rheumatology

Teens

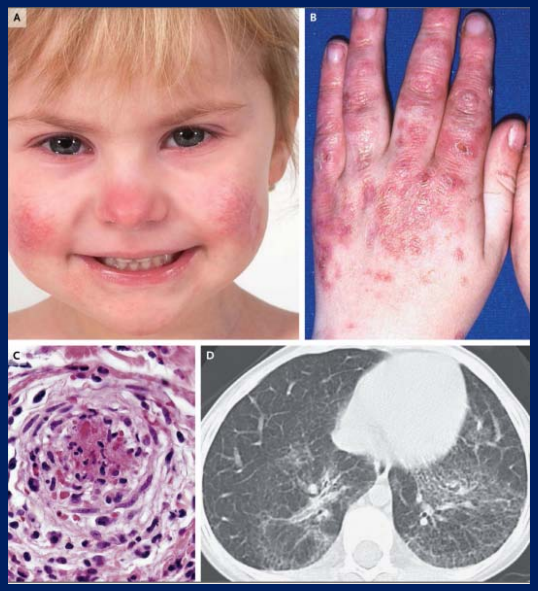
Scleroderma



Rarely JIA, JDM, MCTD, overlap

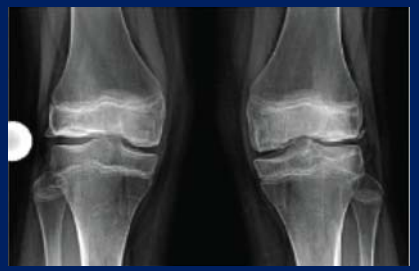
Infants-Toddlers

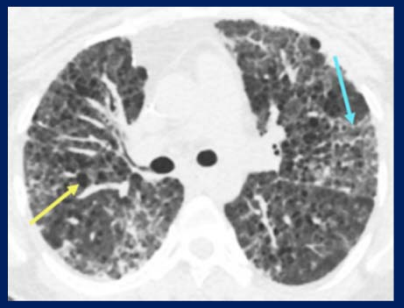
SAVI (TMEM173)



