DIABETIC KETOACIDOSIS TREATMENT CHART

Patient:..... Weight:.....kg

- If the patients is awake, not dehydrated, not vomiting and not metabolic acidotic (s-HCO3 more than 18 mmol/l), it is not necessary to start intravenous insulin and the patient may be managed with a subcutaneous regime.
- The patient needs 2 IV lines in different limbs. One for the insulin infusion and one for rehydration.

A. INSULIN (USE WITH IVAC)

1. Add 50 units of Actrapid (or Humelin R) to 200 ml 0.9% NaCl (every 1 ml contains 0.25 u insulin).
   NB: Flush tubing of insulin infusion with insulin mixture first to saturate receptors for insulin on plastic.
2. Insulin rate (0.1 u insulin per kg per hour):
   - Weight (kg)..... x 0.1 u insulin = ...total units insulin for patient per hour
   - Total units insulin per hour..... ÷ 0.25 units per ml = ...rate of insulin infusion in ml/ hour
3. If glucose < 15 mmol/L decrease the insulin infusion with one to two ml/ hour until the glucose remain stabile at 5 – 15 mmol/l.

B. FLUID REQUIREMENTS (through a separate infusion)

1. Maintenance:

Weight	Daily fluid requirement (ml)	Hourly fluid requirement (ml)
1 – 10 kg	100 ml/kg	4 ml/kg
11 – 20 kg	1 000 ml plus 50 ml/kg for each kg > 10 kg	40 ml plus 2 ml/kg for each kg > 10 kg
21 – 60 kg	1 500 ml plus 20 ml/kg for each kg > 20 kg	60 ml plus 1 ml/kg for each kg > 20 kg

NOTE:

Only give saline fluid boluses if patient is definitely shocked (tachycardia and ↓ BP)

2. Rehydration fluid:

- If 5 % or more dehydrated add additional 50 ml/kg over 24 hours (2 ml/kg/hour).

3. Total volume of intraveneous fluid:

Maintenance fluid = ... ml per hour
Plus Rehydration fluid = ... ml per hour
Minus Rate of insulin infusion = _____ ml per hour
Total rate of second infusion per hour ..... **ml per hour**

4. Type of rehydration fluid:

- If blood glucose> 15 mmol/L give 0.9 % NaCl.
- If blood glucose< 15 mmol/L give 0.45 % NaCl + 5% dextrose (Rehydration fluid)
- If blood glucose< 3 mmol/L AND insulin is at lowest infusion rate (0.05 units/kg/hour) change fluids to 0.45 % NaCl + 10% dextrose (add 20 ml of 50 % dextrose water to each 200 ml 0.45 % NaCl + 5% dextrose).

5. Addition of potassium

- If serum potassium is normal, add 20 mmol of KCl to every litre of fluid as given in B-3 (1 ml of 15% KCl contains 2 mmol K).
- If serum potassium is low (< 3 mmol/L) add 40 mmol of KCl to every litre of fluid as given in B-3 (max dose)
- If serum phosphate is low change KCL to KPO4

D. MONITOR PATIENT

- Chart blood glucose hourly while patient is on insulin infusion.
- Do UK&E 4 hourly while patient is on insulin infusion.
- Monitor neurological status for signs of cerebral oedema 2 hourly: Level of consciousness, pupil sizes, light-pupillary reflex and bradycardia.
- Monitor pulse, BP and hydration status hourly.

E. OTHER

- Nil per os. Clear water is allowed if patient is fully conscious and not vomiting.
- **N.B. DO NOT GIVE NaHCO3.**
- As soon as If the patient is **not metabolic acidotic any more (s-HCO3 more than 18 mmol/l),** awake, not dehydrated and not vomiting, one can stop all infusions, keep a short drip for emergencies and start with SC insulin together with a meal.

Name and signature _____ **Date** _____

Acute Renal Failure (ARF) in Children

Definition.

ARF is a rapid deterioration of renal function associated with the accumulation of nitrogenous wastes in the body and derangement of fluid and electrolyte balance. Urine output may be normal, decreased (oliguria) or increased (polyuria) derangement of fluid and electrolyte balance.

Definition of oliguria

- ≤ 1 ml / kg / hour in neonates
- ≤ 0.3 ml / kg / hour in older children.

Diagnosis of acute renal failure

Paediatric Modified RIFLE (pRIFLE) Criteria

	eCreatinine clearance (eCCL)**	Urine output
Risk	↓ eCCL by 25 %	<0.5 ml/kg/hr for 8 hrs
Injury	↓ eCCL by 50 %	<0.5 ml/kg/hr for > 16hrs
Failure	↓ eCCL by 75 %	<0.5 ml/kg/hr for > 24 hr or anuria for 12 hr

eCCL =estimated creatinine clearance = 40 x length/height (cm) of patient /s-creatinine (µmol/L)

Types of ARF

1. **Pre-renal ARF** due to severe volume depletion and / or hypotension e.g. with loss of extra-cellular fluid, hypoxic ischemic episode, hypoalbuminaemia.
- **Intrinsic ARF** due to acute infectious / inflammatory or cytotoxic insults to the kidney e.g. Haemolytic Uraemic Syndrome, acute glomerulonephritis, nephrotoxins e.g. aminoglycocides, ACEI's, NSAID's and herbal medicines.
- **Post renal ARF** due to obstruction of the urinary tract

Diagnosis

The history will often reveal the aetiology of ARF. Symptoms and signs provide clues to the diagnosis.

