Introduction to Glomerular disease

Dr H Bierman
• Glomerular disease ranges from asymptomatic hematuria and/or proteinuria to fulminant disease with AFR and extra-renal disease.

• Dramatic symptomatic presentations are uncommon.

• Asymptomatic urine abnormalities are common but not so specific – this may also indicate wide range of non-glomerular renal tract disease.
Clinical presentations of glomerular disease

Asymptomatic
Proteinuria 150 mg to 3 g per day
Hematuria > 2 red blood cells per high-power field in spun urine or > 10 x 10⁶ cells/L (red blood cells usually dysmorphic)

Macroscopic hematuria
Brown/red painless hematuria (no clot); typically coincides with intercurrent infection
Asymptomatic hematuria ± proteinuria between attacks

Nephrotic syndrome
Proteinuria: adult > 3.5 g/day; child > 40 mg/h per m²
Hypoalbuminemia < 3.5 g/dL
Edema
Hypercholesterolemia
Lipiduria

Nephritic syndrome
Oliguria
Hematuria: red cell casts
Proteinuria: usually < 3 g/day
Edema
Hypertension
Abrupt onset, usually self-limiting

Rapidly progressive glomerulonephritis
Renal failure over days/weeks
Proteinuria: usually < 3 g/day
Hematuria: red cell casts
Blood pressure often normal
May have other features of vasculitis

Chronic glomerulonephritis
Hypertension
Renal insufficiency
Proteinuria > 3 g/day
Shrunken smooth kidneys
Clinical evaluation of glomerular disease

- History
- Physical examination
- Laboratory studies
- Imaging
- Renal biopsy

The aim is to:
- exclude non-glomerular disease,
- finding evidence of associated multisystem disease,
- establishing glomerular function
Glomerular Disease: History

- **Family history** – hearing loss (Alport); familial IgA nephropathy, FSGS, HUS.

- **Drugs and toxins** – NSAIDS and IF (Minimal change disease), membranous nephropathy (gold, NSAIDS, Hg in skin lightning creams), FSGS (heroin) or HUS (cyclosporin, tacrolimus, oral contraceptive).

- **Recent or persistent infection** – streptococcal, IE, viral.

- **Malignancies** – lung, breast, GIT (membranous); non-Hodgkins (MPGN); renal carcinoma (amyloid). Occasionally first manifestation of malignancy.

- **Multisystem disease**: Diabetes, amyloid, lupus, vasculitis.
Physical examination:

• Dependent pitting edema – nephrotic syndrome, CCF or cirrhosis. Often peri-orbital edema in morning in nephrotic syndrome.

• Edema of abdominal wall and dependent areas like genitals, pleural effusions and ascitis

• > 20% increase in body weight due to fluid accumulation not uncommon
Physical examination:

- Pulmonary signs – think of pulmonary renal syndrome
- Palpable purpura – vasculitis, SLE, cryoglobulinemia, endocarditis
- Low albumin – white nails or white bands (Muercke’s bands)
Laboratory studies:

- Renal function
- Careful examination of urine
- Amount of proteinuria
- Presence or absence of dysmorphic RBC’s and casts
- Serology: ASOT, ANF, anti-dsDNA Ab’s, cryoglobulins and RF, anti-GBM Ab’s, ANCA
- Serum and urine electrophoresis
- Blood cultures, hep B, C HIV
- Complement C3, C4, CH50 (50% hemolyzing dose of complement)
Imaging:

- U/S: ensure 2 kidney’s present, obstruction, anatomical abnormalities, kidney size.
- Renal size usually normal in GN but can be large (>14cm) in nephrotic syndrome associated with DM, HIV, amyloid or acute severe GN.
- Small kidney’s (<9cm) suggest chronic renal disease and should limit enthusiasm for renal biopsy or aggressive immunosuppressive therapy.
Renal biopsy:

- Establish type of renal disease and guide therapy
- In children with typical nephrotic syndrome usually no biopsy initially – minimal change disease most common diagnosis
- In typical post Strep GN esp in epidemic biopsy usually not needed unless poor treatment response
- Anti-GBM GN with pulmonary hemorrhage and high anti-body titres biopsy not needed unless need for prognostic info.
- ANCA with biopsy at other site confirming vasculitis – can withhold biopsy.
- Long standing diabetics with characteristic findings of diabetic nephropathy
- Mild disease – biopsy sometimes not indicated when prognosis good
Asymptomatic urine abnormalities

- Increase with age
- Mostly found coincidently during routine medical examinations
- No evidence for routine population wide screening of urine – renal biopsy and/or therapeutic intervention rarely required if renal function is normal
Asymptomatic microscopic hematuria

- > 2 RBC’s per HPF
- Common in glomerular disease esp IgA nephropathy and thin membrane disease
- Glomerular origin should be thought of if red cells are dysmorphic, RBC casts are present or proteinuria are present.
Asymptomatic microscopic hematuria: evaluation

- U-MC+S to exclude UTI and prostatitis
- Renal imaging to exclude anatomic lesions like PCK, stones, tumor, AV-malformations
- Proteinuria or decreased GFR – suggest glomerular disease
- Sickle cell screen inappropriate populations
- TB
- Serum and urine calcium and uric acid – calcium and uric acid crystals
- Over 40 yrs – always cystoscopy to exclude uroepithelial malignancy
Asymptomatic microscopic hematuria: evaluation

- If all negative glomerular origin in form of IgA nephropathy and thin membrane disease is the most common at any age
- Biopsy will confirm diagnosis but with normal renal function in asymptomatic patient and low-grade proteinuria < 0.5 g/day not needed
- Repeat evaluation every 12 months however needed for rare cases of progression
Asymptomatic non-nephrotic proteinuria

- Hallmark of glomerular disease – proteinuria
- Normal = 150mg protein/24hr
  (20-30mg albumin, 10-20 mg LMW protein freely filtered, 40-60 mg secreted protein like Tamm-Horfall protein and IgA)
- Microalbuminuria = 30-300mg albumin/24 hr – used to detect diabetics at risk fro diabetic nephropathy
- Non-nephrotic proteinuria = < 3.5 g/24 hrs or protein:creat ratio of < 3, not specific for glomerular disease
Asymptomatic non-nephrotic proteinuria

- Selectivity of proteinuria – ratio of IgG to albumin. If highly selective (ratio <10%) is typical of minimal change disease (loss of glom charge barrier but intact glom size barrier).
- In non-selective proteinuria - loss of size and charge barriers is more common.
- Routine testing for protein selectivity is not done.
- Proteinuria can result from increased glomerular permeability or tubulointerstitial disease – but not result in nephrotic syndrome.
- Also increased filtration through normal glomeruli – overflow proteinuria.
Overflow proteinuria

- Typical of urinary light chain excretion
- Myeloma
- Release of lysozyme by leukemic cells
- Negative dipstick for protein but large amount by other tests
Tubular proteinuria

- Tubular interstitial disease - < 2g/d
- Tubular protein – b2-microglobulin and some albumin due to impaired reabsorption of filtered protein
Glomerular proteinuria

1. Functional proteinuria
   - Transient non-nephrotic proteinuria with fever, exercise, CCF, hyperadrenergic or hyper-reninemic states.
   - Is benign
   - Due to increased single nephron flow/pressure

1. Orthostatic proteinuria
   - Children and young adults low grade glom proteinuria may be orthostatic.
   - No protein in first morning sample.
   - < 1g/24 hrs
   - Pathogenesis unknown
   - Biopsy not indicated
Glomerular proteinuria

3. Fixed non-nephrotic proteinuria

- Usually glomerular disease
- If normal GFR benefit of biopsy controversial
- Prolonged follow-up justified as long as proteinuria persists
- Same pathology as with nephrotic syndrome but milder like MPGN without immune deposits.
- Normal light microscopy with only effaced foot processes on EM common. Looks like minimal change but not steroid responsive. No treatment needed.
Asymptomatic proteinuria with hematuria

- Much greater risk for significant glomerular injury, hypertension, progressive renal dysfunction.
- Minor changes on histology less common
- Renal biopsy indicated even if proteinuria between 0.5 and 1 gram/24 hrs if microscopic hematuria present.
Evaluation of isolated asymptomatic proteinuria

