Glomerulonephritis

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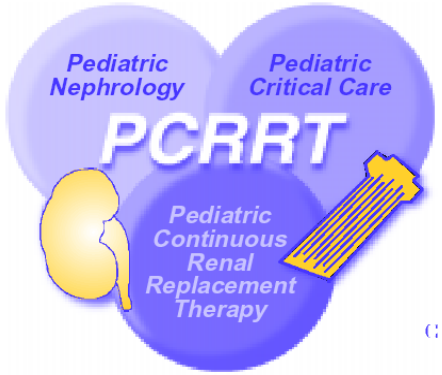


Thank you to

IPNA for support of this conference

Glomerulonephritis

- Presentation
- Evaluation
- Special considerations
  - vasculitis
- Newer classification

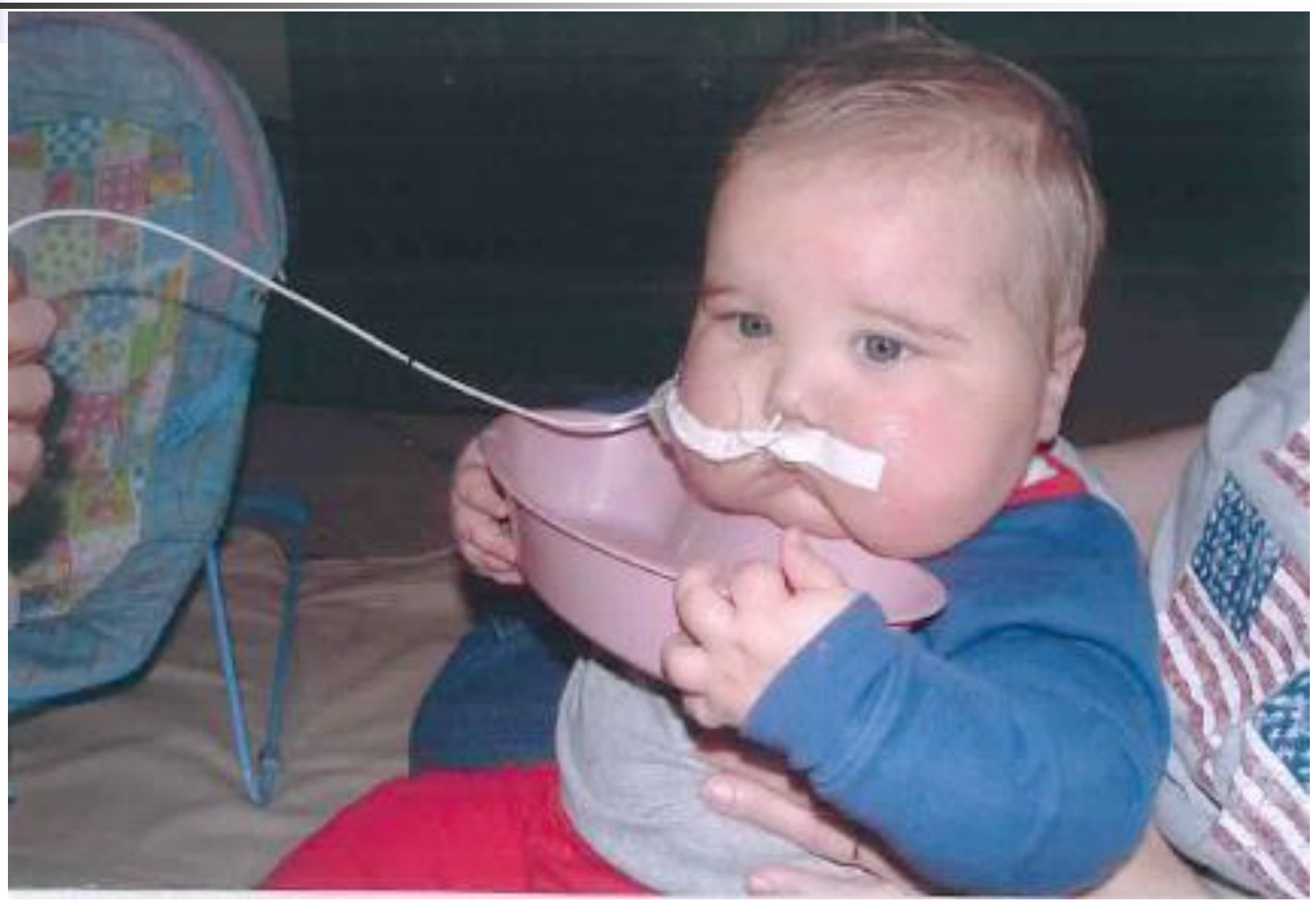
Clinical Presentation

- Edema and grossly bloody urine is what makes patients seek out medical care
- Occasionally respiratory symptoms of cough up to respiratory distress may be present

What kills patients with GN

- Lack of solute clearance
  - hyperkalemia
- Lack of fluid clearance
  - Pulmonary edema, hypertension

What is the evaluation of GN?



H and P!