History

- Antenatal history where appropriate in neonatal ARF
  Health of the mother?
  Drugs taken during pregnancy (ACEI) ?
  Oligohydramnios?
  Foetal distress or asphyxia neonatorum during delivery?
- History of preceding events, symptoms and previous illnesses and treatment

Clinical features which must be looked for

- Dysmorphic features e.g. of Turner Syndrome, Potter Sequence, etc.
- Do anthropometry
- Hydration, capillary filling time, oedema, anaemia, bleeding tendency, petechiae, purpura, jaundice.
- Blood pressure. Hypotension and tachycardia may indicate hypovolemia and shock
- Hypertension is usually associated with fluid overload, intrinsic kidney disease or coarctation of the aorta in the neonate
- Cardiovascular system: Jugular venous pressure, gallop rhythm, pericardial rub, and other signs of heart failure.
- Abdomen: Large palpable kidneys, full bladder, renal artery bruit, presence of an umbilical line.
- Central nervous system: consciousness, convulsions, and loss of vision, focal neurological signs.
- Fundoscopy: hypertensive retinopathy, retinal haemorrhages.
- Signs of an underlying infection, e.g. fever, skin rash etc.

Special investigations

- Urine: Output and macroscopic appearance
  Dipsticks: Haematuria, proteinuria, glycosuria, leucocytes, nitrites
- Urine microscopy: Casts (red blood cell casts, leucocyte, hyaline and granular casts)
- Urine culture
- Urine biochemistry

	Pre-renal failure	Intrinsic renal failure
U-Osmol (mOsmol/L)	↑ > 320	Equal to serum osmol
U- Na (mmol/L)	< 30	> 30
Fe Urea %	< 35 %	> 50 %
FeNa % *	< 1 %	≥ 3 %

* FeNa % = fractional excretion of Na (%) = U-Na / U-Creatinine x S-Creatinine / S-Na x 100
Remember S-Creatinine is measured in µmol/L and for the calculation the value should be + by 1000)

- Blood investigations:
  S-urea, urate, creatinine, electrolytes and osmolarity, glucose, calcium, phosphate and ALP
  Full blood count, differential and platelet count
  Clotting profile
- Cultures and DIC work-up as indicated
- Check ECG on the vital signs monitor to exclude life threatening hyperkalaemia
- Chest X-Ray to evaluate cardiomegaly, pleural effusions, pulmonary oedema.

Treatment of ARF

- Maintain tissue and organ perfusion, maintain blood pressure and intravascular fluid volume, improve tissue oxygenation and avoid nephrotoxic drugs.
- Fluid management

Well-hydrated patient and no abnormal extrarenal fluid losses	Volume depleted patient	Anuric patient
Maintenance fluid only. Replace insensible water loss: Neonate and young baby 30 - 40 ml/kg/day Older child 20 - 25 ml/kg/day	IV fluid bolus, e.g. 0.9 % NaCl or Ringers lactate 20 ml/kg stat and continue with 10 ml/kg/hour IV to replace fluid deficit.	**Electrolyte free solution, i.e. 5 or 10 % D/W to replace insensible losses.**

Replace fluid losses with an appropriate solution, e.g. diarrhoea causing fluid loss: use ½ Darrows 5 % D/W ; for naso-gastric drainage use 0.45% NaCl in 5 % D/W
Monitor fluid balance by weighing the child every 12 hours

- Treat hyperkalaemia when S-K > 6.5 mmol/L
  (i) Nebulized salbutamol
  (ii) Kayexalate 1 g/kg in D/W per os or rectally
  (iii) 50% D/W: 2 ml/kg IV over 20 min ± 0.1 U/kg Insulin
  (iv) $NaHCO_3$ (8.5 %): 2ml/kg IV diluted 1:1 with sterile water

- Treat metabolic acidosis with 8.5% $NaHCO_3$ 2 ml/kg diluted in IV fluid over 4 hours when when S-pH ≤ 7.1.
- Treat hypertension (See protocol on hypertension)
- Treat infection - avoid nephrotoxic antibiotics.
- Exclude specific causes of convulsions, e.g. hypoglycaemia, hyper- or hyponatraemia, hypocalcaemia or hypertension and treat accordingly. Treat uraemic convulsions with Sodium Gardenal or Lorazepam (Ativan).
- Unless acute blood loss has occurred, anaemia should only be treated when Hb < 7 g/dl.
  Give packed red blood cells 10 ml/kg over 6 hours
- Manage pulmonary oedema and volume overload with fluid and salt restriction and give IV furosemide.
  Digitalis is ineffective in this setting.
- Diet: Restrict NaCl, K and phosphate intake. Restrict protein intake when S-urea > 25 mmol/L.
  Daily requirements of protein 1-1.5 g/kg; carbohydrate 2 - 3 g/kg; fat 2 g/kg.
  Infants should preferably be given breast feeds or a humanised milk formula.
- Severe polyuria (urine output > 4 ml/kg/hr) due to tubular dysfunction and impaired urinary concentration occurs during the recovery (diuretic) phase of acute tubular necrosis. Replace fluid and electrolyte losses, e.g. K, Cl and Na. In this setting ½ Darrows in 5 % D/W is usually the appropriate solution to use.

Indications for dialysis

- **Absolute indications for dialysis:**
  Fluid overload and pulmonary oedema
  Anuria > 24 hours
  Central nervous system signs, e.g. convulsions or coma
  Uraemic diathesis
  Uraemic pericarditis

- **Relative indications for dialysis:**
  Hyperkalaemia or hyponatraemia not responding to conservative treatment
  Persistent metabolic acidosis pH < 7.1 or S-HCO3 < 10 mmol / L
  Uncontrollable hypertension
  Severe hyperphosphataemia and hypocalcaemia

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DKA REGIMEN PRESCRIPTION

NB: TO BE STARTED AFTER INITIAL FLUID RESUSCITATION

PATIENT STICKER

A. FLUIDS: (USE DIAL-A-FLOW)

0.9% NaCl ☐ 0.45% NaCl ☐ 5% Dextrose ☐

Set dial-a-flow @ _____ ml/h

If glucose ≤ 14 or s-Na^+ > 150 mmol/l then change fluids to 5% Dextrose.

