



WELCOME TO

ERKNet Advanced Webinars on Rare Kidney Disorders

Date: 04 May 2021

Topic: Acute post-streptococcal GN

Speaker: Michael Somers

Moderator: Elena Levtchenko

Acute Post-Streptococcal Glomerulonephritis

Michael JG Somers, MD
Gunnar B Stickler Chair in Pediatric Nephrology
Associate Chief, Division of Nephrology
Boston Children's Hospital
Harvard Medical School



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Case One -- Thomas

- Thomas is a healthy 6-year-old boy who was treated for strep throat 2 weeks ago
- He presents now with a two-day history of increasing swelling and the onset of tea-colored urine
- On exam, his weight is up 2 kg from his visit for strep throat. His BP is elevated to 140/90. He has mild extremity edema
- Urinalysis reveals 3+ hematuria and 2+ proteinuria on dipstick with > 50 rbc/hpf with occasional rbc casts
- A urine protein-to-creatinine ratio is 1



Case One -- Thomas

- Other laboratories are notable for normal electrolytes and kidney function, a low normal serum albumin, depressed C3 complement level, and an elevated ASO
- He is admitted for blood pressure management and treated with furosemide and amlodipine
- Within 36 hours, his BP is 90%ile and his weight is down 1.5 kg; he is discharged home on furosemide
- At two weeks follow-up, he no longer has gross hematuria, his BP is at the 50%ile, and his weight at baseline and the furosemide is stopped



Case One -- Thomas

- At two months follow-up, he has a normal BP and physical exam and a urinalysis with 1+ hematuria, negative proteinuria, and a normal sediment, and his C3 complement level is normal
- At one year follow-up, he has a normal BP, normal physical exam, and normal urinalysis



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Case Two -- Ian

- Ian is a healthy 10-year-old boy who was treated for strep throat 2 weeks ago
- He presents now with a two-day history of vomiting, poor fluid intake, and reduced output of dark urine
- On exam, his weight is up 2 kg from his visit for strep throat. His BP is elevated to 150/95. He has mild extremity edema
- Urinalysis reveals 3+ hematuria, 2+ proteinuria, too numerous to count rbcs/hpf, with occasional rbc casts and many granular and hyaline casts



Case Two -- Ian

- Other laboratories are notable for mild hyponatremia, hyperkalemia, and acidosis with a BUN of 60 mg/dL (22mmol/L) and a creatinine of 2.5 mg/dL (220umol/L); the C3 is depressed and ASO elevated
- He is admitted for AKI and blood pressure management
- Over the next 12 hours, he becomes oligoanuric and unresponsive to furosemide, remains hypertensive despite provision of IV hydralazine, and his BUN and creatinine increase further
- A renal biopsy shows >90% crescents and he receives pulse dose IV methyl prednisolone



Case Two -- Ian

- He stops making any urine and intermittent hemodialysis is started for increasing azotemia and ongoing volume excess
- He receives ongoing dialysis and supportive medical care but never regains urine output and a repeat kidney biopsy after 8 weeks shows irreversible injury consistent with ESKD
- He maintains intermittent hemodialysis for 6 months and then receives a living donor kidney transplant



Same Disease – Different Outcomes

- Both boys with preceding strep pharyngitis promptly treated
- Both boys developed gross hematuria and volume overload, but Ian had dramatic AKI from RPGN
- Thomas recovered clinically while Ian progressed to ESKD in the same time frame

What should you know about
acute post-streptococcal
glomerulonephritis?



Learning Objectives

- Recognize the pathophysiology of acute post-streptococcal glomerulonephritis (APSGN) as a paradigm for an immune complex nephritis
- Understand the epidemiology of APSGN and its clinical presentations
- Describe the diagnostic evaluation and management strategies in APSGN
- Explain the outcomes seen with APSGN in children and necessary kidney follow up care



Poll Question 1



My exposure to the topic of acute post-streptococcal glomerulonephritis is:

- a) None**
- b) Only lectures/reading**
- c) < 5 patients**
- d) ≥ 5 patients**



Boston Children's Hospital
Until every child is well™

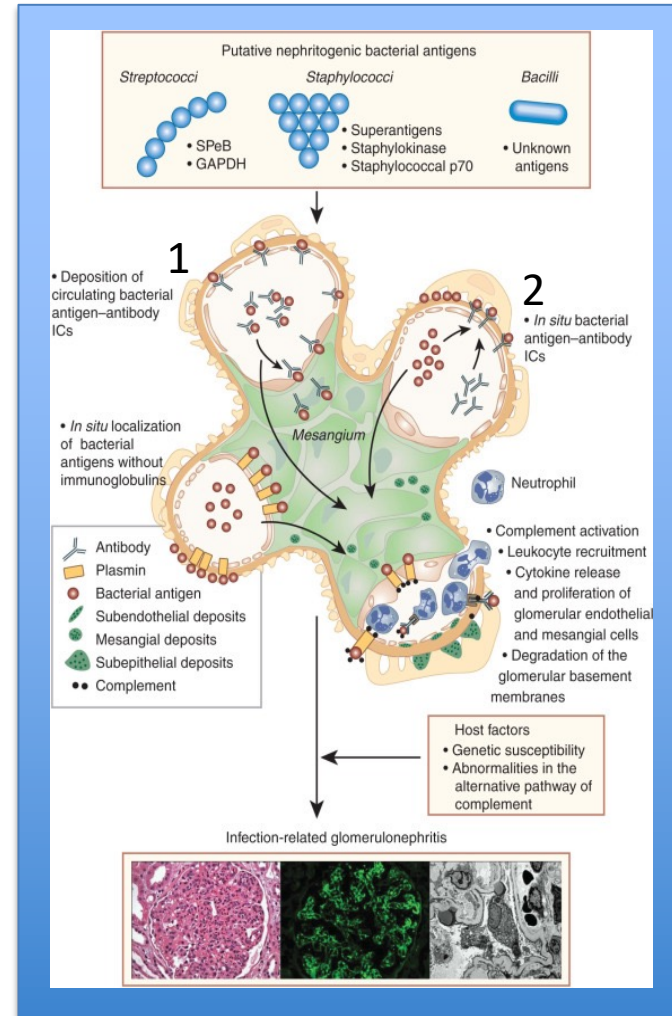


HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Pathophysiology

How could an immune response to a strep infection result in GN?

- 1) Circulating immune complexes that include a streptococcal antigen deposit pre-formed in the kidney
- 2) Streptococcal antigens deposit within the GBM with subsequent antibody binding and immune complex formation
- 3) Antibodies to streptococcal antigen cross react to the glomerulus instead allowing immune complex formation (molecular mimicry)
- 4) Streptococcal neuraminidase modifies native IgG, perhaps by changing terminal sialic acid, and creates an IgG with autoimmune potential



Kidney International 2013 83792-803DOI: (10.1038/ki.2012.407)
Copyright © 2013 International Society of Nephrology



Boston Children's Hospital
Until every child is well™



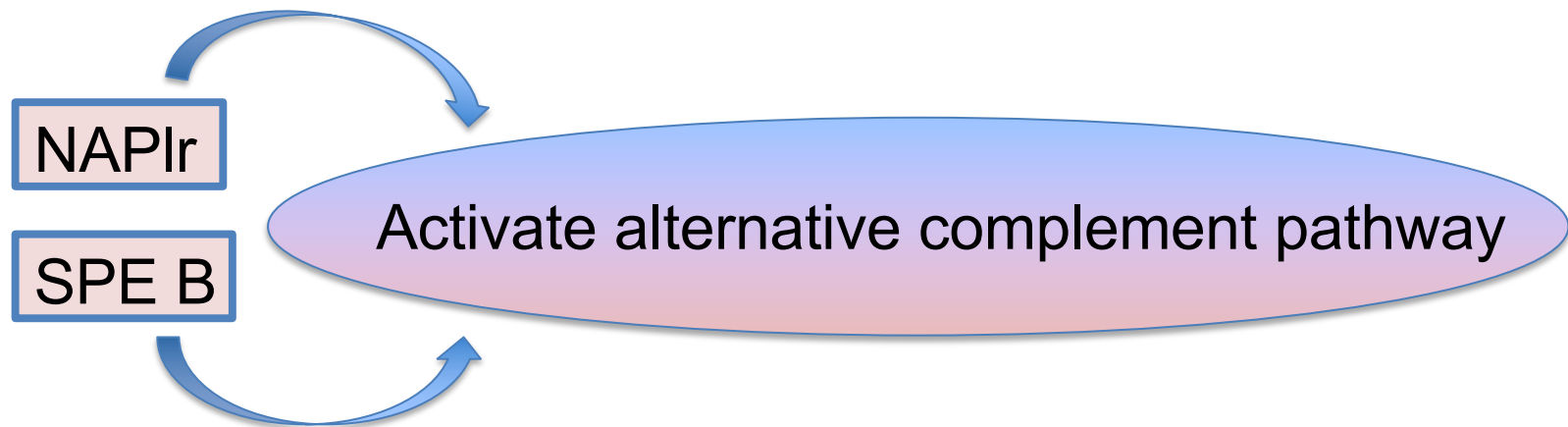
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Pathophysiology