NEJM 2014;371:507–18

COPA

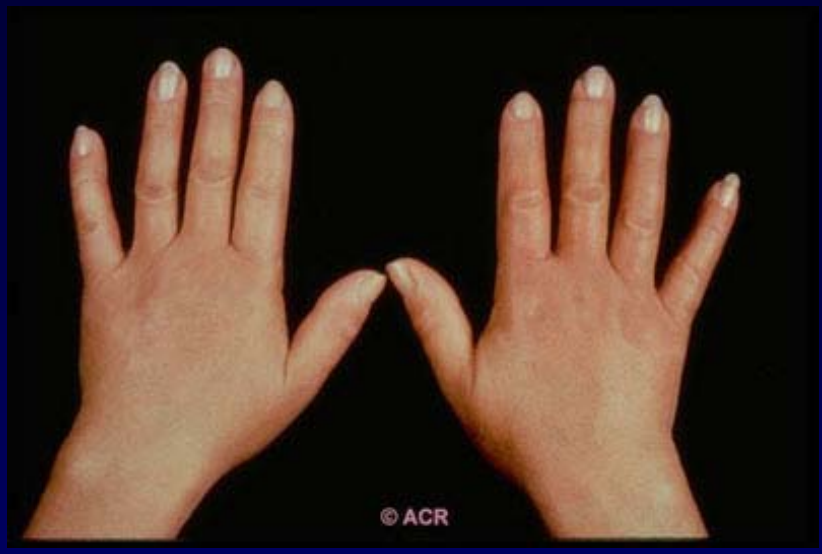




Nat Genet 2015;47:654-60

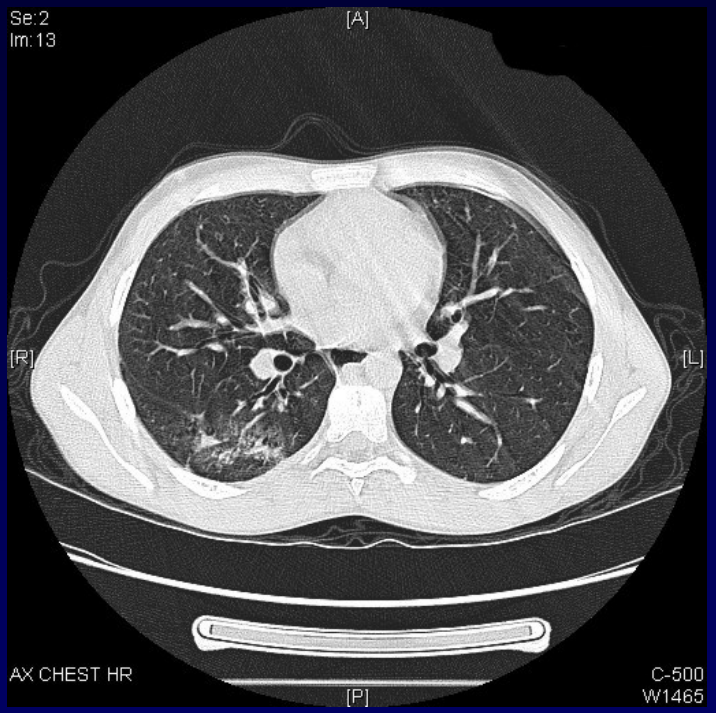
Systemic Scleroderma

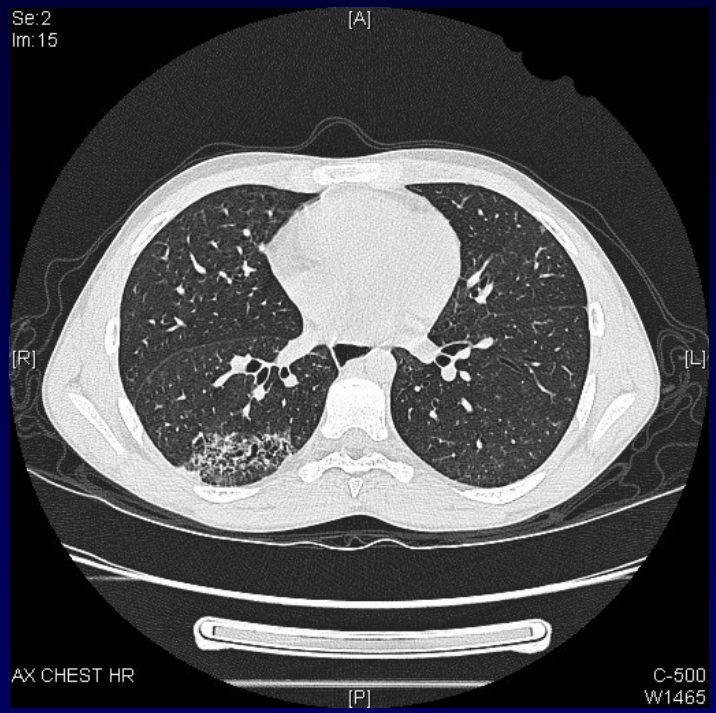
- Multisystem disease involving skin, lung, GI, MSK, kidneys
- Rare in children but pulmonary involvement common and often fatal
- ILD and pulmonary arterial hypertension
- Insidious onset of symptoms



JClinEpi 2019
Arthritis Care Res 2012; 64(4):519-24
Rheumatology2009; 48: 96 +119