Asymptomatic proteinuria

Quantitate protein excretion
Measure glomerular filtration rate (GFR)

Normal GFR
Non-nephrotic proteinuria

Recumbent overnight

Orthostatic proteinuria
No further action

Reduced GFR

Dipstick negative

Serologic tests
Ultrasound

Renal biopsy

Persistent fixed proteinuria

Reassess at 6-12 months
Urine protein
GFR
Blood pressure

If GFR or BP abnormal, if proteinuria increases

If normal GFR and BP persists: reassess annually

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Macroscopic hematuria

- Episodic painless macroscopic hematuria associated with glom disease is often brown “smoky” rather than red
- Clots are unusual
- Exclude other causes of red/brown urine: hemoglobinuria, myoglobinuria, food dyes (beetroot)
- Macroscopic hematuria due to glom disease mainly seen in children and young adults and rarely over 40
Macroscopic hematuria

- Requires urological evaluation including cystoscopy unless history typical of glomerular disease
- IgA nephropathy most common but can occur with many other glomerular and non-glomerular diseases including acute interstitial nephritis
- Usually painless and loin-pain suggests other pathology like stones
Macroscopic hematuria

• IgA nephropathy – hematuria usually episodic occurring within a day of upper resp infection (synpharyngitic)

• Clear distinction between this history and the 2-3 week latency between infection and post strep GN

• Post strep GN usually also has other features of nephritic syndrome
Nephrotic syndrome

- Nephrotic syndrome is pathogenomic of glomerular disease.
Asymptomatic
- Proteinuria 150 mg to 3 g per day
- Hematuria > 2 red blood cells per high-power field in spun urine or > 10 x 10^6 cells/L (blood cells usually dysmorphic)

Nephrotic syndrome
- Proteinuria: adult > 3.5 g/day; child > 40 mg/h per m^2
- Hypoalbuminemia < 3.5 g/dL
- Edema
- Hypercholesterolemia
- Lipiduria

Rapidly progressive glomerulonephritis
- Renal failure over days/weeks
- Proteinuria: usually < 3 g/day
- Hematuria: red cell casts
- Blood pressure often normal
- May have other features of vasculitis
Nephrotic syndrome

- Renal function can be normal but in many cases renal function progressively decline if left untreated.
- Nephrotic syndrome negatively affects renal function but also has metabolic effects leading to poor health.
- Disease can be self limiting or respond completely to treatment (minimal change disease).
- For most patients it is a chronic condition.
- Not all patients with >3.5g/24 hrs have the full syndrome and their serum albumin can be normal; this is due to varied protein metabolism and production between patients.
# Nephrotic syndrome: Etiology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associations</th>
<th>Serologic tests helpful in diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease</td>
<td>Allergy, atopy, NSAIDs, Hodgkin's disease</td>
<td>None</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>African Americans</td>
<td>HIV antibody</td>
</tr>
<tr>
<td></td>
<td>HIV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heroin</td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Drugs: gold, penicillamine, NSAIDs</td>
<td>Hepatitis B surface antigen, anti-HCV antibody</td>
</tr>
<tr>
<td></td>
<td>Infections: hepatitis B, C; malaria</td>
<td>Anti-DNA antibody</td>
</tr>
<tr>
<td></td>
<td>Lupus nephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignancy: breast, lung, gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis (Type I)</td>
<td>C4 nephritic factor</td>
<td>C3 ↓, C4 ↓</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis (Type II)</td>
<td>C3 nephritic factor</td>
<td>C3 ↓, C4 normal</td>
</tr>
<tr>
<td>Cryoglobulinemic MPGN</td>
<td>Hepatitis C</td>
<td>Anti-HCV antibody, rheumatoid factor, C3 ↓, C4 ↓, CH50 ↓</td>
</tr>
<tr>
<td>Amyloid</td>
<td>Myeloma</td>
<td>Serum protein electrophoresis, urine immunoelectrophoresis</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Other diabetic microangiopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

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Nephrotic syndrome: Etiology