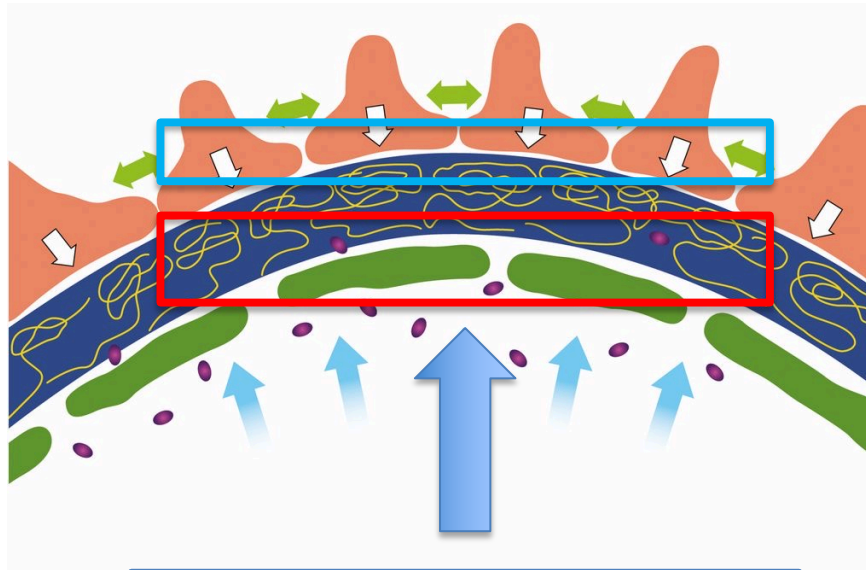
Proposed Nephritogenic Antigens

Nephritis-associated plasmin receptor (NAPlr)
glycolytic enzyme

Streptococcal pyrogenic exotoxin B (SPE B)
proteinase

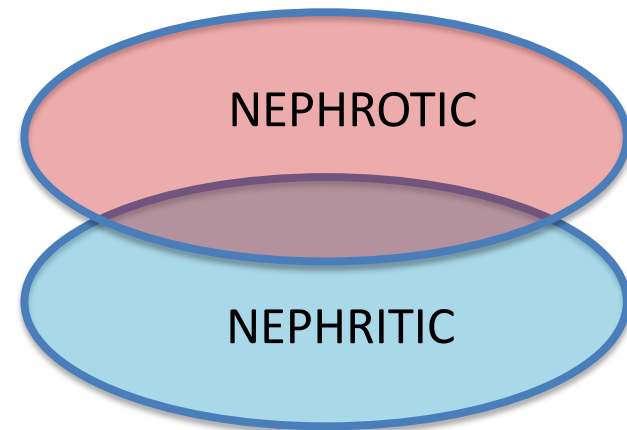


Pathophysiology



Immune complex deposition in subepithelial location associated with proteinuria

Immune complex deposition in subendothelial location associated with inflammation and hypocomplementemia

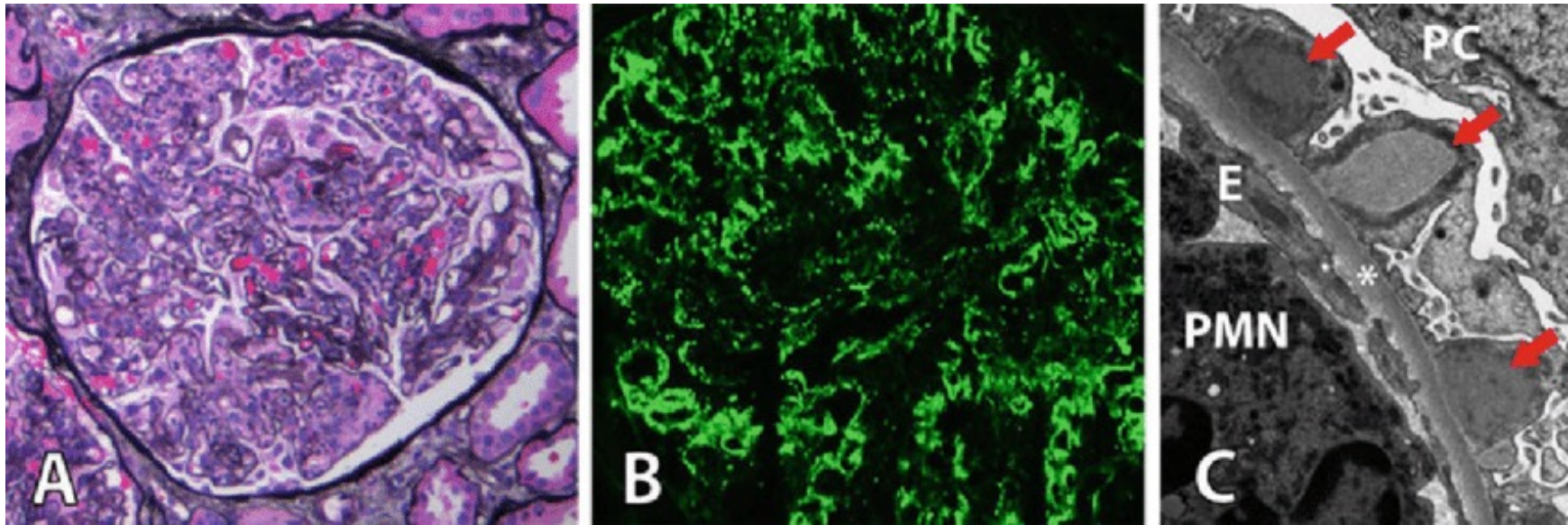


Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

APSGN: Immune Complex Nephritis



- A. **Light microscopy:** proliferative and often exudative GN; findings vary within clinical spectrum; crescents less common
- B. **Immunofluorescence:** diffuse C3 and IgG is typical; C3 deposition often described as “starry sky”
- C. **Electron microscopy:** subepithelial electron-dense humps as well as subendothelial deposits

Pathology pictures from Rodriguez-Iturbe B et al, “Acute postinfectious glomerulonephritis in children,” in Pediatric Nephrology, 7th ed. Berlin: Springer-Verlag, 2015



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Poll Question 2



In a child with acute post-streptococcal glomerulonephritis with a negative throat culture and no active infection, would you provide antibiotics?

