# Acute Renal Failure

## HISTORY OF PRESENTING ILLNESS

There are 3 distinctive forms of acute renal failure, with different histories. They all share some components:

| Thirsty | Haematuric (frank red) | Getting hard to pee of late |
| Dizzy | Tea-coloured myoglobinuria | Obstructive symptoms, dribbling and whatnot |
| Oliguric | (Especially with MYALGIA or some sort of severe TRAUMA) | Urgency |
| Hypotensive | Frothy urine | Frequency |
| In Heart Failure (low output) | Oedematous | Hesitancy |
| Recently has been vomiting | Hypertensive | Hematuria |
| Diarrhoea-ing | Recent Infection (? THROAT ?) | Renal colic or Hx of stones |
| Haemorrhaging | Recent IV contrast study | Previous gynae surgery |
| Coagulopathic eg. DVT | Drugs used recently, eg. | Only one kidney (other one donated, diseased or simply never existed) |
| May be dehydrated because: | - NSAID + ACE-Inhibitor + Lasix | DRUGS eg. |
| - septic | - Gentamicin (or any aminoglycoside) | - Acyclovir |
| - Elderly | - Aspirin + Caffeine (alcoholics) | - Methotrexate |
| - Comatose | - Cyclosporin (immune suppression) | - Sulfonamides |
| - Sedated | - Amphotericin (anti-fungal, in HIV) | All form tubular crystals |
| - Idiot intern forgot to write anything up in the fluid chart | By the end of your history-taking its should be blindingly obvious where the problem is. |

## Physical Examination

**FIRST THINGS FIRST: WHATS THE BLOOD PRESSURE??**

### PRE-Renal Cause

- JVP way low?
- Skin turgor all gone?
- Mucosa dry as a bone?
- Tachycardia?
- Postural hypotension?
- Pale as a sheet?
- ...could your patient be dehydrated, or bleeding internally somewhere?

**LOOK FOR:**

- Purpura, rash, keratitis:
  - Systemic vasculitis?
- Oedema
- Hypertension
- Sore red throat with the typical pus of strep pharyngitis
- Ischaemic limbs
- Signs of major trauma
- Stigma of diabetes

### INTRA-Renal Cause

- Distended bladder
- Renal angle tenderness
  - (Murphy’s kidney punch)
- Surgical scars (how many kidneys left?...)

**LOOK FOR:**

- Are they Atrially Fibrillating?
  - If yes, are they properly heparinised / warfarinised?
- Track Marks of the Junkie?
  - (Endocarditis with septic emboli?)
- Have they recently fractured a big long bone? (marrow fat embolus)
  - COULD THEY HAVE THROWN A CLOT into their last working kidney?

### POST-Renal Cause

If none of those;

- Are they mid-liver-failure?
  - i.e is all the body fluid sequestered in their abdomen as ascites, and that’s why they aren’t perfusing their kidneys?
- ARE THEY SEPTIC and just too old to develop a raging temperature?

Alternatively,

- Are they vasculopathic? I.e...
  - Have they got atheromae everywhere? Is there a RENAL ARTERY BRUIT?
  - Could they have haemorrhaged into a renal artery atheroma?

If that’s not their problem;

- Are they Atrially Fibrillating?
  - If yes, are they properly heparinised / warfarinised?
- Track Marks of the Junkie?
  - (Endocarditis with septic emboli?)
- Have they recently fractured a big long bone? (marrow fat embolus)
  - COULD THEY HAVE THROWN A CLOT into their last working kidney?

Or maybe...

- Are they mid-liver-failure?
  - i.e is all the body fluid sequestered in their abdomen as ascites, and that’s why they aren’t perfusing their kidneys?
- ARE THEY SEPTIC and just too old to develop a raging temperature?

**LOOK FOR:**

- Purpura, rash, keratitis:
  - Systemic vasculitis?
INVESTIGATIONS

URINE OUTPUT:

ANURIA: Not many things will make you completely ANURIC.
- complete obstruction of urethra by a huge angry prostate
- Rapidly Progressive Glomerulonephritis
- Total obstruction of the renal arteries (or your last renal artery)
- Bilateral Diffuse Renal Cortical Necrosis (for whatever reason)

OLIGURIA: Most ARF patients will be oliguric. This includes
- partial obstruction of last remaining ureter by a stone
- partial renal artery stenosis
- renal embolism (for whatever reason)
- HEPATORENAL SYNDROME (in liver disease, where the sequestration of fluid in ascitic compartments leads to over-activity of the RAAS system and hence vasoconstriction of the renal vessels)

NORMAL OUTPUT: A lot of ARF patients will be making urine as usual.
- Acute Glomerulonephritis (there’s still enough urine, it’s just turned red)
- Nephrotoxic Acute Tubular Necrosis eg. after contrast study
- Ischaemic Acute Tubular Necrosis eg. after volume depletion / heart failure
- Rhabdomyolysis ATN – normal urine volume at first, but it is tea-coloured.