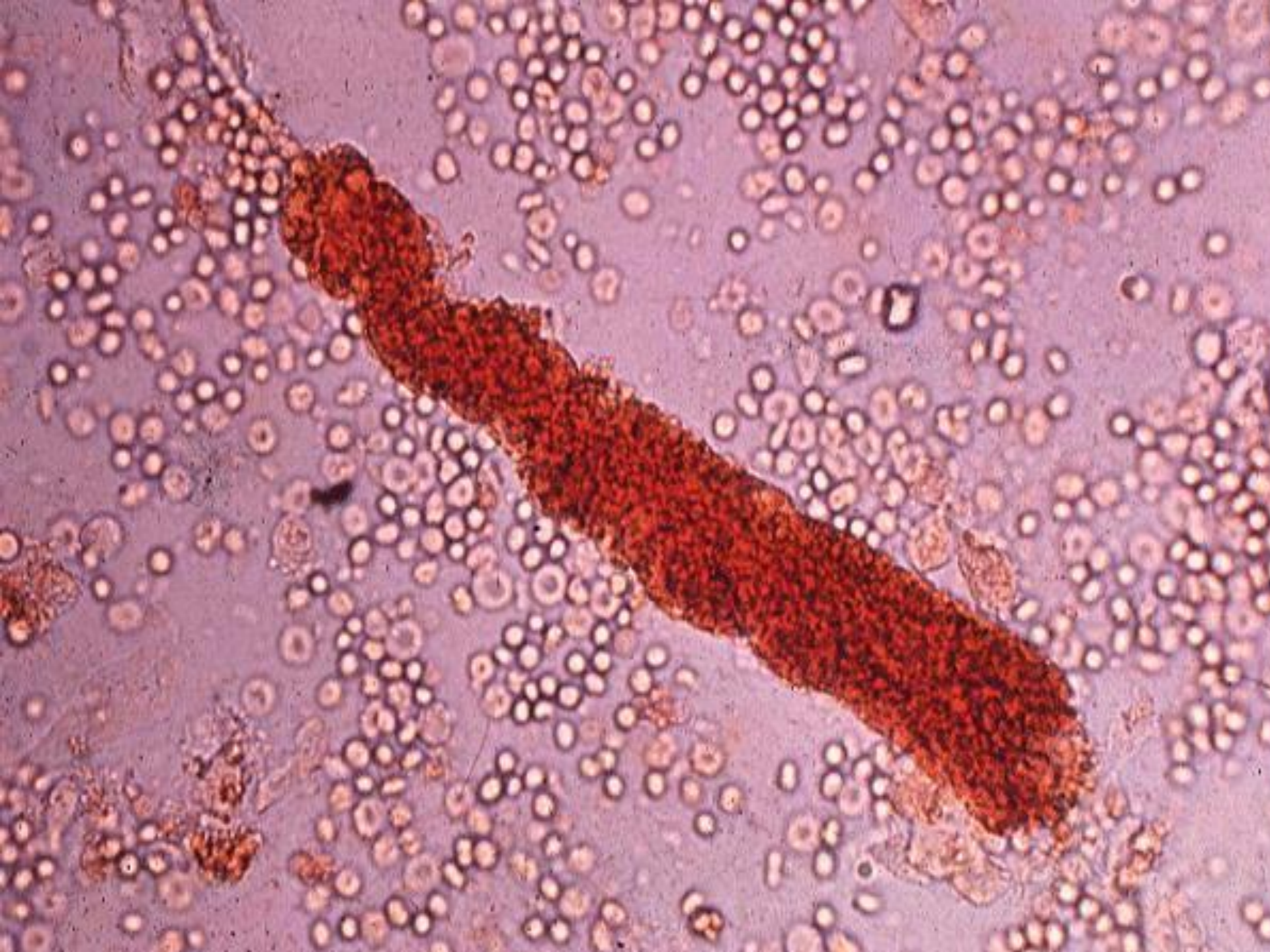
- Do they have risk factors for GN
  - Recent infectious exposure
    - Strep or other infections
  - Family hx of vasculitis
    - SLE, autoimmune diseases

H and P!

- What is their volume status?
  - ?BP
  - Do we have a previous wt for comparison
  - Do they have pulmonary congestion
  - Do they have heart failure

What is the evaluation

- PE with BP
- Lab work
  - urinalysis looking for RBC casts
  - Basic metabolic panel, CBC, complement 3 and 4
  - If indicated
    - Vasculitis labs (ANA, AntiDNA, ANCA, ACE)



Pulmonary Renal Syndromes

- Those GN associated with Sino-pulmonary disease with hemoptysis in excess of pulmonary edema
  - Wegener's
  - Anti GBM disease (Good Pastures)
  - SLE
  - Churg Struss

Hypo-complement GN (low C3)

- PIGN (PSGN, AGN) with normal C4
- SLE with low C4
- MPGN (not called C3 nephropathy) with low or normal C4

Post–Infectious (low C3) Glomerulonephritis

General Aspects

- Epidemiology:
  - Follows 1-2 % of cases of pharyngitis
  - Higher attack rates have been reported
  - Different serotypes of streptococci associated with
  - pharyngitis & pyoderma - associated cases
- Infectious agents that may be involved:
  - Streptococcus, pneumococcus, mycoplasma
  - Coxsackie B, influenza, mumps, enterovirus

Post-Infectious Glomerulonephritis

Key Findings

- Presenting Symptoms:
  - Gross hematuria, edema most common complaints
  - Headache, vomiting, & seizures may also be seen
- Physical Exam:
  - Hypertension & Edema are seen in up to 90% of patients
- Laboratory Studies:
  - Hematuria (gross or microscopic), proteinuria
  - Renal insufficiency
  - Low C'3 (also seen in SLE and MPGN)

Post-Infectious Glomerulonephritis

Management

- Reasons for hospitalization:
  - Symptomatic hypertension
  - Renal insufficiency, if significant and/or progressive
  - Electrolyte abnormalities
- Usually only supportive measures needed:
  - Diuretics, dietary sodium restriction
  - Oral and/or intravenous antihypertensive medications
  - Dialysis, Renal Biopsy as indicated

Post-Infectious Glomerulonephritis

Outcome & Follow-up

- Most features resolve predictably:
  - GH, HTN, renal insufficiency all will resolve in 2-3 weeks
  - Proteinuria may last longer
  - Patients with severe ARF should also recover
  - Microscopic hematuria may persist for 2-3 years
- Long-term prognosis excellent
  - Rare patients will be left with persistent renal insufficiency
  - Repeat complement (C'3) should be obtained in 6-8 weeks to document resolution
    - If C'3 persistently low, patient may have MPGN and should then undergo a renal biopsy

Vasculitis
Classification Schemes

- Clinical Classification Scheme
  - Symptoms and organ systems involved
    - Sinopulmonary, asthma, dermatologic, musculoskeletal, gastrointestinal, or renal limited
    - Sino/Pulmonary Renal Syndrome:
      SLE
      - Wegeners
      - Churg-Struss
        - Usually have peripheral eosiniphilia
      - Goodpastures Disease (anti-GBM Disease)

Vasculitis

Classified by Vessel Size

- Large Vessel Vasculitis (Takayasu's Arteritis)
  - Involves aorta & renal arteries-> Hypertension
- Medium Vessel Vasculitis (Kawasaki and cPAN)
  - Involves renal arteries & occasionally renal arterioles-> Hypertension but not usually involve glomeruli
- Small Vessel Vasculitis (HSP, SLE, ANCA diseases)
  - May involve renal arterioles, glomerular capillaries & post capillary venules-> Necrotizing glomerulonephritis