- a) Yes**
- b) No**



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Epidemiology

Age

- Most cases between 2-18 years of age
- Peak prevalence 6-8 years of age
- Uncommon in very young (perhaps related to less strep carriage/colonization or potential immune factors)

Sex

- Preponderance of boys
- Some case series up to 80% boys, but most often around 60%
- Unclear why since overall prevalence of group A strep does not vary between boys and girls



Epidemiology

Scope of disease

- 500,000 cases annually worldwide
- 5,000 deaths

Disparities in prevalence

- >90% of cases from economically disadvantaged areas
- Incidence of 2 vs 24 cases/100,000 population in geographic areas with more developed vs less developed economies

Seasonal variation

- More respiratory-associated cases in colder months and more skin-associated cases in warmer months



Epidemiology

Epidemic disease

- Periodically described, most often in areas with higher baseline rates of disease
- Research efforts associated with several epidemic outbreaks (Red Lake Reservation in Minnesota, indigenous community in Central Australia)
- Epidemic disease may alter typical approach to diagnosis and management

Nephritogenic strains of strep

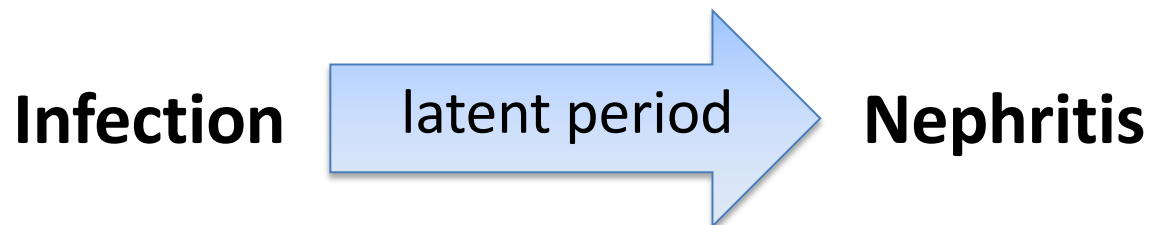
- M types 1, 2, 4, 12 with respiratory disease
- M types 47, 49, 55 with skin disease



Clinical Presentation

Interval between infection and nephritis

- Latent period often between 1 and 6 weeks, but subclinical disease makes time course difficult to pinpoint
- Anecdotal reports that respiratory-related illness typically has onset sooner than skin-related
- Several studies have shown similar latent period of about 10 days between nephritis related to pharyngitis and nephritis related to impetigo



Clinical Presentation – Preceding Illness

Israeli Cohort

125 children

- 45% pharyngitis
- 25% URI
- 15% asymptomatic
- 10% gastroenteritis
- 5% impetigo

Armenian Cohort

474 children

- 51% URI
- 23% pharyngitis
- 13% impetigo
- 8% asymptomatic
- 5% cervical adenitis

10-15% with no recognized illness



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Clinical Characteristics at Presentation