Scleroderma- Interstitial Lung Disease

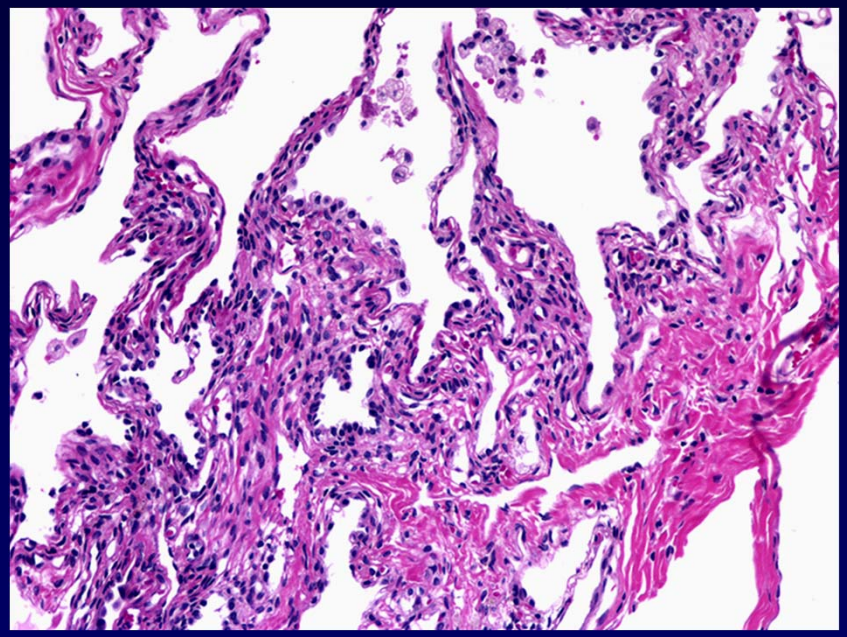




Insidious onset of symptoms: dyspnea, dry cough
PFT: restrictive pattern with low DLCO
CT: honeycombing, traction bronchiectasis

Scleroderma: NSIP Pathology

- 76% NSIP and 11% UIP pathology for adult scleroderma
- Lung biopsy usually not required & pathology not predictive of prognosis or response to therapy
- Consider aspiration and infection as causes of diffuse lung disease

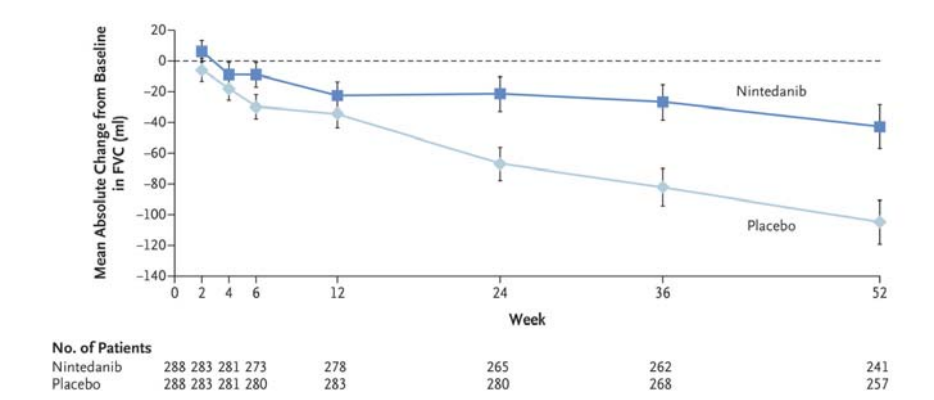


Bouros D et al. AJRCCM 2002 Jun 15;165(12):1581-6

Scleroderma: Therapy

- First line: MMF +/- low dose prednisone
- Second line: Cyclophosphamide
- Refractory disease:
  - Nintedanib (anti-fibrotic) & Rituximab
  - HSCT (but not severe lung disease)