B. INSULIN: (ALWAYS USE AN IVAC)

1. 20 units ACTRAPID in 200 ml 0.9% NaCl = 0.1 U/ml.
   i. Dose = 0.1 U/kg/h = 1 ml/kg/h
   ii. 1 ml x _____kg = _____ml/h through IVAC.
2. Chart blood glucose *hourly* until it is ≤ 14 mmol/l then *2 hourly*.
3. Chart urine ketones *4 hourly*.

Finger Prick Glucose (mmol/l)	Adjust IV Actrapid
5.6	Reduce by 10 ml/h and give 25 ml 50% Dextrose
5.6 – 8.9	Reduce by 10 ml/h
9 – 12.2	No change
12.3 – 15.6	Increase by 10 ml/h
> 15.6	Increase by 10 ml/h and give 8 Units Actrapid IV bolus

C. POTASSIUM:

Add _____ mmol potassium chloride in each vaculitre.

Blood K^+ (mmol/l)	mmol/l KCl per litre fluid
≤ 3	40
3.1 - 4	30
4.1 - 5	20
5.1 – 5.5	10
> 5.5	Omit

NB: Never give > 20 mmol KCl per hour IV.

D. OTHER:

Strict intake and output.

DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

MBCHB III

NEPHRITIC SYNDROME

INTRODUCTION TO NEPHRITIC & NEPHROTIC SYNDROMES:

Collectively these conditions are primarily **Glomerular Diseases** although the tubules may also sometimes be involved. (The glomerulonephritides, glomerulopathies or nephropathies).

Presents clinically as:

A. The nephrotic syndrome – Minimal change nephrotic syndrome. (MCNS)

B. The nephritic syndrome - Acute glomerulonephritis (AGN or APSGN)

C. The nephritic-nephrotic syndrome

D. Asymptomatic proteinuria

E. Asymptomatic haematuria

Asymptomatic proteinuria or haematuria may be the earliest sign of developing glomerular disease. May take months before clinical symptoms develop. May also be the only sign of a transitory glomerular disease.

NB: Although there are many causes for haematuria and proteinuria in children, the nephrological/medical causes (i.e. glomerular diseases and urinary tract infections) are by far the most common. Nephrological causes must thus be sought from the beginning. Delay in making a diagnosis can result in unnecessary investigations and procedures. If a nephrological cause cannot be established, a urological/structural/malignant cause must then be sought.

PATHOGENESIS OF GLOMERULAR DISEASES

A. **Minimal change *nephrotic* syndrome (MCNS.)**

This is attributed to "physiological" change (neutralisation) in the normal electronegative charge of the glomerular basement membrane (GBM) which then allows the smaller electronegatively charged protein-molecules (mainly albumin) to “leak through” into the urine (selective proteinuria). Apart from the fusion of the epithelial foot processes under EM, the glomerular histology is essentially normal.

B. **The <u>nephritic</u> and nephritic-*<u>nephrotic</u>* syndromes**

These conditions are nearly always secondary to immune-complex conditions or diseases. The difference in the clinical pictures between these two conditions is chiefly due to the <u>duration</u> of antigen exposure and the antibody response elicited (Simplified! Many other mediators/factors involved).

a) *The <u>nephritic</u> syndrome*. Acute "single dose" antigen exposure (e.g.. Beta-haemolytic Streptococci) tends to cause an acute "self-limiting" proliferative and exudative glomerulonephritis that can lead to <u>acute renal failure</u>. (Inability of the glomeruli to filtrate efficiently).

b) The nephritic-*<u>nephrotic</u>* syndrome. Chronic persistent antigen exposure with chronic low-grade antibody response can result in <u>gradual</u>, progressive glomerular and GBM <u>damage</u>. This may lead to "mechanical loss" of all protein fractions in the urine (non-selective proteinuria) (as well as neutralisation of the electronegative charge of the G.B.M.) and often blood. This is thus a <u>nephrotic syndrome</u> resulting from a chronic glomerulonephritis. NB: This situation usually begins with asymptomatic proteinuria/haematuria, and then develops into a nephrotic syndrome, and may result in chronic renal failure. (Progresses over months/years, depending on the histology).

ANTIGENS

Sources and types:

Although various antigens have been incriminated in the aetiology of acute and chronic glomerulonephritis, many remain unknown or indeterminable.

- Antigens
  - Exogenous- Bacteria (Streptococci)
    - Viruses (Hepatitis B)

    Parasites (Quartan malaria in West & East Africa)

    Spirochaetes (Congenital & Endemic Syphilis)

    Drugs (heavy metals)
  - Endogenous- DNA and a variety of organ & renal cells such as in SLE. (Auto-antibodies are formed against the cells).
    - GBM itself, such as in Goodpasture's syndrome. (Rare).
  - Unknown - (Antigens and pathogenetic mechanisms)

Antibodies are formed against antigens. Immune complexes bind with complement and cause glomerular injury.

If the antigen disappears after a "single dose" exposure → acute self-limiting glomerulonephritis presents as acute and renal failure. If the antigen persists → chronic glomerulonephritis which usually presents as a nephrotic syndrome.

ACUTE NEPHRITIC SYNDROME IN CHILDREN

Synonym: Acute post-streptococcal glomerulonephritis (APSGN), acute nephritis, acute post-infective glomerulonephritis.