Hematuria

- Microscopic or gross
- Discolored urine reported in up to 80%

Hypertension

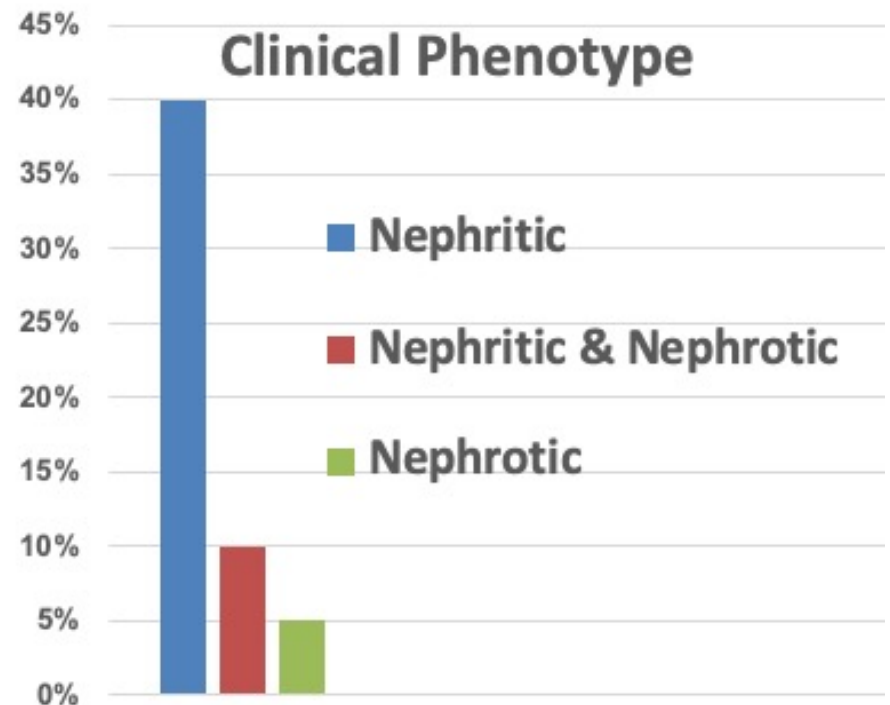
- Reported in 60-75%

Azotemia/Increased Cr

- Reported in 30-40%

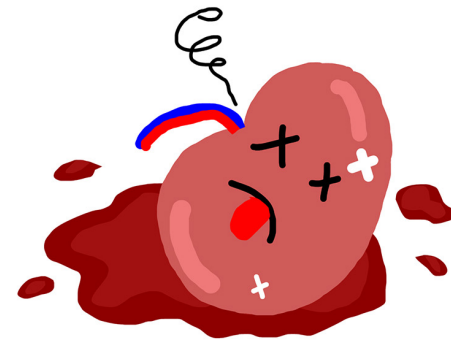
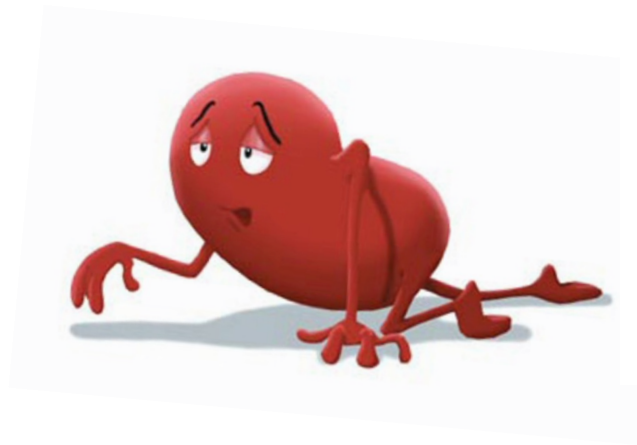
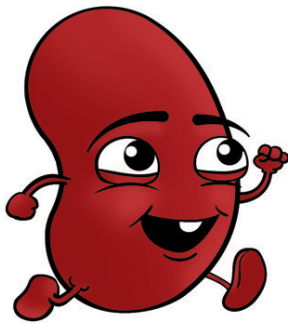
Oliguria

- Reported in 25-35%



Clinical Course – Spectrum of Disease

Asymptomatic  **Kidney Failure**



Boston Children's Hospital
Until every child is well™

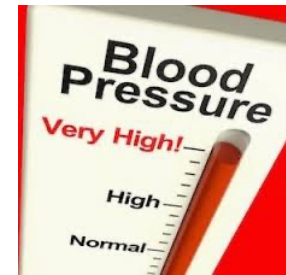


HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Clinical Course: Serious Sequelae

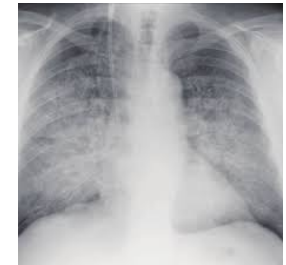
Encephalopathy/Seizures

- Around 5% of most large cohorts
- Generally related to hypertension



Symptomatic Pulmonary Edema/CHF

- 5-15% of most large cohorts
- Chest radiograph changes in up to 50%



Dialysis

- 1-2% of most large cohorts
- Most often related to RPGN



Diagnostic Evaluation

Physical Exam

- Focus of active infection requiring treatment
- Findings related to volume overload: BP, edema, auscultation

Laboratory Studies

- Urinalysis: hematuria (dysmorphic rbc and rbc casts) and variable proteinuria (UPC normal to nephrotic)
- Bloodwork: C3, ASO/antiDNase, albumin, creatinine

Imaging

- Potential need for chest radiograph
- Consideration of kidney ultrasound



Diagnostic Testing

| Test Result | APSGN Cohort (n=74) | Hospitalized Controls (n=60) |
|-------------------------|------------------------|---------------------------------|
| C3 Level Depressed | 99% | 0% |
| ASO Titer Increased | 70% | 18% |
| Throat Culture Positive | 13% | 10% |

**C3 depression is most common
positive lab finding**



Boston Children's Hospital
Until every child is well™



**HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL**

Diagnostic Evaluation

Laboratory Studies Longitudinally

C3 complement:

- Level can be profoundly low at diagnosis but rebounds to normal within weeks
- Depressed level beyond 3 months should prompt consideration of other diagnoses and potential biopsy

ASO titers

- Increase within a week of initial infection
- Peaks within 3-5 week

AntiDNase titers

- Increases by 2 weeks after infection onset
- Peaks within 6-8 weeks
- Some reports of increased utility after skin infections



Poll Question 3



In a child with acute post-streptococcal glomerulonephritis and controlled blood pressure, would you restrict physical activity?