URINALYSIS:

SEDIMENT WILL BE NORMAL IN MOST CASES OF PRE and POST RENAL FAILURE.
There is no reason for anything to be happening in the urine if somebody has blocked the blood supply to the kidney, or blocked off the outflow of urine through the urethra (eg. the prostate).

HOWEVER: Multiple red cells of a normal shape suggest post-renal calculi.
(bled from the shredded walls of the ureter as the calculus scrapes along them)

In INTRA-RENAL FAILURE, the SEDIMENT HAS MEANING:
- Granular casts - ATN, glomerulonephritis, interstitial nephritis.
- RBC casts - Glomerulonephritis, malignant HTN
- Rouleaux RBC casts = multiple myeloma
- WBC casts - Acute interstitial nephritis, pyelonephritis
- Eosinophiluria - Acute allergic interstitial nephritis, atheroembolism
- Crystalluria - Acyclovir, sulfonamides, methotrexate, ethylene glycol toxicity, IV contrast

FBC

MAINLY FOR COMPLETENESS. Most changes with acute renal failure will not change the blood count, with the following exceptions:
- Hb will be reduced in chronic renal failure that has turned acute.
- Also look at the RBC indices; you expect normochromic normocytic anaemia
- WCCs will be meaninglessly elevated in SEPSIS (you knew it was sepsis before you saw the FBC)

EUC is WHERE THE MONEY IS: Creatinine and Urea will be HIGH
Creatinine elevation pretty much defines ARF. You can pretty well guess that they also will be

ECG: tall peaked T waves reaching as high as the QRS
Look like knives- no rounded tip, very sharp
Extremely high K+ = the whole ECG becomes sinusoidal

HYPERKALEMIC and
- HYPOCALCEMIC and
- HYPERPHOSPHATAEMIC
**IMAGING:**

**Renal Ultrasound**
This consumes time, and may not teach you very much. **MASSIVE HYDRONEPHROSIS** will show up with ultrasound (eg. in long standing urinary retention). **TINY DEAD KIDNEYS** will be expected if the patient has had chronic renal failure for years and has recently suffered an exacerbation (eg. chronic glomerulonephritis).

**Renal Vein + Artery Doppler**
You may discover to your delight that there is indeed a huge thrombus occluding the renal artery. OR you may find that there is significant stenosis.

**Renal Artery Angiogram (percutaneous or MRI)**
Indications are very much the same as above. A Percutaneous angiogram also offers some help in clearing the blockage (eg. angioplasty or stenting). However harsh iodinated angiography dye may kill off the last of your kidney, whereas gentle Gadolinium MRI contrast will not do any harm. Mmmm, Gadolinium.

**CT scan** may show hydronephrosis and maybe even the site of the blockage, as you follow the distended ureter down the slices.

**Chest X-ray** will tell you if you need to be worried about pulmonary oedema; it will also point the way towards some weird diagnoses (eg. Wegener’s Granulomatosis or Goodpasture Syndrome which can cause an acute glomerulonephritis).

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**So, you still have NO IDEA why your patient is deteriorating.**

It may be necessary to resort to **RENAL BIOPSY.** Especially if glomerulonephritis is suspected. This procedure carries all the risks implied in puncturing a deep organ with a big needle. A questionnaire among Antipodean nephrologists revealed that about 30% of them would prefer to wait until 4 weeks into the ARF before they would biopsy.

**Barrier Keywords:**

- Immunofluorescence
- Electron Microscopy

**Contraindicated if:**
- Only one functional kidney
- Hideous coagulopathy (just wont clot)
- Small kidneys on ultrasound (fibrotic)

With a renal biopsy, a skilled pathologist will be able to return to you with a diagnosis from one among a massive number of acute glomerular and tubulointerstitial problems, the list of which would take a semester to describe.
EMERGENCY MANAGEMENT OF ACUTE RENAL FAILURE

... should begin before a definitive diagnosis is made.