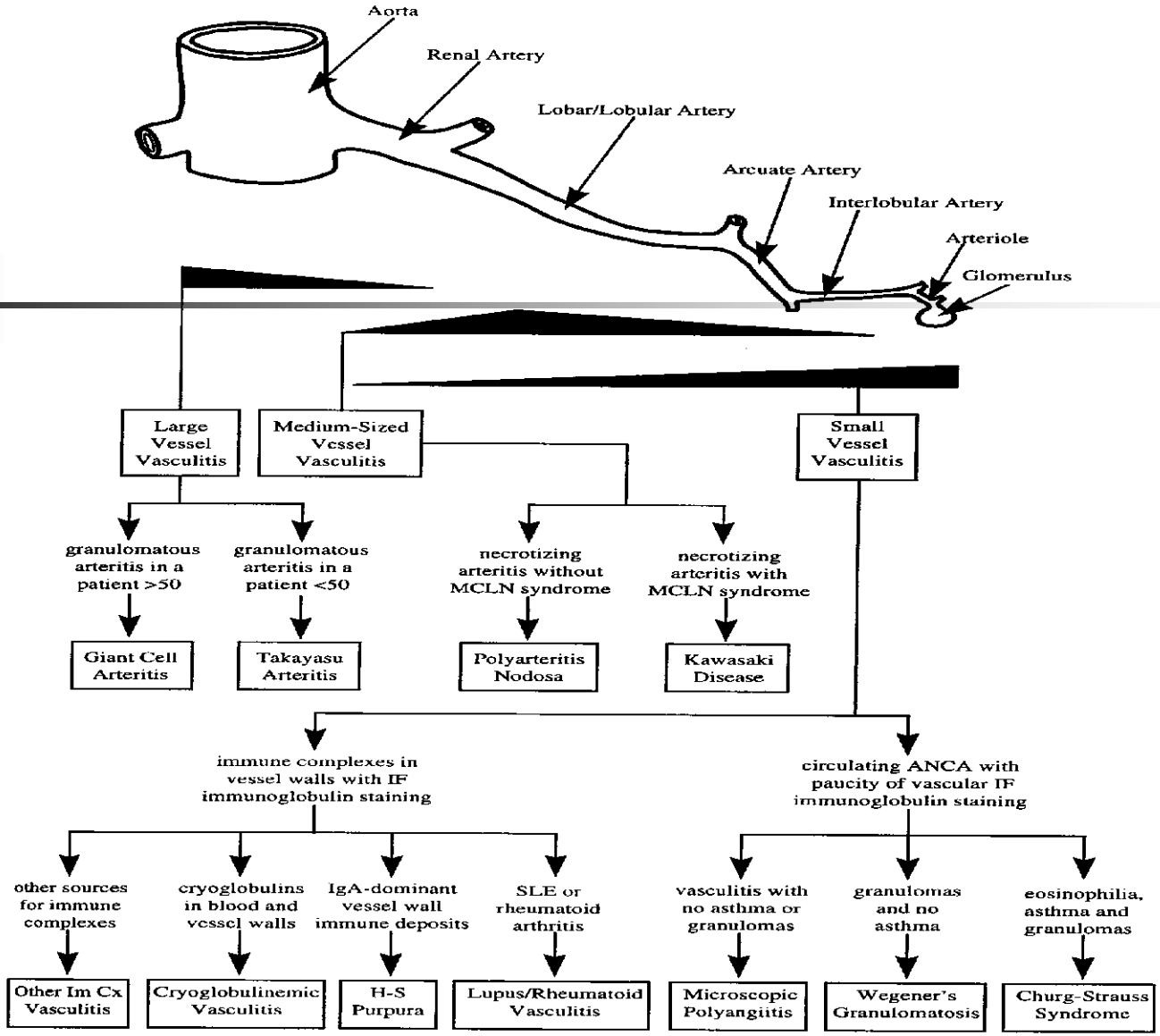
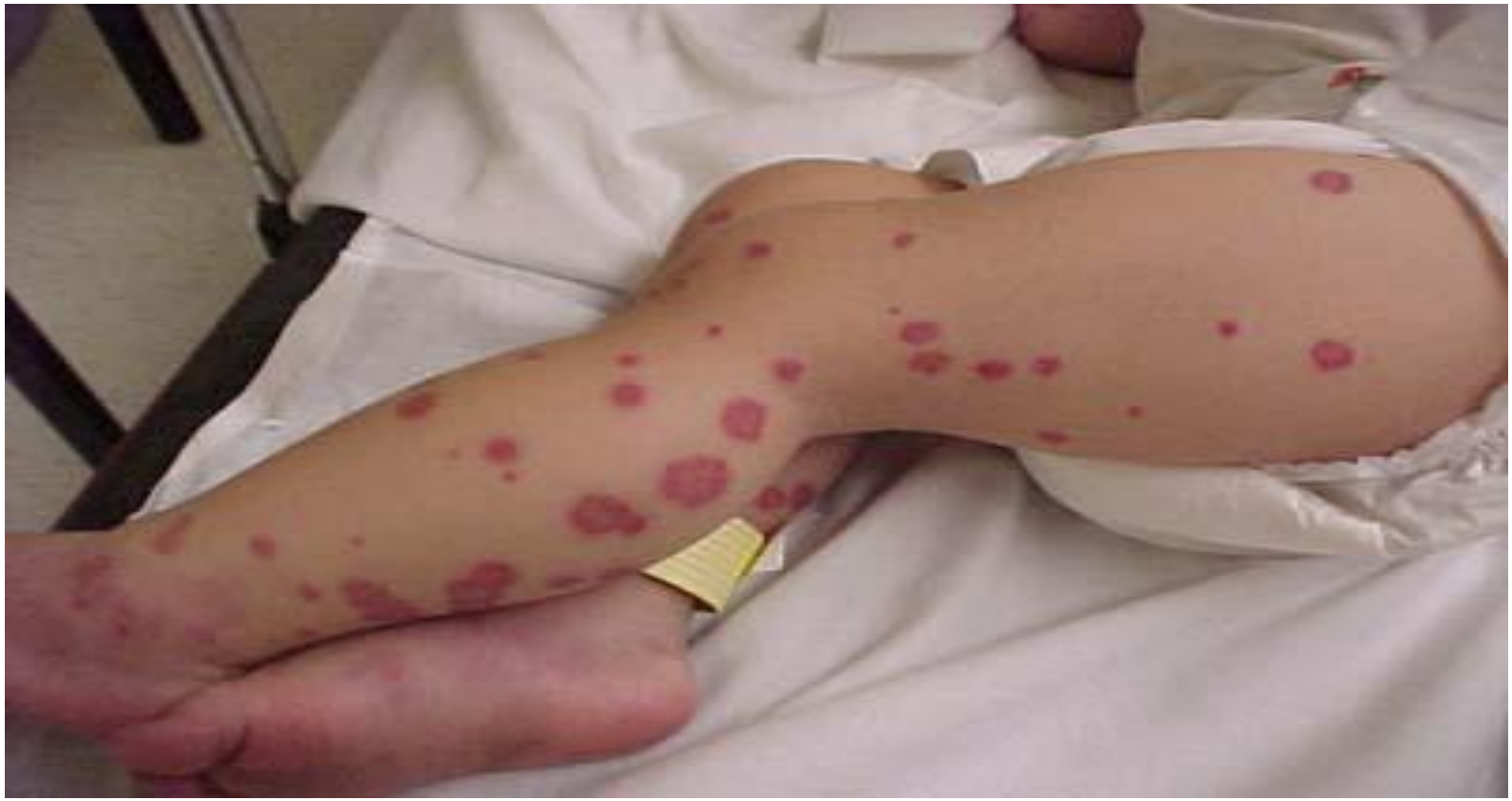