Classical clinical picture is characterised by:

Smokey macrohaematuria

Mild to moderate proteinuria

Oedema (fluid overload) with or without cardiovascular complications/heart failure.

- Hypertension
- Oligo-anuria with renal failure

NB: Any combination and degree of symptoms possible, even just subclinical microhaematuria.

AETIOLOGY

- More than 90% after group A Beta-haemolytic streptococcal infection of the throat or skin.

  (APSGN) Streptococcal M-type

  - Throat 12 ┐ especially, but can also be caused
  - Skin 49 ┘ by other M-types.

  Skin infections (Impetigo) are the most common cause in R.S.A.

  In contrast to rheumatic fever, only a few M-types are "nephritogenic". M-type specific immunity is acquired after infection and thus recurrent episodes are unusual.

- Can also be followed by <u>other bacterial and viral infections</u> e.g. glandular fever, hepatitis A & B, measles, mumps, chicken pox, staphylococcal, pneumococcal, typhoid, Brucella, Strep-viridans (SBE), leptospirosis, Yersinia.

- Can also be caused or mimicked by <u>other disease conditions</u>, e.g. Henoch-Schonlein syndrome, haemolytic-uraemic syndrome, SLE, polyarteritis nodosa, Goodpasture's syndrome, Alport syndrome (hereditary nephritis), benign recurrent haematuria syndrome.

PATHOLOGY

Inflammatory reaction caused by deposition of immune complexes in glomeruli → proliferation, exudation and injury. Mesangial and endothelial proliferation. Polymorph infiltration and exudation.

→ Kidneys enlarge and glomeruli swell.

Tubules ± normal.

(Occasionally epithelial proliferation/crescent formation can lead to progressive GN).

- Capillary lumens are compressed and occluded as a result of this swelling and cannot maintain normal filtration.

Electron microscopy:

Immune complexes are seen as "humps" on the epithelial side of the basement membrane. Fusion of epithelial foot-processes.

Immunofluoresence:

Granular deposits of IgG and C3.

The consequence of this is:

- GBM injury → Smokey macrohaematuria and moderate non-selective proteinuria.

- Mesangial and endothelial proliferation and swelling → the capillary lumens are compressed → inability to excrete K^+, Na^+ and H_2O, urea, creatinine, etc. and GFR decreases.

- Tubules relatively normal → Na^+ and H_2O reabsorption (GT imbalance)
- Diminished GFR and tubular reabsorption results in:
  - → Oligo-anuria
  - → Hypervolaemia
    - Oedema
    - Cardiac failure/pulmonary oedema
    - Hypertension/encephalopathy/convulsions
  - → Acute renal failure

CLINICAL PICTURE (APSGN)

Onset: 7 - 21 days after Streptococcal infection of the throat or especially skin (impetigo), infected scabies, insect bites, chickenpox sores as well as scarlet fever, otitis media, etc.) (7 - 14 days after throat infection and 14 - 21 days after skin infection).

NB:

a) Haematuria at onset of acute pharyngitis, i.e. short latent period of only 1 - 4 days, is against APSGN – more in favour of Benign recurrent haematuria syndrome or flare up of other underlying renal diseases.

b) History of prior sore throat or skin infection is not always obtained.

Age:

2 - 10 years old, peaking at 5 - 7 years of age. Unusual under 2 years of age.

Gender:

M : F = 2 : 1 after throat infection, but 1 : 1 after skin infection.

Incidence:

Risk after streptococcal infection is 1 - 2%.

Precise incidence is actually unknown since up to 50% may be subclinical in an epidemic. Always perform immunological investigations for APSGN in children presenting with asymptomatic haematuria.

Symptoms:

"Classical picture" – Usually sudden onset. Typical complaints of "swelling of the face" (puffy eyes) and "blood in the urine" (dark brown resembling Coke or black tea, throughout micturition and usually painless). Other areas (legs) of oedema and reduction in urine excretion (oliguria) are noticed less frequently by the parents.

Fever is unusual but there are sometimes complaints of listlessness, pallor, cough and vague abdominal and stomach pain.

Other additional manifestations are usually due to:

a) Cardiac failure/pulmonary oedema e.g. shortness of breath, dyspnoea/orthopnoea, cough etc.
b) Hypertension e.g. headache, visual disturbances, irritability, projectile vomiting, changing levels of consciousness, convulsions and coma.

c) Renal failure and uraemia e.g. Retention of salt and urea often stimulates the thirst centre; in other cases, "uraemia" can also cause anorexia, nausea and vomiting – oedema can be "vomited away" (Refer also to the ARF lecture notes).

SIGNS:

Any combination and degree possible. Signs of prior Streptococcal infection (especially of the skin). Pallor usually results from a dilutional anaemia. Oedema varies from none to severe - ascites is actually unusual in acute nephritis.

Hypertension occurs in 30 - 50% of cases and can result in hypertensive encephalopathy. Rapidity of BP increase is more important than the degree of hypertension - convulsions can occur at a relatively low level.

Mechanism of hypertensive encephalopathy. The cerebral blood flow is normally kept reasonably constant over a wide fluctuation of blood pressure. If B.P. falls → arteriolar dilatation. If B.P. rises → arteriolar contriction. This vasoconstriction can only protect the brain to a certain degree. If the blood pressure becomes very high (above 'autoregulatory plateau')then the high pressure is transmitted to the capillary bed causing forced vasodilatation (and therefore increased brain blood volume) and cerebral oedema.