1. **URINARY CATHETER:** if the problem was an obstructive prostate, you just solved it. Now just a matter of sitting out the diuresis phase and waiting for your elective TURP.

2. **HYPOVOLEMIA is your enemy, FLUID OVERLOAD is also your enemy.**
   It is necessary to take great care with the fluid management of someone in ARF of any aetiology. HYPOVOLEMIA should be reversed until the JVP is seen. **USE NORMAL SALINE.**
   Having given a bag of saline stat, see if the patient has responded (i.e., is there now more urine being produced?)
   **NO RESPONSE TO FLUID CHALLENGE:** try a loop diuretic.
   Still nothing?
   **TIME TO CONSIDER DIALYSIS.**

   If you did manage to coax your anuric dehydrated patient back into oliguria, Continue the fluid replacement according to output: 100ml out = 100ml in
   **THIS SHOULD MAINTAIN PERFUSION OF THE KIDNEYS AND IMPROVE WASH-OUT** (which is the beneficial movement of weird debris out of the tubules and into the toilet)

3. **WHATS THE pH?** Diseased kidneys cannot regulate acid-base balance. You must act as your patients kidneys, topping up the bicarbonate as needed. ACIDOSIS may be aggravated by the pulmonary oedema due to your overzealous fluid management, as well as the renal pathology. Make certain the patient is able to regulate at least the respiratory component of the pH equation.

4. **WATCH THE ELECTROLYTES.** ARF patients die from cardiac causes.
   **HYPERKALEMIA:** stack all the methods of lowering potassium known to you one on top of another, especially if the patient has K+ approaching 7.0
   This means:
   - Give 10% dextrose (healthy young person should be able to generate their own insulin)
   - Or… Give 10% dextrose AND rapid-acting insulin
   - Resonium resin orally. (scavenges K+ from gut wall)
   - **Salbutamol (ventolin)** – beta agonists in general will increase K+ uptake
   - **Loop Diuretic** (will cause K+ wasting from tubules)
   Last ditch effort is DIALYSIS.

**CONTROVERSIAL MEASURE:**
**DOPAMINE** goes in and out of favour: rumoured to dilate renal arteries. Lower doses stimulate mainly dopaminergic receptors that produce renal and mesenteric vasodilation; cardiac stimulation and renal vasodilation produced by higher doses. **Pure anecdote, most recent study failed it in terms of urine output benefit, and showed that it had pro-arrhythmic effects.** Best renal vasodilator is still fluid replacement until euvoolemia.

It is meaningless to speak of prognosis and epidemiology of this problem, as it is too wide a spectrum of disorders to be considered beneath the same umbrella term “acute renal failure”. Rhabdomyolysis as the cause of acute renal failure is almost unheard of in the Australian community, where renal vein thrombosis and acute glomerulonephritis are the norm. ATN, however, is the complication of almost every acute renal impairment.
HIDEOUS INJURIES
Crush injury, pressure sores, freezing injuries, extensive burns, psychopathically excessive exercise, vascular disease causing whole-limb ischaemia, widespread sepsis, inflammatory myopathy, blast injury eg, bomb explosion, alcoholism, and over-use of MDMA in a rave dance-club setting

Torrential leakage of cellular contents

Widespread cell destruction, on a massive scale, and thus

Sodium and water move into the damaged muscle:
MANY LITRES MAY BECOME SEQUESTERED!

Injury-related haemorrhage
(or, drugged +/- drunken dehydration)

HYPOVOLEMIA

HYPTENSION

RENAL HYPOPERFUSION
Due to vasoconstriction secondary to RAAS activation

Reduced GFR,
thus reduced rate of wash-out

Myoglobin in the bloodstream scavenges NO, and this causes reduced vasodilation

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Reduced urine concentrating mechanisms still haven't come back online. This is the so-called DIURESIS PHASE.

Major pathology happens here:
Now you got iron-rich protein congealing up your tubule. This has numerous unsavoury CONSEQUENCES:

MECHANICAL:
Tubules crammed full of myoglobin casts become dilated with backpressure, and the fragile tubular brush border is destroyed by the crude effect of having proteinaceous waste forced through it.

Eventually the macrophages will come and bulldoze down the dead tubules and clean out all the myoglobin.