- Nephrotic range proteinuria without low albumin and edema has the similar etiologies.
- Although predominant in childhood, minimal change disease remains common at all ages. Increased prevalence of FSGS in African Americans.
- FSGS is becoming more common and MPGN less common.
## Age-related variations in nephrotic syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease</td>
<td>78</td>
<td>23</td>
<td>15</td>
<td>21</td>
<td>16</td>
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<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>8</td>
<td>19</td>
<td>55</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>2</td>
<td>24</td>
<td>26</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis (MPGN)</td>
<td>6</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Other glomerulonephritis</td>
<td>6</td>
<td>14</td>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Amyloid</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

Data adapted from Haas et al.\(^6\) and Cameron\(^5\).

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Nephrotic syndrome: Hypoalbuminemia

- The result of:
  1. Urinary losses
  2. Increased reabsorption and catabolism by tubular cells in proximal tubuli
  3. Increased synthesis by liver is blunted by nephrotic syndrome

- Increased protein intake does not improve protein metabolism – the hemodynamic response is increased glomerular pressure, increasing protein losses.
Nephrotic syndrome: Hypoalbuminemia

- Consequence: fall in serum albumin.
- Increased protein synthesis in response to renal losses is non-discriminatory – proteins not lost may actually increase.
- Determined by molecular weight – the larger the molecule, the less likely it will be lost through kidney – increased plasma levels the result.
- This leads specifically to hypercoagulability and hyperlipidemia.
Nephrotic syndrome: Edema
Formation of nephrotic edema

**Underfill**
- Proteinuria
  - Hypoalbuminemia
  - Plasma colloid oncotic pressure ↓
    - Starling forces
    - Reduced plasma volume
      - Vasopressin ↑
      - Atrial natriuretic peptide (ANP) normal/low
      - Renin–angiotensin system activated
      - Aldosterone ↑
      - Water retention
      - Sodium retention
      - Edema

**Overfill**
- Primary tubular defect causing sodium retention
  - Normal/raised plasma volume
    - Vasopressin normal
    - ANP ↑
    - Aldosterone ↓

*The kidney is relatively resistant to ANP in this setting, so it has little effect in countering sodium retention*
Metabolic consequences of nephrotic syndrome:

1. Negative nitrogen balance
2. Hypercoagulability
3. Hyperlipidemia and lipiduria
4. Endocrine
Metabolic consequences of nephrotic syndrome: negative nitrogen balance

- Measured by low S-albumin
- Wasting illness – muscle wasting masked by edema
- Loss of 10-20% of lean body mass common
- Albumin turnover increased by tubular catabolism of filtered protein rather than merely protein loss.
- Increased intake increases synthesis but also loss and aggravates disease.
- Low protein diet reduce proteinuria but in long run can worsen negative nitrogen balance.
Metabolic consequences of nephrotic syndrome: Hypercoagulability

Coagulation abnormalities in nephrotic syndrome

- **Coagulation proteins**
  - Raised: fibrinogen, factors V, VII, von Willebrand factor, protein C, α2-macroglubulin
  - Unchanged/reduced: prothrombin factors IX, X, XI, XII, antithrombin III

- **Hepatic synthesis ↑**
- **Urine clearance ↑**
- **Platelet aggregability ↑**

- **Hypertension**
- **Accelerated atherosclerosis**

- **Volume contraction**
  - Hemococoncentration

- **Immobility**

- **Arterial thrombosis**
- **Venous thromboembolism**

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Metabolic consequences of nephrotic syndrome: Hypercoagulability

- Altered levels of coagulation factors and altered platelet function
- Netto result = hypercoagulable state aggravated by:
  1. Immobility
  2. Infection
  3. Hemoconcentration
Metabolic consequences of nephrotic syndrome: Hypercoagulability

- Venous thrombosis and embolism is common as well as arterial thrombosis.
- 10% of adults and 2% of children will have thrombotic event.
- Increased fibrinogen causes increased ESR – levels of >100 not uncommon – ESR loses its clinical value as marker of acute phase response.
Metabolic consequences of nephrotic syndrome: Hypercoagulability