The upper range of normal (i.e. the 95th percentile) for systolic blood pressure can be calculated as follows: (Age in years X 3) + 100. Diastolic B.P. is: (Age in years X 1.5) + 70

Degree of systolic hypertension:

Mild hypertension	: 95th percentile + (1 - 15%)
Moderate hypertension	: 95th percentile + (16 - 30%)
Severe hypertension	: 95th percentile + (31 - 50%)
Hypertensive crisis	: 95th percentile + (> 50%) or 30 mmHg > than 95th percentile

In practice the systolic B.P. is much easier to measure accurately, and most management decisions are made on the basis of systolic B.P.

Also signs of cardiac failure and renal failure.

MISLEADING PICTURES:

- Asymptomatic haematuria (Up to 50% in epidemics in siblings. Important in the differential diagnosis of haematuria – Always perform complement C_3 level).

- Convulsions as a consequence of hypertensive encephalopathy are often attributed to other causes e.g. epilepsy.

- Congestive cardiac failure – can also be attributed to other causes or may be misdiagnosed as pneumonia. (In cardiac failure without heart murmurs – Think first of fluid overload due to renal failure resulting from APSGN and/or hypertension).

- No oedema, or even dehydration, as a result of anorexia and vomiting from the severe uraemia.

- Clinical and biochemical nephrotic syndrome in 2 - 5% of cases. Usually transitory (self-limiting).

- Urine findings may be minimal or misleading, e.g. more white blood cells (pyuria) than red blood cells or more protein than blood in the urine.

URINE FINDINGS:

Macrohaematuria in ± 80% of hospitalised children (100% on Labstix).

Microscopy: Red blood cell casts in ± 60%. Hyaline and granular casts often occur, but casts are <u>not</u> essential for the diagnosis.

NB: The presence of "glomerular" (dysmorphic or deformed) red blood cells on phase-contrast microscopy is particularly important in die absence of casts.

White blood cells are often present and may sometimes outnumber the red blood cells. (Do not confuse with UTI).

Non-selective proteinuria 1 -3(+): Usually less than 1 g/m^2/24 hours, although may sometimes be more and may occasionally initially occur without haematuria. Do not confuse with nephrotic syndrome. (Nephrotic syndrome may also sometimes present with macrohaematuria!).

Urine osmolality is often increased as the urine concentrating ability is maintained (normal tubular function). Do not confuse with pre-renal failure.

Urine culture is negative even though there are many white blood cells.

Throat and Skin Swab MCS

Positivity varies between 10 - 50% - ? technique. Less often from throat than skin, since infection has already subsided there.

BLOOD INVESTIGATIONS:

- Haematology: Normochromic anaemia. Hb 9 - 10 g/dl as a result of dilution. Often leukocytosis. Sedimentation rate is increased for up to 3 months, but is of little prognostic value.

- Blood chemistry: Renal function tests - Electrolytes, acid-base, urea and creatinine, calcium and phosphate (ARF lesion). Albumin often slightly lower as a result of haemodilution. (Not lower than 25 g/l). Cholesterol normal (transitory nephrotic phase in ± 5% of cases).

- Immunological parameters:

a) Serum complement: Total complement and C_3 are decreased in nearly 100% of active cases. C_4 is usually normal since complement activation takes place mainly via the alternative pathway. NB: A normal C_3 level is **very much against** the diagnosis of APSGN and another cause must be sought for the picture, even if the ASOT is increased. C_3 should normalise within 6 - 8 weeks.

(ANF negative: Circulating immune complexes are increased. RF often increased. This and other serological tests are routinely unnecessary).

b) Antibody response against Group A streptococcal extracellular antigens.

* ASO titre - Increased in 60 - 70% of cases, but more often after throat infections.

  Begins to increase 10 - 14 days after the infection, peaks within 4 weeks and normalises within 1 - 6 months. (Increases are blunted by early antibiotic therapy).

* Anti-DNase B titre - Increases in 90 - 95% of cases, especially following skin infections.

c) Immunoglobulin G (IgG) increases in + 90% of cases (not a routine investigation).

NB: Documentation on the aetiology especially by means of complement C_3, but also by means of ASOT determinations, as well as by throat/skin swab culture is important in order to exclude later confusion. This is especially valid for the more atypical cases, as well as with asymptomatic haematuria; this also eliminates the use of unnecessary radiological/urological investigations. Follow-up of these patients should include confirming the normalisation of abnormal tests.

Radiological investigations:

Chest x-rays: cardiomegaly, pulmonary oedema and pneumonia. Sonar etc. are unnecessary if the diagnosis has already been established at the onset.

ECG:

Cardiomegaly. Hyperkalaemia. Myocarditis.

TREATMENT:

Monitor: Blood pressure. Pulse. Weight.

Intake and output.

Daily urine investigation.

Bed rest in acute phase.

Penicillin for 10 days p.o. Treat impetigo and scabies.

Fluid balance: (Refer to ARF lecture for details)

- Oedema without cardiac failure - **only insensible loss** (1lycal) until oedema resolves.

  a) 10 - 25 ml/kg/24hours

  Newborns = 25 ml/kg/24hours. 5-year olds = 15 ml/kg/24hours.

  10-year olds = 10 ml/kg/24hours.

  b) 300 ml/m^2/24hours

- Cardiac failure/lung oedema - **No fluids**.

  Oxygen.

  ? Ventilation and ?dialysis with ultrafiltration – Seldom necessary unless resistant anuria or administration of too much fluids.

- Effect diuresis - Furosemide (Lasix) 1 - 5 mg/kg initially I.V. (slowly) and then 6 hourly as necessary depending on the response. Oral absorption of furosemide is poor with fluid overload. Maintenance per os after severe oedema has resolved is acceptable. Diuretic therapy also shortens the hospital stay. NB Avoid Mannitol! Spironolactone is contraindicated in APSGN or renal failure due to its potassium-sparing effect).