Loss of brush border:
Its full of enzymes, eg. carbonic anhydrase, which produces your renal bicarbonate- and so THE ABILITY TO REGULATE ACID-BASE BALANCE IS LOST which contributes to the heme-depositing tubule-clogging aciduria

PROLONGED ATP DEPLETION (i.e. you DONT get the kidneys re-perfused) = CORTICAL NECROSIS = no recovery

BIOCHEMICAL
Myoglobin is a protein, and the tubule attempts to transport it back into the bloodstream using its normal mechanism of ATP-dependant transport. There being so much of it, the ATP reserves of the blood-starved tubule are depleted rather quickly. ATP depletion means you can't power all those ion pumps, and thus control of electrolyte concentration is lost.

CELLULAR + GENETIC:
Iron, of which myoglobin is full, seems to be toxic to the tubule epithelium. By itself its a free radical, and it will generate new free radicals when you reperfuse the kidneys with your well-intentioned litre of IV saline- because oxygen will actually be able to get down there. Superoxide Dismutase will cope with this...for a while. Then, the oxidative stress will burn the DNA and the lipid bi-layers. This is irreversible.

Otherwise...
Lots of mitosis and a little fibrosis: the kidneys restore their architecture; tubule cells recover their ion pump functions AFTER the tubules are cleared up, and thus there is a period of massive polyuria, while the urine concentrating mechanisms still haven't come back online. This is the so-called DIURESIS PHASE.
Acute Glomerulonephritis

- Abrupt onset of obvious macroscopic hematuria
- Oliguria
- Sudden decrease in glomerular filtration rate →
- Proteinuria below nephrotic range (<3g/day)
- OEDEMA occurring as a result of sodium retention and not hypoalbuminaemia

ITS ALMOST ALWAYS A POST-INFECTIONOUS SITUATION!

Triggering Events:
- POST-INFECTIONOUS eg. post-streptococcal
  - Mainly in young children with a runny nose
  - Occurs ~2 weeks after the initial infection
  - Mediated by immune-complex deposition AND by the accumulation of streptococcal antigens in the glomerular filtration membrane... which then attract all kinds of immune retribution, mainly in the shape of angry complement and macrophages.

Natural History

Strep infection;
- 1-2 weeks later: onset of oedema + hemoproteinuria
- 1-2 weeks of oedema and hemoproteinuria with massively elevated creatinine and Na+
- 1-2 weeks of wild diuresis
- 1-2 weeks of continuing creatinine abnormalities, tapering off;
- 6 months of hematuria
- X years of proteinuria (variable; persists for 10 years in 2% of patients)

Diagnostic Side-Dishes

Certain immunological changes take place in post-infectious GN, and these can be employed to point the way towards a diagnosis.

- COMPLEMENT components, esp. C3 are depressed during the early course. THESE SHOULD RETURN TO NORMAL 6-8 weeks after onset IF THEY HAVE NOT: !! RED FLAG !! it may be lupus nephritis

- STREPT ANTIBODIES wont diagnose post-strep GN for you, but they will tell you if a strep infection has taken place recently. ...Look for antibodies to...
  - Streptolysin O (be warned- only 66% of streptococci wield this weapon)
  - Streptokinase
  - Hyalouronidase
  - Nicotinamide Dinucleotidase

MANAGEMENT IS SUPPORTIVE and consists of...

MANAGING FLUID OVERLOAD with diuretics
MANAGING HYPERTENSION which results from fluid overload with conventional agents

Creatinine: measure of GFR
released from skeletal muscle at a steady rate; high level is associated with large muscle mass and exercise

- high creatinine better be found in a large well-muscled patient, not a frail 90 yr old woman.
- THUS in a hypovolemic patient the GFR will drop and thus the serum creatinine will RISE
Normal creatinine = GFR must be OK

FILTRATION RATE: ~100 ml per minute; = Carefully controlled!

Very steady between 90 and 200 systolic
only extremes of blood pressure influence the GFR.
INCREASED BP = reflex contraction of smooth muscle in afferent arteriole, thus reduced flow still means GFR maintained at the same level

BIOPSY with immunofluorescence and electron microscopy is the ONLY MEANS OF DIAGNOSIS...

RESOLVES SPONTANEOUSLY! No cause for dismay

Only 1 or 2% of post-strep GN patients progress to ESRF
Asymptomatic Hematuria in Glomerulonephritis

BEWARE! Asymptomatic hematuria can mean ANY DAMN THING. Glomerulonephritis is JUST ONE POSSIBILITY. BUT!... if there is also PROTEINURIA, you must keep GN in the back of your mind.

