PHYSIOLOGY

- lie opposite the L_1-L_2 vertebral bodies, right being ~ 1 cm lower

a. length ~ 11.5-12.5 cm

b. nephrons ~ 1.3×10^6
~ 15% being ***long-looped***

c. renal blood flow ~ 1.25 l/min
~ 25% of resting CO

d. GFR **~ 125 ml/min** or 180 l/day
~ 20% of ERPF (625 ml/min)
- GFR estimated by ***creatinine clearance***
- ***inulin*** would be ideal, however requires infusion to steady state & cumbersome

e. renal VO_2 ~ 18 ml/min
~ 7% of basal VO_2 → global ERO_2 **< 10%**

f. hydrostatic pressure
i. glomerular capillary ~ 45 mmHg
ii. glomerular oncotic ~ 25-35 mmHg
iii. Bowman's capsule ~ 10 mmHg
- filtration pressure equilibrium is reached ~ 2/3 along the glomerular capillary

Renal - Physiology			
Na^+ excretion	normal	~ 100-200	mmol/d
	minimum	**~ 5-10**	mmol/d
K^+ excretion	normal	~ 30-100	mmol/d
	minimum	**~ 20**	mmol/d
osmolar load		~ 8-12	mosm/kg/d
		~ 600	mosm/d
urine osmolarity		~ 40-1200	mosm/l
obligate urine volume		~ 0.3-0.5	ml/kg/hr
		~ 500	ml/d
urine SG		~ 1003-1030	
pH		~ 4.5-8.0	mean ~ 6
urea		~ 5-10	mmol/kg/d
protein		< 0.7	g/l
WBC's		< 3/µl | 3000/ml	< 1/HPF
RBC's		< 1/µl | 1000/ml	< 1/HPF

■ ***Creatinine***

• ***creatine*** is an amino acid, derived from,

1. exogenous ingestion - small amount
2. synthesis in the liver - from glycine & arginine ? ornithine

• creatine is taken-up by ***skeletal muscle*** ~ 150 mg / 100 g muscle
• regularly turned-over, nonenzymatically, between,

$$\text{CPK} \longleftrightarrow \text{creatine} \longleftrightarrow \text{creatinine}$$

• ***creatinine*** is an anhydride, cyclised degradation product of creatine
• daily production / excretion is relatively constant ~ **8-25 mmol/d** (15-20 mg/day)
• this rate of production varies ~ 10% for a given individual, largely $\propto$ skeletal muscle mass
• muscle content is low ~ 0.3 mmol/l, due to rapid diffusion out of the sarcolemma
• serum levels rise when the GFR is reduced by ~ 50%,

$$\delta[\text{creatinine}](\%) \sim 1 / \delta\text{GFR}(\%)$$

• ie., plasma creatinine $\rightarrow$ ~ doubles for each 50% reduction in nephron mass
• normal serum level ~ 0.06-0.11 mmol/l (see table following)
• this is elevated to a greater extent in renal or post-renal failure, than in pre-renal failure
• levels fall in pregnancy due to dilution & $\uparrow$ GFR
• the normal ***urea:creatinine ratio* ~ 70-150:1**
• varies 10-25% in normal adults, decreasing with age,

$$Cl_{CR} \approx 133 - (0.64 \times \text{Age}) \quad (\text{ml/min/1.73m}^2)$$

• serum creatinine is a ***poor reflection*** of GFR because,

a. excretion is by filtration and tubular ***secretion***
b. with a fall in GFR - tubular secretion increases
   - V_{dSS} increases
c. production varies with - muscle mass
   - age
   - catabolic state
   - muscle damage (myositis, rhabdomyolysis, myopathies)
d. false increase with non-creatinine chromogens (Jaffe colour absorption)
   - ketones - ***acetoacetate***
   - cephalosporins
   - flucytosine
e. creatinine excretion impaired by cimetidine, cotrimoxazole

Normal Values	**Neonate**	**Adult**
GFR • premature • at birth • at 1 month	10-20 ml/min/m^2 0.7-0.8 ml/min/m^2 1-2 ml/min/m^2 50 ml/min/m^2	**60-80 ml/min/m^2** 75-185 ml/min/1.73m^2 (95%CI | 70kg → 1.7m^2)
Maximum Urine Concentration	450-600 mosmol/l	1400 mosmol/l
Plasma Creatinine	• maternal at birth[1] • infant ~ 18-35 µmol/l • child ~ 30-60 µmol/l • youth ~ 45-90 µmol/l	• male ~ 55-120 µmol/l • female ~ 45-95 µmol/l
pH	7.35	7.4
[HCO_3^-]	20 mmol/l	25 mmol/l

[1] decreases due to low muscle mass and high rate of anabolism

- ***Urea***

• clearance varies with GFR → reabsorption ~ 40-60%
• handled by simple diffusion, both secreted & reabsorbed in different regions of nephron

- ***Distal Nephron***

• basolateral Na/K-ATPase is mineralocorticoid sensitive
• responsible for reabsorption of ~ 5% of filtered Na^+
• in absence of ***aldosterone*** ~ 50% of distal Na^+ is reabsorbed

→ maximal Na^+ excretion ~ 750 mmol/d (~ 1500 mmol/d enters DT)

■ ***Atrial Natriuretic Hormone***

- 152 AA preprohormone → 126 AA prohormone (atriopeptigen)
  → 19-28 AA bilogically active peptides
- the predominant circulating hormone is the **28 AA *atriopeptin***
- specific ***ANH receptors*** located in vascular, renal and adrenal tissue → ↑ **cGMP**
- does not inhibit NaK-ATPase & effects are not inhibited by NSAIDs (ie. not PG mediated)
- effects at physiological levels,
  1. ***natriuresis*** & modest kaluresis
  2. ↓ MAP ∝ vasodilatation
  3. inhibition of renal salt/H_2O retaining systems
     i. ↓ renal renin release
     ii. ↓ aldosterone synthesis & release
     iii. ↓ ADH release

- in health, plasma levels respond to Na^+ intake
- in disease, ***increased*** ANP levels are found in,
  1. hypervolaemic disorders
     i. hyperaldosteronism
     ii. CCF
     iii. CRF
  2. essential hypertension
  3. pre-eclampsia
  4. SIADH - urinary $[Na^+] > 20$ mmol/l
  5. hyperthyroidism
  6. cirrhosis - with onset of HRS, levels decline modestly
  7. PAT

■ ***Prostaglandins***

- major proportion is $\mathbf{PGE_2}$ synthesised in the ***medulla***
- inhibition by NSAIDs does little to GFR/RBF in normal individuals
- in hypovolaemic states, ***PG inhibitors*** →
  1. increased incidence of ARF
  2. papillary necrosis & CRF
  3. hyporeninaemic hypoaldosteronism → ***hyperkalaemic RTA*** (type IV)
  4. acute interstitial nephritis & nephrotic syndrome

DIURETICS

- except for the osmotic agents they are all extensively ***protein bound***
- except for ***spironolactone***, they are secreted by the pars recta PT and act from ***within*** the lumen

- ***Indications***

1.	all agents →	oedematous states	- CCF - nephrotic syndrome - ascites - cerebral oedema
2.	diluting segment agents		- hypertension - diabetes insipidus - RTA - hypercalcuria
3.	loop agents		- renal failure - hyponatraemia - hypercalcaemia, hyperkalaemia, hypermagnesaemia - bromide or iodide intoxication
4.	carbonic anhydrase agents		- metabolic alkalosis - glaucoma - high altitude disease
5.	potassium sparing agents		- hyperaldosteronism, 1° or 2°
6.	osmotic agents		- cerebral oedema - renal tubular toxins

Benzothiazides

- synthesised as an extension of studies into carbonic anhydrase inhibitors
- inhibit ***chloride*** transport in the ***cortical portion*** of the thick ascending limb of the loop of Henle
- only ~ 10% of the filtered load of Na^+ is handled by this segment, ***∴ceiling effect***

  → parallel dose-response curves, having equivalent maximal ***chloruretic*** effects

- with the closely related ***phthalimidine derivates*** (chlorthalidone) used mainly for ***hypertension***
- although termed diuretics, their main action in ***chronic therapy*** appears to be ***vasodilatation***
- this is maximal at the ***lower*** dose range, and in this regard they are superior to loop agents

- ***Mechanism of Renal Action***

1. increase excretion of ***chloride & sodium***
2. accompanying loss of ***free water***
   - in patients with diabetes insipidus, they ***decrease*** urinary water excretion
   - ie. fluid leaving the early DT is not as dilute
3. acute increases in ***potassium*** excretion
4. variable potency as carbonic anhydrase inhibitors - clinically insignificant
5. ***GFR*** may be reduced - direct vasodilatation of renal vasculature
6. enhanced reabsorption of ***urate*** in PT & decreased active secretion
7. decreased excretion of ***calcium*** - direct action on DT
   + volume contraction with ↑ PT reabsorption
8. decreased excretion of ***magnesium***

- ***Antihypertensive Action***

• given ***acutely*** in moderately large doses they result in decreased,

1. plasma volume & cardiac output
2. GFR & renal blood flow
3. mean arterial pressure

• ***chronically***, the doses required for antihypertensive efficacy is far less than that required for saluresis, kaluresis and loss of free water
• the urinary filtration fraction, renal vascular resistance and plasma renin activity rise modestly
• some of the initial reduction in plasma volume is recovered, with a mean reduction of ~ 5%
• CO & GFR return to pretreatment values
• potentiate the antihypertensive action of agents acting via other mechanisms
• antihypertensive effect in any given patient is unpredictable, however they are unlikely to be effective alone in severe hypertension

• the exact mechanism of their antihypertensive action is ***unclear*** & effects are probably multiple
• as plasma renin, noradrenaline and aldosterone all rise as compensatory mechanisms, therefore reduction in these is not involved
• ***saluresis*** appears to be the critical factor, as infusion of saline but not dextran, returns BP to pretreatment values

- ***Clinical Toxicity***

1. biochemical ***side-effects***
   i. hypokalaemia ± contraction alkalosis
   ii. metabolic alkalosis
   iii. azotaemia
   iv. hyperglycaemia - ↓ insulin secretion & ↓ glycogenesis
   - ↑ glycogenolysis
   v. hyperuricaemia
   vi. hypercalcaemia & hypophosphataemia - rarely with hyperparathyroidism
   vii. hyperlipidaemia
2. purpura, dermatitis, photosensitivity reactions - erythema multiforme
3. depression of the formed elements of blood - thrombocytopaenia
4. interstitial nephritis
5. necrotizing vasculitis
6. cholestatic hepatitis
7. pancreatitis

High-Ceiling / Loop Diuretics

- three commonly used agents, frusemide, bumetanide and ethacrynic acid
- these are structurally quite distinct and ***do not*** form a chemical class, only a pharmacological one