- Renal vein thrombosis (RVT) is an NB complication of nephrotic syndrome.
- Occurs in 8% of nephrotic individuals but if sought for specifically the prevalence increases to 10-50%.
- Acute RV-thrombosis symptoms – flank pain, hematuria, ARF (if bilateral).
- More often develops slowly and asymptomatic.
- RVT should not be screened for routinely.
- Pulmonary embolism = NB complication.
Hyperlipidemia and lipiduria
Lipid abnormalities in nephrotic syndrome

Circulating lipids

- VLDL deposition in vascular tissues ↑
- Catabolism ↓ Endothelial lipoprotein lipase ↓
- Oxidized LDL ↑
- Atherogenicity ↑
- Urine clearance of smaller HDL3
- Cholesterol removal from tissue to liver impaired
- Atherogenicity ↑

VLDL, very-low-density lipoproteins
HDL, high-density lipoproteins
IDL, intermediate-density lipoproteins

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Hyperlipidemia and lipiduria

- Integral part of nephrotic syndrome.
- Clinical stigmata like xanthelasma may have rapid onset.
Hyperlipidemia and lipiduria

- Levels of s-cholesterol > 13 is common.
- Highly atherogenic lipid profile.
- 5-fold increase in coronary risk – except minimal change disease patients (short duration of illness).
- Contribute to progressive renal disease – lipid deposition in glomeruli and interstitium.
- Protection against CVS risk and renal risk via statins. May slow progression of renal disease.
Hyperlipidemia and lipiduria

- Lipiduria – refractile accumulation of lipid in cellular debris and casts (oval fat bodies and fatty casts).
- This is a consequence of proteinuria and not plasma lipid abnormalities.
Endocrine and other effects of nephrotic syndrome: Vitamin D

- Loss of Vit D binding protein – low plasma 25-OHvitD.
- Free Vit D usually normal and overt osteomalasia or uncontrolled hyperparathyroidism is very unusual unless renal failure present.
Endocrine and other effects of nephrotic syndrome: thyroid

- Loss of thyroid binding globulin – reduced total circulating thyroxine. Normal free thyroxine and TSH.
- No clinical alteration in thyroid status.
- Occasional cases of copper, iron, or zinc deficiency have been described due to loss of binding proteins.
Endocrine and other effects of nephrotic syndrome

- Drug binding might be altered by decreased albumin.
- Most drugs don’t need dose adjustments except clofibrate which can cause severe myopathy in nephrotic patients at normal dosages.
- Altered protein binding may change dosage of warfarin required for adequate anticoagulation.
Nephrotic syndrome: infection

- Prone to bacterial infection
- Before steroids sepsis was major cause of death in nephrotic children; still problem in developing world
- Primary peritonitis caused by pneumococci is characteristic of nephrotic children
- Over age 20 most people have antibodies against pneumococci capsular Ag therefore less common after this age
- Also streptococci and gram negative bacilli (not staphylococcus)
Endocrine and other effects of nephrotic syndrome

• Cellulitis in areas of severe edema is common – B-hemolytic streptoccci

• Explanation for increased infection risks:
  1. Large fluid collections – bacteria grow easily
  2. Nephrotic skin is fragile – site of entry
  3. Edema dilute local humoral immune factors
  4. Loss of IgG and complement factor B (of alternative pathway) in urine – loss of ability to eliminate encapsulated organisms such as pneumococci
  5. Zn and fe lost – needed for normal lymphocyte function
  6. Polymorph and T-cell dysfunction are also present
Acute and chronic changes in renal function in nephrotic syndrome:
Acute renal failure
## Acute Renal Failure

### Acute renal failure in nephrotic syndrome

- Pre-renal failure due to volume depletion
- Acute tubular necrosis due to volume depletion and/or sepsis
- Intrarenal edema
- Renal vein thrombosis
- Transformation of underlying glomerular disease, e.g., crescentic change superimposed on membranous nephropathy
- Adverse effects of drug therapy
  - Acute allergic interstitial nephritis secondary to various drugs, including diuretics
  - Hemodynamic response to NSAIDs and ACE inhibitors
Chronic Renal Failure

- With exception of minimal change disease most cases are at risk of progressive renal failure
- Degree of proteinuria one of biggest risk factors for progression
- Risk less if < 2g/day and increases in proportion to degree of proteinuria
- Marked risk if > 5g/day
- Because proteinuria identifies severe glomerular disease and causes renal damage *per se* via toxic interstitial nephritis
- Measures that reduce proteinuria reduce disease progression – ACE inhibitors
In nephrotic syndrome the glomerular injury manifests as increased capillary permeability to protein.