- After the oedema has disappeared - stop diuretics! A child can then regulate its own fluid intake, but intake and excretion must still be documented.

NB: - Avoid intravenous fluids. - Do not perpetuate the oedema.
- Thirst is no indication of the fluid requirements (often thirsty).

Diet: Restrict Na^+ and K^+. Limit protein intake to "normal" requirements, i.e. ± 1.5 g/kg/day – Do not malnourish.
High calorie intake.

Renal failure: E.g.. Hyperkalaemia, metabolic acidosis, hypocalcaemia etc. Refer to the ARF lecture.

Hypertension: Treat if above 140/90 - 150/100 (It is not necessary to treat mild hypertension).

- Hypertensive crisis is defined as a systolic BP > 95 centile for age height and sex and/or a diastolic pressur greater than 1.5x normal. Hypertensive crisis can be divided into:

  a)Hypertensive emergencies: with end organ damage(eg hypertensive encephalopathy, retinal bleeds, blindness, pulmonary oedema etc)

  b)Hypertensive urgency: May have symptoms of headache, nauseau, disturbed vision but without the above mentioned physical signs.

In situation a) the blood pressure should be brought down immediately. Antihypertensives that can be used for this are:

a) Nifedipine (Adalat) 0.2 (0.15 - 0.3) mg/kg sublingual or oral 2 - 6 hours (maximum single dose 5 - 10 mg). (Most commonly used at TCH)
b) Labetolol IVI 0,5-3mg/kg/hr infusie
c) Dihydralazine (Nepresol) 0.15 - 0.25 mg/kg IM 4 - 6 hourly can also be used. (Beware of hypotension).).Infusie:0,75-5mcg/kg/min

d)Na Nitroprusside IVI 0.5 – 8 µg/kg/min

In situation b) the blood pressure can be brought down more slowly with antihypertensives like

a) Amlodipine po
b) Atenolol po

Beware of sudden large reduction in BP (>25%) as this may lead to cerebral underperfusion
One to three doses of acute therapy is usually sufficient. Watch out for sudden "late" blood pressure increases after 2 - 5 days. Moderate hypertension may be sustained for 10 - 14 days. If the tendency towards hypertension remains, maintenance therapy together with a diuretic (Lasix) must be administered.

- <u>Moderate hypertension and maintenance therapy</u>:
  - Long-acting calcium channel blocker such as Amlodipine (Norvasc®) or
  - Beta-blockers such as atenolol (Tenormin/Tenbloka).
    - do not use in cardiac failure.

  NB: ACE-inhibitors are <u>absolutely</u> contraindicated in acute renal failure.

- Bed rest until:

  Adequate diuresis/oedema resolves

  Urea ± normal (Usually within 2 weeks, but may take longer)

  Blood pressure normal

  Semi-bed rest until macrohaematuria resolves. Thereafter bed rest is of little value. Can go back to school. Sport only when microhaematuria resolves.

Macrohaematuria: Lasts a few days to 4 - 6 weeks.

Can flare up again :
* too much exercise
* intermittent infection (U.R.T. I.) and fever
* too much protein load in diet.

Flare-ups do not indicate a relapse or a poor prognosis. Treat with temporary bed rest and/or antibiotics. Give reassurance.

- Microhaematuria: Usually resolves within 3 - 6 months. May persist for a year or even longer.

- Immunological parameters: Complement measurements should normalise within 6 - 8 weeks. ASO titre and IgG levels sometimes take longer, but should demonstrate a tendency to decrease.

PROGNOSIS:

Immediate mortality ± 1%; almost always as a result of cardiovascular complications/heart failure. A few cases develop irreversible crescentic glomerulonephritis.

Long-term prognosis: The age of onset and the degree of renal failure influence the long-term morbidity to an extent. As a whole, ± 95% of children recover completely. Adults have a higher incidence of both short and long-term complications. Protracted uraemia and/or anuria carry a higher risk of complications such as hypertension – These cases should be followed-up long term.

Factors indicating a poorer prognosis or incorrect diagnosis:

1. Severe renal failure at onset. Urea greater than ± 40 mmol/l.
2. Anuria lasting more than 10 days.
3. Oliguria, uraemia or hypertension longer than 4 weeks (Also deteriorating renal function).
4. Macrohaematuria longer than 6 weeks.
5. Persistent heavy proteinuria and/or nephrotic syndrome lasting more than 4 weeks.
6. Mild proteinuria for more than 6 months.
7. Decreased complement after 8 weeks.
8. History of previous or familial renal disease.

DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

MBCHB III

THE NEPHROTIC SYNDROME IN CHILDREN

DEFINITION:

a) Heavy proteinuria (more than 1000 mg/m^2/24 hours or 40 mg/m^2/hour or 50 mg/kg/hour).

b) Hypoalbuminaemia (< 30 gm/l - oedema only develops after albumin falls below 25 gm/l).

c) Hypercholesterolaemia (Triglycerides and phospholipids are also elevated).

The outstanding clinical characteristic is the rapid onset of oedema. It is often difficult to clinically differentiate this from other causes of oedema.

PATHOGENESIS/AETIOLOGY:

There are two mechanisms:

A. *Minimal change* nephrotic syndrome (MCNS)

Loss of the electronegative charge of the glomerular basement membrane (GBM) allows electronegatively charged protein molecules (mainly albumin) to filter through the GBM into the urine. This albuminuria is known as a selective proteinuria. There is little or no blood in the urine. The blood pressure is usually normal.