▪ *Mechanism of Action*

- inhibit ***chloride*** reabsorption in both ***medullary*** and ***cortical portions*** of the thick ascending limb of the LOH → ~ 15% + 10% of total Na^+ reabsorption
- when GFR is reduced by > 50% the thiazides lose most of their diuretic & antihypertensive action, and a loop agent will be more efficacious
- the site of action is at the ***luminal membrane***, to inhibit the Na^+-K^+-$2Cl^-$ ***cotransport*** mechanism
- frusemide & bumetanide are both ***sulphonamides***
  → ***carbonic anhydrase*** inhibitors *only in very high doses
- frusemide also increases ***venous capacitance***,
  1. ↓ PAOP - possibly via production of ***prostacycline***
  2. ↓ pulmonary oedema
  3. enhanced interstitial → intravascular fluid movement
     - tends to maintain intravascular volume during diuresis

▪ *Clinical Toxicity*

- two important generalisations,
  1. abnormalities of fluid & electrolyte balance are most common
     i. hypokalaemia
     ii. metabolic alkalosis
        - ↑ excretion of ***ammonia*** and ***titratable acid***
     iii. hyponatraemia
     iv. hypocalcaemia, hypomagnesaemia
        - ↑ excretion of both Ca^{++} and Mg^{++} in proportion to the naturesis
  2. side-effects unrelated to the primary action of these agents are rare
     i. hyperuricaemia - usually biochemical, clinical gout rare
     ii. GIT disturbances - with or without ulceration
     iii. depression of the formed elements of blood
     iv. skin rashes - bullous, urticarial
     v. paraesthesias
     vi. liver dysfunction
     vii. allergic interstitial nephritis - reversible renal failure
     viii. mild carbohydrate intolerance - frusemide only
     ix. ***deafness*** - ethacrynic acid >> frusemide >> bumetanide
        - ***synergistic*** with aminoglycosides

Spironolactone

• a ***17-spirolactone steroid*** which is a ***competitive antagonist*** of mineralocorticoids (***aldosterone***)
• the receptor is a cytoplasmic protein which appears to exist in two allosteric forms
• spironolactone (± its metabolite ***canrenone***) bind to this protein, therefore

1. prevent it from assuming the active conformation
2. are effective only in the presence of endogenous or exogenous aldosterone
3. may be overcome by increasing concentrations of mineralocorticoid

• the ***urinary Na^+:K^+ ratio*** serves as a direct index of aldosterone activity
• only ~ 5% of filtered Na^+ is handled in the DT, ∴ maximal diuresis is small
• often used to offset the kaluric/magnesuric effects of loop agents
• spironolactone also increases ***calcium*** excretion via a direct effect on tubular transport
• at very high concentrations, it also inhibits the biosynthesis of aldosterone, and may therefore have a direct diuretic action, however this is not observed clinically

- ***Clinical Toxicity***

a. principal toxic effects relate to ***hyperkalaemia***
b. gynaecomastia - due to androgen-like activity
c. minor GIT symptoms

- ***Clinical Uses & Dosage***

a. hypertension
b. refractory oedema - usually in conjunction with another diuretic
   - especially states of secondary hyperaldosteronism
c. diagnosis & management of primary hyperaldosterone states

• oral tablets as 25, 50 and 100 mg
• average daily doses ~ 100 mg/d in adults, and 3.3 mg/kg for children

▪ ***Other Potassium Sparing Agents***

• ***amiloride*** and ***triamterene*** appear to have identical mechanisms of action
• interfere with transport in the late segments of the nephron,

a. modest natriuresis - mainly accompanied by chloride

b. under normal conditions, there is little change in potassium excretion

c. when potassium excretion is high,

i. increased dietary intake

ii. concomitant use of a potassium wasting diuretic

iii. excessive mineralocorticoid activity

these agents result in a marked ***decrease*** in potassium excretion

NB: their action is similar to that of spironolactone, however,

i. they ***are not*** antagonists of aldosterone

ii. their principal effect appears to be to inhibit the luminal electrogenic entry of ***sodium*** in the distal tubule → decreased electrochemical gradient

iii. they also inhibit distal secretion of hydrogen ion
→ resulting in alkalinisation of the urine

▪ ***Carbonic Anhydrase Inhibitors Acetazolamide***

• major effects in the proximal tubule, at the luminal brush border
• the reduction in pulmonary CO_2 excretion is transient & clinically unimportant
• diuretic action is weak due to compensation by later tubular segments
• increases urinary excretion of Na^+, K^+ and HCO_3^- without altering chloride
• produce a clinical type II RTA

▪ ***Osmotic Agents Mannitol***

• non-absorbable, non-metabolised carbohydrate with MW ~ 182
• in controlled studies, prevention of ARF, or reduction in duration or mortality of ARF has ***not*** been demonstrated, except possibly post-transplantation
• majority of action is due to inhibition of NaCl & H_2O reabsorption in the ***ascending LOH***
• side effects,

a. initial ECF overload - exacerbation of CCF

b. hypotension - late volume depletion
- vasodilatation 2° hyperosmolality

c. factitious hyponatraemia
- not truely "factitious", actually hyperosmolar hyponatraemia

d. hyperosmolality

e. acute renal failure

Anuria

- ***Common***

a. "apparent" anuria 2° to dehydration

b. blocked catheter

3. bladder neck obstruction - benign / malignant

4. trauma - urethral
   - bladder

5. acute renal disease in patient with one functioning kidney

- ***Uncommon***

1. urethral obstruction - bladder calculus
   - stricture

2. bilateral ureteric obstruction - calculi
   - papillary necrosis
   - retroperitoneal fibrosis
   - retroperitoneal tumour
   - surgical misadventure

3. bilateral vascular obstruction - renal artery thrombosis
   - renal vein thrombosis
   - aortic dissection

4. acute renal failure - parenchymal diseases
   * usually oliguria, not anuria

5. congenital GUS anomalies

- ***Diagnosis***

a.	history		- pain, haematuria, urinary symptoms - surgery - drugs
b.	examination		- palpate bladder & kidneys - prostate - fluid status - lower limb ischaemia - place | flush | replace catheter
c.	investigations		
	i.	FBE	- infection, WCC - haemolysis, anaemia, thrombocytopaenia - eosinophilia - ESR
	ii.	electrolytes	- urea, creatinine - Na^+, K^+, HCO_3^- - LFT's, LDH
	iii.	AXR plain	- kidney position/size - calcification aorta/renal - bladder shadow
	iv.	abdominal U/S	- hydronephrosis - kidney size & morphology
	v.	perfusion scan	

Oliguria

Def'n: urine output **< 0.3-0.5 ml/kg/hr** < 400 ml/d
< 16 ml/hr

Knaus, OSF → *ARF*

1.	urine output	≤ 479	ml/24 hr or ≤ 158 ml/8 hr
2.	urea	≥ 36	mmol/l
3.	creatinine	≥ 270	µmol/l

- ***Common Causes***

1. hypovolaemia, dehydration
2. hypotension
3. sepsis
4. acute tubular necrosis
5. mechanical - catheter problems

- ***Aetiology***

1. ***prerenal*** - hypotension
   - dehydration, hypovolaemia
   - cardiac failure
   - sepsis
2. ***postrenal*** - obstruction, calculi
   - fibrosis
   - trauma, urethral damage
   - abdominal hypertension
3. ***intrinsic renal disease***
   - i. congenital - APKD, medullary sponge kidney
   - ii. ATN - haemorrhage
     - sepsis, shock
     - nephrotoxins
     - burns
     - pancreatitis
   - iii. glomerulonephritis
   - iv. hepatorenal syndrome
   - v. vascular events - emboli
     - thrombosis
     - fibrosis
4. raised intra-abdominal pressure

- ***Investigation***

a. history - CRF, preceding renal function
   - trauma, surgery

b. examination - volume status, perfusion
   - cardiac output, sepsis
   - catheter flush

c. uninalysis - M,C&S
   - SG, protein, Hb
   - sediment microscopy, casts

d. plasma / urine electrolytes and osmolality

e. specific investigations - plain AXR
   - renal U/S
   - IVP
   - renal biopsy
   - CT scan
   - technetium DPTA scan

Polyuria

Def'n: urine output > 5000 ml/d
> 200 ml/hr
> 500 ml/hr in severe cases

- mild polyuria, < 200 ml/hr, is common and usually ***benign***
  → seen in the recovery phase of many illnesses or postoperatively
- severe polyuria is less common and usually implies DI or polyuric renal failure

Common Causes

1. ↑ ECFV
   - excessive oral fluids, Na^+ intake
   - reabsorption of 3rd space losses
   - return of bowel function
   - supine posture
2. ↑ RBF
   - inotropes
   - theophylline
   - relief of raised intra-abdominal pressure, post-obstruction
3. ↓ tubular reabsorption
   i. acute renal failure
      - polyuric renal failure (Cr > 0.2)
      - recovery phase of ATN
   ii. diuretics
   iii. osmotic agents
      - mannitol, hyperglycaemia
   iv. hypothermia
   v. diabetes insipidus
      - central | nephrogenic
      - hypokalaemia, hypercalcaemia

Management

a. history
   - fluid intake
   - PH_X renal disease
   - surgery, trauma
   - drugs, etc.
b. examination
   - fluid status
   - mental state, etc.
c. uninalysis
   - M,C&S, SG, glucose
d. plasma/urine
   - Na^+, K^+ and osmolality
e. plasma biochemistry
   - glucose, Ca^{++}, K^+, $HPO_4^=$
   - urea and creatinine
f. specific investigations
   - CXR, fluid status
   - ADH assay (DDAVP challenge)

- ***Classification***

a. ***water / saline excess***
   i. IV fluids
   ii. reabsorption of 3rd space losses
   iii. hypothalamic thirst disorder
   iv. psychogenic polydipsia
   v. drug induced polydipsia
      - anticholinergics
      - thioridazine, chlorpromazine

b. ***osmotic diuresis***
   i. hyperglycaemia
   ii. uraemia
   iii. drugs
      - mannitol
      - hypertonic dextrose, dextrans
      - IV contrast media

c. ***central DI***
   i. idiopathic ~ 30%
   ii. traumatic ~ 30%
      - CHI
      - surgery
   iii. neoplastic
      - 1° & 2° , especially breast & lung
   iv. vascular lesions
      - post-partum necrosis
      - aneurysm
      - hyperviscosity syndrome
   v. chronic inflammatory
      - TB, sarcoidosis
   vi. hypoxic brain damage

d. ***nephrogenic DI***
   i. congenital and familial
   ii. hypercalcaemic
      - hyperparathyroidism, nephrocalcinosis
   iii. hypokalaemic
      - diuretic abuse
      - Conn's syndrome, ? Bartter's
   iv. renal failure
      - post-obstructive
      - pyelonephritis
      - ATN recovery
      - transplantation
      - polycystic disease
   v. drugs
      - diuretics
      - lithium, demeclocycline
      - methoxyflurane, F^-
   vi. systemic disease
      - amyloid
      - sickle cell disease
      - myeloma

ACUTE RENAL FAILURE

Def'n: any reduction in renal ***excretory function*** sufficient to result in retention of nitrogenous waste:

