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Nephrotic and Nephritic Presentations in Pediatrics

Striving for Healthy Childhood: UAE Enlightens the Way

International Pediatric Summit

سعياً لطفولة سليمة: الإمارات تنير الدرب

Third International Pediatric Summit 2019

Dubai U.A.E.

February 16, 2019

Disclosures

- I have no conflict of interest related to the discussed topic
- I will not endorse off-label use of medications or devices
- I will not use brand names for medications
- I received permission for the educational use of patient photographs

Case 1

- 4 y/o boy, previously healthy
- Increasing facial and body swelling following a mild URTI
- Diagnosed with childhood nephrotic syndrome and treated with standard dose of oral prednisolone
- Returns to ED for abdominal pain and fever
- Rapid deterioration with arterial hypotension
- Referred to Al Jalila, admitted to PICU
  - Appears septic with painful abdomen and moderate ascites, generalized edema
  - Cardiac arrest, resuscitated, ventilated for 2 days
  - Intravenous antibiotic and glucocorticoids (full recovery)

- Key lab findings
  - Profound hypoalbuminemia
  - Blood culture from referring hospital positive for *S. pneumoniae*
- Outcome
  - Full recovery
  - Good response to gluococortiocoid therapy
- Diagnosis
  - Childhood nephrotic syndrome (likely minimal change disease)

Overview of the topic

- Childhood nephrotic syndromes
  - INS/MCD
  - FSGS
  - MPGN
- Nephritic syndromes
  - APIGN
  - IgAV (Schönlein Henoch purpura)
  - IgA nephropathy
  - Vasculitides
  - Immune complex mediated glomerulonephritis
- Rapidly progressive glomerulonephritis

Nephrotic syndrome

Nephrotic syndrome is a disease of the glomerular filtration barrier

Nephrotic range proteinuria >40 mg/h/m^2 (960 mg/day/m^2

- Niaudet >50 mg/kg/day
- Upc >2 g/g (0.2 g/mmol)

Hypoalbuminemia <25 g/L

Edema

- Not apparent in all patients

Hyperlipidemia

- Not always present

Bland urine sediment (primary nephrotic syndrome)

- Lack of glomerular inflammation per biopsy

Nephritic syndrome

- Clinical syndrome
- Association of
  - Hematuria (usually visibly bloody (”gross” or macrohematuria)
  - Proteinuria
  - Arterial hypertension (frequent)
  - AKI due to glomerular inflammation
  - Typically “active” urine “sediment” (RBC or mixed cellular casts)

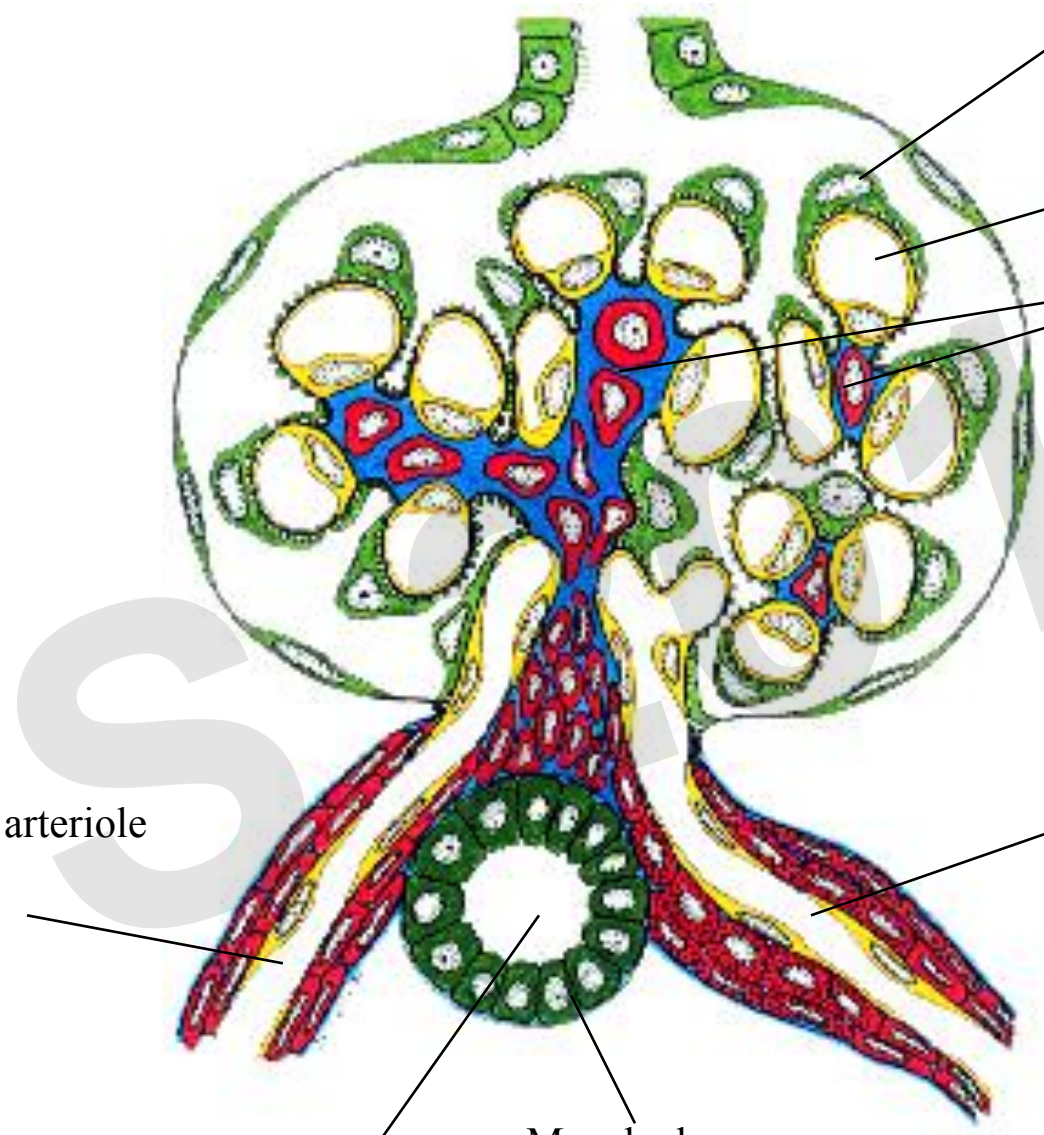
Nephrotic syndrome - a bit of history

- 2/3 would die before treatment became available
  - Infections (loss of immunoglobulins with proteinuria)
  - Malnutrition (loss of nutrients)
- Improvement of outcome with first antibiotics in 1939
- Breakthrough with use of cortisone in early 1950s
  - Death rate decreased to 9% (still high)
  - Clear benefit of cortisone
  - Placebo controlled trials never performed

Clinico-Pathological Classification of Nephrotic Syndromes in Childhood

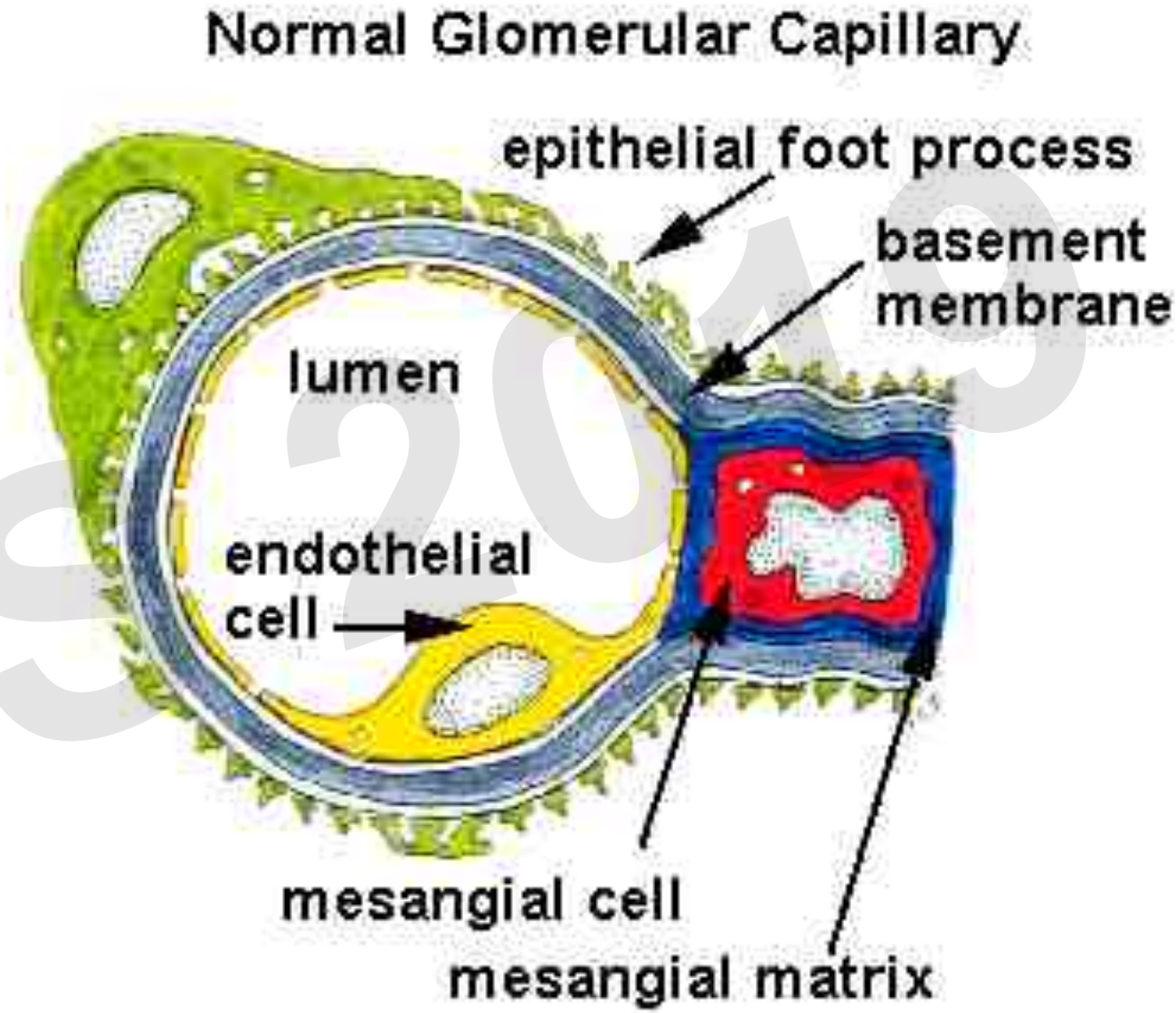
- Primary NS
  - Absence of an identifiable systemic disease (e.g. idiopathic nephrotic syndrome)
  - Nephrotic syndrome as part of a complex (genetic) syndrome ("syndromic nephrotic syndrome")
- Secondary NS
  - Presence of identifiable systemic disease, including (congenital) infections
- Nephrotic syndrome according to age at onset
  - Congenital (< 3 months)
  - Childhood
  - Adolescence and adulthood

