Chronic Renal Failure

History of Presenting Illness

Earliest:
- LETHARGY
- FATIGUE
- OEDEMA
- NOCTURIA
- ANOREXIA
- NAUSEA
- VOMITING
- INFECTIONS
- THROMBI

Latest:
- CONFUSION
- DEMENTIA
- COMA

Most patients present with:
- heavy proteinuria,
- most commonly in the nephrotic range
- insidious in onset.

Differential Diagnoses
- Acute renal failure
- Liver failure
- Congestive heart failure
- Hyperparathyroidism
- Inherited Clotting disorder
- Gastrointestinal malignancy
- Acute glomerulonephritis
- Central Nervous System Lesion

Past History

Want to know about:
- LUPUS, and autoimmune disease in general
- Hypertension
- History of renal disease in family
- CHEST PAIN
- EASY BRUISING
- Recent Fractures
- Shortness of Breath
- Ankle Swelling
- Frequency of Nocturia
- ? hematuria
- frothy urine
- Itching/scratching
- Cognitive decline
- RECENT ILNNESSES (screen for post-strep GN)

Examination

Want to look for:
- Uremic complexion
- Oedema + ascites
- Bruising / ecchymoses
- Infected dialysis fistula
- Anaemia
- Pericarditis
- Bony tenderness
- Neuropathy
- Subcutaneous Ca++ nodules
- Scratch marks
- Kussmaul breathing
- Hydration status

Drugs of particular importance:
- analgesics
- NSAIDs
- gold,
- penicillamine,
- vancomycin,
- lithium,
- ACE inhibitors

Questions about uremia:
- Appetite
- Nausea/vomiting
- SOB
- Oedema
- Weight change
- Muscle cramps
- Bone pain
- Easy bruising
- Mental acuity
- Decreased libido
- Erectile dysfunction
- ADLs
Tests and Investigations: ITS ALL ABOUT THE URINE

URINALYSIS is FIRST!!
→ DIPSTICK (for suspicion)
→ URINE MICROSCOPY for confirmation
→ URINE BIOCHEMISTRY to supplement serum biochemistry:
try to work out what is getting filtered and what is not.

PROTEINURIA = PARENCHYMAL DISEASE

NORMALLY:
Low molecular weight proteins are reabsorbed at the proximal tubule
Some escapes: <150 mg./day
Normal urine contains up to 30 mg of albumin

PROTEINURIA on DIPSTICK ANALYSIS:
= concentration of about 300 mg/L.

SELECTIVE Proteinuria
= you must be >this tall< to enter
Eg. only a certain size of protein is being lost
= this means damage to the glomerulus is mild

HEMURATURIA ALONE = TRACT PROBLEM

NORMALLY:
No more than 5 million RBCs per litre
VISUALLY:
Naked eye can see 5 billion RBCs per L
DIPSTICK TEST:
Sensitive up to 5 million RBCs
MICROSCOPY:
Sensitive up to 0.5 million RBCs
Dysmorphic tattered RBCs = origin of bleed is in the renal parenchyma

Must differentiate:
IS IT RED BECAUSE OF BLOOD?
IS THERE AN ALTERNATIVE SOURCE eg. menses?...

~SPECTRUM OF URINARY SEDIMENT~

NPHROTIC
- proteinuria,
- hypoalbuminaemia,
- oedema

NPHRITIC
- proteinuria,
- hematuria
- hypoalbuminaemia,
- oedema

Non-proliferative glomerular disease
Eg. membranous
Minimal change disease

Proliferative glomerular disease
Eg. mesangial IgA
post-strep GN

PROTEINURIA alone
Hemoproteinuria
HEMURATURIA alone

FBC: looking for
- increased WCC(inflam. process)
- normocytic normochromic anaemia

Kidney Ultrasonography + BIOPSY
looking for
- small diseased fibrotic kidneys (to prove its chronic failure, not acute)
- is it worthwhile to do a biopsy? In late stage renal failure all aetiologies look the same

Contraindications to renal biopsy include
- bilateral small kidneys,
- polycystic kidney disease,
- uncontrolled hypertension
- urinary tract or perinephric infection,
- bleeding diathesis,
- respiratory distress,
- and morbid obesity.

**Diffuse** (all glomeruli) vs. **focal** (only some glomeruli, maybe under 80%)

**Global** (entire glomerulus) vs. **segmental** (a part of a glomerulus)

(Global diseases are usually diffuse, and segmental diseases are usually focal. Unless otherwise specified, the diseases we will describe today are usually diffuse.)