1.	biochemistry	- urea	**> 20 mmol/l**
		- creatinine	**> 0.2 mmol/l**
		- U/P creatinine	**< 20** "filtration failure"
2.	persistent GFR	**< 15-20**	**ml/min**
		< 10-15	ml/min/m^2
3.	urinary indices	- Na^+ & osmolality $\rightarrow$ tubular dysfunction	
4.	urine output	< 0.3-0.5 ml/kg/hr	
		* but "oliguria" ≠ ARF	

▪ ***Causes of Acute Renal Failure***

• LIGW states, 'prerenal' and 'postrenal' failure should be considered as respective ***azotaemia syndromes***, and not included in the causes of ARF, as they do not indicate intrinsic renal disease
• however, prolonged pre/post-renal disease will result in structural renal damage

a. prolonged impairment of ***renal blood flow***
   i. hypovolaemia, dehydration
   ii. hypotension
   iii. cardiac failure
   iv. renovascular disease
   v. intra-abdominal hypertension
   vi. hepatorenal disease

b. ***intrinsic renal disease***
   i. glomerulonephritis
   ii. nephrotoxic tubular disease - ATN
   iii. ischaemic tubular disease ? ATN
   iv. interstitial nephritis
   v. infection - bacteria, TB
   vi. infiltration
   vii. trauma

c. ***obstructive renal disease***
   i. calculi, prostatic, stricture
   ii. trauma, surgical, retroperitoneal fibrosis

d. ***alternative classification***
   i. filtration failure
   ii. tubular dysfunction
   iii. oliguric or non-oliguric

- ***Risk Factors***

1.	***acute disease states***	- sepsis, SIRS - jaundice, liver dysfunction - raised intra-abdominal pressure - renal trauma, soft tissue trauma - transfusion reaction, DIC - anaphylaxis, anaphylactoid reactions - muscle injury, thermal burn, electrocution
2.	***chronic disease states***	- advancing age - diabetes mellitus - renal disease - hyperuricaemia - vascular disease
3.	***physiologic changes***	- advancing age - tachycardia, hypotension - ↑ CVP, ↓ RVPP - high or low CO, SVR - abnormal O_2 extraction ratio - oliguria, polyuria, osmolar diuresis - abnormal urine indices ± fluid balance, oedema - high or low protein intake
4.	***chronic drug therapy***	- NSAID's, diuretics, cyclosporin, ABx
5.	***acute drug therapy***	
	i. ***ATN***	- aminoglycosides, amphotericin, cephalosporins - diuretics, radiocontrast agents, rifampicin - lithium, cisplatin, mithramycin
	ii. ***interstitial nephritis***	- penicillins, cephalosporins, sulphonamides, rifampicin - frusemide, thiazides, triamterene - aspirin, NSAID's - cimetidine, captopril
6.	***procedures***	- aortic, renal cross-clamping - transfusion - surgery (CNS, thoracic, major abdominal/orthopaedic)
7.	***impaired RBF***	- hypotension, malignant hypertension - renal artery occlusion - hepatorenal failure - endotoxaemia - renal vein thrombosis - renal venous hypertension (CVP, IABP, abdo surgery) - HUS, TTP, PAN, DIC

h. ***toxic causes***

i. drugs

- aminoglycosides, amphotericin, allopurinol, cephalosporins, chemotherapeutic agents, hydrallazine, EDTA, lithium, mannitol, methoxyflurane, paracetamol, penicillamine, probenecid, procainamide, propylthiouracil, radiocontrast media, rifampicin, sulphonamides, thiazides, vit. D

ii. toxins

- CCl_4, ethylene glycol, heroin, $HgCl_2$, heavy metals, methanol, organophosphates, toluene, uranyl nitrate

i. ***metabolic causes***

i. electrolytes - hyper-Ca^{++}, hypo-K^{+}
- hyperphosphataemia

ii. metabolites - hyperuricaemia
- pigments (bilirubin, myoglobin, Hb)

iii. high plasma oncotic pressure

j. ***post-renal*** - urethral/bladder neck obstruction
- bilateral ureteral obstruction
- stones, clot, tumour
- papillary necrosis
- retroperitoneal fibrosis
- surgical ligation
- bladder rupture, urethral trauma
- renal pelvic trauma

Acute Tubular Necrosis

- the most common cause of ARF in ICU (~ 70%), most are ***multifactorial***
- the associated ***mortality ~ 30-60%***
- those at ***high risk*** (50-70%) are those associated with,
    1. oliguria
    2. trauma, postoperative
    3. sepsis
    4. underlying poor medical condition
    5. elderly

- those at ***lower risk*** are associated with,
    1. polyuria → mortality ~ 26%, cf. 50% in oliguric ARF
    2. nephrotoxic
    3. obstetric

- ***Aetiology***

    a. factors which interfere with ***renal blood flow***
        i. cardiogenic shock - ischaemia, arrhythmia, myopathy
        ii. hypovolaemia, hypotension, dehydration
        iii. SIRS, severe sepsis, pancreatitis, burns
        iv. severe pre-eclampsia, eclampsia
        v. severe renovascular disease
        vi. scleorderma, malignant hypertension, DIC, TTP, rhabdomyolysis, haemolysis
        vii. hepatorenal syndrome
        viii. intra-abdominal hypertension
        ix. mechanical ventilation
        x. prolonged aortic cross-clamping

    b. ***nephrotoxic agents***
        i. endogenous - myoglobin, haemoglobin, severe hypercalcaemia, urate
        ii. exogenous
            - antibiotics - aminoglycosides, cephalosporins, sulphonamides
              - amphotericin, rifampicin
            - cytotoxics - cyclosporin, cisplatin, methotrexate, mithramycin
            - radiocontrast media
            - other drugs: ACE inhibitors, allopurinol, hydrallazine, EDTA, lithium, mannitol, methoxyflurane, paracetamol, penicillamine, probenecid, procainamide, propylthiouracil, thiazides, vit. D
            - toxins: CCl_4, ethylene glycol, heroin, $HgCl_2$, heavy metals, methanol, organophosphates, toluene, uranyl nitrate

Initiation Phase ATN

- ***Ischaemia***

• initiation phase of both ischaemic and nephrotoxic ATN is thought to relate to renal ischaemia
• ↓ GFR being secondary to afferent arteriolar constriction,

1. sympathetic stimulation
2. intra-renal renin-angiotensin activation
   - ***tubuloglomerular feedback*** prevents large losses of Na^+ which would otherwise occur with failure of reabsorption ("acute renal success")
   - however, frusemide which inhibits TGF does not protect against ATN
   - interruption of the renin-angiotensin axis does not protect against ATN
3. inhibition of renal synthesis of PGE_2
4. ↓ ANH
5. ↑ ADH
6. ↑ adenosine *vasoconstrictor in renal vasculature
7. ↑ endothelin

- ***Nephrotoxins***

• prerenal hypoperfusion markedly increases susceptibility to ATN from nephrotoxic agents
• presumably due to increased tubular concentration (∴tubular cell []'n) & transit time
• protection from toxic agents is afforded by saline loading (± mannitol) which increase proximal tubular flow, cf. frusemide which only increases distal flow
• studies with radiocontrast agents show ***no benefit*** from mannitol, and in the presence of background disease (IDDM) actually enhances toxicity

Maintenance Phase ATN

• GFR commonly **< 5%**
• RBF is usually ~ 25-50% of normal
• factors acting to maintain filtration failure,

1. tubular ***obstruction***
   - micropuncture studies have often (not always) shown increased pressure
2. tubular ***backleak***
   - probably only a minor role in overall reduction in GFR
3. ***vasodilatation*** of the efferent arteriole - minor
4. decreased glomerular membrane ***permeability*** - unlikely, no structural defect

- ***Mechanism of Oliguria***

a. glomerulo-tubular balance

b. decreased glomerular permeability

c. intratubular obstruction

d. interstitial oedema

e. cortical ischaemia

- ***Drugs***

1. aminoglycosides
   - peak levels correlate with bactericidal activity
   - ***trough levels*** correlate more closely with clinical toxicity
   - toxicity less with single daily doses, greater with infusions, due to ***saturable uptake*** mechanism for aminoglycosides
2. amphotericin B
   - toxicity increases with a ***cumulative dose*** **> 2-3g**
   - average dose 0.5 mg/kg/d for 70 kg → 70 days
   - initial disorder is ***distal tubular*** dysfunction with,

   i. nephrogenic DI

   ii. distal RTA

   iii. magnesium & potassium wasting
   - similar pattern seen with ***cisplatin***
3. NSAIDs
   - interfere with renal PG synthesis and increase incidence of ATN in hypoperfusion
4. radiocontrast media
   - potentiate ARF with hypoperfusion, shock states & sepsis
   - appear to be little difference between older agents & newer non-ionic, low osmolality contrast media

- ***Uric Acid Nephropathy***

- three types of renal lesion,

1. interstitial parenchymal urate deposition & CRF
2. nephrolithiasis
3. ATN
   - especially if plasma level rises acutely
   - eg. tumour lysis syndrome, treatment of haematological malignancy

- ***ATN Risk Factors***

a. ***preoperative***

i.	patient factors	- age > 50 - PH_X renal disease, hypertension - diabetes - drugs (as above)
ii.	delayed resuscitation	- prolonged dehydration - hypoxia, hypovolaemia, hypotension
iii.	disease factors	- biliary tract sepsis, jaundice - other sepsis - major trauma

b. ***intraoperative***

i.	prolonged hypovolaemia, hypotension	
ii.	anaesthesia	- GA > LA - mechanical ventilation
iii.	surgery	- site and duration - major intra-abdominal, vascular - cardiothoracic - major trauma

c. ***postoperative***

i.	prolonged hypovolaemia, hypotension, haemorrhage	
ii.	intra-abdominal hypertension ³ **30 mmHg**	
iii.	pancreatitis	
iv.	sepsis	
v.	mechanical ventilation	
vi.	drugs	- as above

d. ***non-surgical ATN***

i.	dehydration, hypovolaemia, hypotension	
ii.	aminoglycoside excess	
iii.	pigmenturia	- rhabdomyolysis, haemolysis
iv.	hepatic failure	

- ***Histological Lesion***

  a. ***nephrotoxic lesion***
     - tubular epithelial necrosis with ***BM sparing***
     - epithelial regeneration takes days
     - frequently non-oliguric

  b. ***ischaemic lesion*** → ***tubulorrhexis***
     - loss of tubular epithelium and BM
     - epithelial regeneration takes weeks
     - found in most cases of ATN