IgA Nephropathy is the commonest GN cause of asymptomatic hematuria

Commonest among young males, 2\textsuperscript{nd} to 3\textsuperscript{rd} decades of life.

- Altered regulation of production or structure of IgA
- Exposure to Antigens at the mucosa, where production of IgA is triggered
- Overproduction of IgA in response to comparatively trivial immune insult
- 50% of IgA GN patients have increased serum IgA
- Abnormal glycosylation: Polymeric IgA class 1 subtypes get glycosylated more easily (?)
- IgA lodges in the GBM and causes trouble: Complement is activated, macrophages are summoned, all hell breaks loose in the glomerulus.
- Circulating IgA complexes =
  - Titres parallel the severity of disease
- Abnormal Glycosylation: Polymeric IgA class 1 subtypes get glycosylated more easily (?)
- Abnormal glycosylation helps the IgA complexes to escape clearance by the reticuloendothelial system, as they are no longer recognised by the asialoglycoprotein receptors.

PRESENTATION and NATURAL HISTORY

- In 50-60\% of cases ASYMPOMATIC GROSS HEMATURIA
- In 30\% of cases, ASYMPOMATIC MICROSCOPIC HEMATURIA
- In 10\% of cases, NEPHROTIC SYNDROME or ACUTE GLOMERULONEPHRITIS
- Simultaneous Respiratory or GIT infection
- 10-20 years later, END STAGE RENAL FAILURE. Especially if:
  - elderly
  - male
  - hypertensive
  - proteinuric
  - already crappy kidneys

AT-RISK GROUP!! Should at least ATTEMPT TO RETARD PROGRESSION TO END STAGE RENAL FAILURE

SO WHAT DO I DO? Supportive management.

- Keep fluid balance in the realms of normality
- Diuretics for overload, saline for dehydration.
- If your patient runs the risk of progressing to ESRF, try corticosteroids or fish oil.
- ACE inhibitors for all!
- Ang II receptor blockers for some.

So many trials, so many mixed results:

- Corticosteroids: decrease proteinuria, but no change in disease progression. Pfft.
- Fish Oil: n-3 fatty acids should limit the production and/or action of cytokines at the glomerulus. Some success. One very wonky trial showed extreme benefit. 6\% fish-oilers doubled their serum creatinine over 4 yrs, versus 33\% of placebo group.
- ACE inhibitors: there is OBVIOUS BENEFIT; All experts agree.
Rapidly Progressive Glomerulonephritis

Just like acute glomerulonephritis, but in fast forward: rapid decline in renal function, and subsequent end-stage renal failure within days or weeks. LUCKILY ITS RARE. 2 to 4% of GN are rapidly progressive.

Natural History

- INSIDIOUS ONSET:
  - Malaise, lethargy, microscopic hematuria
  - Proteinuria in ~30% of patients
- KNOW TO LOOK FOR RARE DISEASES KNOWN TO BE ASSOCIATED WITH RAPIDLY PROGRESSIVE GN:
  - a VASCULITIS of some sort, be it WEGENER’S GRANULOMATOSIS, MICROSCOPIC POLYANGIITIS, or CHURG-STRAUSS SYNDROME
  - CRYOGLOBULINAEMIA
  - SYSTEMIC LUPUS ERYTHEMATOSUS
  - GLOMERULAR BASEMENT MEMBRANE ANTIBODIES
  - GOODPASTURE’S SYNDROME (also haemoptysis)

PATHOLOGICAL HALLMARKS:

- Cellular crescents surrounding the glomeruli.
  - these are made of endothelial cells, mononuclear infiltrate and recruited fibroblasts.
- ALSO:
  - linear deposition of immunoglobulins all along the GBM in 20%
  - granular (blobby) deposition of these Ig’s in the GBM in 30%.
  - In the remainder of pts, no immune deposits of any sort are detectable.

MANAGEMENT is AGGRESSIVE and DETERMINED.

Kick-start with IV corticosteroids and cyclophosphamide
Monitor progress: if response is limited move on to PLASMA EXCHANGE
(thats if you can identify an antibody as the culprit)

Renal survival is most closely related to serum creatinine titres at presentation.

Only 40% of patients escape dialysis at 1 year of follow-up.