Histology:	Light microscopy - normal. Electron microscopy - fusion of the epithelial foot processes.
Aetiology:	Precise aetiology not yet known. Abnormalities in T-cells have been documented. Not an immune complex condition.
Gender:	Slightly more common in boys.
Age:	± 75% between 2 - 6 years of age. Unusual under 1 year of age and increasingly unusual after 10 years of age (less than 20% in adults).
Race:	± 80% Whites and S.A. Indian children ± 30% Coloured children (TBH) < 10% Black children (Namibia)
Response to steroids:	Usually good and the condition tends to eventually burn out.

B. *Nephritic*-nephrotic syndrome.

Structural damage to the glomeruli, due to immune complex mediated diseases, results in all protein molecules filtering through the glomeruli into the urine. The proteinuria is known as non-selective proteinuria. There is usually micro- or macrohaematuria present. A renin-dependent hypertension is often present. The complement C_3 fraction may be decreased and the ANF is positive in SLE.

Histology:	Abnormal. Various entities (see later).
Aetiology:	Immune complex diseases. A persistent antigenaemia with a chronic low-grade antibody response results in nephritic-nephrotic syndrome due to a chronic glomerulonephritis. The antigen can often not be determined. The most common causes in Southern Africa are Hepatitis B, syphilis (congenital or endemic), SLE (especially in girls after 10 years of age) and occasionally typhoid and Henoch-Schonlein syndrome. Acute post-streptococcal GN can have a self-limiting nephrotic phase.
Gender:	Slightly more common in boys. More than 80% of cases of Hepatitis B carriers with NS are boys.
Age:	Any. (75% between 5 - 15 years of age)
Race:	More common in non-white children. (Opposite of MCNS)
Response to steroids:	Usually poor or incomplete.
Course:	Depends on histology and on whether or not the antigen remains. May go into remission, remain nephrotic or result in chronic end-stage renal failure. Often complicated by hypertension. Course may take place over months to years.

HISTOLOGICAL CLASSIFICATION OF GLOMERULAR DISEASES

Not all of these histological pictures necessarily result in the nephrotic syndrome.

A. Minimal change nephrotic syndrome (MCNS)

Histology essentially normal.

B. Focal segmental glomerulosclerosis (FSGN)

Mimics MCNS. Usually associated with moderate hypertension and microhaematuria. Only ±20% of cases respond to immunosuppression. Tends to advance into diffuse, global sclerosis, especially if persistently nephrotic, and may result in chronic renal failure.

C. The proliferative glomerulonephritides

1. Mesangial proliferative G.N.

   Course unpredictable. Low-grade proliferation may respond to immunosuppression and spontaneous remission is also possible. More pronounced proliferation may result in glomerulosclerosis and end-stage renal failure.

2. Endocapillary GN

   Mesangial proliferation plus endothelial swelling (proliferation). Classical acute post-streptococcal GN. May develop a transient nephrotic picture.

3. Crescenteric GN

   Mesangial proliferation plus epithelial proliferation. Clinically this is a rapidly progressive GN with a poor prognosis if crescent formation is extensive.

4. Mesangiocapillary (membranoproliferative) GN

   Mesangial proliferation plus GBM involvement. C_3 complement fraction often reduced. Poor prognosis.

D. Membranous nephropathy

GBM thickening (due to incorporation of immune deposits) with minimal mesangial proliferation. Most cases have been associated with Hepatitis B viraemia (TBH) in the past (reduced significantly since Hep B immunization was introduced). Course varies (see prognosis). May go into spontaneous remission especially if the antigen disappears. Steroids are of no value. (Can also be caused by S.L.E.)

CAUSES

Apart from MCNS, the above-mentioned glomerular lesions (chronic glomerulonephritides) may be caused by the following:

A. Newborns.

1. Congenital nephrotic syndrome – Finnish type.

   Autosomal recessive inheritance. Presents within a few days after birth. Increased maternal alpha-fetoprotein in serum and amniotic fluid. Always fatal.

2. Congenital syphilis. (Also described with CMV infection, nephrotoxins and nephroblastoma).

B. Older children.

1. Secondary to infections. Hepatitis B, endemic syphilis, streptococcus, typhoid, (Quartan malaria in West Africa), Bilhazia and SBE.

2. Secondary to nephrotoxins. Gold and mercury salts, trimethadione, penicillamine, captopril, bee-stings. These causes are unusual.

3. Secondary to collagen diseases – especially SLE in older girls.

4. Malignancies – Hodgkin's lymphoma, leukaemia.

5. Other systemic diseases - Henoch-Schonlein syndrome. (Diabetes mellitus, amyloidosis and sickle cell anaemia are rare causes in children).

MECHANISMS OF OEDEMA

Approximately 80% of the oncotic pressure in normal plasma is attributed to its albumin content.

Reduction in plasma albumin level, especially below 25 g/l, results in reduction in the plasma oncotic pressure and fluid exits the intravascular compartment into the tissues.

NB This can result in intravascular HYPOVOLAEMIA or dehydration.

This intravascular hypovolaemia or dehydration causes decreased renal blood flow and the glomerular filtration rate (GFR) is reduced, thus reducing excretion. This can result in pre-renal renal failure. The hypovolaemia also stimulates the renin-angiotensin system, resulting in secondary aldosteronism. This can lead to salt and water retention, thus worsening the oedema. (ADH secretion may also be increased).

Although many children may later adapt to low albumin levels and become "normovolaemic", they must initially be regarded as potentially hypovolaemic, especially if they are very oedematous, as this may lead to a hypovolaemic crisis.

CLINICAL PICTURE

Presents with rapid onset of oedema, which increases gradually. The oedema is generalised and the distribution is influenced by gravity - The eyelids are typically swollen in the morning and the legs/feet at night. Transudation of fluid into the body cavities results in pleural effusions and ascites, which can hinder respiration. In untreated or refractory cases, massive anasarca can develop. The eyelids can swell totally closed and alarming scrotal or vulval oedema may occur. The urine excretion may decrease and urine becomes frothy.