Complications of ARF/ATN

a. ***oliguria*** - absolute < 400 ml/d ~ 80%
- relative, non-oliguric ~ 20%

b. ***azotaemia***
- normal solute load ~ 600 mosm/d
  maximum [urine] ~ 1200 mosm/l → ~ 500 ml/d obligatory volume
- in catabolic states ~ 1000-1500 mosm/d
  ARF maximum [urine] ~ 350 mosm/l → ~ 3-4 l/d required urine volume
- δ [urea] / d ~ 5-10 mmol/l/d (lower in afebrile, non-catabolic)
- δ [Cr] / d ~ 0.05-0.15 mmol/l/d

c. ***biochemical***

i. ↑ $NaCl / H_2O$ - hypertension, hypo-Na^+, oedema

ii. ↑ $[K^+]$ ~ 0.3-0.5 mmol/l/d (non-catabolic)
- if initially 3.5 mmol/l and symptoms at ~ 6.5 mmol/l, then will take 6-10 days

iii. ↑ $[HPO_4^=]$ ~ 2-2.5 mmol/l
- ↑ cellular release & catabolism / ↓ renal excretion

iv. ↓ $[Ca^{++}]$ ~ 1.5-2.2 mmol/l
- mechanism unclear ? $[Ca^{++}].[PO_4^=] < 5$

v. ↑ $[Mg^{++}]$ - mild, higher if present in dialysate or antacids

vi. ↑ [uric acid]

vii. ***metabolic acidosis*** → ↓ HCO_3^- ~ 1-2 mmol/l/d
- non-volatile acid production is much higher
  → ~ 1 mmol/kg/d of $SO_4^=$ & $PO_4^=$, excluding lactate
- $[HCO_3^-]$ - rarely < 12 mmol/l
- anion gap - rarely > 23

d. ***haematological***

i. normochromic normocytic anaemia → Hct ~ 20-30%
- haemodilution, haemolysis, blood loss
- impaired synthesis, decreased erythropoietin

ii. thrombocytopaenia & platelet dysfunction

iii. leukocyte dysfunction - production usually normal ± leukocytosis

e. ***immunosuppression***
- lymphopaenia, lymphoid atrophy
- reduced IgG, complement
- impaired PMN chemotaxis, normal number
- impaired acute inflammatory response and delayed hypersensitivity
- drug effects, steroids, cyclosporin
- ***infections*** → 30-70%, lung, urine, wound, line

f.	***cardiovascular***	- CCF, hypervolaemia - hypertension, 25% after 2 weeks - arrhythmias, pericarditis, effusion
g.	***GIT***	- anorexia, nausea, vomiting, ileus - haemorrhage ~ 10-30%, usually mild
h.	***neurological***	- lethargy, somnolence, confusion - asterixis, myoclonic twitches, seizures - increased sensitivity to anaesthetic agents

- ***Causes of Pulmonary Infiltrates in ARF***

a.	LVF / CCF	
b.	bacterial pneumonia	
c.	atypical pneumonia	- viral, mycoplasma, Legionaire's disease, etc.
d.	septicaemia	
e.	ARDS	
f.	autoimmune diseases	- Goodpasture's - SLE, polyarteritis nodosa, systemic sclerosis - Wegener's granulomatosis
g.	disseminated TB	

• recent paper stating cANCA +'ve patients more common cause of renal dysfunction & pulmonary haemorrhage cf. Goodpasture's syndrome (Niles, AIM 1996)

- ***Causes of Acidosis in ARF***

a. early
   i. ***tubular dysfunction***, reduced H^+ secretion
   ii. hyperchloraemic metabolic acidosis
   iii. normal anion gap

b. later
   i. ***glomerular dysfunction***
   ii. accumulation of organic acids ($HSO_4^=$, $HPO_4^=$)
   iii. high anion gap acidosis
   iv. rarely → AG > 23 / HCO_3^- < 12 mmol/l

c. other causes
   - ARF 2° low cardiac output → lactic acidosis
   - respiratory failure → respiratory acidosis
   - starvation in RF → ketoacidosis
   - rhabdomyolysis, accumulation of organic acids, hyperkalaemia & high AG acidosis

NB: non-volatile acid production ***~ 1 mmol/kg/day***
HCO_3^- falls 1-2 mmol/l/day in ARF

Investigations

- ***Biochemistry***

Urinary Indices of Renal Failure		
Parameter	**Pre-renal ARF**	**ATN**
urine osmolality	> 500	< 350 mosm/l
U/P osmolality	> 1.8	~ 0.8-1.2
urine SG	> 1.020	~ 1.010-1.015
urine [Na^+]	< 20	**> 40** mosm/l
urine [Cl^-]	< 20	**> 20** mosm/l
U/P urea	> 8	≤ 3 rarely ≤ 8
U/P creatinine	> 40	< 20
RFI	< 1	> 1
FE_{Na}	< 1	> 1

Def'n: RFI = ***renal failure index*** = urine [Na^+] / [U/P creatinine]

FE_{Na} = % fractional excretion Na^+ = [U/P Na^+].100 / [U/P creatinine]

- ***Abnormal Urea/Creatinine Ratio***

Def'n: normal U:C ratio ~ 100:1 (R: 70-150)
> 200:1 is indicative of ***pre-renal*** disease

1. high ratio
   - i. ↑ urea
     - dehydration, hypovolaemia
     - GIT bleeding
     - catabolic states, sepsis
     - hyperalimentation
     - drugs: tetracyclines, steroids
   - ii. ↓ creatinine
     - elderly, low muscle mass
2. low ratio
   - i. ↓ urea
     - liver failure, protein malnutrition
     - hepatorenal syndrome
   - ii. ↑ creatinine
     - rhabdomyolysis
     - acute muscular diseases
     - ketones, cephalosporins (factitious)

- ***Urinary Sediment***

1. cast types
   - i. hyaline casts — fever, diuretics, exercise; renal diseases
   - ii. red cell casts — glomerulonephritis
   - iii. white cell casts — pyelonephritis
   - iv. waxy casts — chronic renal disease
2. clinical syndromes
   - i. ATN — granular, cellular & pigmented casts; epithelial cells
   - ii. GN — RBC's, RC-casts, proteinuria, lipid
   - iii. pyelonephritis — WBC's, WC-casts, proteinuria
   - iv. interstitial nephritis — WBC's, WC-casts, cellular casts; ***eosinophils***, epithelial cells, protein and lipid

- ***Imaging***

1. ultrasound
   - 93-98% sensitivity for detection of renal tract obstruction
   - also assesses renal size, cortex/medullary morphology
2. CT scan
3. IV pyelogram
4. radio-isotope perfusion scan
5. renal angiogram

NB: 2-5 may effectively assess renal perfusion, vascular supply

- ***Renal Biopsy***

1. glomerulonephritis
2. vasculitis
3. SLE
4. Goodpasture's syndrome
5. TTP
6. interstitial nephritis
7. oliguria lasting > 8 weeks

Renal Failure - Frusemide

- ***Beneficial Effects***

  a. ↑ tubular and urine flow

  b. ↑ Na^+ and osmolar clearance

  c. ↓ tubular O_2 demand

  d. ***decreases GFR*** ∝ tubuloglomerular feedback (TGF)
  → ↓ O_2 demand

  e. ?? conversion of oliguric to non-oliguric renal failure

- ***Deleterious Effects***

  a. hypovolaemia

  b. hypokalaemia, hyponatraemia

  c. direct ***nephrotoxicity*** - idiosyncratic ***interstitial nephritis***

  d. ***ototoxicity*** > 4 mg/min, or (250 mg → 60 mins)
  > 80-100 µg/ml

  e. additive toxicity with other drugs, esp. aminoglycosides

  f. ***decreased GFR*** - TGF (↑ Na^+ excretion → ↓ GFR)

• beneficial uses in ***non-renal failure***,

  a. fluid overload states - absolute & relative (CCF)

  b. cerebral oedema

  c. hyperkalaemia

  d. hypercalcaemia ? this is no longer recommended

  e. ?? renal protection - ↓ O_2 demand

• problems with most frusemide studies,

  a. diagnosis of ARF unclear
     - especially distinction of ATN from pre-renal ARF

  b. different risk groups
     - obstetric & medical have better prognosis than surgical and post-traumatic

  c. uncontrolled, or retrospective controls

  d. variability in drug dosages

  e. small numbers

- ***Brown, Ogg, Cameron Clin. Nephrol. 1981***

• randomised controlled trial of high dose frusemide, 1 ± 3 g/day
• predominantly surgical and post-traumatic renal failure, ie. ***high risk***
• continuous frusemide infusion,

1. non-oliguric converted to ***polyuric*** renal failure ~ 80%
   or polyuria maintained ~ 100%
2. ***no difference*** in,
   i. the number of dialysis runs required → 7 vs 6
   ii. mortality
   iii. biochemical renal recovery
3. 2 patients suffered ***ototoxicity***

- ***Klienknecht et al. Nephron 1976***

• randomised controlled trail, high dose frusemide, 1.5-6 mg/kg q4h
• 50% surgical or traumatic, 22% obstetric
• ***no difference*** in the number of dialysis runs required, nor the oliguric period

- ***Lucas et al. Surgery 1977***

NB: "frusemide does not protect against renal failure"

• frusemide 0.5 mg/kg given to 45 post-traumatic (incipient) renal failure patients after ***volume loading***,

1. resulted in an increase in Na^+ and osmolar clearance
2. ***no change*** in,
   i. GFR
   ii. RBF
   iii. intrarenal distribution of blood flow
3. 10% developed ***hypotension*** 2-10 hrs following administration

• questions ??

1. adequacy of the volume loading used
2. would results have been the same if volume status was maintained

Renal Failure - Prophylaxis & Protection

- ***Methods***

1. ***physiological***
   - i. blood volume
   - ii. cardiac output → RBF/GFR
   - iii. O_2 delivery
   - iv. sodium excretion
   - v. nutrition
2. ***physical***
   - i. detection / management of intra-abdominal hypertension
   - ii. detection / management of post-renal obstruction
   - iii. limitation of aortic clamp times
   - iv. avoidance of embolisation
   - v. minimise direct trauma
3. ***pharmacological***
   - i. avoid nephrotoxins - antibiotics, pigments, contrast dyes, etc.
   - ii. avoid inhibitors of autoregulation - NSAID's
   - iii. diuretics
   - iv. renodilators
   - v. other agents - free radical scavengers
     - Ca^{++}-channel blockers, etc.
4. ***dialytic therapies***
5. ***monitoring*** ?? improvement in outcome

- ***Physiological Defence***

1. defence of blood volume - IV fluids (Na^+ containing[§])
   - euvolaemia or mild hypervolaemia
2. maintenance of CO ± MAP - IV fluids
   - R_X of arrhythmias
   - inotropes
3. high sodium excretion[§] - ↓ tubular reabsorption → ↓ renal VO_2
   - theoretical, ***volume*** more important
4. maintain DO_2 - normal [Hb], S_pO_2 and avoidance of hypercarbia/acidosis
5. nutrition ? probable benefit in ***outcome***, not absolute

- ***Diuretics***

1. ***mannitol***
   - found to be protective in many animal studies
   - both for ischaemic (NA & renal artery clamping) and nehprotoxic models
   - few human studies, most uncontrolled
     → reversal of oliguria but ***not*** renal function
   - proposed mechanisms of action,

   i. osmotic diuresis

   ii. "anti-sludging" tubular cytoprotection

   iii. ↑ renal vasodilatory PG synthesis

   iv. free-radical scavenger

   - LIGW states, ***no controlled trials***,
     ∴"not recommended as a renal protective agent"
   - Conger, AJKD 1996, "possible benefit post-transplantation, no proven benefit in any other scenario, possibly detrimental in radiocontrast studies"