FIGURE 1 Predominant distribution of renal vascular involvement by systemic vasculitides and diagnostic clinical and pathologic features that distinguish among them. The width of the black triangles indicates the predilection of small, medium, and large vessel vasculitides for various portions of the renal vasculature. Note that medium-sized renal arteries can be affected by large, medium, and small vessel vasculitides, but arterioles and glomeruli are affected by small vessel vasculitides alone based on the definitions in Table 1. MCLN; mucocutaneous lymph node syndrome.

Jennette JC and Falk RJ. "Renal involvement in systemic vasculitis" in Primer on Kidney Diseases, 2nd Edition, National Kidney Foundation, 1998.

13 y/o female

- 2 mos hx of Abdominal pain without bloody stools
- Lower extremity purpuric rash
- Intermittent joint complaints but no true arthritis
- “active urine sediment”
  - Hematuria and proteinuria



HSP/AP

- Age of onset-75% < 10 y/o
- Rash-100%
- Arthritis-~ 60%
- Abdominal Vasculitis-75%
  - Gut edema/purpura-100%
  - Intussusception-5%
- Renal ~ 80%
  - GN

HSP/AP

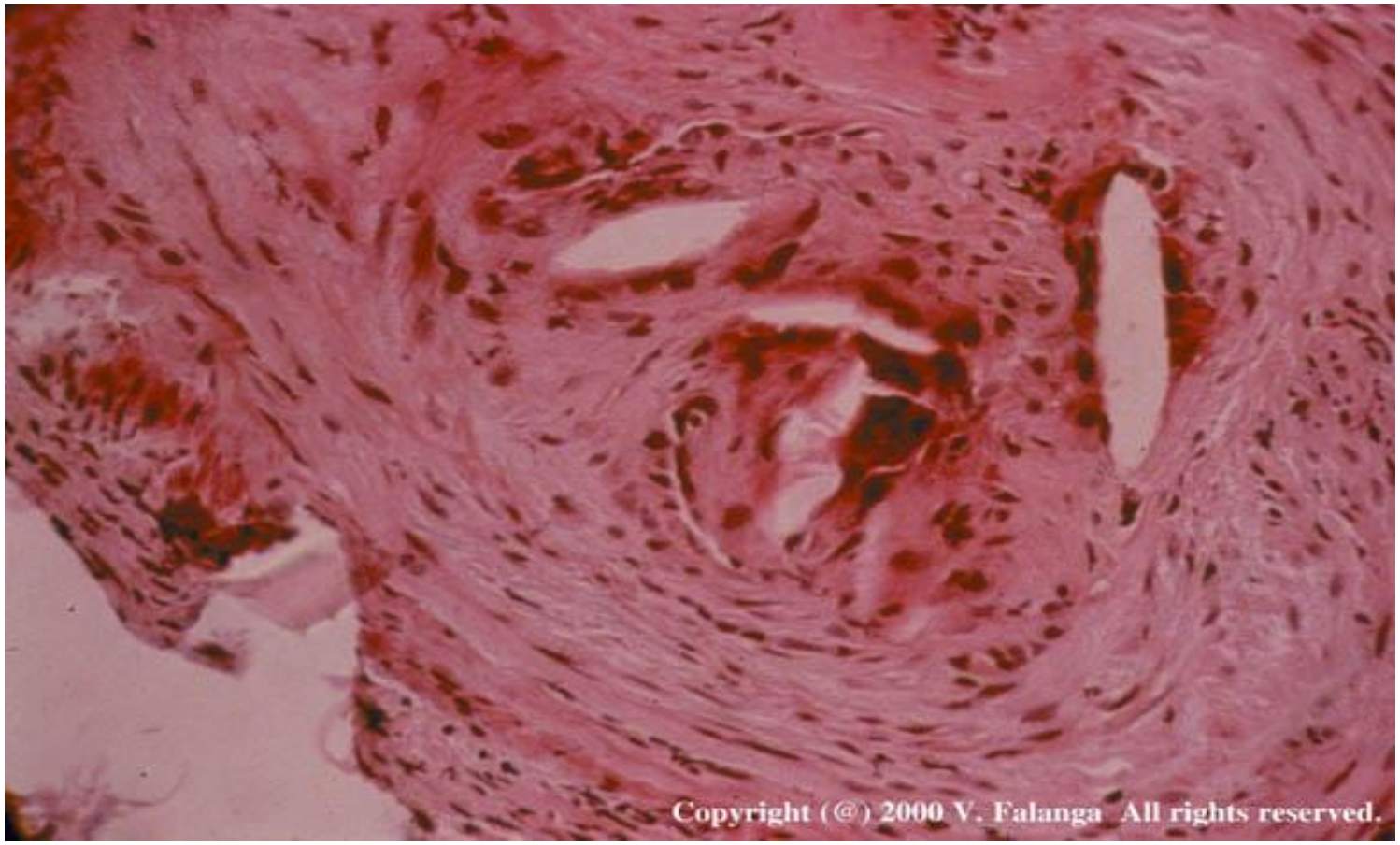
- Normal complements
- ANCA positive in 30% of children with HSP