* **Hyalinosis** (*fibrinoid*): deposits of plasma proteins. (This stuff doesn’t stain blue with *trichrome* or black with "silver", distinguishing it from fibrosis and sclerosis respectively.)

**Sclerosis**: enough increase in basement membrane - mesangial matrix material to compromise the lumens of capillaries. (The distinguishing feature is that this stains positive with silver.)

**Fibrosis**: type I collagen, i.e., an organized scar. (Blue on "trichrome". Unlike hyalinosis and sclerosis, this is essentially PAS-negative.)

---

**Diffuse Proliferative Glomerulonephritis**

- Large, irregularly spaced subepithelial deposits
- Endothelial cell edema
- Neutrophils
- Some cellular proliferation leading to the appearance of hypercellularity on H&E
- Coarse granularity ("lumpy-bumpy")

*Usually nephritic syndrome*

---

**Anti-GBM Disease** (Goodpasture’s, etc.)

- Do not expect to see any immune deposits, or any specific changes, on electron microscopy.
- Goodpasture’s means there is also anti-basement membrane disease of the lung (thoroscopy).

*Experimental: Masugi nephritis*

*Usually rapidly progressive glomerulonephritis*

---

**Mesangial Glomerulonephritis**

- Deposits primarily in the mesangium, with some proliferation of the mesangial cells.
- Most often IgA is the major immunoglobulin.
- Mesangial pattern (*tree in winter*)

*Usually asymptomatic hematuria*

---

**Minimal Change Disease**

- Usually idiopathic.
- Reveal kid’s disease.
- Foot processes are fused/obliterated.
- No immune deposits.

*Nephrotic syndrome: Expect selective proteinuria*

---

**Membranoproliferative GN Type II**

- The split GBM presents "tram tracks."
- The "dense deposit" is a broad band with C3 but usually no Ig.

*Detect Deposits: Worms C3 stain only

*Usually nephritic-nephrotic*

---

**Rapidly-Progressive Glomerulonephritis... Etiologies**

- **RPGN I**: Anti-GBM disease
  - Goodpasture’s, etc.
- **RPGN II**: Immune complex disease
  - Post-strep, very bad lupus, etc., etc.
- **RPGN III**: Vasculitis
  - Wegener’s, polyarteritis nodosa
  - Look for segmental necrosis

---

**Focal-Segmental Glomerulosclerosis**

- "Sclerosis" means extra mesangial matrix and thickened GBM’s obliterate the loops.
- Foot processes are always obliterated/fused.
- No interesting immune deposits

*Nephrotic syndrome*

---

**Bad Lupus Glomerulopathy**

- Anything but anti-GBM
- The subendothelial mesangial deposits are the famous "wire loops."

-Coarse granularity, often mixed chunks

-Hematuria or nephritic syndrome or RPGN
Disease Definition
Membranous glomerulonephritis is an antibody mediated disease in which the immune complexes localize to the subepithelial aspect of the capillary loop. That is, between the outer aspect of the basement membrane and the podocyte (epithelial cell).

How is this diagnosis made? ⇒ by BIOPSY (no other way)

Management:

Maintenance:
- fluid restriction
- dietary restriction (more protein!)
- diuretics (loop first, then thiazides)
- STEROIDS + cyclosporins (to reduce inflammatory damage)

Palliative: DIALYSIS
Hemodialysis
- every 3 days for 4-5 hrs
- home, hospital or satellite centre
- blood infections are a worry
- ruined veins, etc.

Peritoneal (CAPD)
- 3-4 times per day for 45 mins
- Continuous Ambulatory Dialysis
- Peritonitis and tube site infections (Pseudomonas and Candida are the commonest)
- Do-It-Yourself, thus relies on 100% sterile accuracy tri-daily …!

Curative:
TRANSPLANTATION: living or cadaver donor
- great if you survive dialysis for several years while you wait
- 8% of people per year get theirs (500, of which 300 from cadavers)

Prognosis
Clinical Course
The course of untreated idiopathic membranous glomerulonephritis is variable. Of patients presenting with the nephrotic syndrome and a normal serum creatinine:
- 30% will have a spontaneous complete remission and a stable GFR for up to 20 years.
- 25% will have a spontaneous partial remission with a stable GFR.
- 20-25% experience persistent nephrotic syndrome with stable or very slowly progressive loss of GFR.
Twenty to 25% of patients progress to end-stage renal failure over a 20 to 30 year follow-up.

Patients in whom a causitive agent is identified usually respond to treatment of the underlying disorder, or withdrawal of the offending agent.