2. ***frusemide***
   - animal studies variable → some benefit in ***ischaemic***, but not in nephrotoxic injury
   - conflicting results for prophylactic use in surgical patients
   - effects are negligible once ***volume*** is aggressively controlled
   - no overall benefit in established oliguric renal failure
   - theoretical benefit in ***critical ischaemic lesion*** (↓ O_2-demand)

   NB: Brown, Ogg & Cameron (Clin. Nephrology, 1980)

   i. non-oliguric converted to polyuric renal failure ~ 80%
   polyuric renal failure maintained ~ 100%

   ii. no difference in the number of ***dialysis runs*** required (7 vs 6)

   iii. no difference in ***mortality***

   iv. no difference in biochemical ***renal recovery***

- however, in this study, the controls received 1g of frusemide over 4 hrs
- there were only 50 patients total, ~ 25 in each group
- if we accept that non-oliguric renal failure has a better prognosis than oliguric renal failure, then why didn't conversion to the former improve prognosis ??
- all patients were in established ARF, no good RCT looking at 'prevention'

1. ***low dose dopamine***
   - ↑ DO_2 via modest ↑ CO (~ 20% on low dose), and usually an ↑ RBF
   - potential ↓ renal VO_2 due to inhibition of Na^+ reabsorption
   - potential renal vasodilator in normal man, but ?? not in ***septic*** patients
   - conflicting animal evidence regarding protective effect
   - known ***diuretic effect*** → demonstrated in uncontrolled human studies
   - no controlled human studies looking at long term renal function or mortality
   - adverse effects include,

   i. extrarenal side-effects
      - tachyarrhythmias
      - ↑ PCWP, RV & LV afterload
      - ↑ shunt fraction & ↓ P_{aO2}
      - ↓ central respiratory drive
      - ↓ TSH release & ? other anterior pituitary function

   ii. impairs TGF mechanism, thereby may worsen regional O_2 supply/demand

   iii. the induced diuresis is not always associated with an increase RBF

   iv. diuresis may mask, or augment hypovolaemia & renal hypoperfusion

   - similar ↑ RBF achievable with inotropes ***not*** affecting tubular function
   - tubular & DA_1-receptor effects blocked by commonly used drugs

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NB: "if ***dopamine***, or other ***diuretics*** are used in the setting of ARF, then greater attention must be paid to the basic elements of critical care - blood volume, renal perfusion pressure (MAP) and cardiac output - as urine output can no longer be used as a guide to the adequacy of RBF" (Duke, Bersten AIC 1992)

▪ ***Other Agents***

- Ca^{++} entry blockers, proven ***lack*** of benefit in ARF
- may be of some benefit post-transplantation (Conger, AJKD)
- agents investigated but inadequate studies,

1. ATP-$MgCl_2$
2. inosine
3. clonidine
4. chlorpromazine

Management ARF

1. ***dialysis***
   - indications
   i. fluid overload | pulmonary oedema
   ii. hyperkalaemia
   iii. metabolic acidosis, refractory to R_X
   iv. uraemic symptoms | complications (Ur > 50 mmol/l)
   v. hyperuricaemia
   - aim in maintenance phase for - creatinine ~ 200-400 µmol/l
     - urea ~ 20-40 mmol/l
2. management of ***uraemic complications***
   i. pericarditis, effusion
   ii. anaemia, thrombocytopaenia, bleeding tendency
   iii. encephalopathy, myopathy, neuropathy
   iv. peptic ulcer disease
   v. infections | sepsis
3. biochemical homeostasis
4. nutrition
   - some poorly controlled studies suggest improved survival with use of TPN
5. monitor drug therapy / avoid nephrotoxic agents
6. normalise intra-abdominal pressure - aim for < 20 cmH_2O

NB: maintenance of volume status & biochemical normality during polyuric recovery phase

- other therapies of little or no use,
   1. Ca^{++} chanel blockers * except transplants
   2. adenosine receptor antagonists - aminophylline
   3. oxypentifylline
   4. chlorpromazine
   5. clonidine
   6. ATP-$MgCl_2$
   7. ANF

Nephritic Syndrome

- ***Essential Features***

1. usually sudden onset
2. ***haematuria*** and RBC casts
3. ***hypertension*** > 140/90 mmHg (or > 20% increase)
4. biochemical renal insufficiency
   i. ↑ creatinine > 0.14 mmol/l
   ii. uraemia > 20 mmol/l
5. mild ***oedema*** - usually facial
   - rarely generalized
6. mild ***proteinuria*** < 3 g/d
7. ↑ ESR
8. hypergammaglobulinaemia
9. low ***complement*** levels,
   i. low $C_{3,4}$ → "classical" pathway activation
   ii. low C_3 / normal C_4 → "alternative" pathway

NB: ***alternate pathway*** activation seen in ***membranoproliferative GN***

- ***Aetiology Common***

a. post-streptococcal GN
b. Goodpasture's syndrome
c. SLE
d. Henoch-Schönlein purpura
e. polyarteritis nodosa

Nephrotic Syndrome

- ***Essential Features*** ® ***Leaky Glomeruli***

  a. ↑ creatinine and urea
  b. generalized ***oedema***
  c. heavy ***proteinuria*** > 3.5 g/d
  d. hypoalbuminaemia < 20 g/l
  e. hyperlipidaemia / lipiduria
  f. ± hypertension
  g. ***no*** haematuria
  h. oliguria
  i. usually insidious onset

- ***Aetiology***

  a. ***primary glomerular lesions*** **~ 75%**
     i. membranous GN ~ 40%
     ii. minimal change GN ~ 15% adult / 80% children
     iii. focal glomerulosclerosis ~ 15%
     iv. proliferative GN
        - membranoproliferative ~ 7%
        - mesangioproliferative ~ 5%
        - other - crescentic, focal

b. ***secondary glomerular lesions*** **~ 25%**

i. ***diabetes mellitus***

ii. infections
- post-streptococcal, bacterial endocarditis, shunt infections
- leprosy, syphilis, HBV, EBV, malaria, schistosomiasis, filariasis

iii. drugs
- gold, penicillamine, probenecid, antivenoms / antitoxins
- contrast media, captopril, street heroin

iv. collagen-vascular disease
- SLE, PAN, Henoch-Schönlein purpura, Goodpastures'
- necrotising vasculitis (inc. Wegener's), dermatomyositis

v. malignancy
- Hodgkin's & NH lymphomas, leukaemia, carcinoma (breast, GIT), melanoma
- Wilm's tumour, multiple myeloma

vi. familial
- sickle cell disease**,** Alport's syndrome (sensorineural deafness)

vii. miscellaneous
- sarcoidosis, amyloidosis
- pre-eclampsia, renovascular hypertension
- thyroiditis, myxoedema, morbid obesity
- renal transplant rejection
- vesico-ureteric reflux

DIALYTIC THERAPIES

- ***Indications***

1. acute reversible ***renal failure*** - especially in critically ill
   i. hyperkalaemia
   ii. fluid overload | pulmonary oedema
   iii. refractory metabolic acidosis
   iv. uraemic symptoms / complications
   v. hyperuricaemia
2. ***fluid overload*** states - refractory to conventional therapy
3. ***drug overdosage***
   i. lithium
   ii. methanol, ethylene glycol, isopropanol
   iii. salicylates
   iv. rarely - theophylline, barbiturates
4. ***plasmapheresis***
   i. hyperviscosity syndromes
   ii. GB syndrome
   iii. myasthenia
5. ***haemoperfusion***
   - theoretical advantages for lipid soluble / highly protein bound molecules
   - studies have ***not*** shown improved morbidity/mortality
   - severe ***thrombycytopaenia*** is a common side-effect
   - recently developed ***polystyrene resins*** (Amberlite XAD-4) have high affinity for lipid soluble compounds and have a clearance ~ **2x** charcoal
6. research
   i. hepatic encephalopathy
   ii. septicaemia / SIRS

- ***Techniques***

Def'n: ***dialysis*****:** ***solute*** diffusion through a semipermeable membrane, driven by the electrochemical activity gradient for each molecular species

ultrafiltration**:** ***solvent & solute*** transfer through a semipermeable membrane, driven by the hypdrostatic & osmotic pressure difference across the membrane

1. ***SCUF*** - slow continuous ultrafiltration
   - usually only used for excess fluid removal
   - clearance of urea, with 3000 ml/hr filtrate, is only 50 ml/min
2. ***haemofiltration*** *CAV or CVV + **HF**
   - uses ultrafiltration only to remove solvent & solute
   - filtrate replacement either pre/post-filter
   - pre-filter dilution may increase urea clearance up to 20%
   - results in better CVS stability, see later
   - major advantages are simplicity, no requirement for dialysate solution
   - major disadvantages are potential fluid imbalance due to large volumes filtered
3. ***haemodialysis*** *CAV or CVV + **HD**
   i. intermittent
      - conventional haemodialysis = dialysis + ultrafiltration

   ii. continuous
      - most commonly used in ICU → CVVHD
4. ***haemodiafiltration*** *CAV or CVV + **HDF**
5. peritoneal dialysis

- ***Filter Membranes***

a. surface area ≥ BSA x $0.75m^2$ for maximal solute clearance

b. material
   i. cellulose - cuprophane
      - regenerated cellulose, cellulose acetate

   ii. synthetic - polyacrylnitrile (PAN)
      - polymethylmethacrylate (PMMA)
      - polysulphone, polyamide, polycarbonate

c. geometry
   i. hollow fibre - minimize extracorporeal blood volume

   ii. plate

- ***Membrane Selection***

• synthetic membranes →

a. ↓ platelet sequestration
b. ↓ neutrophil activation
c. ↓ IL-1 production from monocytes
d. higher ***hydraulic permeability***, ∴ preferred for HF
e. more effective solute clearance
f. longer filter life
g. more rapid resolution of ARF & lower mortality (Hakim *et al.*, J.A.Soc.Neph. 1994)

Haemofiltration

- ***Advantages***

1. cardiovascular stability
2. correction of,
   i. electrolyte & acid-base abnormalities
   ii. fluid overload
3. creation of "fluid space" for TPN, ABP, drugs, etc
4. low & middle MW molecule clearance
   i. renal and hepatic failure metabolites
   ii. mediators of systemic inflammatory response syndrome
5. maintenance of oncotic pressure - albumin replacement
6. avoids rises in ICP with haemodialysis

- ***Problems***

1. slow electrolyte removal
2. large volumes removed - potential for hypo/hypervolaemia
3. systemic anticoagulation
4. thrombocytopaenia
5. technical difficulties
   i. access
   ii. haemorrhage, thrombosis
   iii. infection
   iv. other complications