Rash

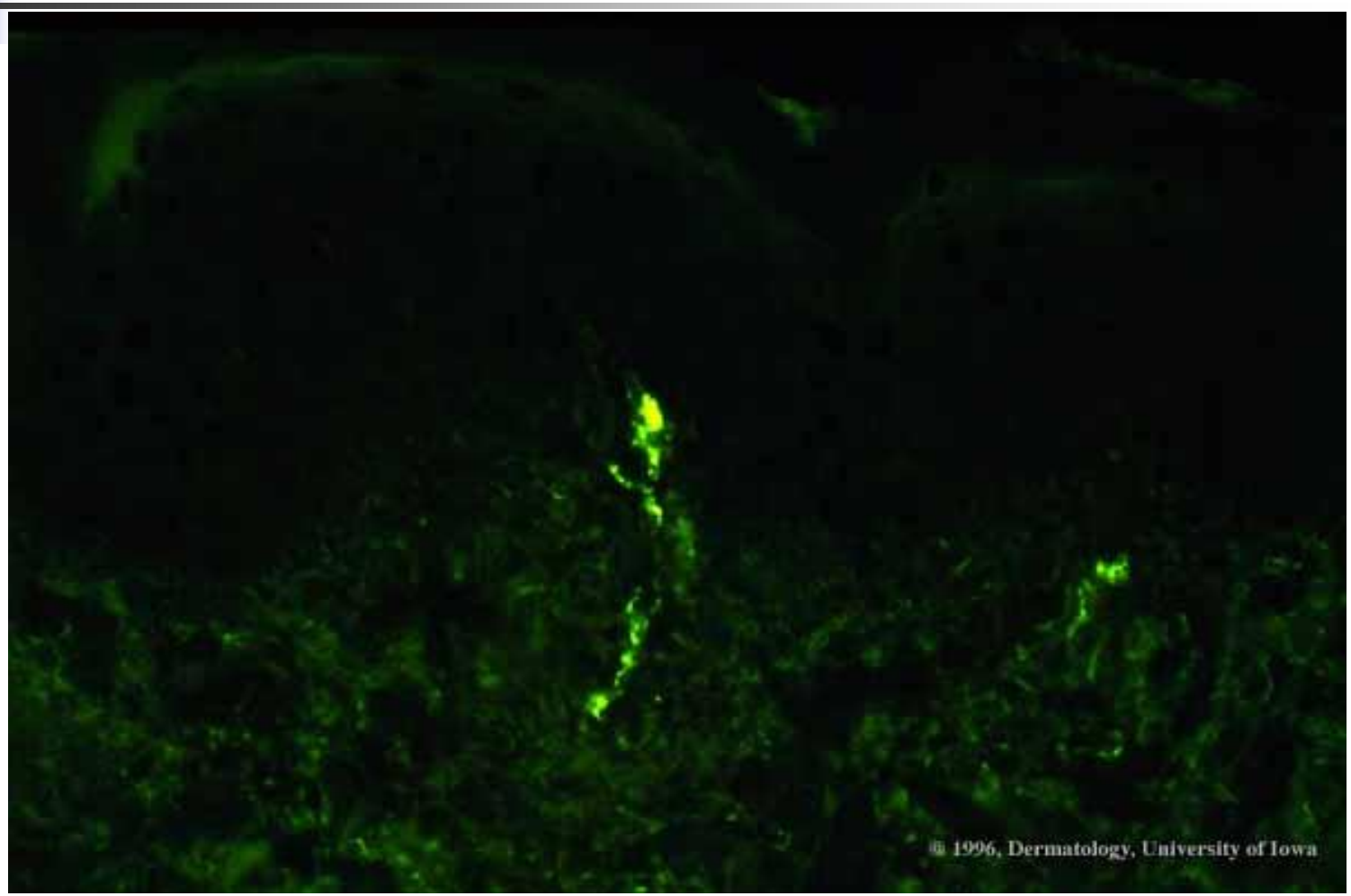
- Treatment
  - Supportive
  - No role for steroids
- Follow-up-50% recurrence within 3 mos of initial insult with or without other systemic complaints

Skin Bx suggestive but not diagnostic

Leukocytoclastic Vasculitis



IgA deposition alone with vascular wall suggestive but not diagnostic



Joints

- Treatment
  - Supportive
  - NSAIDS
  - No role for steroids
- Follow-up
  - Resolution within 4-6 weeks

GI

- Treatment
  - GI symptoms resolve with po/iv steroids
    - 50% Rx vs 14% nonRx.
    - Rosenblum & Winter Pediatr 1987
  - Risk of intussusception may decrease with po/iv steroids
  - GI bleeding and perforation rare occurrences
    - Blanco et al, Arth & Rheum, 1997

Renal

- What is its presentation?
  - Hematuria alone
    - ~ 40%
  - Hematuria with proteinuria –GN
    - ~ 60%
  - HTN associated
    - Depends upon the degree of renal involvement
  - Nephrotic range proteinuria +/- NS
    - Rare but concerning

SLE

- More Frequent in Females
  - Adults (Female:Male-9:1)
  - Children (Female:Male-4.5:1)
- Asians > AA > Hispanics > Caucasians
- Approximately 50% of adult patients with SLE develop lupus nephritis (LN)
  - 9% at presentation
- ~80% of children develop LN

(Font et al. Ann Rheum Dis 1998;57:456-9)

How do you make the diagnosis?

- A high index of suspicion
- Physical exam
  - Hypertension
  - Edema
  - Skin and joint involvement
- Laboratory data
- Tissue biopsy

SLE should be called an auto-antibody Syndrome

- ANA (30% of school aged kids positive)
- Anti-DNA/Double Stranded DNA
- Anti-cardiolipin antibody (VDRL)
  - Local data 100% positive at onset
- Anti SM, RHO, LA
- CH50/CH100, C3, C4, ?? C2
- ANCA positive in 30%

Tissue Analysis

- Skin
  - Leukocytoclastic vasculitis (not specific)
  - HSP, PAN, SLE, Wegeners, Drug induced
- Renal
  - LM
    - WHO I-VI
  - IF confirms diagnosis
  - EM confirms IF

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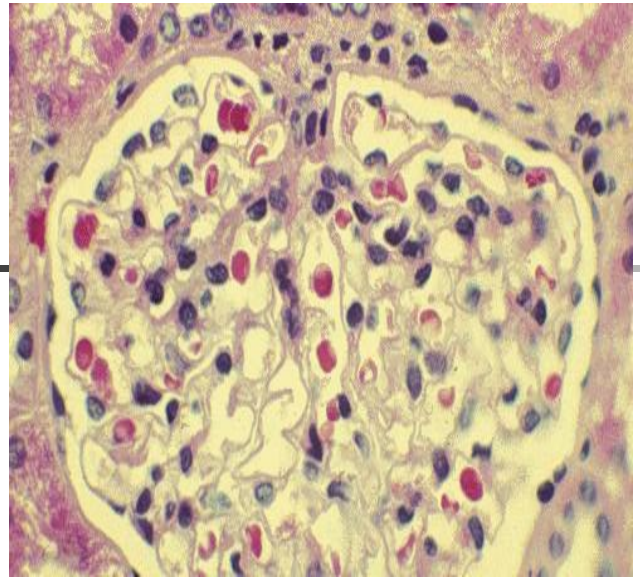