Normal Glomerular Histology

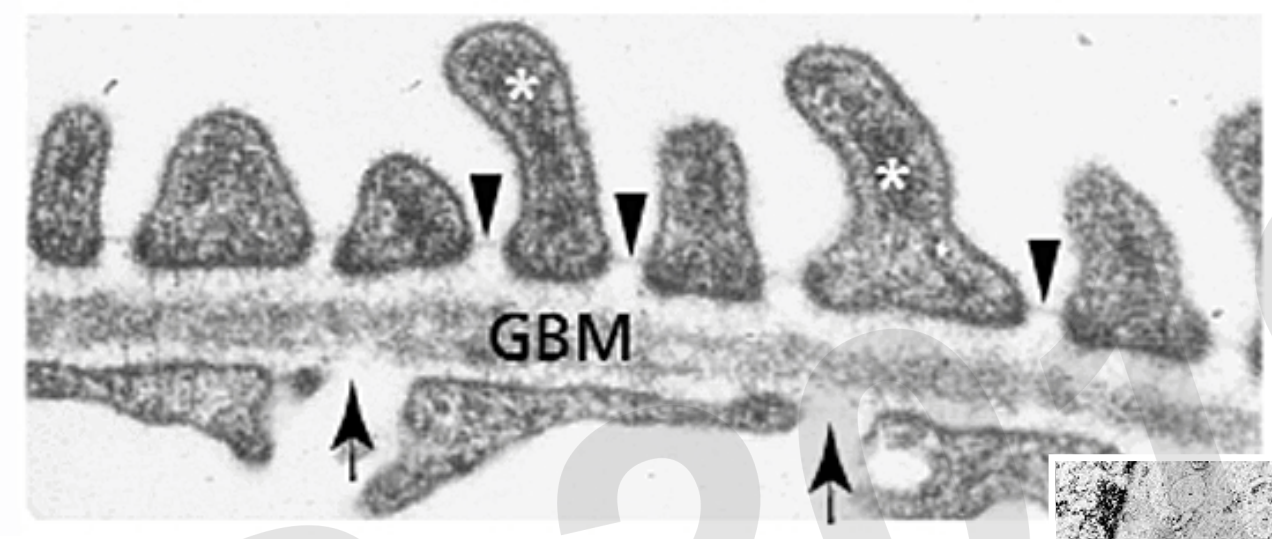


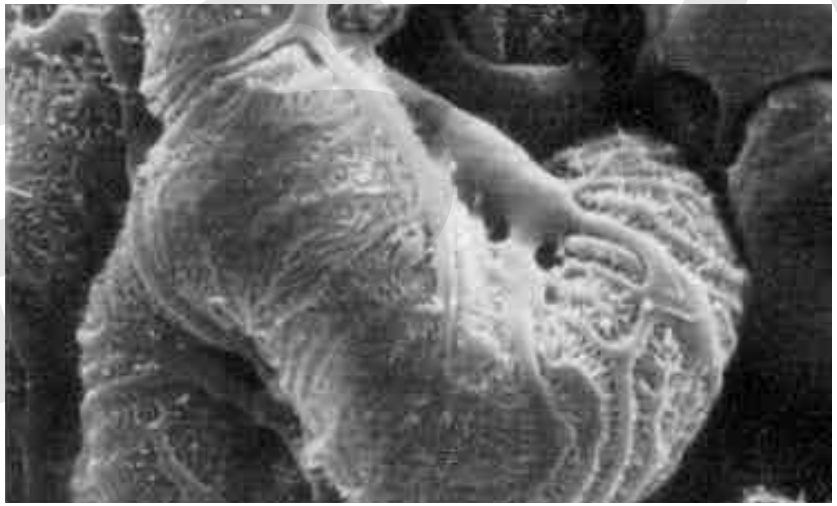
From: http://ns.gamewood.net/rnet/renalpath/ch1.htm

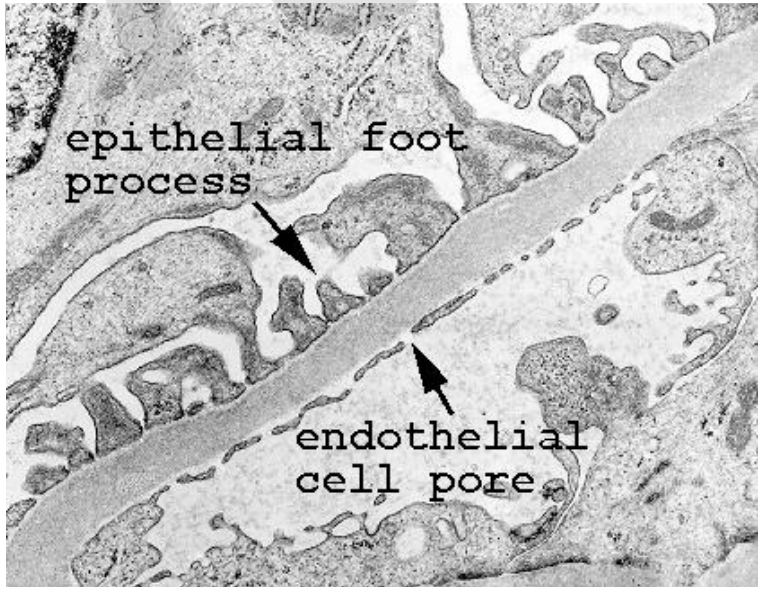
Normal Glomerular Histology



The glomerular filtration barrier

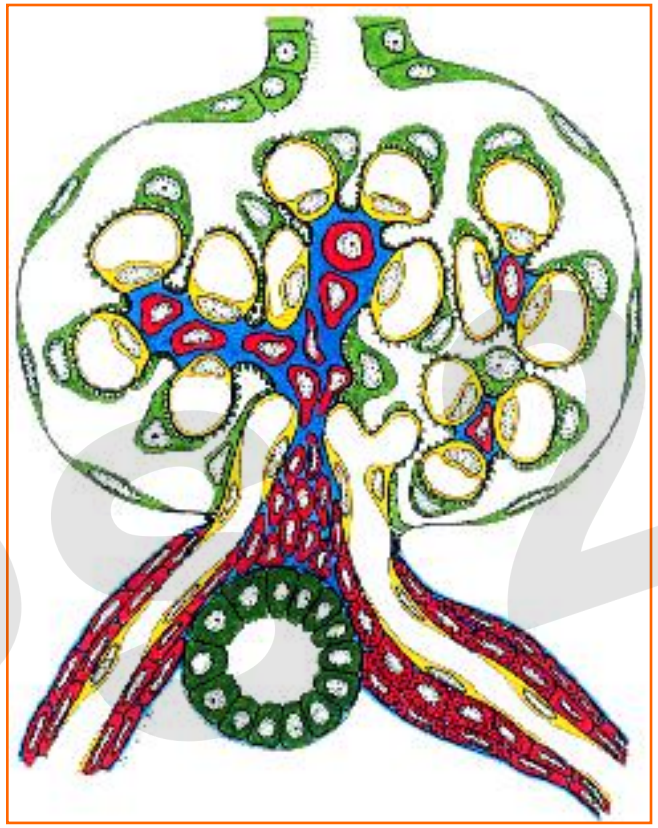






Images from: Somlo S, Mundel P. Getting a foothold in nephrotic syndrome. *Nature Genetics* 2000; 24, 333 - 335