Epidemiology
Membranous glomerulonephritis is more common in adults and most patients are older than 30 years at diagnosis. Membranous glomerulonephritis accounts for 35-50% of cases of adult nephrotic syndrome.
CHRONIC RENAL FAILURE IS RAMPANTLY PREVALENT AMONG THE ABORIGINAL COMMUNITY
⇒ Related to maternal malnutrition (thus, underweight infants born with far fewer nephrons are more predisposed to CRF earlier in life; 1 more Kg of birth weight = 250,000 more nephrons!)
PLUS for whatever reason DIABETES IS ALSO RAMPANT; + ON THE RISE!!!
**IgG subclass 4**

- is the culprit
  - the rarest of the circulating IgG subclasses
  - accounts for only 3-6% of total IgG.
  - unique in its inability to activate classical complement pathway.

**THIS IS IMPORTANT!!**

Classical pathway is responsible for preventing immune complex deposition
- C3 binds to the antigen/antibody complexes, then links the complex to the CR1 Receptor on erythrocytes, which then circulate to the liver where the immune complexes are destroyed.

**IgG is also a LOW AFFINITY antibody**

Hence it is able to dissociate pre-GBM, then penetrate the GBM and allegedly re-aggregate afterwards (inside the membrane).

---

**TUBULAR DAMAGE:**

**NORMALLY:**

Some proteins slip through the GBM
- Eg. low mol. weight proteins with neutral charge

The low molecular weight proteins are usually reabsorbed by the proximal tubule.

In Membranous Glomerulonephritis:
- The poor tubule tries to reabsorb (pinocytose) the extra protein out of the urine and is thus overloaded with it.

(vis. histological finding: *vacuolisation*” of the tubule)

**THIS MUCH PROTEIN IS TOXIC:**
- Toxic on its own eg. heme
- The act of pumping it depletes ATP
- THUS the tubules atrophy and die
- then release cytokines
  - thus attract FIBROBLASTS
  - FIBROSIS

---

**Antibody-associated Glomerular Injury**

- **Trapping of soluble circulating Ag-Ab complexes in the glomerulus**
- **Injury by Ab reacting in situ within the glomerulus**

- **Site of immune complexes largely determine glomerular response:**
  - Subendothelial → activate complement, acute inflammatory response
  - Mesangial → mesangio proliferative response
  - Subepithelial → induce production of basement membrane material

---

**4 stages:**

**Stage 1:**

Scattered subendothelial deposits (subendothelial meaning behind the GBM, on the urine side of things)

**Stage 2:**

Large uniform deposits; Spikes of epithelium between them

Foot processes are being destroyed by the membrane attack complex (invoked by complement cascade, the alternative pathway).

**Stage 3:**

DEPOSITS ENCRIMPED and incorporated into the glomerular basement membrane; this is the famed “membranous transformation”

**Stage 4:**

Complete absorption of antibody complexes into the now-homogenous, irregular basement membrane.

---

**NORMALLY:**

The filtering in the GBM is done by
- a size-barrier (i.e. the type IV collagen mesh)
- a charge barrier (i.e. the polyanionic inclusions in the mesh and the nephrin on the podocyte foot processes)

**In Membranous Glomerulonephritis:**

the defect in membranous glomerulonephritis results mainly from a loss of size selectivity. -NEJM 1998

---

**Exposure to endogenous or exogenous antigen(s)**

- in the Heymann mouse model this is a glomerular epithelial glycoprotein called *megalin*, but it has no equivalent in humans
  - induction of low affinity IgG immune response

@ **KIDNEY:**

low affinity of the IgG4 allows dissociation of the complexes
  - thus their FILTRATION through the GBM and fixation in it
  - then, re-aggregation?…PLUS hemodynamic stress eg. tortuous capillaries also increase the likelihood of immune complex deposition) either way…

---

**Genetic component:**

HLA DR3 = risk factor
Also Cancer, SLE, lead, mercury, gold, penicillamine, hep B/C, and syphilis

---

**Stage 3:**

DEPOSITS ENCRIMPED and incorporated into the glomerular basement membrane; this is the famed “membranous transformation”
**CHRONIC RENAL FAILURE and its many COMPLICATIONS**

**DECLINE IN GLOMERULAR FILTRATION RATE**
As measure of the time elapsed since the beginning of the end

**100mls**

- **Tubular Endothelium Damage:**
  - Tubules attempt to reabsorb the excess protein by means of ATP-dependent pinocytosis; thus depletes ATP quickly, becomes starved and **ATROPHIES**
  - **PLUS:** protein toxicity induces cytokine production and thus **FIBROSIS**