- ***Methods to Improve Clearance***

a. increase filter blood pressure / flow - pumped
- short, wide-bore lines

b. ***pre-dilution*** - non-classical haemoperfusion

c. ultrafiltrate "suction"

d. counter-current dialysate - ie. haemodialfiltration

e. plate filter

Haemodialysis

1. intermittent vs continuous
2. CAV vs CVV *vascular access
3. anticoagulation

- ***Dialysate***

• acetate or lactate are added due to poor stability of ***bicarbonate*** in solution
• normal individuals can metabolise up to **300 mmol/hr** of acetate, largely in skeletal muscle
• this is significantly reduced in critically ill patients
• high ***acetate*** levels →

a. fatigue, dizziness, headache, nausea

b. hypoxia

c. hypotension

NB: ∴lactate often used in critically ill

• ***lactate*** metabolised mainly in the liver, ∴solutions should be avoided in hepatic failure
• bicarbonate solutions result in fewer problems, however Ca^{++} & Mg^{++} cannot be added directly

- ***Gambro Solution #1***

1.	Na^+	140	mmol/l	
2.	Cl^-	102	mmol/l	
3.	**K^+**	**1.0**	**mmol/l**	
4.	Ca^{++}	1.6	mmol/l	* no protein, ∴predominantly ionized
5.	Mg^{++}	0.82	mmol/l	
6.	**lactate**	**45**	**mmol/l**	* both D & L-lactate
7.	glucose	10.9	mmol/l	
8.	osmolality	285	mosmol/kg	

Disequilibrium

- usually patients with moderate to severe azotaemia dialysed too rapidly
- results in ***cerebral oedema*** due to rapid reduction in ECF ***urea*** with insufficient time for diffusion
- causes headache, dizziness, agitation, N&V, seizures and coma

Hypoxaemia

- occurs during the first 1-2 hrs, usually more marked with ***acetate***
- ? because greater capacity for metabolism

a. loss of CO_2 in the dialysate

b. consumption of CO_2 with regeneration of HCO_3^- from lactate/acetate

c. subsequent ***hypoventilation***

d. membrane dependent mechanisms - C' activation, platelet activation, etc.

Compounds Removed by Haemodialysis

a. antibiotics
   - aminoglycosides
   - most cephalosporins & penicillins - not cefamandole or cloxacillins
   - metronidazole, chloramphenicol, sulphonamides
   - some anti-TB drugs
   - acyclovir

b. hypnosedatives - phenobarbitone
   - lithium, meprobamate

c. antiarrhythmics - procainamide, quinidine, disopyramide

d. antihypertensives - diazoxide, nitroprusside
   - methyldopa

e. endogenous metabolites- lactic acid, uric acid, etc.

f. others - immunosuppressive agents
   - alcohols, paraquat
   - aspirin, theophylline (?), cimetidine

CAVH vs. Conventional Dialysis Techniques

- ***Advantages CAVHD***

1. cardiovascular stability
2. better middle molecule clearance
3. no disequilibrium syndromes
4. technical
   - simpler, less equipment
   - less expensive
   - training of personnel

- ***Problems Conventional Haemodialysis***

1. haemodynamic instability
2. hypoxia
   - neutrophil activation
   - platelet margination
   - ↑ ***shunt fraction***
3. disequilibrium syndrome
   - rapid fluid shifts
   - rapid electrolyte shifts
4. blood loss
5. vascular access
6. equipment
7. trained personnel

Dialytic Therapies

Mode	Blood Flow ml/min	Dialysate Flow ml/min	Cl-MW D	Cl-urea ml/min	Fluid loss litres
Kidney	1250		< 50,000	> 60	1.5
HD[1]	200-300	500	< 1,500	150	2-7
CAVHF	100-200		< 40,000	7-15	20-30
CVVHD	150-250	15-30	< 5,000	15-30	2-12
CVVHDF	150-250	15-30	< 40,000	15-30	2-12

[1] conventional 4 hr haemodialysis averaged over 24 hours

Peritoneal Dialysis

- used for both acute and chronic renal supplementation
- technical difficulties,

a. difficult insertion - previous surgery, adhesions
b. haemorrhage
c. bowel perforation
d. drainage failure
e. difficult/contraindicated with - recent surgery, drains
- intra-abdominal infection

- ***Efficiency***

a. slow fluid and solute removal
b. less predictable effect than other dialytic therapies
c. hyperglycaemia - markedly hyperosmolar dialysate fluids
d. protein loss

- ***Problems Peritoneal Dialysis***

1. slow fluid and solute removal
2. less predictable effect
3. catheter related infection - peritonitis
4. drainage failure
5. respiratory embarrassment
6. hyperglycaemia
7. protein loss
8. difficult/relatively contraindicated with - recent surgery
- abscess
- abdominal drains, etc.

- ***Other Complications***

a. catheter related infection - peritonitis
b. respiratory embarrassment - ↓ FRC
- pleural effusion
- especially in children

CHRONIC RENAL FAILURE

- ***Common Causes***

1. diabetic nephropathy ~ 28%
2. hypertension ~ 24%
3. glomerulonephritis ~ 21%
4. polycystic kidney disease
5. analgesic nephropathy

- ***Retained Potentially Toxic Metabolites***

a. urea - probably only a "marker" in CRF

b. polypeptide "middle molecules" - MW's ~ 300-3500

c. ***guanine*** derivatives - guanidine, methyl/dimethyl-guanidine
- ***guanidosuccinic acid***
- creatine, creatinine

d. nucleotide metabolites

e. aromatic ***amino acid*** derivatives - tryptophan, tyrosine, phenylalanine

f. aliphatic amines

g. elevated hormone levels - PTH
- glucagon, insulin
- GH, LH, PRL

- ***Clinical Effects***

a. GFR ~ 50%
- asymptomatic
- mild elevation of creatinine ($\propto$ 1/GFR)

b. GFR ~ 25-30%
- hypertension
- anaemia
- polyuria, nocturia
- $\uparrow$ creatinine, urea
- $\uparrow$ glucose, urate, TG

c. GFR **~ 15-20%**
- overt renal failure
- metabolic acidosis
- fluid overload
- GIT, CVS, CNS complications
- K^+, $HPO_4^=$ & urate rise as GFR < 25%

- ***Clinical Features***

1. those ***corrected by dialysis***
   - i. fluids & electrolytes
     - Na^+ & fluid overload
     - metabolic acidosis
     - hyperkalaemia, intracellular potassium ***deficit***
     - hyperphosphataemia, hypocalcaemia
     - glucose intolerance
   - ii. hypothermia, fatigue, lethargy
   - iii. asterixis, muscle irritability, myoclonus, coma
   - iv. CCF, pericarditis, uraemic lung
   - v. anorexia, nausea, vomiting, gastroenteritis
   - vi. coagulopathy, platelet dysfunction
2. those which may be ***unchanged by dialysis***
   - i. renal osteodystrophy, 2° hyperparathyroidism
   - ii. hyperuricaemia, hyperlipidaemia
   - iii. protein, calorie malnutrition
   - iv. growth and sexual dysfunction
   - v. peripheral neuropathy
   - vi. paralysis, seizures
   - vii. accelerated atherosclerosis
   - viii. hypertension, cardiomyopathy
   - ix. pallor, pruritus, ecchymoses
   - x. anaemia, lymphopaenia, immunosuppression
   - xi. peptic ulcers
   - xii. splenomegaly, hypersplenism
   - xiii. restless leg syndrome

c. those ***"exacerbated" by haemodialysis***
   - i. hypotension
   - ii. muscle cramps
   - iii. disequilibrium syndrome (cerebral oedema)
   - iv. dialysis dementia ? aluminium toxicity from older filters
   - v. atherosclerosis
   - vi. GIT haemorrhage
   - vii. hepatitis, ascites
   - viii. neutropaenia, low complement

- ***Metabolic Effects***

  a. impaired Na^+/K^+-ATP'ase activity
  b. hypothermia, ↓ BMR
  c. glucose intolerance, insulin resistance - hyperglycaemia, occasionally ketosis
  d. protein intolerance
  e. high TG, normal cholesterol

- ***Immunosuppression***

  a. lymphopaenia, lymphoid atrophy
  b. normal neutrophil number but impaired chemotaxis
  c. decrease in acute inflammatory response & delayed hypersensitivity
  d. ↓ IgG and complement levels
  e. drug immunosuppression - steroids, cyclosporin

- ***Coagulopathy***

  a. impaired platelet function ? guanidosuccinic acid
  b. low levels of ***PAF III***
  c. impaired prothrombin activity

- ***Indications for Dialysis***

a. short term dialysis

i. symptomatic renal failure
- pericarditis
- metabolic acidosis
- uraemic symptoms

ii. acute biochemical alterations
- $[K^+]$ > 7.0 mmol/l
  - or associated with arrhythmias
  - or rapidly increasing
- pH < 7.15
- [Cr] > 0.6 mmol/l
- [urea] > 40 mmol/l, or rapidly increasing

b. other therapy

i. fluid overload - CCF, hypertension

ii. drug intoxication
- salicylates, lithium
- barbiturates, ethanol, methanol
- theophylline

iii. biochemical - uncontrolled hyper-Ca^{++}/K^+

c. chronic dialysis

i. failed conservative management

ii. creatinine > 0.6-0.8 mmol/l

iii. GFR < 3 ml/min

iv. progression of bone disease

v. progression of CNS disease
- neuropathy
- encephalopathy

vi. uraemic pericarditis

vii. awaiting transplantation

GLOMERULONEPHRITIS

- ***Clinical Presentation***

1.	acute ***nephritic*** syndrome	- hypertension, oedema - proteinuria, haematuria, rbc casts
2.	***nephrotic*** syndrome	- heavy proteinuria, hypoalbuminaemia, oedema
3.	chronic renal failure	* ie. presentation may be ***fulminant*** or ***indolent***
4.	loin pain	
5.	constitutional features of CRF	
6.	acute oliguric renal failure	- very rarely

- ***Histological Presentation***

a.	minimal lesion	- "normal" LM presentation
b.	membranous	- no cellular proliferation
c.	focal glomerulosclerosis	
d.	proliferative GN	- diffuse - focal - mesangial - rapidly progressive - chronic endothelial

- ***Implicated Antigens***

a.	bacterial	- β-haemolytic Streptococci, Staphlococci - TB - syphilis - Salmonella
b.	viral	- HBV - varicella, mumps - EBV, Coxsackie B
c.	protozoal	- malaria - shistosomiasis - toxoplasmosis
d.	autoimmune	- SLE, PAN, SS - thyroiditis - cryoglobulins
e.	drugs	- penicillamine - heroin

HAEMOLYTIC-URAEMIC SYNDROME / TTP

Def'n: disease of unknown aetiology with target organ dysfunction secondary to marked ***platelet aggregation*** in the microcirculation (Dabrow & Wilkins 1993)

- TTP first described by Moschocowitz in 1925
- HUS first described by Gasser *et al.* in 1955
- now considered different expressions of the same underlying disease process