Focal Segmental Glomerulosclerosis

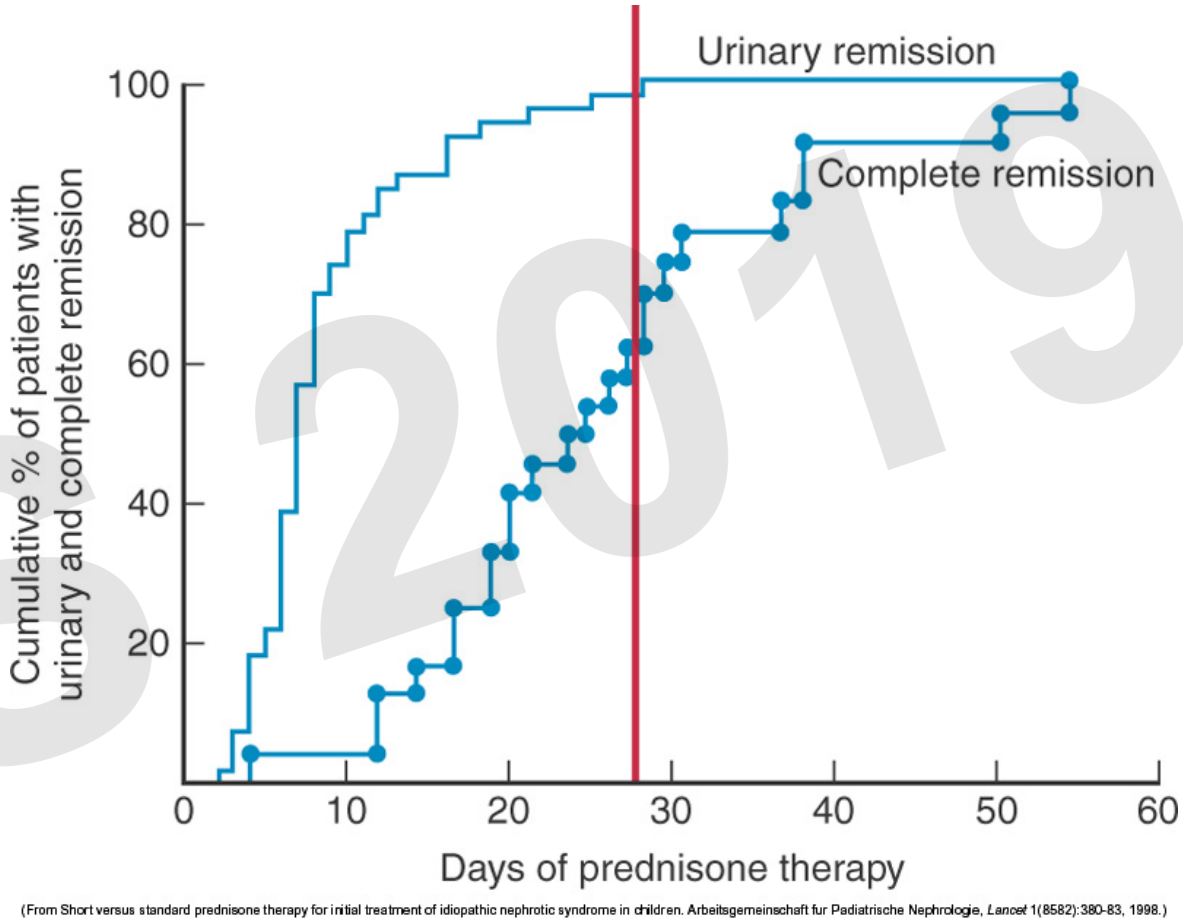


The diagram depicts **perihilar segmental sclerosis**, which is continuous with the afferent arteriole

Nephrotic syndrome in children

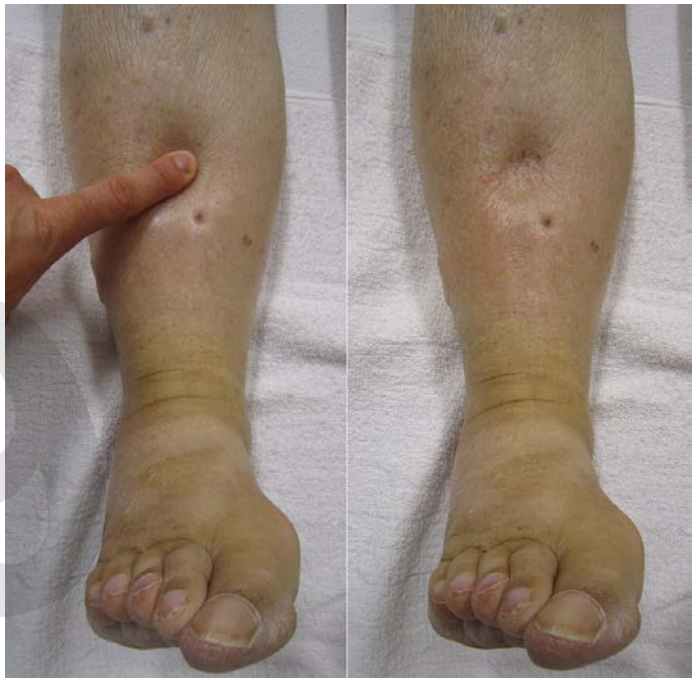
- Cumulative prevalence 16/100,000 children
- Clinical diagnosis
  - Large proteinuria (>40 mg/h/m^2 = >1 g/d/m^2 body surface area)
    - Normal < 4 mg/h/m^2 (<100 mg/d/m^2)
  - Hypoalbuminemia (<25 g/L)
  - Edema
- Idiopathic childhood nephrotic syndrome
  - 80 % Minimal change disease (MCD)
  - 10 % Focal segmental glomerulosclerosis (FSGS)
  - 10 % other etiologies

Initial treatment response to prednisone in MCD



From Geary/Schaefer "Comprehensive Pediatric Nephrology", 2008; Fig. 16-1 – modified.
Original data: Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie, Lancet 1998; 1(8582):380-383)