By contrast – in nephritic syndrome there is evidence of glomerular inflammation with:

1. Reduced GFR
2. Non-nephrotic proteinuria
3. Edema
4. Hypertension (secondary to sodium retention)
5. Hematuria with RBC casts
Nephritic syndrome

• Classical presentation seen in acute post-streptococcal GN in children
• Rapid onset over a few days of:
  1. Oliguria
  2. Weight gain
  3. Generalized edema
  4. Brown urine with no clots
  5. Urine with protein, RBC’s and RBC casts
  6. Serum albumin is normal – rarely nephrotic range proteinuria
  7. Increased circulating volume with hypertension and pulmonary edema without signs of cardiac disease
### Differentiation between nephrotic syndrome and nephritic syndrome

<table>
<thead>
<tr>
<th>Typical features</th>
<th>Nephrotic</th>
<th>Nephritic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Insidious</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Edema</td>
<td>++ + + +</td>
<td>++</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Raised</td>
</tr>
<tr>
<td>Jugular venous pressure</td>
<td>Normal/low</td>
<td>Raised</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>++ + + +</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>May/may not occur</td>
<td>+++</td>
</tr>
<tr>
<td>Red-cell casts</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Low</td>
<td>Normal/slightly reduced</td>
</tr>
</tbody>
</table>
Nephritic syndrome

- This differentiation is usually straightforward but can overlap esp in MPGN
### Nephritic syndrome: Etiology

<table>
<thead>
<tr>
<th>Common glomerular diseases presenting as nephritic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
</tr>
<tr>
<td>Other postinfectious disease</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Abscess</td>
</tr>
<tr>
<td>'Shunt'</td>
</tr>
<tr>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>Systemic lupus</td>
</tr>
</tbody>
</table>
Nephritic syndrome: RPGN

- Glomerular injury is so severe that renal function deteriorates over days or weeks.
- Patient may present as uremic emergency with progressive disease and renal failure or develop renal failure while being investigated for extra-renal disease associated with GN.
- Histology in RPGN is Crescentic GN: proliferative cellular response outside glomerular tuft but inside Bowman’s space known as crescent because of its shape on cross section.
# RPGN: Etiology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Association</th>
<th>Serologic tests helpful in diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodpasture’s disease</td>
<td>Lung hemorrhage</td>
<td>Antiglomerular basement membrane (anti-GBM) antibody (occasionally antineutrophil cytoplasmic antibodies (ANCA) present)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Upper and lower respiratory involvement</td>
<td>cANCA (cytoplasmic)</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Multisystem involvement</td>
<td>pANCA (perinuclear)</td>
</tr>
<tr>
<td>Pauci-immune crescentic glomerulonephritis</td>
<td>Renal involvement only</td>
<td>pANCA</td>
</tr>
<tr>
<td>‘Immune complex’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Other multisystem features of lupus</td>
<td>Antinuclear antibody, anti-double stranded DNA antibody, C3 ↓, C4 ↓</td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Pharyngitis, impetigo</td>
<td>Asotiter, streptozyme antibody, C3 ↓, C4 normal</td>
</tr>
<tr>
<td>IgA nephropathy/Henoch–Schönlein purpura (HSP)</td>
<td>Characteristic rash ± abdominal pain in HSP</td>
<td>Serum IgA ↑ (30%), C3 and C4 normal</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Cardiac murmur; other systemic features of bacteremia</td>
<td>Blood cultures, ANCA (occasionally) C3 ↓, C4 normal</td>
</tr>
</tbody>
</table>