- known associations,

a. infection, septicaemia * feces for pathogens
   i. children - especially *Shigella sp., Salmonella*
   ii. adults - enterohaemorrhagic *E. coli*
   - VTEC 0157:H7 produces ***vero cytotoxin***
   - pneumococcal infection
   iii. viruses - Coxsackie, echoviruses

b. drugs - OCP, cisplatin, mitomicin C, cyclosporin A

c. malignant hypertension

d. pregnancy

e. radiation

f. autoimmune disorders - SLE, scleroderma

▪ ***Pathogenesis***

- plasma contains a ***transmissible factor*** which aggregates platelets
- this is ***not*** complement or antibodies
- unknown mechanism results in widespread ***endothelial damage*** (key lesion)

→ release of ***HMW-vWF*** → platelet aggregation

- excess ***ULvWF***, possible due to missing enzyme in its processing, eg protease inhibitor
- multi-organ infarction / ischaemia, mainly renal in HUS
- arterioles filled with ***hyaline thrombosis***(fibrin & platelets)

- ***diarrhoea negative HUS***, frequently associated with severe pneumococcal infection
- characteristically become far more ill than the *E.coli* associated HUS
- mechanism is felt to be due to exposure by ***neuraminidase*** producing strains of pneumococcus of a usually hidden T antigen (***Thomsen-Friendenreich antigen***) found on platelets, red cells and endothelial cell surfaces
- most people have naturally occuring antibodies to this T "cryptantigen", which rapidly leads to the damage associated with HUS.
- avoid transfusing serum in any form (no FFP/cryo) unless exsanguinating, and wash all RBC's
- this will avoid giving the patient a fresh new supply of IgM to bind and damage the cells with T antigen still available

- ***Clinical Features***

a. fever

b. nausea, vomiting, diarrhoea, abdominal pain

c. arthralgia

d. bleeding, petechiae

e. renal failure & uraemia

f. jaundice

g. rarely hepato/splenomegaly

h. cerebrovascular events - especially in TTP

NB: HUS usually → children & more severe renal failure
fever & CNS signs are usually ***absent***

TTP usually → young female, adults & more thrombotic events, especially CNS

- ***Laboratory***

a. microangiopathic ***haemolytic anaemia***
   - anaemia, fragmented rbc's, reticulocytosis
   - thrombocytopenia
   - ↓ haptoglobin, ↑ haemopexin, haemalbumin present

b. ***normal coagulation profile*** - c.f. DIC
   - isolated deficiencies may occur

c. hyperbilirubinaemia, ↑ LDH

d. ANA ~ 20% +'ve

e. biopsy → characteristic vascular changes
   - skin, mucous membranes, gingiva, renal

- ***Diagnosis***

1. anaemia - microangiopathic picture
2. evidence of haemolysis
3. severe thrombocytopaenia
4. uraemia
5. ***normal*** coagulation profile and absence of FDP's

- ***Treatment Modalities***

1. routine management of,
   i. anaemia
   ii. renal failure
   iii. hypertension
   iv. electrolyte & fluid balance
2. early, uncomplicated disease → ***prednisolone***
3. severe disease
   i. ***plasmapheresis***
   ii. plasma transfusion
   iii. vincristine for refractory TTP/HUS
   iv. high dose IgG inhibits platelet aggregation
   v. splenectomy
4. antiplatelet drugs ***not effective***

- ***Prognosis***

- usually lasts days → weeks, rarely months
- fatal if left untreated, but treatment is effective in most
- Hayward *et al.* 1994,

a.	remission	~ 96%
b.	late TTP/HUS related problems	~ 50%
c.	ESRF	~ 8%
d.	relapse	~ 21%

HEPATORENAL SYNDROME

Def'n: potentially ***reversible*** renal failure associated with severe liver failure, without obvious other cause, characterised by,

1. oliguria with low urine Na^+
2. high urine osmolality but unresponsive to fluids / inotropes
3. may progress to ATN

NB: this is distinct from ***pseudohepatorenal syndrome***, where both liver and kidneys are primarily affected by the underlying disease process

▪ *Clinical Features*

a. mortality ~ 95%
   * recovery associated with improvement of liver function

b. oliguric renal failure with H_2O/Na^+ retention

c. high urine osmolality with $[Na^+] < 10$ mmol/l

d. low SVR, low cardiac output, hypotension

e. hypervolaemia

f. decreased response to vasopressors

g. high circulating renin, angiotensin II, aldosterone
   - these may ***decrease*** with the onset of HRS

h. increased renal excretion of noradrenaline & TBX_{B2}

i. ***decreased*** renal production / urinary excretion of $\mathbf{PGE_2}$
   - normally ***increased*** in cirrhosis with ascites
   - ie. intrarenal PG's protect GFR against high circulating angiotensin/aldosterone

▪ *Precipitating Factors*

1. usually occurs with,
   i. chronic alcoholic cirrhosis
   ii. fulminant hepatic failure - any cause
2. paracentesis ? probably marker only, syndrome associated with ascites!
3. diuretics ? intravascular volume depletion
4. NSAIDs ? impaired renal PG synthesis
5. sepsis ? relative hypovolaemia
   ? chronic endotoxaemia

Proposed Mechanisms

Arteriolar Vasodilatation Hypothesis 1988

- intense arteriolar vasodilatation 2° to hepatic failure → ***arterial underfilling***
- distinct from hypovolaemia → ↑ PRA / AI&II / aldosterone
  ↑ NA, ADH
  → intense ***renal vasoconstriction***

- Na^+ & H_2O retention worsen oedema and ascites
- the kidneys respond with ↑ PG synthesis (vasodilatory) which delays the onset of ARF
- this accounts for the marked sensitivity to NSAID's and other PG inhibitors

Secondary Tubular Dysfunction

- the disorder is completely reversible with return of liver function
- successful ***transplantation*** of HRS kidneys
- the enzymuria & β_2-microglobinuria seen in HRS is not seen in ATN or pre-renal failure
- however, absence of histological tubular damage in some studies
- other studies show ATN-like changes, bile vacuoles in tubular cells and hypertrophied JGA

Mediator Imbalance

- xenon studies show maldistribution of RBF → renal ***cortical hypoperfusion***

a. ↓ PGE_2 - fall in substrate & enzyme activity
   - cf. normal in ATN

b. ↑ TBX_{A2} ? 1° or 2° to hypovolaemia & high circulating catecholamines
   * little evidence to support this (Maxwell & Kleeman)

c. ↓ renin-angiotensin activity - low renin substrate in HRS
   - improved filtration with FFP or AII infusion
   ? opposite of arteriolar vasodilatory mechanism

d. ↓ ***"glomerulopressin"*** - hormone , MW ~ 500, synthesised in the liver
   - increased by AA infusion & glucagon
   - reduces afferent aa. tone and ***increases GFR***
   - synthesis blocked by NSAID's

Intra-Abdominal Hypertension

- increased renal vein pressure
- improved filtration with paracentesis + colloid or peritovenous shunt

- ***High SNS Tone & Reversible Cortical Ischaemia***

• probably not involved,

1. fall in ANF - levels are only marginally reduced
   - infusion ***does not*** improve filtration
2. high renin-angiotensin II ?
3. aldosterone - levels correlate poorly with the degree of Na^+ retention
4. chronic endotoxaemia

Treatment

a. largely supportive → ***prevention***
   i. optimise volume status
   ii. treat septicaemia
   iii. avoid nephrotoxic agents

b. paracentesis + FFP | Albuminex-20%

c. peritoneovenous (LeVeen) shunt
   - ↑ preload, cardiac output
   - ↑ RBF, GFR
   - high operative mortality
   - may result in marked thrombocytopaenia
   - ***no*** improved survival

d. ***liver transplant***

• other modalities tried with little or no success,

a. vasodilators - dopamine

b. lumbar sympathectomy

c. vasopressors - transient improvement

d. A-II inhibitors - marked hypotension
   - no increase in GFR

e. Ca^{++} entry blockers * no lasting effect

f. PGE_2 infusion

g. TBX_{B2} inhibitors

h. water immersion - increases venous pressure

i. dialysis

j. plasma exchange

RHABDOMYOLYSIS

Def'n: the disintegration or dissolution of muscle,
associated with the excretion of ***myoglobin*** in the urine

- ***Aetiology***

1. trauma / ischaemia / exhaustion
   i. crush injuries | compartment syndromes
   ii. arterial embolism | thrombosis, torniquets, antishock trousers
   iii. burns
   iv. electric shock
   v. hyperthermic syndromes
      - heat stroke
      - malignant hyperthermia
      - malignant neurolept syndrome
   vi. drug induced
      - suxamethonium in myopathic disorders
      - myopathy - alcohol, salicylates, amphetamines
        - aminophylline, phencyclidine, LSD, heroin
      - overdose of any sedative agent & pressure effects
   vii. envenomation
   viii. overuse
      - prolonged exercise, pretibial syndrome
      - status epilepticus
      - tetanus
      - delerium tremens
2. infection / inflammation
   i. viral myositis
   ii. gas gangrene
   iii. acute polymyositis
   iv. Legionaires' disease
3. metabolic defects
   i. severe hypophosphataemia, hypokalaemia, hyperosmolality
   ii. myxoedema, thyrotoxicosis
   iii. McArdle's syndrome
4. familial myoglobinuria

NB: systemic release of ***myoglobin*** by itself is ***not nephrotoxic***, however when combined with hypotension and renal hypoperfusion may result in ATN

- ***Investigations***

1. muscle ***compartment pressures***
   - normal < 10 mmHg
   - if > 30-40 mmHg, or
     > BP_{Dias} - 30 mmHg → ***fasciotomy***
2. biochemistry
   - hypocalcaemia, hyperphosphataemia, hyperkalaemia
   - hyperuricaemia
   - ↑ LDH, AST
   - CK-MM > 5x or greater
   - metabolic acidosis
   - thrombocytopaenia & haemoconcentration
3. myoglobinuria
   - false negative tests may occur in up to **36%** of cases
   - both haemoglobin & myoglobin test positive to urine "dipstick"

- ***Management***

1. early, aggressive IVT to support intravascular volume & urine output
   - saline loading → prevent hypovolaemia / dehydration
2. mannitol
   - theoretically increases proximal tubular flow & reduces effects of pigmenturia
   - supported by some animal data on nephrotoxic models
   - supported by the "Israeli" school but no controlled trials to support use
   - human trials in prevention of angiographic dye ARF ***worsen*** outcome
3. bicarbonate
   - alkalinisation of urine improves solubility of myglobin, ∴ reducing cast formation
   - animal studies showing reduction in ATN
   - like mannitol, no controlled trials to support use
4. acetazolamide

- ***Crush Injuries & Renal Failure***

1. activation of renin-angiotensin system, ↑ catechoamines & ADH
2. nephrotoxicity of ***myoglobinuria*** & ***uricosuria***
   - potentiated by acidifcation & concentration in tubules
3. acute increase in plasma Ca^{++}-$PO_4^{=}$ product
   - may result in suppression of renal function
4. ***microthrombi*** in renal vasculature