Supportive/Rescue therapy

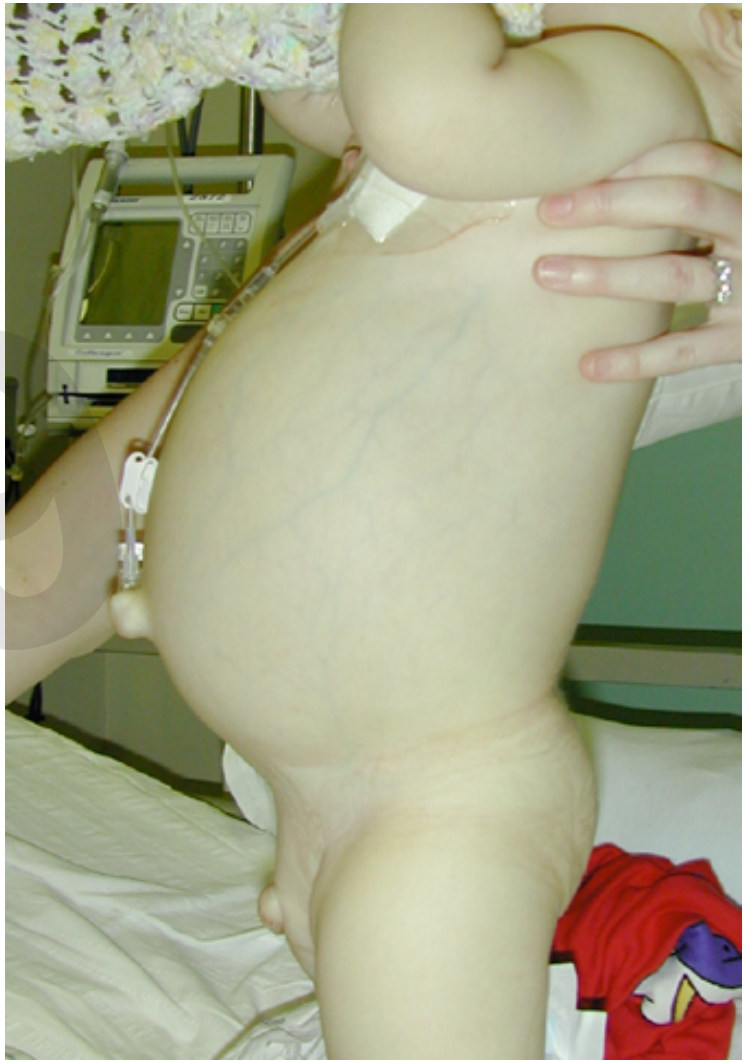


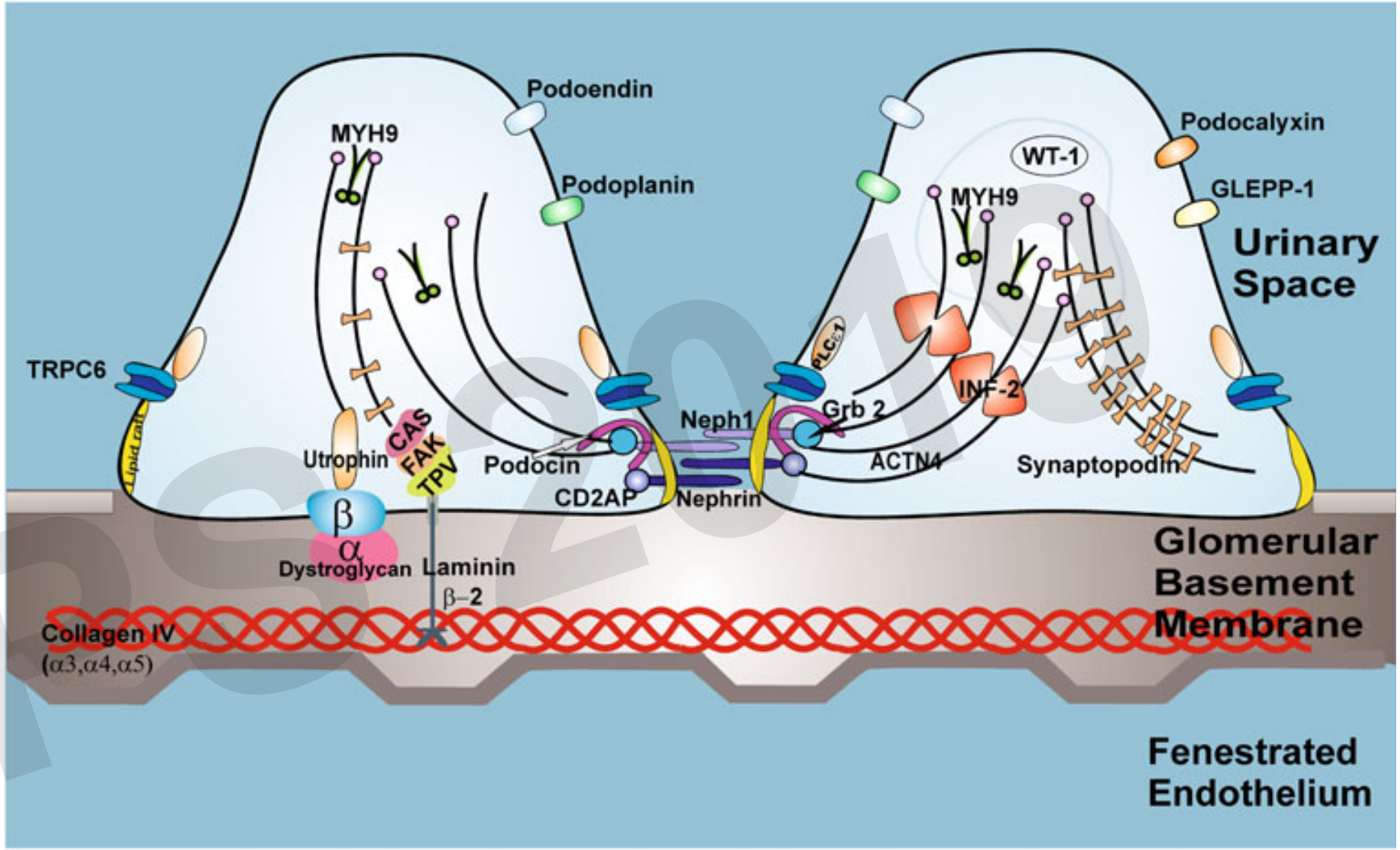
- Albumin infusion (with furosemide)
  - Volume depletion with adverse effects
  - Ischemia due to poor perfusion/hypoxia
    - Mesenterium (abdominal pain)
    - Kidneys (elevated creatinine)
  - Severe edema, including ascites / scrotal edema

Problem # 1
Lack of treatment response

About 10% of children do not respond to prednisone

- Glucocorticoid “resistance”
- Often due to FSGS or other glomerular disease
- Kidney biopsy for diagnosis
- Alternative treatment





Gbadegesin R et al. Pathogenesis and therapy of focal segmental glomerulosclerosis: an update. Pediatr Nephrol 2011; 26: 1001-1015

Problem # 2
Relapsing Nephrotic Syndrome

About 30 % relapse frequently (≥4 times/12 months)

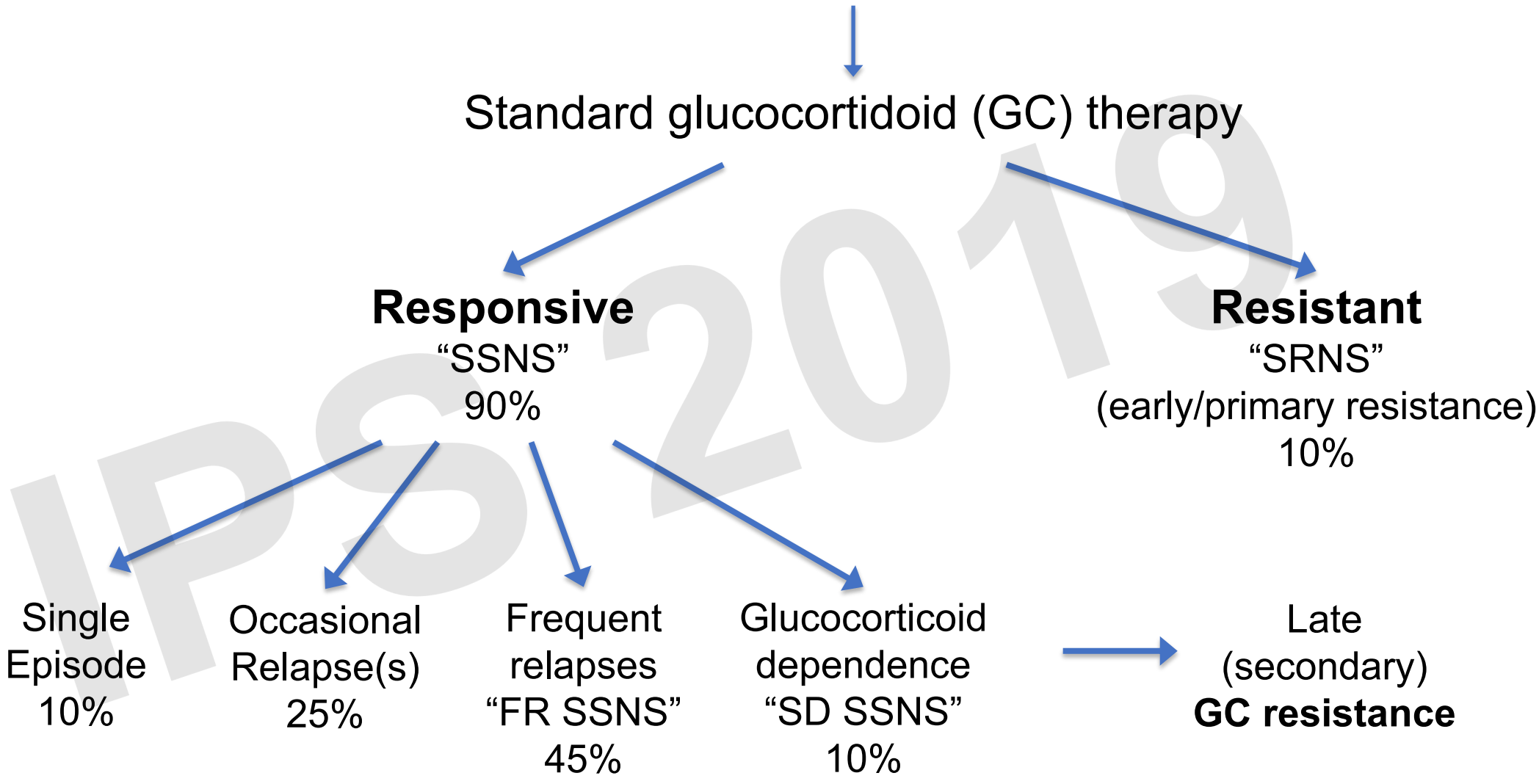
- "Frequently relapsing nephrotic syndrome" (FRNS)

- 10-20 % relapse during treatment or immediately after "standard" course of prednisone
  - "glucocorticoid-dependent nephrotic syndrome" (SDNS)

Problem # 3
Nephrotic Syndrome and Infection

- Infectious complications
  - Peritonitis, cellulitis
- Infection prevention
- Immunizations
  - Varicella, *S. pneumoniae*, *H. influenzae*
  - Seasonal influenza
  - Does immunization lead to relapse ?
  - Vaccine efficacy while receiving prednisone ?
  - Live vaccine *Pro* and *Con*
- Antibiotic prophylaxis ?

Childhood Idiopathic Nephrotic Syndrome (cINS)



Treatment of frequently relapsing or glucocorticoid-dependent nephrotic syndrome

- "Second line" agents
  - Mycophenolate mofetil (MMF)
  - Calcineurin inhibitors (tacrolimus, cyclosporine A)
  - Cyclophosphamide
  - Levamisole
  - Rituximab

Practical, outcome-oriented classification of "primary" nephrotic syndromes

- Glucocorticoid-responsive nephrotic syndrome (MCD, some FSGS)
- Genetic forms of nephrotic syndrome/FSGS
  - Mutations affecting glomerular barrier (structural or functional podocyte or GBM genes)
    - Congenital (often AR)
    - Adult onset (often AD)
    - Syndromic
- "Non-genetic", recurrent ("rapidly progressive") FSGS (R-FSGS)
  - Permeability factor/extrarenal cause
- "Non-genetic", non-recurrent FSGS

Case 2

- 5 y/o boy, previously healthy
- Cough 4 days prior to ED, 1 day of fever, moderate respiratory distress
- Pneumonia with consolidations R > L
- Absolute neutrophil count and CRP are moderately elevated,
- Admitted for IV antibiotic treatment
- 3 days later
  - While patient appears clinically stable, he voids dark bloody urine

Case 2
What is your approach to this patient ?