- a) Yes**
- b) No**



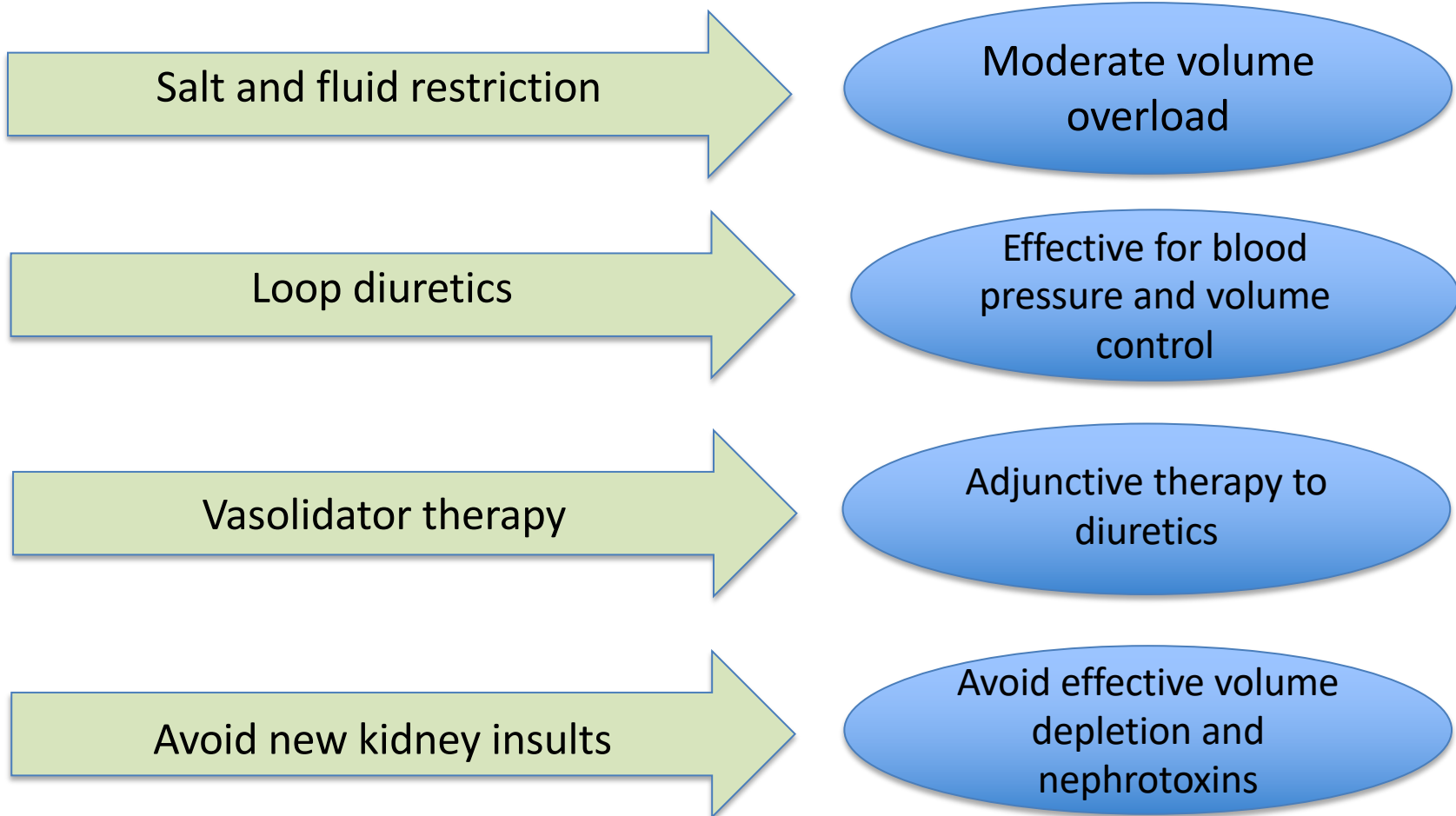
Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Management:

General Medical Care



Management:

Unsupported Historical Management

Routine antibiotic provision to patient

Rare active bacterial infection at diagnosis

Routine antibiotic provision to family

Outside of epidemics or other special clinical circumstances

Routine protracted bedrest

No evidence for efficacy

Routine limitation to sports

Unless BP uncontrolled or another specific contraindication

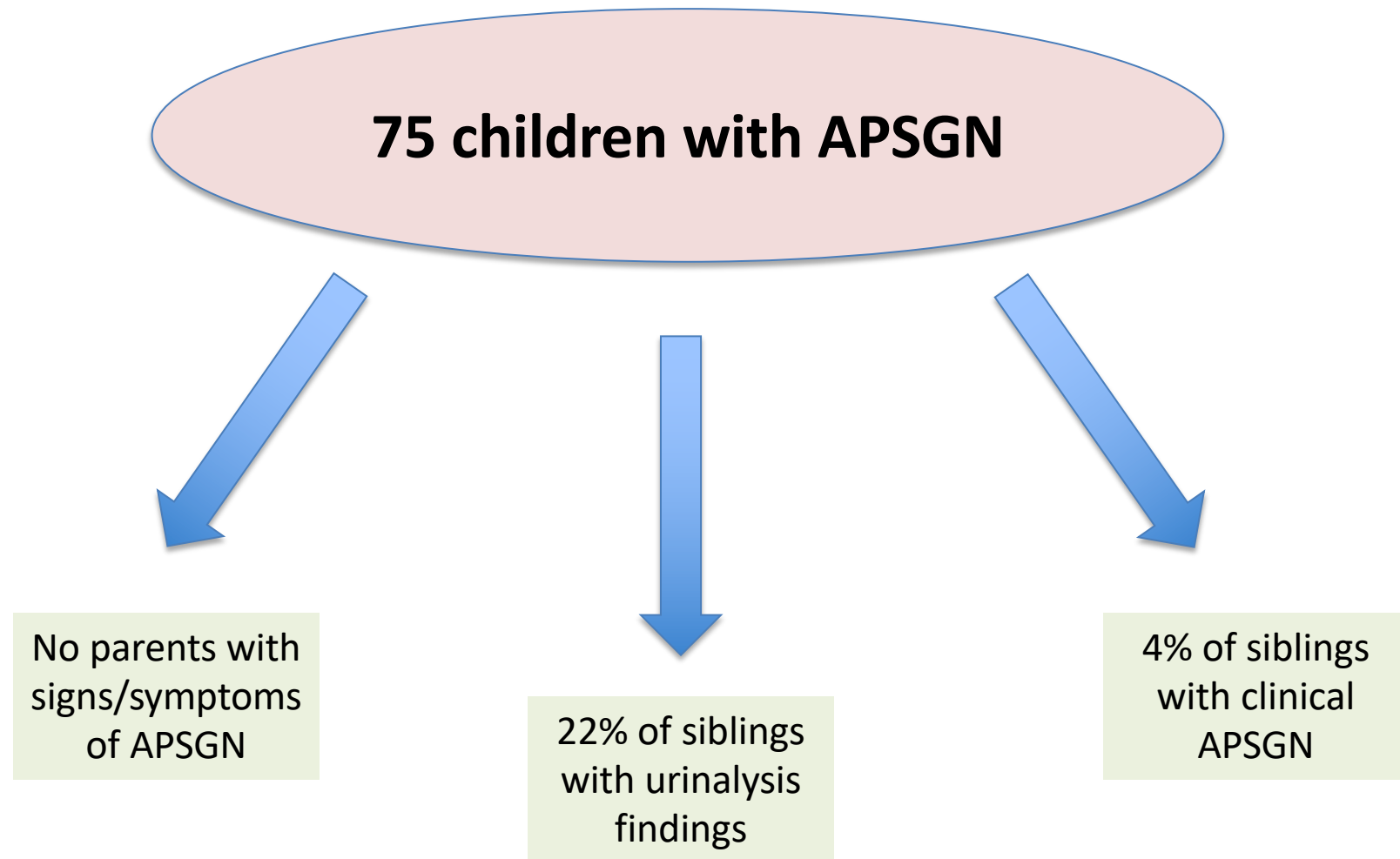


Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

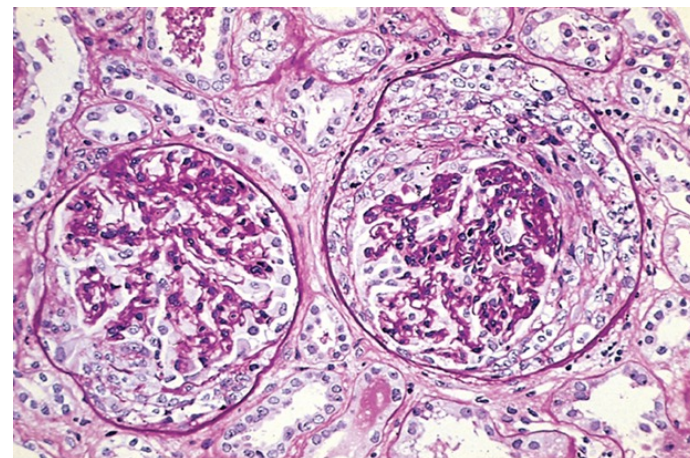
Family Outcomes



Management: RPGN

Uncommon finding but needs to be considered in setting of decreasing kidney function

- Certain populations may be more at risk for a variety of not well understood factors
- Maori community in New Zealand