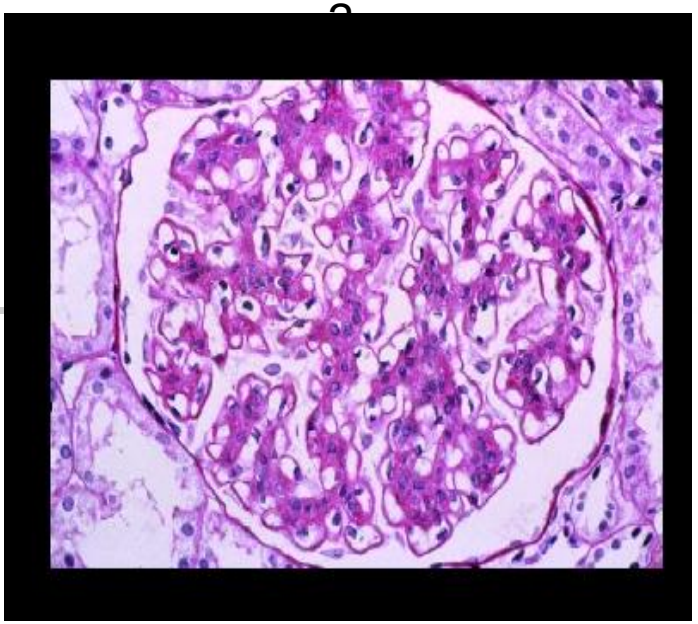

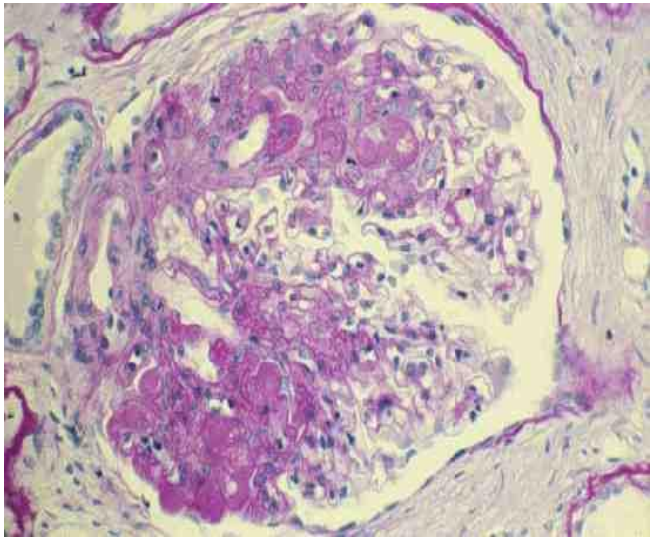

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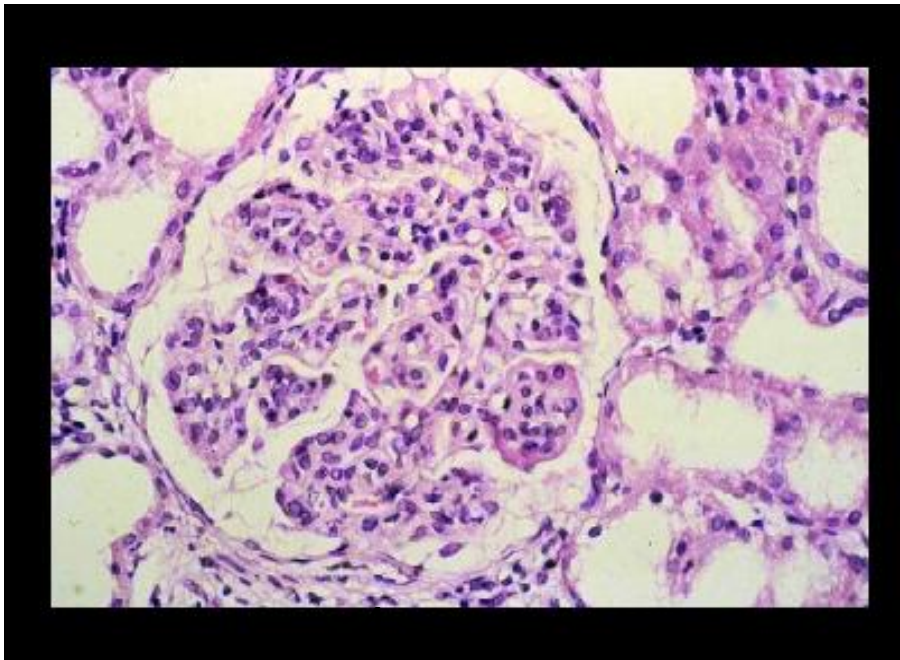
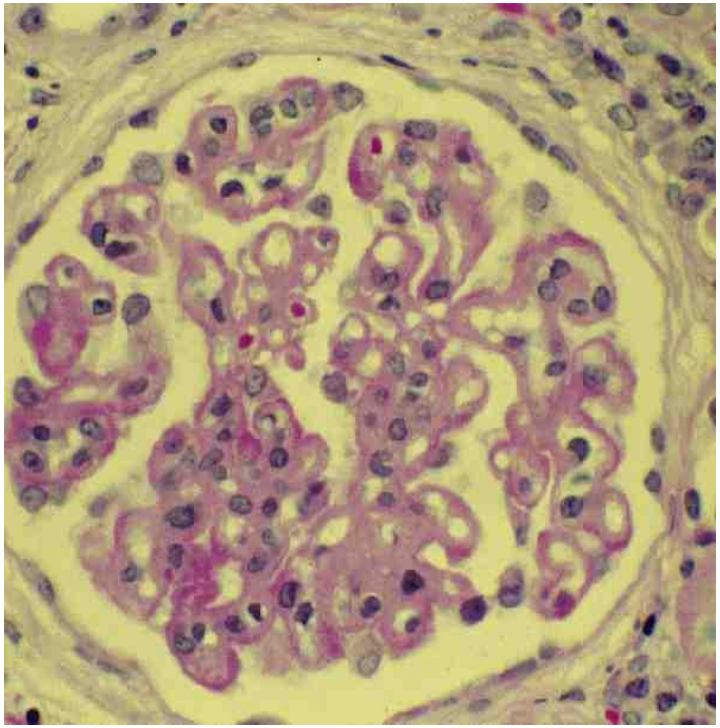
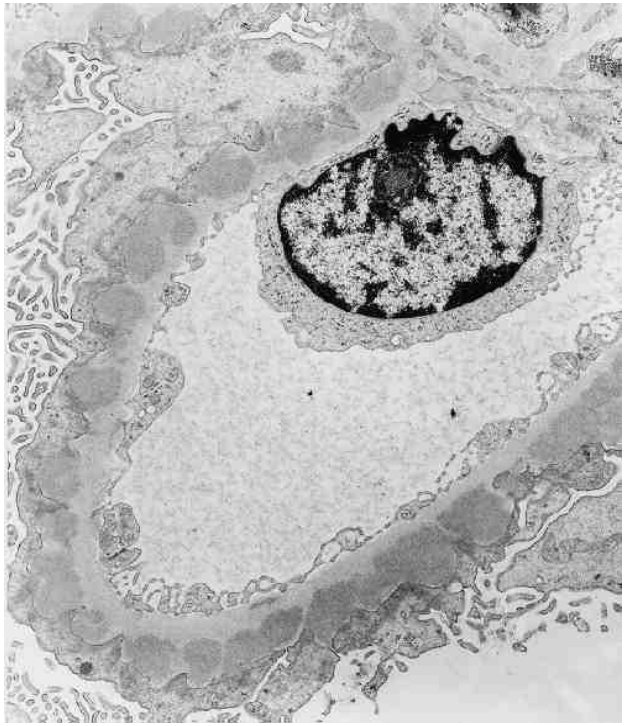