- ***Management Israel (Nephron 1990)***

1. early aggressive volume replacement, preferrably at the scene of injury
   - immediate resuscitation
   - N.saline or Ringer's lactate @ 1500 ml/hr adult
     @ 20 ml/kg/hr child
2. forced mannitol-alkaline diuresis
   - 5% Dextrose + NaCl 70 mmol
     + mannitol 20% 50 ml = 10g
     + bicarbonate 8.4% 50 ml = 50 mmol
     @ **500 ml/hr**
   - 12 l/day → 600g dextrose = 2400 kcal
     840 mmol NaCl + 600 mmol $NaHCO_3$
     120 g mannitol
3. acetazolamide - if plasma pH > 7.45
   - due to enhancement of metastatic calcification

- claimed improvement in survival against historical controls
- no prospective randomised study to support this protocol
- almost certainly associated with electrolyte disturbances

RENAL TUBULAR ACIDOSIS

Type I Distal RTA

- inherited as an ***autosomal dominant***, "classic" RTA
- inability to maximally acidfy the urine, or excrete daily acid load

▪ ***Clinical Features***

a. ***low anion gap acidaemia*** - pH < 7.35

b. hyperchloraemia and hypokalaemia

c. urine pH > 5.4, even after acid load - NH_4Cl ~ 100 mg/kg
   - absence of urinary infection

d. ***complications***
   i. chronic acidaemia → ↑ Ca^{++} excretion
   ii. 2° hyperparathyroidism
   iii. nephrocalcinosis, calculi ~ 60-70%
   iv. vit.D deficiency, osteomalacia, rickets - especially children

▪ ***Treatment***

a. $NaHCO_3$ ~ 0.5-2.0 mmol/kg/day

b. *or,* Na^+/K^+-citrate → ↓ CO_2 production in GIT

c. large K^+ supplement usually ***not*** required

Type II Proximal RTA

- generalized tubular disorder, may be ***congenital*** or ***acquired***
- reduced H^+ secretion, impaired HCO_3^- reabsorption (reduced T_M)
- mild ***low anion gap acidosis***, also have ***amino aciduria*** and ***phosphaturia***
- treatment need only be commenced when the $[HCO_3^-] < 18$ mmol/l

→ $NaHCO_3$ ~ 5-10 mmol/kg/d + K^+ supplement

▪ ***Type III - RTA***

- a combination of type I & type II RTA (very rare, possibly doesn't exist!)

- ***Type IV - RTA***

- the urine acidifies during periods of marked acidaemia, however there is ***hyperkalaemia***
- metabolic acidosis may be associated with hypotension
- usually seen with ***hyporeninaemic hypoaldosteronism***,
    1. diabetic nephropathy
    2. hypertensive nephrosclerosis
    3. chronic tubulointerstitial nephropathies

- also seen in Addison's disease & advanced age

NB: ***hyperkalaemia*** inhibits renal tubular generation of ***ammonia***, thereby reducing urinary buffer and worsening the acidosis

Renal Tubular Acidosis			
	Type I	Type II	Type IV
"site" of lesion	distal	proximal	distal
low anion gap acidosis	yes	yes	yes
minimum urine pH	> 5.5	< 5.5	< 5.5
% filtered HCO_3^- excreted	< 10%	> 15%	< 10%
plasma K^+	low	low	***high***
Fanconi syndrome	no	***yes***	no
nephrocalcinosis / stones	***yes***	no	no
daily H^+ excretion	low	normal	low
ammonium excretion	high for pH	normal	low for pH
daily HCO_3^- replacement	< 4 mmol/kg	> 4 mmol/kg	< 4 mmol/kg

Causes of RTA

- ***Proximal***

1. isolated HCO_3^- wasting
   - i. idiopathic - genetic / hereditary
     - sporadic
   - ii. low carbonic anhydrase activity - drug induced, acetazolamide
     - deficiency, cf ospeoporosis
   - iii. hyperkalaemia
2. generalised proximal tubular defect
   - i. hereditary defects - Fanconi-like syndromes
   - ii. toxic damage
     - heavy metals - Pb, As, Hg
     - drugs - aminoglycosides, 6-mercaptopurine, paraquat
   - iii. dysproteinaemias - m.myeloma, amyloidosis, MGUS
   - iv. immunologic
     - autoimmunopathy - CAH, SLE, RA
     - renal transplantation
     - interstitial nephritis
   - v. hyperparathyroidism - 1° hyperparathyroidism
     - deficiency of, or resistance to Vit.D

- ***Distal***

1. idiopathic
2. nephrocalcinosis *may be a result of, or produce the disease
   - medullary sponge kidney, idiopathic nephrocalcinosis
   - chronic hydronephrosis, analgesic nephropathy, renal transplantation
   - hyperthyroidism, 1° hyperparathyroidism
3. drugs - amphoterecin B, lithium
4. low NH_3 availability
   - i. defect in NH_3 generation
     - ↓ ATP synthesis
     - inhibition of glutamine metabolism - hyperkalaemia
     - decreased availability of glutamine - malnutrition, GI disorders
     - fuel competition - ketoacidosis, TPN
   - ii. defect in NH_3 transfer
     - interstitial nephritis
     - hyperkalaemia

5. low H^+ secretion
   i. H^+-pump defect
      - interstitial renal disease
      - low aldosterone activity - usually results in hyperkalaemia
   ii. voltage defect
      - low Na^+ delivery
      - inhibitors of Na^+ reabsorption
      - low aldosterone activity
   iii. H^+ backleak
      - hereditary disorders
      - drugs - amphoterecin B

- ***Hyperkalaemic RTA***

1. primary aldosterone deficiency
   i. combined with cortisol
      - Addison's disease, idiopathic
      - bilateral adrenalectomy
      - bilateral adrenal destruction - haemorrhage, tumour, infection, infiltration
      - congenital enzyme defects
   ii. isolated aldosterone deficiency
      - cortisone methoxidase - types I & II, familial
      - transient hypoaldosteronism of infancy
      - chronic idiopathic hypoaldosteronism
      - heparin induced
2. secondary hyporeninaemic hypoaldosteronism
   i. diabetes mellitus
   ii. tubulointerstitial nephritis
   iii. nephrosclerosis
   iv. drugs
3. mineralocorticoid resistant hyperkalaemia
   i. generalised DT dysfunction
      - obstructive nephropathy
      - sickle cell disease, amyloid
      - interstitial nephritis
   ii. pseudohypoaldosteronism - hypovolaemic
   iii. chloride shunt - hypervolaemic
   iv. drugs
      - spironolactone
      - amiloride, triamterene

Bartter's Syndrome

1. autosomal ***recessive*** - frequently symptomatic in childhood
2. renal juxtaglomerular apparatus hyperplasia
3. high plasma ***renin*** activity, angiotensin I/II & aldosterone secretion
4. ***normal BP***
   - decreased vascular response to noradrenaline & angiotensin II[§]
5. ***hypokalaemia*** ± alkalosis
   ± hypomagnesaemia
   - weakness & periodic paralysis
   - polyuria ∝ nephrogenic DI
   - overproduction of ***prostaglandins*** → altered Na^+/K^+ handling

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NB: the principal defect is reduced NaCl absorption in the ***thick ascending LOH***
→ volume depletion & TGF → ↑ renin-angiotensin-aldosterone

- increased NaCl delivery to the late DT, with raised aldosterone, produces ***severe*** K^+ wasting
- defective function of TA-LOH results in ***hypomagnesaemia*** & exacerbation of K^+ wasting
- ***hypokalaemia*** → ↑ PGE_2, PGI_2
  → further increase in renin secretion

- angiotensin-II & aldosterone → ↑ renal kallikrien
  → ↑ plasma ***bradykinin***
- ***normal BP*** reflects,
  a. ↓ vasopressor activity of angiotensin-II - ? diminished by downregulation
  b. vasodepressor actions of PGE_2 & bradykinin

- ***Treatment***

  a. oral K^+ / Mg^{++} supplementation
  b. propranolol / atenolol - ↓ renin release
  c. captopril - ↓ angiotensin II
  d. spironolactone - antagonise aldosterone
  e. PG synthesis inhibition - indomethacin, ibuprofen
     - aspirin

  NB: → ***~ opposite to RTA***

Renin - Angiotensin System

▪ ***Renin***

- a glycoprotein ***acid protease*** released by the juxtaglomerular apparatus
- MW ~ 40000, acts to cleave the Leu-Leu bond in ***angiotensinogen*** to form ***angiotensin I***
- plasma elimination half life, $t_{½\beta}$ ~ 15-30 min
- stimuli to release include,

1. increased sympathetic tone - β_1-agonists
2. reduced hydrostatic pressure in the ***afferent arteriole***
3. increased Cl^- at the macula densa - tubuloglomerular balance
4. low angiotensin II level - reduced -'ve feedback on JGA

- common clinical stimuli include,

a. total body Na^+ deficit

b. upright posture

c. disease states
- renovascular disease
- CCF, hypovolaemia, hypotension
- chronic liver disease
- pre-renal ARF
- Bartter's syndrome

d. drugs
- most anaesthetic agents
- vasodilators
- α/β-adrenergic blockers
- captopril, enalpril, saralasin
- diuretics
- theophylline
- chlorpromazine
- OCP

▪ ***Angiotensinogen***

- an a_2-**globulin**, glycoprotein, synthesised by the liver
- ? also synthesized locally by the macula densa for local release
- ***angiotensin I*** is formed from the **10AA** at the ***amino terminus***
- production is increased by,

a. steroids with glucocorticoid effect

b. oestrogens, pregnancy

- effectively "renin substrate"
- levels may be derranged in hepatorenal syndrome

Angiotensin II

- produced by cleavage of 2AA from angiotensin I by ACE in the lung, ie. **8AA *peptide hormone***
- ? ACE also present in the kidney
- plasma elimination half life, $t_{½\beta}$ ~ 1-2 min
- inactivated by many different enzymes in many tissues including RBC's
- actions include,

a. potent vasoconstrictor (2nd to ***endothelin***)- inhibited by saralasin

b. ↑ efferent > afferent arteriolar tone in the kidney

c. ↓ GFR and ↑ Na^+ reabsorption through GTB

→ ↓ RBF > GFR, ∴↑ ***GFR/RBF ratio***

d. ↑ renal PGI_2 production

→ counteracts adverse renal effects and maintains RBF

e. negative feedback on renin release at JGA

f. ***aldosterone*** release from ZG of adrenal cortex

g. facilitation of SNS via presynaptic AII receptors

h. weak direct inotropic and chronotropic effects

i. hypothalamic CNS effects

i. ↑ SNS discharge

ii. thirst stimulation

iii. ↑ ADH release

Angiotensin III

- produced by cleavage of 1AA from angiotensin II
- more potent aldosterone release than angiotensin II
- vasoconstrictor effects more potent on the arterial beds of the kidney, skin, muscle, and splanchnic circulation
- less effect on cerebral, coronary and pulmonary circulations