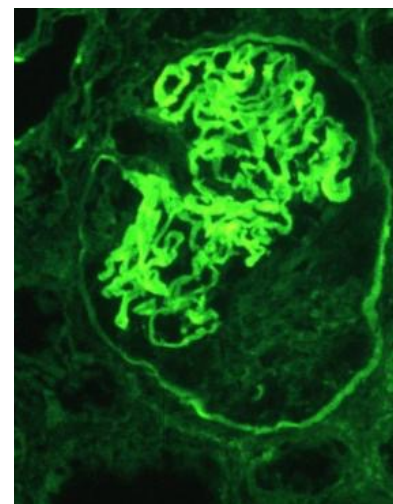


No good evidence-based practice

- Use of typical historical treatment for RPGN

Pulse intravenous methylprednisolone

- Most common therapy and included without supporting studies in KDIGO guideline

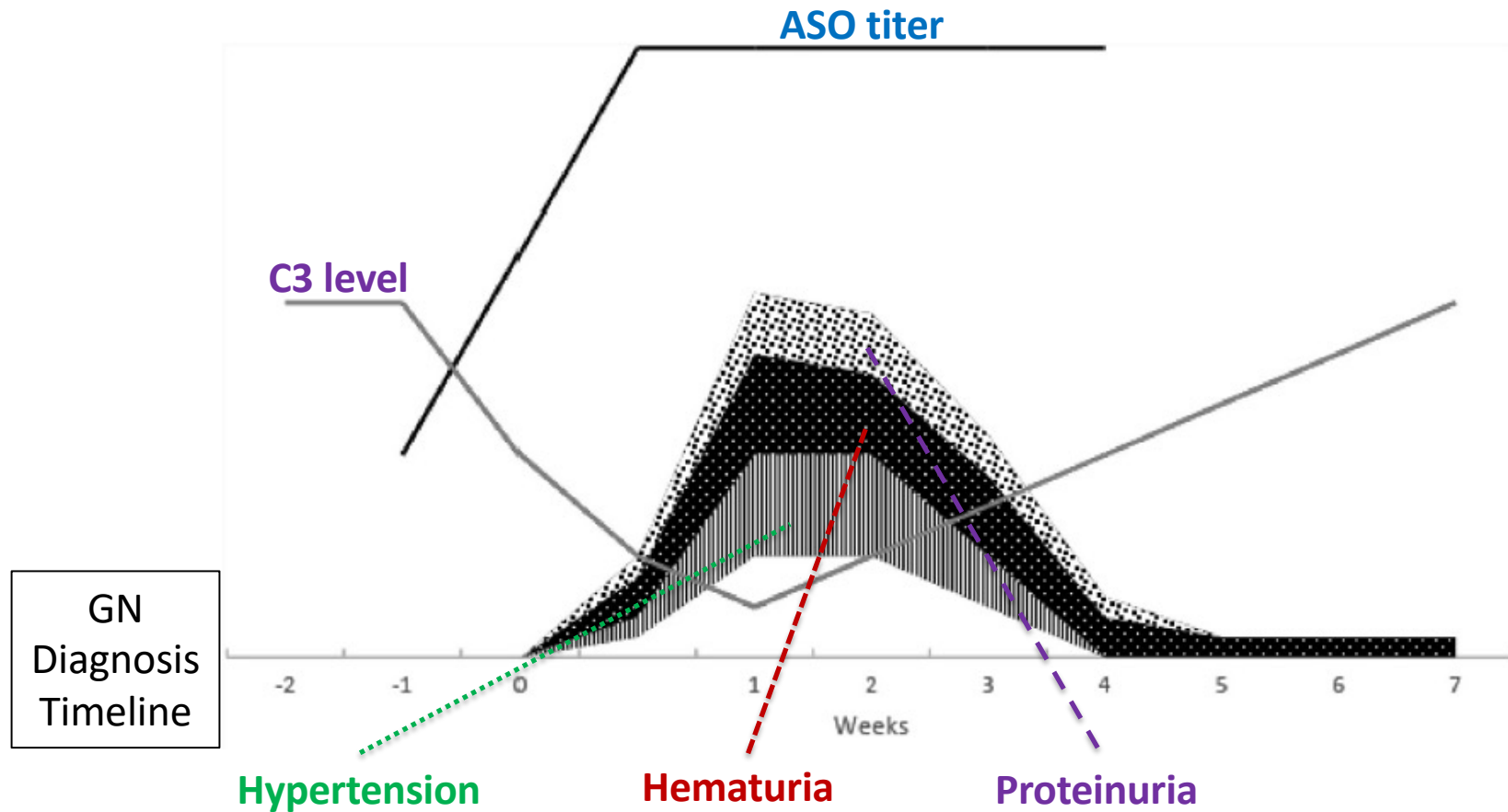


Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Clinical Course



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

General Clinical Expectations

Most clinical signs and symptoms resolve spontaneously and within weeks

Hypocomplementemia >3 months should raise concern for a chronic hypocomplementemic GN

Recurrent gross hematuria is common with new acute illness early after diagnosis

Recurrent APSGN is quite rare

ESKD from APSGN is uncommon



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Long-term Kidney Outcomes

Almost all affected children will have no clinical or laboratory residuals of nephritis by 1-2 years

As with any AKI episode, even if there is a full initial recovery, a predisposition to CKD exists

Chinese Cohort

110 children with 15-20 years of APSGN follow-up

- 7% proteinuria
- 5% hematuria
- 5% hypertension
- 1% decline in GFR/ESKD



**Surveillance of those
at high risk for
progression**



KEEP
CALM
AND
LOVE
YOUR
KIDNEYS



Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Next Webinars



ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **11 May 2021**

Speaker: **Savino Sciascia**

Topic: **TMA in Anti-phospholipid syndrome**

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

Date: **01 June 2021**

Speaker: **Marina Noris**

Topic: **Atypical Hemolytic Uremic Syndrome**

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

Date: **15 June 2021**

Speaker: **Rosa Vargas Poussou**

Topic: **Dent Disease**

Subscribe the ERKNet and IPNA Newsletter and don't miss Webinars!