1. Call a urology consultant and request a cystoscopy
2. Obtain an abdominal X ray
3. Do a kidney stone work up
4. Ask the rheumatologist for help
5. Obtain a urine culture and change the antibiotic
6. Last resort: contact the (pediatric) nephrologist

Case 2

Key lab results

- Diminished serum C3
- Hight ASOT

Diagnosis

- APIGN (APSGN) due to pneumonia
- Likely caused by *S. pyogenes*

Gross hematuria in children

- It is usually not bladder cancer
- Rarely due to strictly “urological” etiology
- Urine appearance
  - Fresh blood (bright) or dark (tea coloured) ?
- Does the patient describe pain ?
  - Location, time, related to micturition and when during micturition ?
- Is the hematuria associated with a current or recent infection ?
- Systemic signs
  - (Vasculitc) rash, petechiae, arthralgia, edema, arterial hypertension ?
- Has hematuria occurred in the past ?

Acute postinfectious glomerulonephritis (APIGN)

- APIGN is the most common form of acute glomerulonephritis in childhood
- Pathogenesis
  - Immunologically mediated, inflammatory disorder of the renal parenchyma
  - Characterized by alternative complement pathway activation and exudative, proliferative glomerulonephritis
  - Manifestation after a latent period of 1–3 weeks after upper respiratory tract infection/pharyngitis or 3–5 weeks after pyoderma
  - Caused by group A hemolytic streptococci (*S. pyogenes*) and other infectious organisms

APIGN - Clinical Features

- Triad of
  - (gross) hematuria
  - Arterial hypertension
  - Generalized edema (acute nephritic syndrome)

Spectrum clinical presentation ranges from microhematuria to nephrotic syndrome, severe renal failure, and encephalopathy or seizures due to hypertension (posterior reversible encephalopathy syndrome, PRES).

APIGN - Laboratory evaluation

- Important lab tests
  - Renal function
  - Urinalysis
  - C3 and C4
  - Microbiological studies
    - Throat swab, skin swab, blood culture – if indicated
    - Serological studies (ASOT, ADB)
    - Antigen detection / nucleic acid tests

Treatment and prognosis

- Treatment
  - Symptomatic
  - Hypertension and fluid retention: diuretics = first line
  - Anti-hypertensives if needed
- Antibiotics
  - do not change course of (or prevent) disease but may limit spread of nephritogenic strains of betahemolytic Streptococci
- Prognosis
  - Excellent outcome in >95 % of cases
  - Progression to end-stage renal disease or recurrence of APIGN is extremely rare

IgAV / SHP (Schoenlein Henoch Purpura)

- Most common vasculitis in children
- Manifestations
  - Purpura and/or petechiae
  - Abdominal pain (submucosal vasculitis)
  - Non-deforming arthritis
  - Nephritis
- Hematuria (mostly microscopic) in 80% of children
- Full picture of nephritis and/nephrotic syndrome in < 10%
- Hematuria and proteinuria resolve within 3 mo of onset of purpura
- Nephrotic syndrome and rapid rise of S-cr (RPGN) are associated with CKD or ESRD

Z Rheumatol 2007 · 66:716–724
DOI 10.1007/s00393-007-0179-z
Online publiziert: 1. Juni 2007

W. Keitel
Gommern-Vogelsang

Johann Lukas Schönlein (1793–1864)

Der degradierte Ehrenbürger

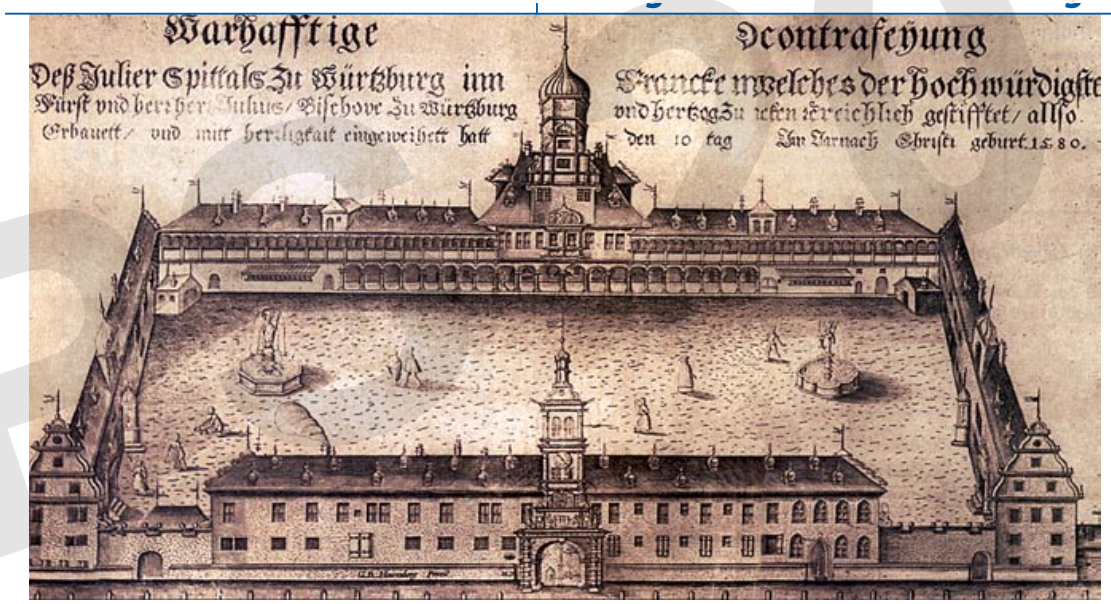


Abb. 2 ▲ Julius Hospital Würzburg von Fürstbischof Julius Echter von Mespelbrunn 1580 eingeweiht

JOHANN LUKAS SCHÖNLEIN
(1793–1864)

Abb. 1 ▲ Titelbild des Ausstellungskataloges „... und ewig erklingen wird sein Ruhm...", Staatsbibliothek Bamberg 1993 [30]

New classification of SHP as IgA vasculitis

Chappel Hill Consensus Conference 2012

Box 3.9 Classification of Childhood Vasculitis[a]

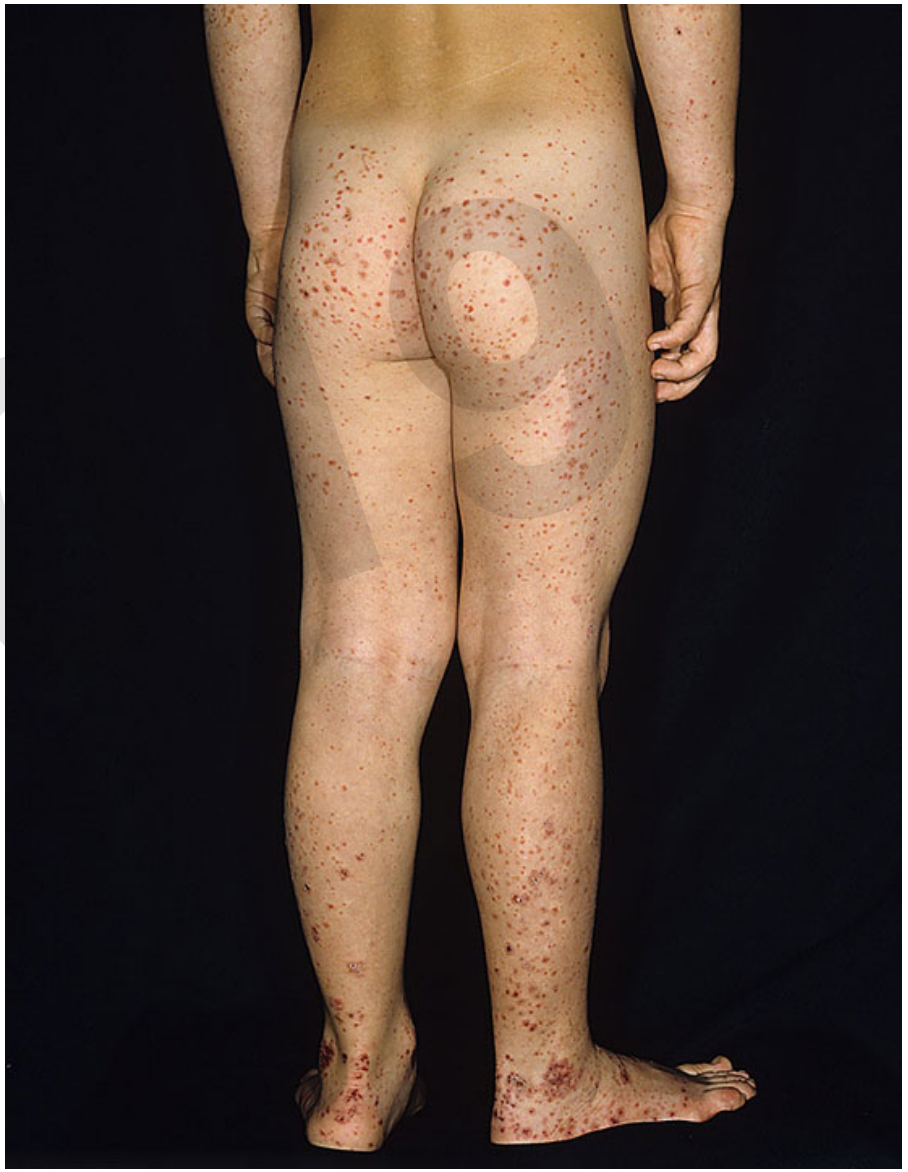
Childhood vasculitis can be classified based on the size of the blood vessel affected:

1. Large vessel vasculitis (LVV)
   - (a) Takayasu arteritis TAK, (see Sect. 3.6.5.1)
   - (b) Giant cell arteritis (GCA)
2. Medium-sized vessel vasculitis
   - (a) Childhood polyarteritis nodosa (cPAN) (see Sect. 3.6.5.2)
   - (b) Kawasaki disease (KD) (see Sect. 3.6.5.3)
3. Small vessel vasculitis (SVV)
   - (a) Pauci-immune vasculitis/ANCA-associated vasculitis (AAV) (see Sect. 3.6.3)
     - (i) Microscopic polyangiitis (MPA) (see Sect. 3.6.3.4)
     - (ii) Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) (see Sect. 3.6.3.5)
     - (iii) Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome) (see Sect. 3.6.3.6)
     - (iv) Renal limited vasculitis (pauci-immune necrotizing and crescentic GN (NCGN))
   - (b) Immune complex vasculitis
     - (i) Schönlein–Henoch purpura (SHP)/Schönlein–Henoch nephritis (SHN or IgA vasculitis, IgAV) (see Sect. 3.6.2)
     - (ii) Cryoglobulinemic vasculitis (CV)
     - (iii) Anti-glomerular basement membrane (anti-GBM) disease (see Table 3.12)
4. Vasculitis associated with systemic disease
   - (a) Lupus vasculitis (lupus nephritis, LN) (see Sect. 3.6.4)
   - (b) Vasculitis associated with chronic juvenile arthritis, mixed connective tissue disease and overlap syndromes
5. Vasculitis associated with probable etiology
   - (a) Vasculitides associated with infections, malignancy, drugs, hypersensitivity

[a]Based on the 2012 Chapel Hill Consensus Conference (CHCC 2012)

Bitzan M. "*Glomerular Diseases*" (chapter 3). In:
Manual of Pediatric Nephrology (eds. Phadke K, Goodyer PR, Bitzan M). Springer, Berlin, Heidelberg 2014

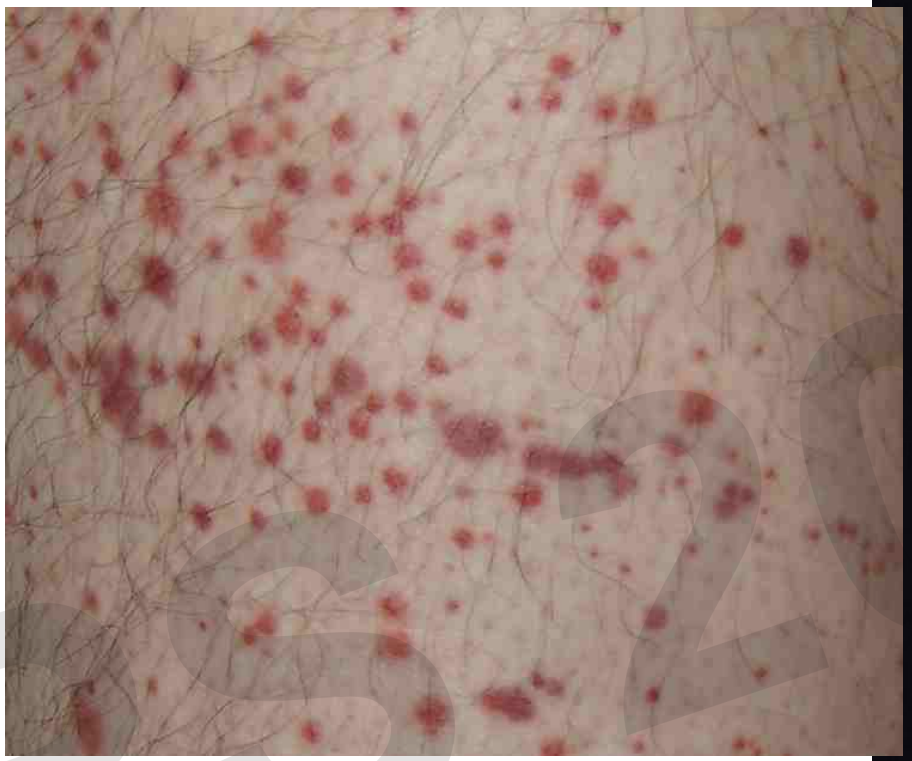
IgAV- Leukocytoclastic vasculitis

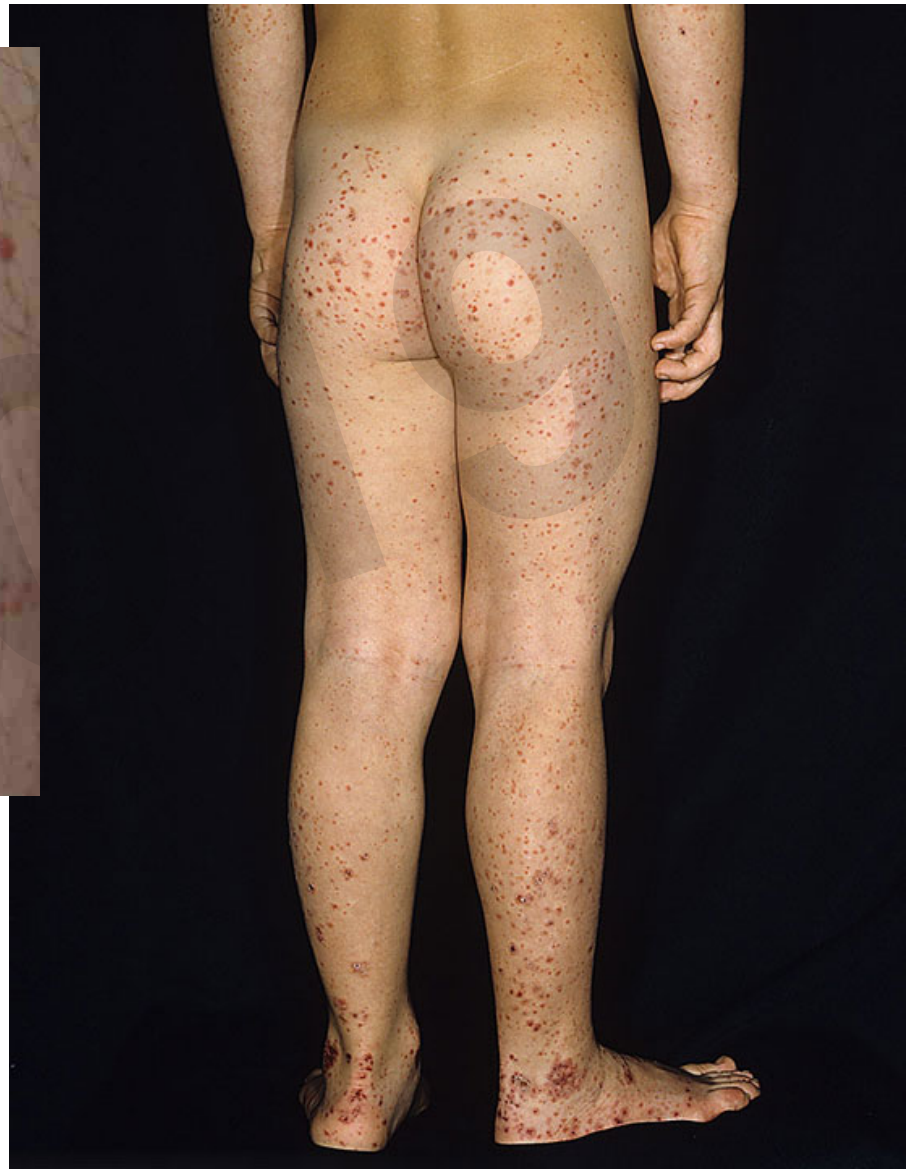


http://en.wikipedia.org/wiki/Image:Purpura.jpg

Author: Dr Ben Tallon, Dermatologist/Dermatopathologist, Tauranga, New Zealand, 2011
http://www.dermnetnz.org/topics/leukocytoclastic-vasculitis-pathology/