Note the overlap between the diseases in this figure and those in Table 19.5. A number of glomerular disease may present with either a nephritic syndrome or with RPGN.
Treatment of glomerular disease

• General supportive
  1. Reduce proteinuria
  2. Control edema
  3. Treat blood pressure
  4. Treat metabolic consequences

• Disease specific
  1. Immunosuppressive therapy
  2. Plasma exchange
  3. Adequate treatment of infection to eliminate persistent presence of AG
Treatment of nephrotic edema

• Before the days of diuretics small tubes were inserted under the skin via needles and the patient stood in drum while fluid seeps out. Not very SATISFACTORY!
Treatment of nephrotic edema

• MAINSTAY of treatment is moderate sodium restriction (60-80 mmol/24hrs) together with diuretics
• Hypovolemia usually not a problem provided fluid removal is gradual and controlled
• Weigh patient daily to measure progress
• Children – be cautious – more prone to hypovolemic shock
Treatment of nephrotic edema

• Nephrotic patients are resistant to diuretics:
  1. Loop diuretics must reach tubuli to be effective
  2. Transport from peritubular capillaries requires protein binding which is reduced in hypoalbuminemia
  3. Once in renal tubuli 70% binds to protein in urine and is excreted and lost

• Oral diuretics are preferred – effect is dependent on AUC which is greater for oral drugs

• In severe nephrosis reduced GIT absorption due to GIT edema – then rather IV infusion

• Remove $\leq 2$ kg/day – move on to next class of diuretic to achieve this goal
Management of edema in nephrotic syndrome

Oral loop diuretic
- e.g., Furosemide 40 mg bd
- Bumetanide 1 mg bid
  - No response

Double dose until diuresis
OR
Ceiling dose reached
- Furosemide 250 mg bid
- Bumetanide 5 mg bid
  - No response

Reduce stepwise to maintenance dose as diuresis continues

Add: Oral thiazide
- e.g., Hydrochlorothiazide 50 mg bd
- Metolazone 2.5–5 mg daily
  - No response

Change loop diuretic to IV bolus bid
  - No response

Add: 20% human albumin
50–100 mL IV followed by IV bolus diuretic
  - No response

Mechanical ultrafiltration

*Spironolactone is less effective in nephrotic syndrome than in cirrhosis and is often poorly tolerated because of gastrointestinal side effects

Monitor serum K+
If hypokalemia:
Add: K supplements
OR: Amiloride 5–20 mg daily
OR: Spironolactone 50–200 mg daily*
Treatment of proteinuria

- Benefits of reducing proteinuria:
  1. If reduced below nephrotic range serum proteins normalize reversing metabolic consequences
  2. Reduced renal impairment progression – ACE inhibition reduced intra-renal hypertension (seen in renal impairment)
  3. Proteinuria is toxic to tubulo-interstitium
  4. If proteinuria can be reduced with less toxic therapy less need for more disease specific treatment which could have other negative effects
Treatment of proteinuria

• Agents reducing proteinuria do so hemodynamically:
  1. Reducing afferent arteriolar dilatation (NSAID’s, low-protein diet, dipyridamole)
  2. Blocking efferent arteriolar constriction (ACE, ARB, direct renin inhibitors)
  3. ACE inhibitors also reduce increased glomerular capillary wall permeability

• This therapy reduce the GFR – reduction in GFR is however generally less than reduction in proteinuria
Treatment of proteinuria

- ACE-inhibitors most commonly used – reduce proteinuria 40-50%, esp. if patient on salt restricted diet
- Anti-Hpt drugs will reduce proteinuria in relation to drop in systolic BP but ACE/ARM’s do so independently of BP
- ACE and ARB’s have additive effect in reducing proteinuria (ON TARGET)
Treatment of proteinuria

• Therapy less commonly used:

1. NSAID’s (reduce intra-renal PG synthesis – chemical nephrectomy)

2. Dipyridamole (adenosine mediated afferent arteriolar vasoconstriction)

• Caution: ACE and NSAID can cause severe drop in GFR with ARF. ACE – hyperkalemia, NSAIDS – salt retention and diuretic resistance.
Treatment of proteinuria

• Low protein diet will reduce proteinuria – caution – can induce malnutrition

• In rare cases where nephrotic syndrome is so severe that patient is dying of its complications one needs to resort to nephrectomy – usually chemically by NSAID/ACE. Reduce proteinuria by removing residual GFR.