Renal Outcome

- Renal-with appropriate Rx ESRD incidence < 10% but….
  - WHO IV if untreated > 65% ESRD
  - WHO III if untreated ~ 40% ESRD
  - WHO V variable outcome
  - WHO I, II < 10% ESRD (may progress)
- CNS
  - Variable depending on cause

Rx of Lupus

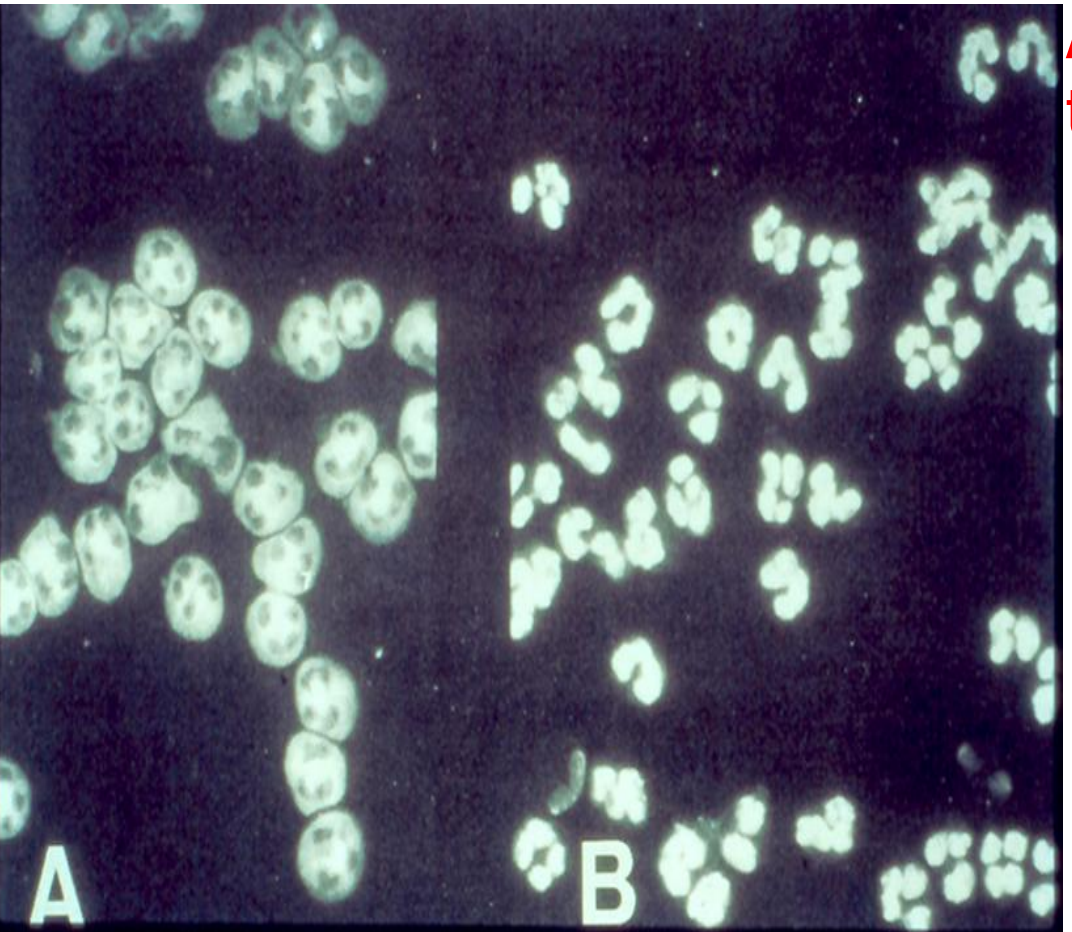
- Corticosteroids
- Plaquenil
  - Steroid sparing agent
- Cytotoxic agents
  - Cyclophosphamide
  - Azathioprine (Imuran)
  - Mycophenolate mofetile (MMF, Cellcept)
- Methotrexate
  - ? Joint

Wegener Granulomatosis
ANCA Specificity

- Cytoplasmic ANCA are not specific
  - However, in patients with vasculitis approximately 90% of cytoplasmic ANCA are PR3-ANCA
- Neither cANCA nor PR3 antibodies are specific for WG
  - They are found in other forms of vasculitis- MPA
- **Recommendation**: In the clinical setting of vasculitis, both indirect IF ANCA testing and more specific ANCA testing be done.

Indirect Immunofluorescence ANCA Testing

** 50% of Children with Weg Are ANCA negative at the time of clinical presentation!!



Immunofluorescent staining of serum incubated with ethanol fixed neutrophils.