**70mls**

- **Hyperkalemia,** thus neuromuscular and cardiological complications

**30mls**

- **Increased levels of PARATHYROID HORMONE → hyperparathyroidism**
- **Loss of Erythropoietin**
  - Thus, Normocytic Normochromic Anaemia
- **Calcified Atheroma**
  - = 50% of deaths in chronic renal failure are the result of CARDIOVASCULAR complications

**25mls**

- **Hyperphosphataemia**
- **Ureaemia**
  - Guanidinosuccinic acid
  - **Ammonia**
- **Impaired Clotting**
  - Failure to crosslink platelets with VWF
- **Confusion, dementia, coma**
- **Hypertension**
- **Nausea, Vomiting, Anorexia**

**20mls**

- **Na+ disregulation:**
  - Narrowed homeostatic range:
    - Dying tubules versus uncontrollable RAAS

**10mls**

- **Hyperkalemia, thus neuromuscular and cardiological complications**
- **Risk of Asystole**

**5mls**

- **Compliances of hemodialysis:** beta-2-microglobulin, a normal component of the MHC HLA molecule, is prone to collecting @ the kidney thus causing AMYLOIDOSIS... plus infections of the vulnerable fistula, hemolysis in the machine, and heparinisation

**Compliances of ambulatory peritoneal dialysis** is continued peritonitis, thus adhesions...

---

**~ALL DIALYSIS IS UNDER-DIALYSIS~**
Table 270-2: Uremic "Toxins"

By-products of protein and amino acid metabolism

- Urea-80% of total (excreted nitrogen)
- Guanidino compounds
- Guanidine
- Methylguanidine
- Dimethylguanidine
- Creatinine
- Creatine
- Guanidinosuccinic acid
- Urates and hippurates
- End products of nucleic acid metabolism
- End products of aliphatic amine metabolism
- End products of aromatic amino acid metabolism
- Tryptophan
- Tyrosine
- Phenylalanine
- Other nitrogenous substances
- Polyamines
- Myoinositol
- Phenols
- Benzoates
- Indoles
- Advanced glycation end products
- Inhibitors of ligand-protein binding
- Glucuronoconjugates and aglycones
- Inhibitors of somatomedin and insulin action

- DNA, histones and nucleosomes (DNA-histone complexes) in lupus nephritis
- Trapped bacterial, viral and parasitic antigens
- Certain drugs
- Circulating immune complex deposition (type III reactions): deposition of circulating pre-formed immune complexes within glomeruli
  - Serum sickness reactions, postinfectious GN, mesangiocapillary GN type I, cryoglobulinaemic GN (eh. hepatitis C antigen-antibody complexes).
  - Cationic immune complexes are able to cross capillary walls from the capillary lumen thus bind to subepithelial sites (eg. membranous GN), anionic and neutral complexes are trapped in
    - Mesangium (eg. IgA nephropathy)
    - Subendothelial sites (eg. mesangiocapillary GN);
    - Immune complexes that persist for long periods in the circulation are most likely to deposit in glomeruli; thus IgG subclass 4 is best for this (it's not cleared by the [erythrocyte→liver] transport system
  - High hydrostatic pressures generated within the glomerular capillary make it a common site of immune complex deposition.

Mediators of glomerular damage
- Complement activation
- Leucocyte infiltration
- Platelet activation
- Activation of coagulation cascade
- Release of reactive oxygen species
- Cytokine and chemokine secretion

The glomerulus has a limited range of responses to inciting stimuli. These include:
1. Coagulation, fibrin deposition and crescent formation
2. Cellular proliferation: mesangial, epithelial and/or endothelial
3. Deposition of mesangial matrix or basement membrane material
4. Vasoactive mediator release and altered glomerular filtration
**Chronic Glomerulonephritis**

PROGRESSIVE loss of renal function associated with inflammation.
CREEPS UP ON YOU: most commonly an incidental finding, for example:

- **Routine Urinalysis:**
  - Proteinuria and hematuria

- **Routine FBC:**
  - Normocytic normochromic anaemia

- **Abdominal Imaging:**
  - Bilateral small kidneys

Usually a chronic GN results from the resolution of an acute GN. Initial injury = reduction in the number of working nephrons. Therefore your GFR ain’t what it used to be, and the remaining nephron units detect this and hypertrophy to compensate. So now you are working your few remaining nephrons much harder: the same amount of blood needs to get filtered, but the filter is much smaller and thus the blood is forced through it at a greater pressure. This is fine for a while, but we all know what happens to arterioles under constant hemodynamic stress: SCLEROSIS. Thats right, the glomeruli literally work themselves into an early grave. Hence the progression to end-stage renal failure (ESRF)

**DISEASE DEFINITIONS: “STAGING”**

- **Stage 1:** kidney damage with a normal GFR (>90 mL/min). The action plan is diagnosis and treatment, treatment of comorbid conditions, slowing of the progressing of kidney disease, and reduction of cardiovascular disease risks.