SENSCIS Trial*



*NEJM 2019; 380:2518-28

NEJM 2018; 378:35-47

AnnRheumDis 2017; 76(8): 1327-1339

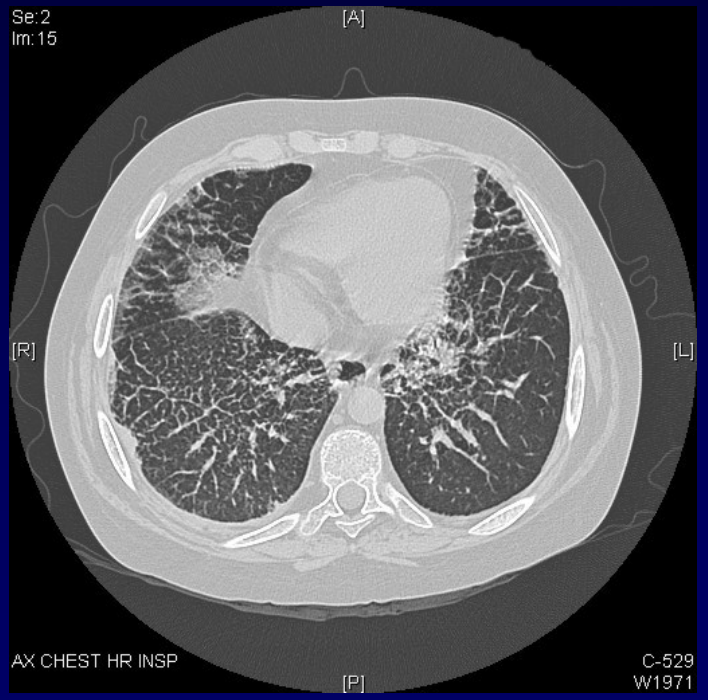
Scleroderma- Importance of early detection of lung disease

- Pulmonary fibrosis is now main cause of death, may start in childhood
- Initially disease is asymptomatic
- Lung disease seems to respond to therapy
- Controversy: should mild lung disease be treated?

Juvenile Idiopathic Arthritis (JIA)

- Minor pulmonary function abnormalities common but symptomatic or progressive lung disease is rare
- Pleuritis very common with systemic JIA onset-limited course
- Severe progressive interstitial lung disease is rare but can be fatal and occurs almost exclusively with systemic onset disease

ILD in Systemic JIA



Pulmonary Interstitial Cholesterol Granulomas (PICG)
Schultz R et al. Ped Pulm 32:397-402, 2001

Epidemiology of sJIA ILD

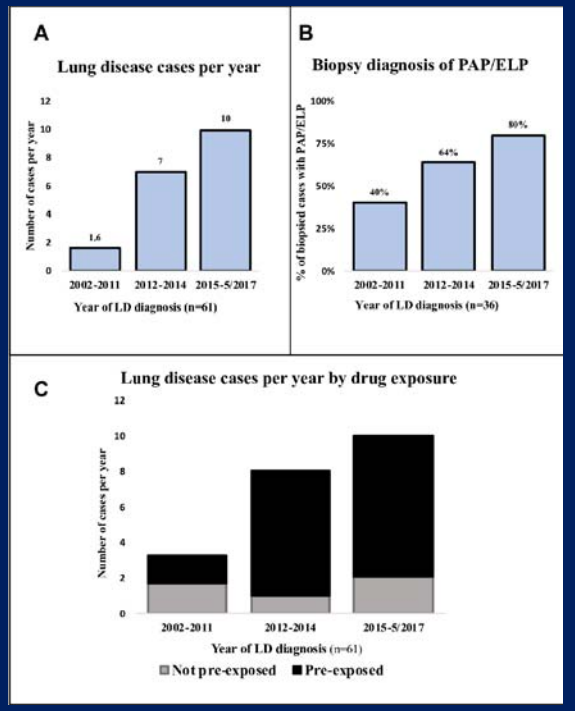
- Also called “PICG”: Progressive Pulmonary Interstitial and Intra-alveolar Cholesterol Granulomas

- 4 published Case Reports PICG 1996-2010
  - No IL1 or IL6 therapy

1. First retrospective case series (n=25, 68% dead) 2013 Kimura et al

2. 2nd Cincinnati cohort 2010-2019 (n= 18, alive)
   - Median follow-up one year (0.5-13) after LD
   - Detailed mechanistic work of tissue/BALF