IgAV- Leukocytoclastic vasculitis





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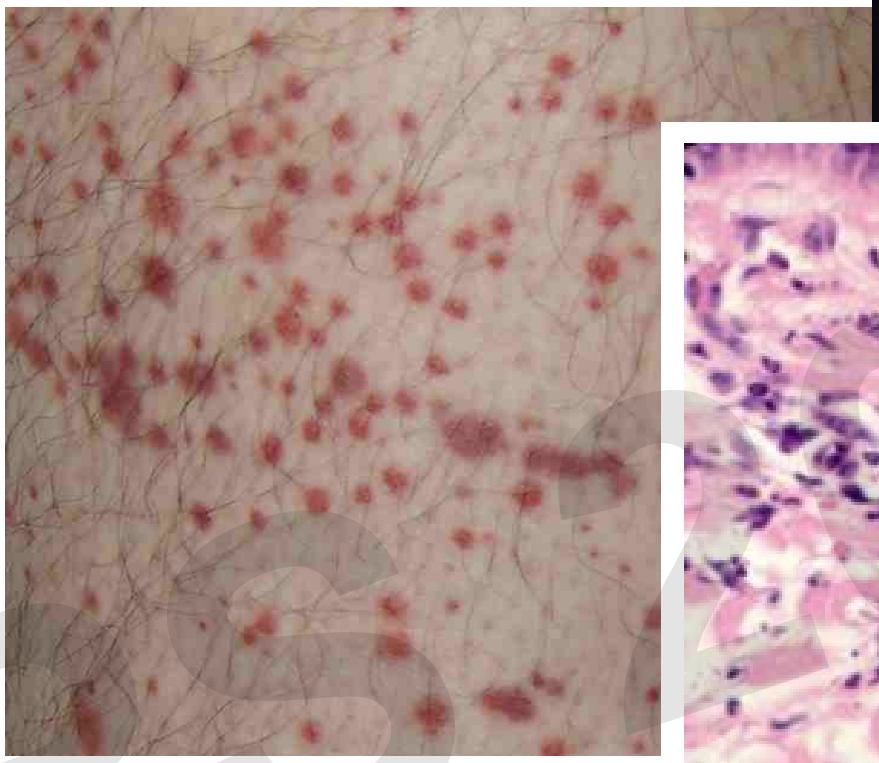
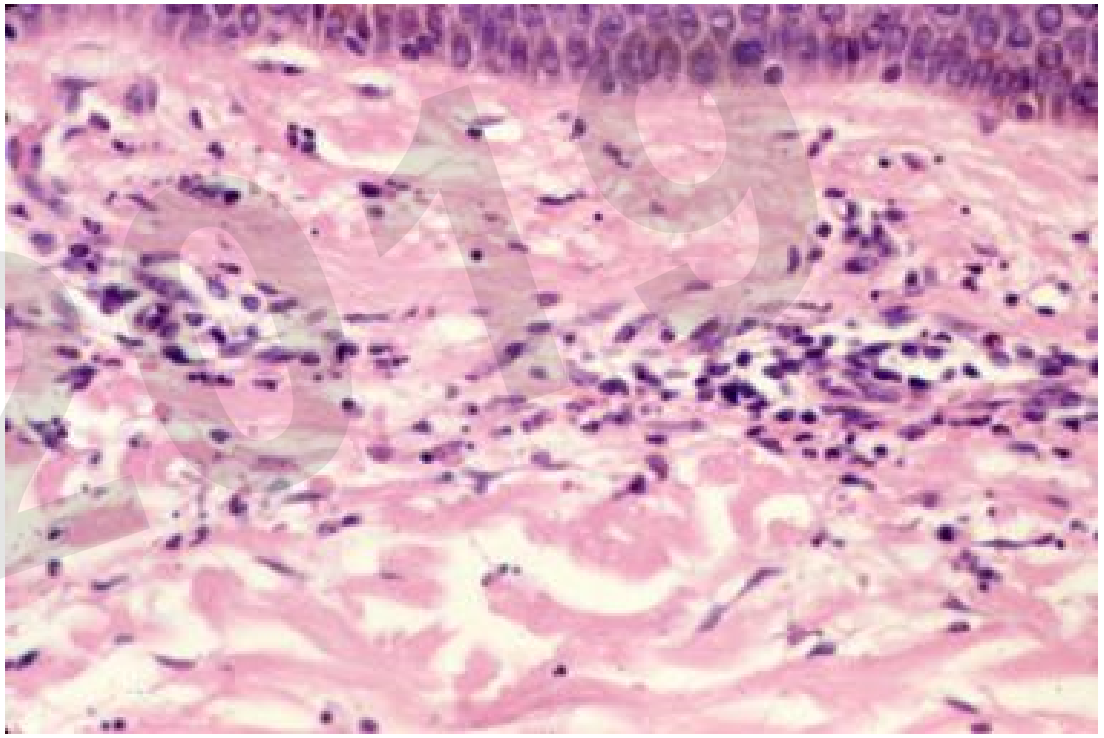
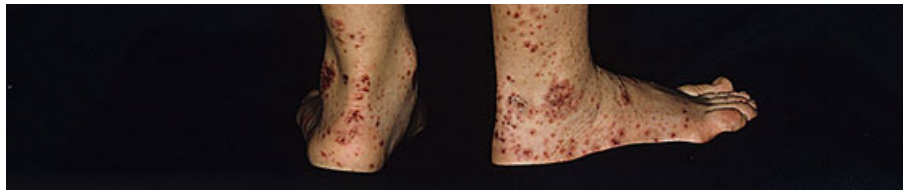




Histopathology of leukocytoclastic vasculitis.



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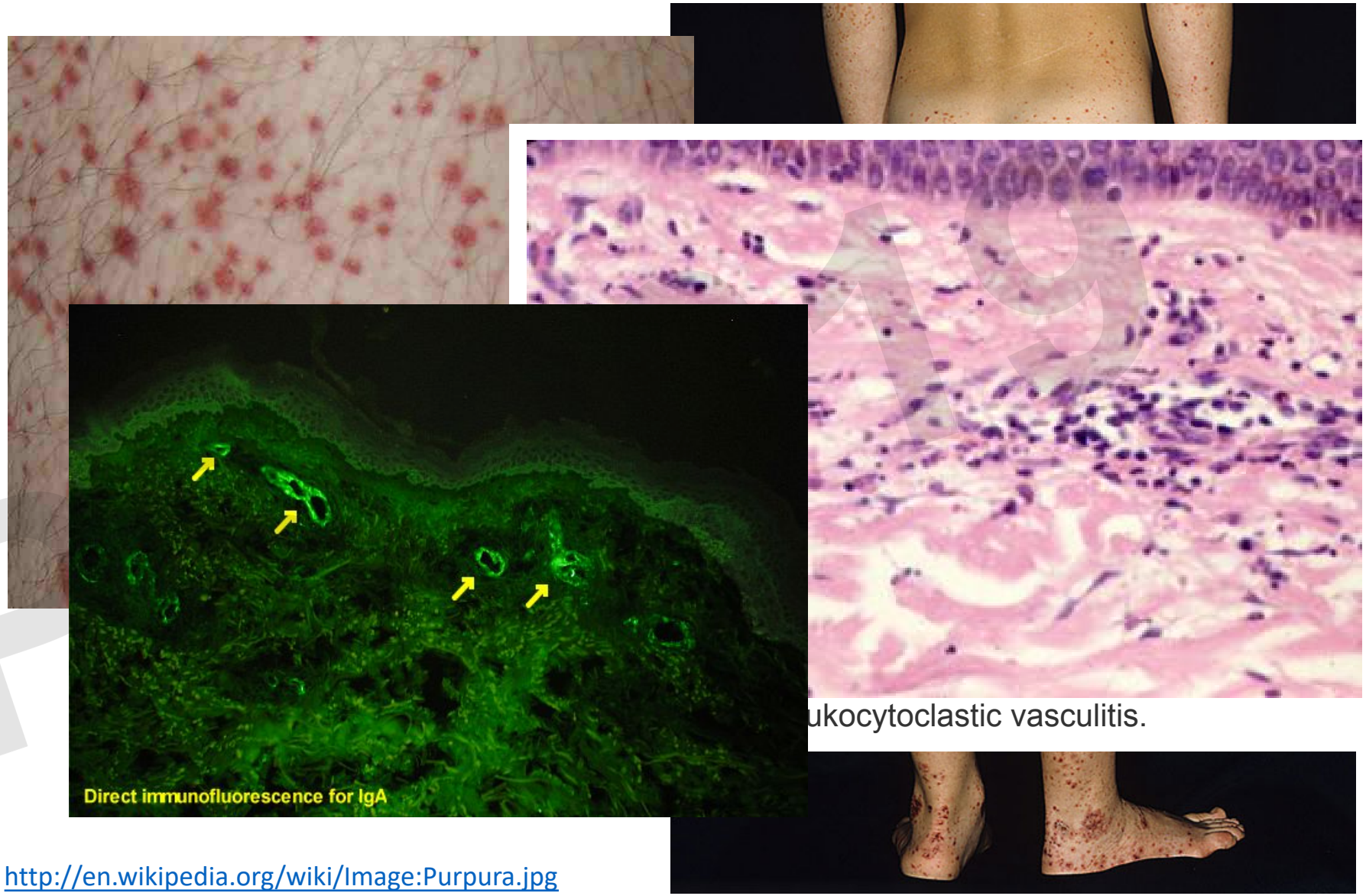