- **Stage 2:** kidney damage with a mild decrease in the GFR (60-90 mL/min). The action plan is estimation of the progression of kidney disease.

- **Stage 3:** moderately decreased GFR (30-59 mL/min). The action plan is evaluation and treatment of complications.

- **Stage 4:** severe decrease in the GFR (15-29 mL/min). The action plan is preparation for renal replacement therapy.

- **Stage 5:** kidney failure. The action plan is kidney replacement if the patient is uremic.

**General approach:**

Find and treat the systemic cause.
No apparent cause?

→ TREAT UREMIA

→ DELAY END-STAGE RENAL FAILURE

→ DIALYSIS

→ TRANSPLANTATION

**MONITORING PROGRESSION:**

**URINALYSIS:** to calculate protein loss using protein / creatinine ratio

Eg. 300 protein and 150 creat. = 300 / 150 = 2 (g protein/day)

**EUC:** to calculate GFR using online creatinine clearance calculator in CIAP

Use this to monitor response to therapy; GFR = all important

**ALSO look at calcium (low?), phosphate (high?)**

**FBC** looking for normochromic normocytic anaemia

**Albumin:** to monitor effect of protein loss

**COAGS:** watch out for thrombophilia ..may also want to do a kidney ultrasound:

**GOALS OF MANAGEMENT:**

- Reduce blood pressure (ACE-I, lasix, etc)

- Replace EPO and activated Vitamin D

- Manage hyperlipidaemia (reduce CVS risk factors)

- Consider calcitriol and alfacalcidol
The **NEPHROTIC SYNDROME**

Leakage of 3 grams of protein per day.

**Pathophysiology**

You have a charge barrier and a size barrier. Normally nothing larger than 70kD and nothing polyanionic can get through. With GBM damage, both of these barriers can be disrupted.

**SEQUELAE and STRATEGIES FOR THE MANAGEMENT THEREOF**

**Oedema:** due to protein loss uncompensated by liver synthesis and tissue mobilisation of albumin

**Sodium Retention:** due to increased distal resorption; ? due to activated RAAS?

*Must get rid of the extra sodium. Loop diuretics and salt restriction are the go.*

*Might even want to combine frusemide with a thiazide or a K-sparing diuretic.*

**NOTE:** frusemide has a short half life. Use it 2-3 times a day in large doses.

**BEWARE:** abrupt natriuresis can cause a sudden hypovolemia and even ARF! Plus by excreting so much water you will hyperconcentrate the blood, so give these diuretics in tandem with heparin and TED stockings.

**Thromboembolic Complications:** especially renal vein thrombosis! This is due to a number of factors, only one of which is the increased excretion of anticoagulation proteins (eg. antithrombin III) into the urine. There is aso unexplainable thrombocytosis (? Due to hyperconcentration of blood cells? Remember, all that water moving out into the interstitial spaces leaves behind the cells in the blood.);

*Must prevent thromboembolism. Just give them heparin, evidence shows that the number of fatal emboli prevented is greater than the number of fatal bleeding events induced. Also consider aspirin (because much of the antithrombin III has been excreted and heparin has fewer targets to bind with).*

**Infectious Complications:** you are peeing out all of your immunoglobulins and complement cascade components. Especially dangerous in children.

*Sadly, still no justification for prophylactic antibiotics, as you may end up simply selecting for resistant organisms. Use ad-hoc intravenous antibiotics.*

**Hyperlipidaemia:** due to overproduction and under-catabolism of LDLs. Undercatabolism seems to result from urinary excretion of ...something. Something vital to lipid catabolism. Exactly what it is has not been determined yet. Nor do we know what causes the increased synthesis of blood lipids.

*Manage this with a soy-based low fat diet and statins. ACE-inhibitors also help indirectly, by reducing protein excretion.*

**ACE Inhibition:** indicated even in normotensive patients. The BP-lowering effects take place within 24hrs, but the antinephrotic protein-saving effects take a month. The anti-nephrotic effect is totally unrelated to the blood-pressure effects, its a completely different poorly understood mechanism. It can be enhanced with a low-sodium diet and diuretics.

**Common Causes**

− Diabetic Nephropathy
− Minimal Change Glomerulopathy (idiopathic)
  − Loss of charge selectivity
− Membranous glomerulonephritis (often linked to neoplasia)
  − Carcinomas, lymphoma, leukaemia, myeloma, sarcoma...
  − Loss of size selectivity
− Primary Renal Amyloidosis
− HIV
− Preeclampsia