3. 3rd case series+ (n=61, 45 unique, 36% dead)
   - Identified in 37 international centers
   - Multi-D review of history, imaging, pathology +/- WES

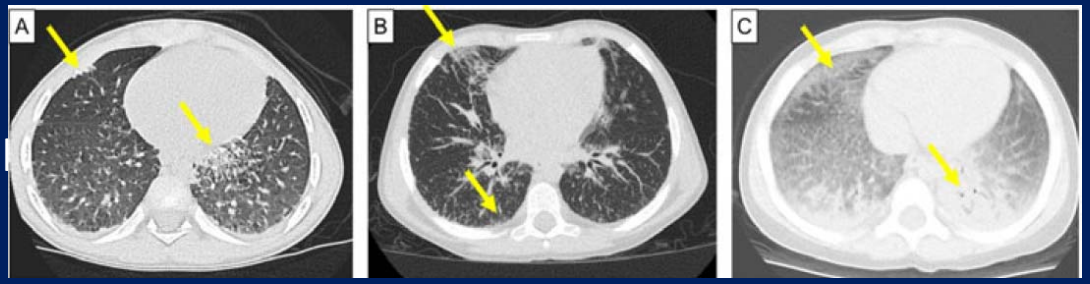


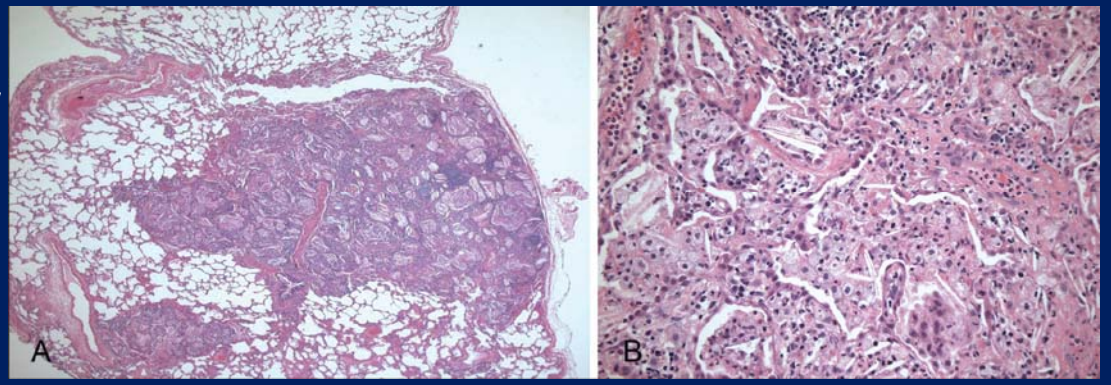
1. 2013**ACR** 2013;65:745-52
2. **2019 ArthRheum 71:1943-1954**
3. **2019 AnnRheumDis 2019; 0:1-10**

sJIA Interstitial Lung Disease

A novel inflammatory lung disease with distinct clinical and immunological features

- Insidious onset: clubbing, dyspnea, cough
- HRCT: patchy but extensive disease, subpleural & interlobular septal thickening, GGO, lymphadenopathy, “crazy paving”
- Pathology: patchy lymphoplasmocytic infiltrates, features of PAP & ELP, vasculopathy
- Immunology: increased MAS & serum IL-18, reactions to tocalizumab, BALF neutrophilia with IFNɣ signature