Staining Patterns are:
A: Cytoplasmic (coarse, granular) =cANCA
B: Perinuclear = pANCA

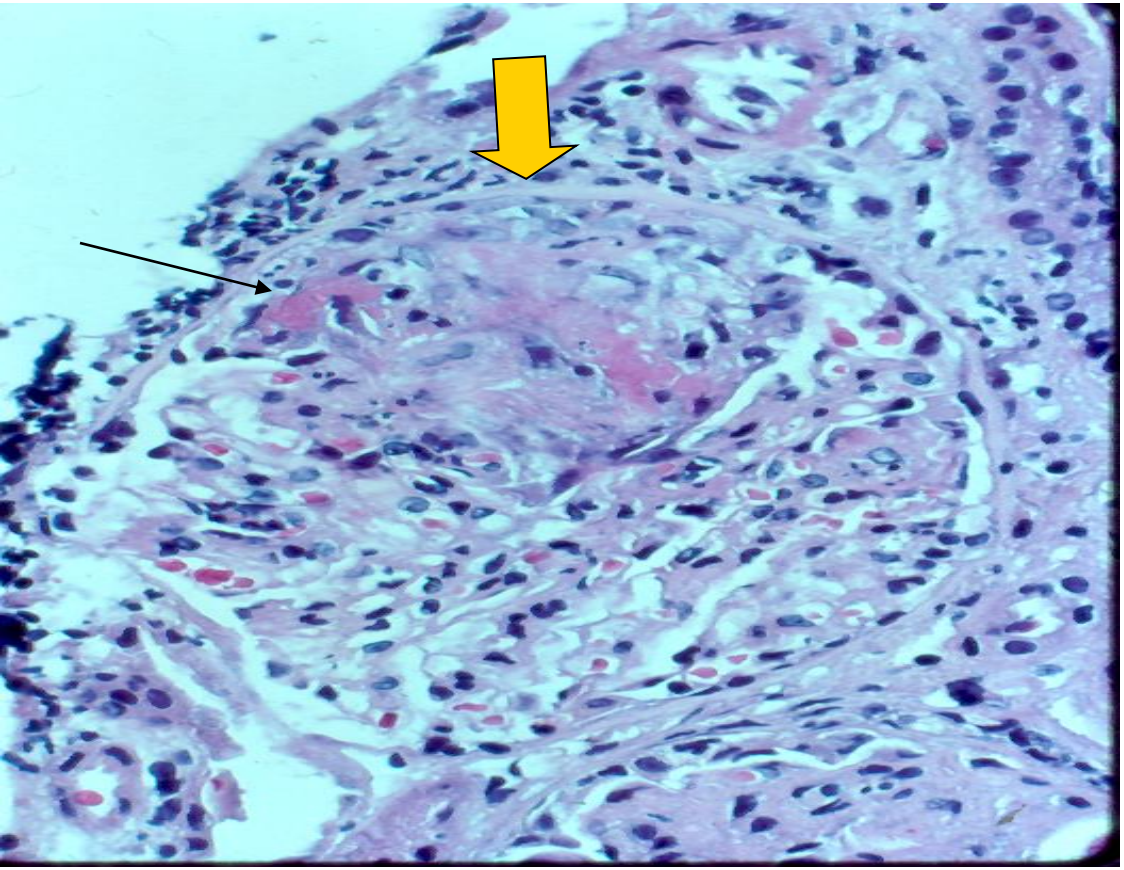
Note: In most vasculitis patients,
cANCA corresponds to **Proteinase 3**
&
pANCA corresponds to **Myeloperoxidase**

Falk RJ, Jennette JC: *NEJM* 1988

Wegener Granulomatosis
Pathologic Features

- Necrotizing vasculitis
  - Small arteries and veins together with granuloma formation are the hallmark lesions
  - Granulomatous necrotizing lesions are most commonly found in the respiratory tract
- Lung involvement may include bilateral nodular cavitary infiltrates
- Pauci-immune necrotizing and crescentic glomerulonephritis

Focal Necrotizing and Crescentic GN in Adolescent Female with Wegener Granulomatosis



Large Arrow:
Focal Crescent Formation

Small Arrow:
Hemorrhage/Necrosis

Treatment Summary of ANCA Associated GN & Vasculitis

- **Prednisone** (1-2 mg/kg/day, max 80 mg) for 1-2 months-taper to qod
- **CTX** for 6-12 months before changing to AZA/MMF
  - Duration and form of CYP is related to the severity of disease at presentation
  - **Non-life threatening disease**: Monthly IV CYP for 6 months + steroids
    Remission achieved-> transition to AZA at 2 mg/kg/day + slow steroid taper
  - **Life threatening disease**: Daily oral CYP for 1 year + steroids
    Remission achieved-> transition to AZA at 2 mg/kg/day + slow steroid taper
  - Remission is defined as lack of symptoms, stable renal function, benign urinalysis (except for some proteinuria), and a stable ESR
  - A repeat renal biopsy looking for histologic confirmation of inactive disease is usually performed before transitioning a patient off of CYP
- **Adjunctive Agents**
  - All patients are placed on TMP/Sulfa and ACE Inhibitor if K+ and Creatinine permits

Treatment of ANCA Associated GN & Vasculitis-

Adjunctive Summary

- **Trimethoprim/sulfamethoxazole (T/S):**
  - Utilized as prophylaxis for *Pneumocystis carinii* pneumonia, which occurred in 4% of adult WG patients
  - Reduces respiratory relapses in adults with WG
    - Possibly due to treatment of nasal carriage of *Staph aureus*, which was associated with serious sinopulmonary infections in the early NIH studies

- **ACE Inhibitors:**

- Fauci AS et al. *Annals of Internal Medicine*, 1983; 98:76-85.
- Stegeman CA et al. *New England Journal of Medicine*, 1996; 335:16-20.
- Hoffman GS et al. *Annals of Internal Medicine*, 1992;116:488-498

Outcome of ANCA Associated GN and Vasculitis

- Pediatric experience in the US, a cumulative incidence of end stage renal disease (ESRD) of ~ 30%
- Those developing ESRD typically presented with very advanced disease.
- Review 7 patient, single center experience exhibited a lower incidence of ESRD (14%)
  - Valentini et al, Pediatr
- In the last 3 years we have diagnosed 7 new children all with pulmonary bleeds, 3 initially dialyzed
  - All off dialysis with varying degree of CKD

Vasculitis Evaluation

	HSP	SLE	Wegeners
Skin involvement	+	+	+
Joint	+	+	+
GN	+	+	+
C3	Normal	Low	Normal
C4	Normal	Low	Normal
Anti-DNA	Neg	+	Neg
ANA	Low pos *	Pos	Low pos *
ANCA	Low pos *	Low pos *	Positive (50%)

* Background noise positive but not diagnostic

New Classifications of the same old disease

- Immune Complex-Mediated GN
  - IGA
  - SLE
  - PIGN
  - Fibrillary GN
- ANCA-associated GN
  - PR3 ANCA positive
  - MPO-ANCA positive

(Sethi S et al, NDT, 2018 in press)

New Classifications of the same old disease

- Anti-GBM GN
- Monoclonal Ig-GN
  - Proliferative GN with IGG deposition
- C3 glomerulopathy
  - C3GN
  - DDD (MPGN type 2)

(Sethi S et al, NDT, 2018 in press)

Conclusion

- GNs can be aggressive and lethal
- Attention to solute and volume status (BP) is imperative
- Compliment directed decision making is in the evaluation