• Bilateral renal artery embolization can be done if above not adequate.

• Bilateral nephrectomy – significant peri-operative mortality
Correction of hypo-proteinemia

- Difficult to increase protein intake to maintain positive protein balance – patients usually have anorexia and easy satiety due to gut edema and ascites.
- Sustained high protein intake may be detrimental to renal function.
- Low protein diet reduce proteinuria and may improve serum protein but take care to avoid malnutrition – YOU NEED A DIETICIAN EXPERIENCE IN RENAL PATIENT CARE.
- (0.8 – 1 mg/kg/d) with high carbohydrate intake to maximize protein utilization.
Treatment of hypercoagulability

- Increased risk when albumin falls below 20
- Immobility and undercurrent illness aggravates the risk
- Analysis suggest benefit to anti-coagulate long term as long as albumin is below 20
- Anti-coagulate during hospitalization – prophylactic dosages
- Once thrombotic event occurs long term anti-coagulation for 6-12 months or longer should albumin not recover
Treatment of hypercoagulability

- Higher dosages of heparin may be needed – dependent on anti-thrombin III which is reduced in nephrotic syndrome
- Warfarin for long term anti-coagulation – careful – altered protein binding may reduce dose needed to achieve INR of 2-3
- Acute renal vain thrombosis may try thrombolytic therapy of embolectomy (surgical) – not convincing evidence that it improves renal survival long term
Treatment of hyperlipidemia

- Not direct evidence that nephrotic syndrome and hyperlipidemia increase CVS risk, extrapolation of evidence suggest benefit in treating hyperlipidemia
- Diet restriction only modest effect
- Statins reduce LDL and some may increase HDL and reduce Tgl
- Fibrates unacceptable myositis risk
- Bile acid sequestrants (cholestyramine) may lower LDL further and increase HDL but usually not tolerated due to GIT side affects
- Second line treatment = probucol, newer fibrates (closely monitor for muscle injury)
- Conventional dosing
Infection

- High index of suspicion
- Spontaneous bacterial peritonitis is common – ascites should be tested and cultured if suspicion of systemic infection
- Bacteremia is common even if signs are localized (cellulitis ex)
- ESR of little value (raised in Nephrotic syndrome)
- Raised CRP and PCT of value
- IV antibiotics stated as soon as cultures are taken (should include penicillin (pneumococci))
- With recurrent infections and IgG less than 600mg/dL – some proof to give monthly IV Ig 10-15g to keep levels > 600
Hypertension

- Common in GN
- Universal as chronic GN progress to end-stage renal disease
- Sodium and water retention NB and high-dose diuretic with dietary salt restriction is essential part of treatment
- Aim of treatment is to reduce CVS risk and renal disease progression
- MDRD study – patients with >1g proteinuria do better with BP <125/75
- ACE-inhibitors/ARB’s = first choice
- Non-dihyropyridine calcium channel blockers also reduce proteinuria and BP
Disease specific therapy

General principles:

• Most glomerular diseases has immune pathogenesis – treatment aimed at suppressing systemic and local immune responses

• Where foreign antigen is ineffectively removed treatment aimed at eliminating it ex. IE (antibiotics), IF-alpha (cryoglobulinemia ass with Hep C)

• The more severe and acute the GN the more successful the immunosuppression

• Little success with chronic GN
Disease specific therapy

• With rapid deteriorating RF the toxicity of drugs acceptable for short period – “little to loose”
• Treatment is not specific and suppress immunity globally
• Mainstay of treatment:
  1. Steroids
  2. Azathioprine
  3. Cyclophosphamide
Disease specific therapy

- Cyclosporine no proven place in GN but established in transplant
- Mycophenolate Mofetil newer anti-metabolite emerging as new agent in GN especially lupus
- Cancer risk with immunosuppression
- Time of exposure limited to as short as possible
That’s it