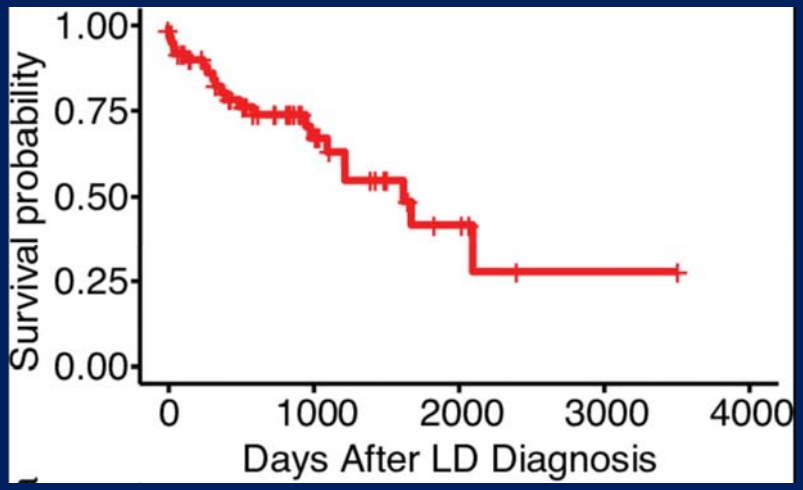
ArthRheum 2019; 71:1943-1954

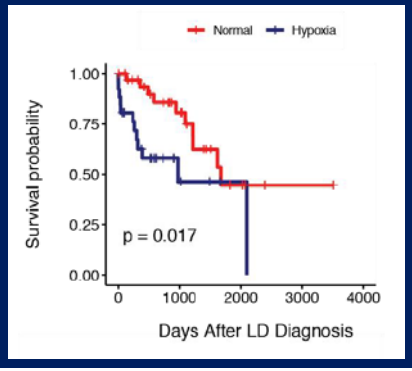
CanRespJ 2010; 17 (3): e42-44

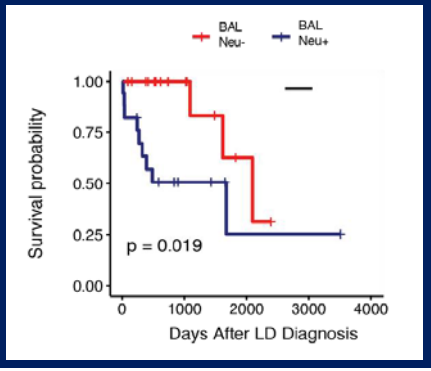
Prognosis of sJIA ILD

1. Cincinnati cohort (n=18, 1 yr f-u):
   - ~ half stable over time
   - ~ quarter worsen
   - ~ quarter improve (no MAS)

2. Saper-Mellins case series (n=61 LD)
   - 42% survival at 5 years
   - Hypoxia and BAL neutrophilia (>40%) associated with worse prognosis



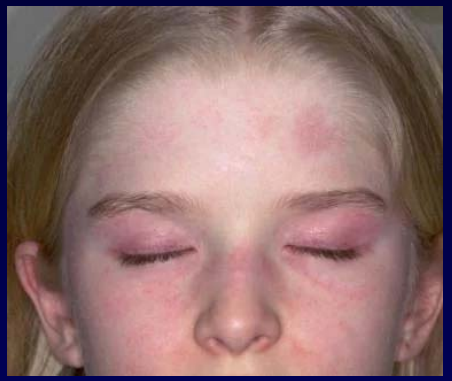




1. **2019 ArthRheum 71:1943-1954**
2. **2019 AnnRheumDis 2019; 0:1-10**

Juvenille Dermatomyositis (JDM)

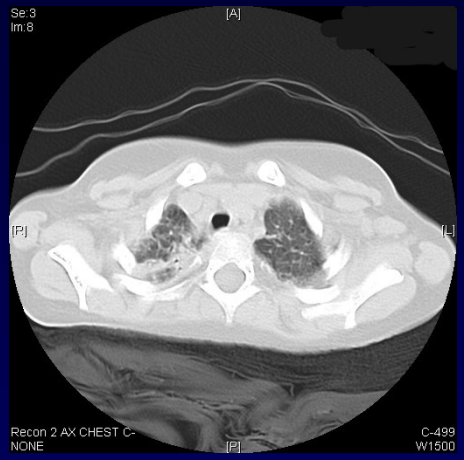
- Characterized by myopathy with vasculitis involving skin and muscles
- Lung involvement rare in JDM but common in adult onset DM- associated with anti-Jo-1 autoantibodies
- Case reports of ILD in childhood: COP, fatal interstitial pneumonitis with air leak*