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Author: Dr Ben Tallon, Dermatologist/Dermatopathologist, Tauranga, New Zealand, 2011

http://www.dermnetnz.org/topics/leukocytoclastic-vasculitis-pathology/

KDIGO Clinical Practice Guideline for Glomerulonephritis

11.1 Treatment of HSP nephritis in children

11.1.1: We suggest that children with HSP nephritis and persistent proteinuria 0.5-1 g/d per 1.73 m2, are treated with ACE-C or ARBs. (2D)

11.1.2: We suggest that children with persistent proteinuria, >1 g/d per 1.73 m2, after a trial of AC E-I or ARBs, and GFR >50 ml/min per 1.73 m^2, be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see Chapter 10). (2D)

11.2: Treatment of crescentic HSP nephritis in children

11.2.1: We suggest that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for IgA (see Recommendation 10.6.3). (2D)

AJKD 2012

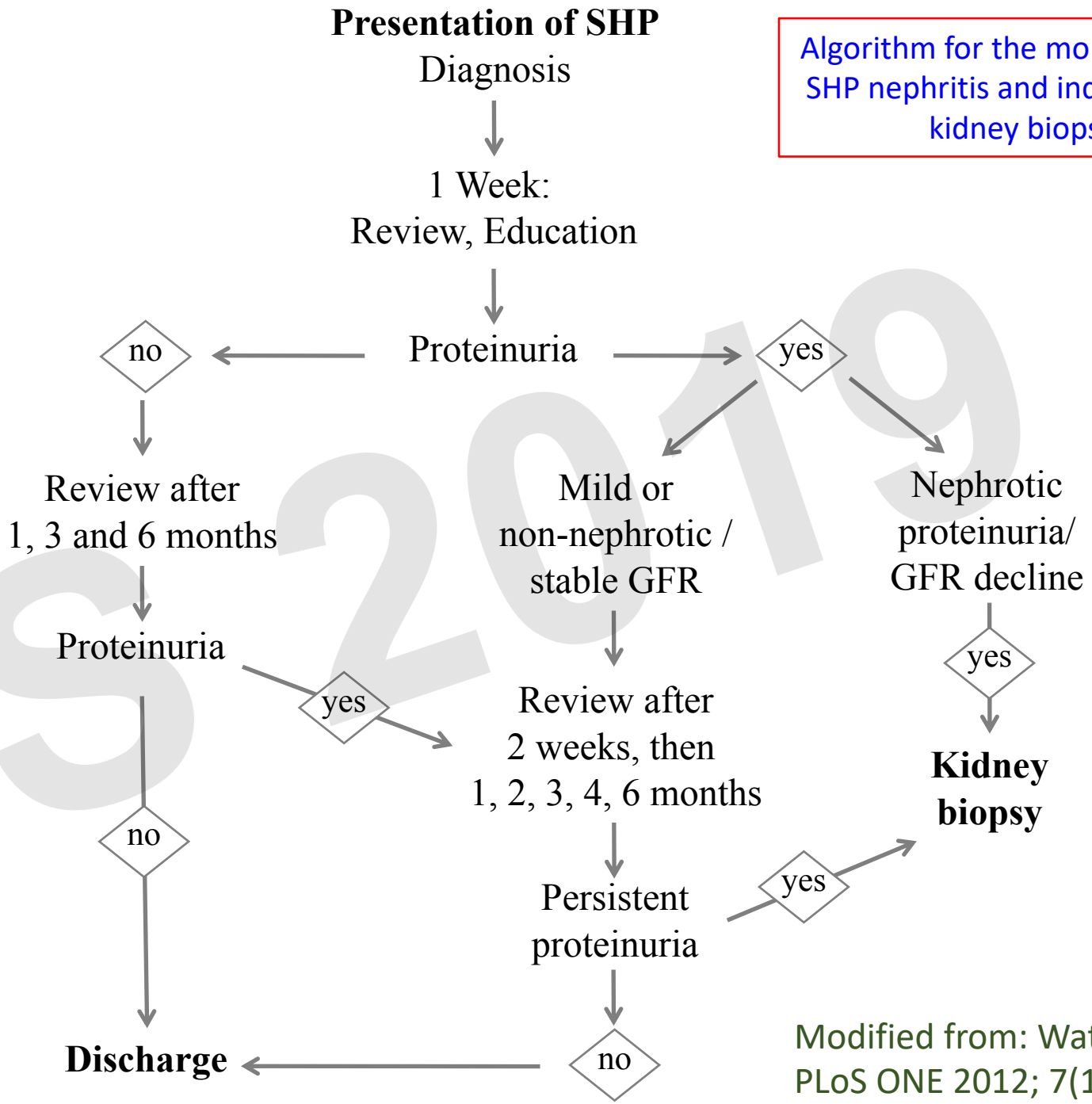
When to worry and how to treat ?

The risk of evolution into CKD for the combination of onset with [1, 2]

- nephrotic and nephritic syndrome (up to 50%)
- nephrotic syndrome (up to 40 %)
- nephritic syndrome and/or heavy non-nephrotic proteinuria (up to 15%)

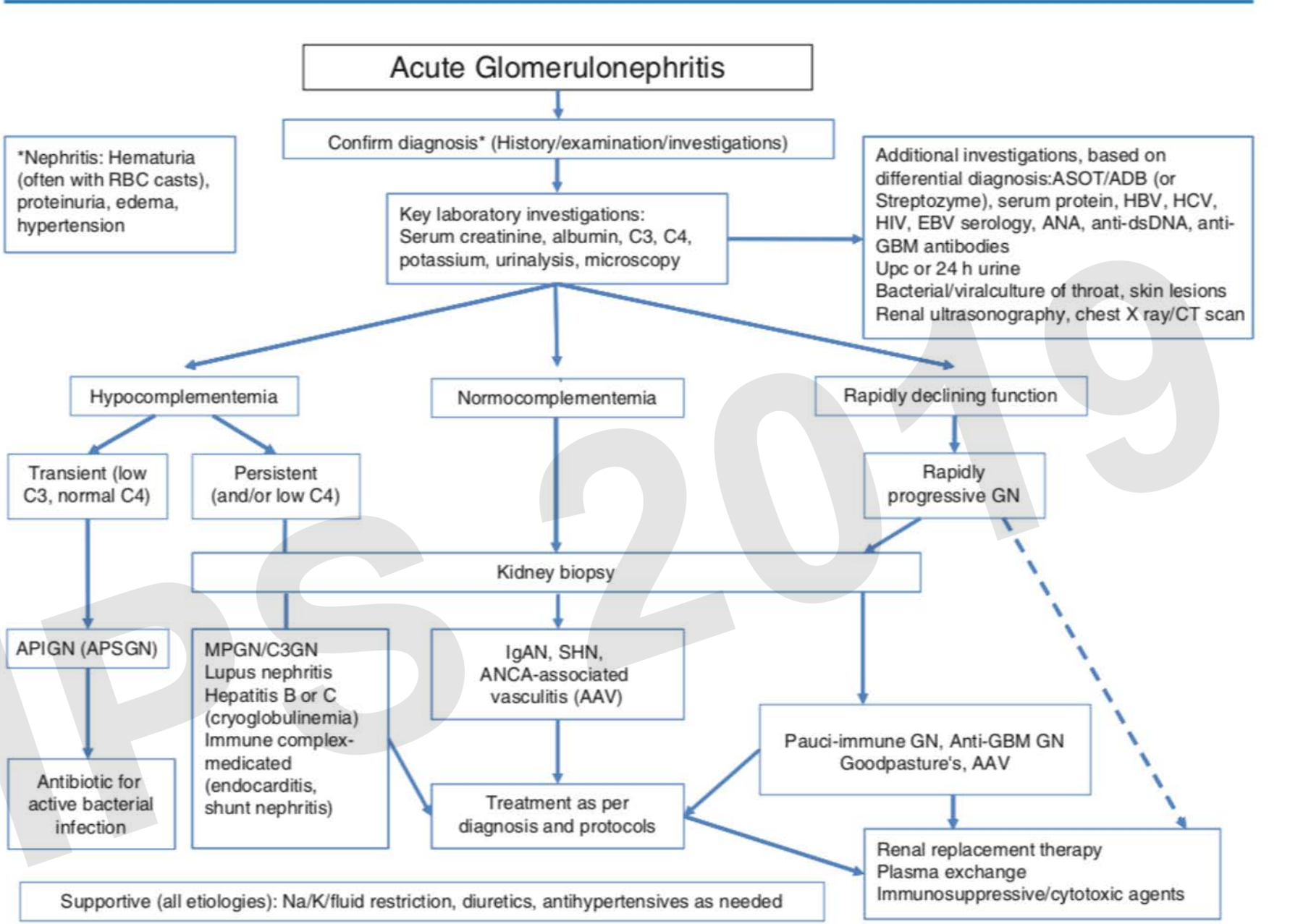
1 Davin & Coppo. *Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch–Schönlein purpura nephritis*. Pediatr Nephrol 2013; 28:1897–1903

2 Goldstein AR et al. *Long-term follow-up of childhood Henoch–Schönlein nephritis*. Lancet 1992; 339:280–282



Algorithm for the monitoring for SHP nephritis and indication for kidney biopsy

Modified from: Watson L et al. PLoS ONE 2012; 7(1): e29512



From: Manual of Pediatric Nephrology (Eds. Phadke/Goodyer/Bitzan)

For additional questions