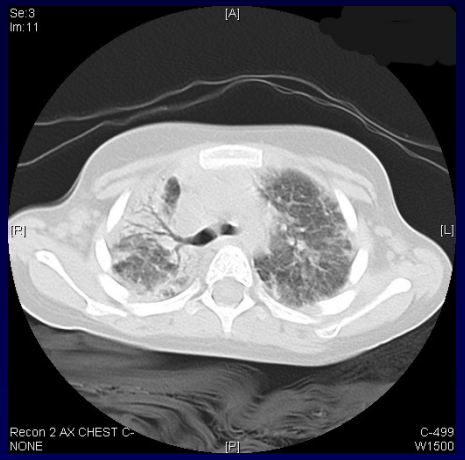


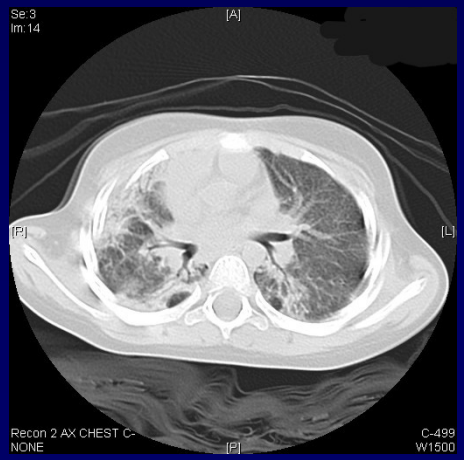
Heliotropic Rash

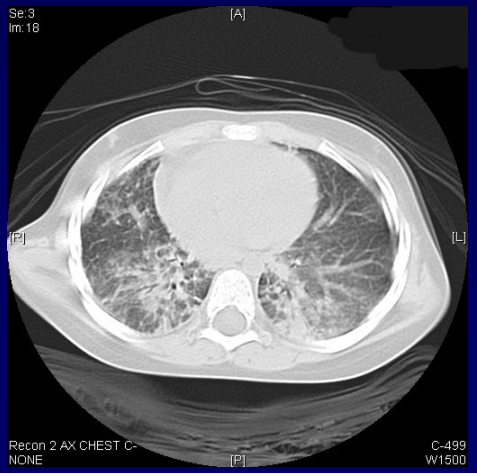
*Kobayashi N et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. Rheumatology (Oxford). 2015;54(5):784-91

ILD (COP) as Initial Presentation of Juvenile Dermatomyositis



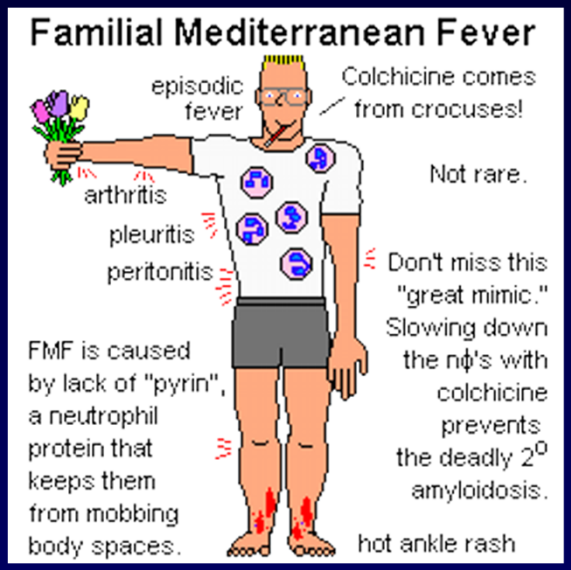






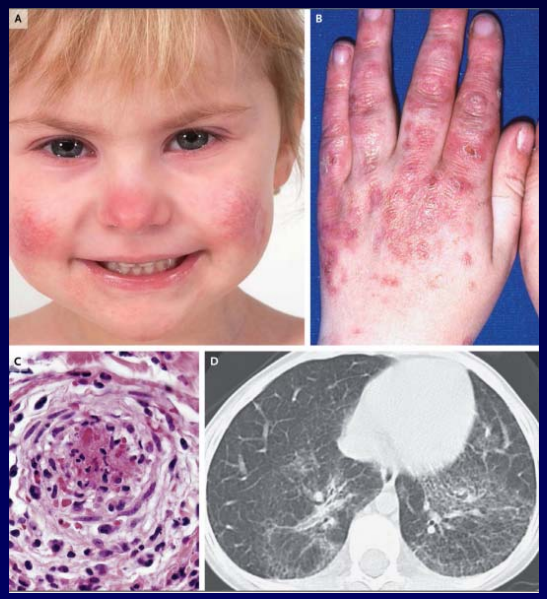
Lungs & Inherited Autoinflammatory Disease

FMF & TRAPS



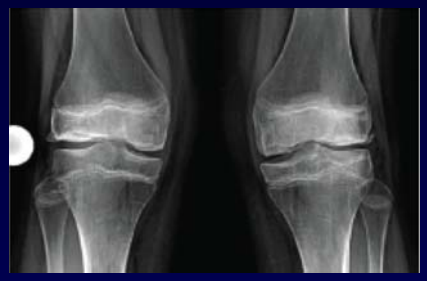
Pleuritis is common
x 1-3 days

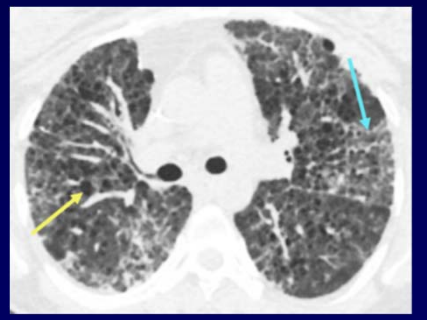
SAVI*



Onset in infancy, fevers, vasculitic rash, ILD

COPA**





"Atypical lupus" ; "Atypical JIA"
Arthritis, ILD, pulmonary hemorrhage, autoantibodies, familial (AD)

*NEJM 2014;371:507–18 **Nat Genet. 2015;47(6):654-60, ERJ Open Res. 2018 Jun 27; 4(2). pii: 00017-2018

Pulmonology vs Rheumatology: Synergy in Management Approaches

- Physiologic versus immunologic based specialty[1]
- Differences in medication prescriptions[1]:
  - Pulse steroid therapy approach
  - High dose hydroxychloroquine approach
- Multicenter networks for rare lung disease are at infancy stage (except for cystic fibrosis)[2,3]

1. Vassallo R, Thomas CF. *Curr Opin Rheumatol.* 2004;16(3):186-191.
2. Hamvas A, et al. *Pediatr Pulmonol.* 2014;49(4):400-409.
3. Luisetti M, et al. *Respir Med.* 2012;106(6):759-768.

PEARLS to Recognize and Manage Lung Manifestations of Rheumatological Disease *

- Pulmonary vasculitis presents as DAH, pulmonary nodules or tracheo-bronchial stenosis +/- renal and other symptoms
- Pulmonary vasculitis usually associated with ANCA +ve small vessel vasculitis (except IPC)
- Thrombosis is associated with lupus and vasculitis

***Dell's PEARLS based on published case reports, case series and personal anecdotes**

PEARLS to Recognize and Manage Lung Manifestations of Rheumatological Disease *

- NSIP histopathology should prompt work up for CTD
- sJIA and JDM associated ILD can be rapidly fatal
- Consider genetic testing for autoinflammatory disease in patients with ILD associated with vasculitic rash, “atypical” lupus or JIA, especially if familial disease or consanguinity
- Talk to your rheumatologists for therapy choices in the induction and maintenance phases!

***Dell’s PEARLS based on published case reports, case series and personal anecdotes**

Acknowledgements

Toronto SickKids Hospital
Pediatric Vasculitis Team

CHILD Network