Microhaematuria may occur in ± 20% of cases and mild hypertension in ± 10% of cases of MCNS, however this is not a characteristic finding. Macrohaematuria and significant hypertension are suggestive of glomerular damage (chronic glomerulonephritis) as the cause of the nephrotic syndrome.

The children are often listless and appear pale, however they are not necessarily anaemic. Fever is not a characteristic finding and is suggestive of secondary infection.

Hypovolaemic crisis: Severe listlessness, irritability and cold extremities. Sudden anorexia, abdominal discomfort/pain and frothy diarrhoea (due to protein-losing enteropathy) are severe signs. Postural hypotension may develop, but paradoxical hypertension (due to vasoconstriction) may also be present. The haematocrit (Hb) increases due to haemoconcentration. Urine Na^+ concentration is very low (< 10 mmol/l) and the plasma urea increases due to pre-renal renal failure. Urgent treatment is necessary.

Tendency towards infections: Due, amongst others, to defective lymphocyte function and decreased plasma IgG, there is an increased tendency towards infections. Tuberculosis must be excluded before steroids are administered. There is also an increased tendency for cellulitis, as well as an increased incidence of primary peritonitis and septicaemia due to Streptococcus pneumoniae and gram-negative bacteria.

Thrombosis: Both arterial and venous thromboses can occur due to increased blood viscosity and hypercoagulability. There is also thrombocytosis and increased platelet adhesiveness. Fibrinogen and clotting factors V, VII & VIII are increased, while antithrombin III is decreased. Thrombotic phenomena occur less commonly in children than in adults. Aspirin 75 mg/day may prevent thromboses.

Malnutrition: Loss and malabsorption of nutrients can result in children with chronic refractory NS becoming malnourished. Severe muscle atrophy, which is often masked by the oedema, can develop. Dull hair, striae, anaemia, poor appetite and growth retardation may develop. Persistent ascites may result in umbilical and inguinal hernias, as well as rectal prolapse.

SPECIAL INVESTIGATIONS

Haematology: Increased platelets and sedimentation rate, but further normal. Anaemia in chronic cases. (Hb increases with hypovolaemia).

Blood chemistry:

K^+ - A tendency towards hypokalaemia due to secondary aldosteronism.

Na^+ - Sometimes decreased due to increased water intake and ADH secretion. Total body sodium is almost always increased, however.

Urea - Decreased, normal or increased. (Increased urea with normal creatinine indicates pre-renal renal failure).

Creatinine - Normal unless renal failure sets in.

Protein - Albumin less than 25 g/l. (The albumin level does not necessarily correlate well with the degree of oedema). Alpha-2 globulin increased. IgG decreased & IgM increased.

Lipids - Cholesterol, phospholipids and triglycerides increased. LDL & VLDL is increased & HDL normal.

Complement: Total complement, C_3 & C_4 normal in MCNS
Total complement & C_3 decreased, C_4 normal in APSGN.
Total complement, C_3 and C_4 decreased in S.L.E.
C_3 decreased in mesangiocapillary GN

Other investigations indicated:

Hepatitis B, VDRL, ANF, anti-DNA and ENA for SLE (especially older girls). Sometimes Widal ASOT.

Urine:

Microscopy: Granular casts and oval fat-bodies frequent in MCNS. An active sediment with dysmorphic red blood cells and casts is suspicious of glomerular lesions.

Urine culture: Infection may be present.

DIFFERENTIAL DIAGNOSIS

A. First differentiate from other causes of generalised oedema.

1. Increased hydrostatic pressure: Inability to excrete Na^+ & H_2O, resulting in intravascular fluid overload.
   - Cardiac failure
   - Renal failure especially APSGN
2. Reduced colloid osmotic pressure due to decreased plasma albumin level.
   - Defective intake - kwashiorkor
   - Defective synthesis - cirrhosis
   - Increased loss
     - Kidneys - Nephrotic syndrome
     - Intestinal canal – Protein-losing enteropathy
3. Allergic (angioneurotic) oedema

B. If a diagnosis of NS is made, a distinction between the different causes must be made.

NB The clinical picture of acute post-streptococcal GN and the nephritic-nephrotic syndrome is very similar. Both frequently have oedema, haematuria and proteinuria as well as hypertension, and the clinical distinction can be very difficult. Determination of the albumin level is critically important, especially if impetigo is also present.

Fluid overload in APSGN can dilute the albumin level down to almost 25 g/l. Levels lower than 25 g/l must be regarded as nephrotic. Then measure the cholesterol level: If increased, this is suggestive of nephrotic syndrome.

KIDNEY BIOPSY

Kidney biopsy is not performed routinely in children with a clinical picture of MCNS, but definitely when a nephritic-nephrotic syndrome is suspected.

Indications:

Children under 1 year of age and older than ± 10 years of age.
Black children (more often in coloured children).
Macrohaematuria and active urinary sediment.
Persistent hypertension.
Reduced renal function not due to hypovolaemia/pre-renal failure.
Hypocomplementaemia.
When Hepatitis B, ANF (anti-DNA) or VDRL are positive (systemic diseases)
No response to steroids.

TREATMENT

Supportive:

A. Activity:

Although bed rest may have a "diuretic" effect, strict bed rest is usually not necessary. Activity must be restricted; however movement is necessary to mobilise the oedema.

B. Diet:

- Adequate protein intake up to 3 gm/kg/day must be maintained. Excessive high protein intake is not advantageous and a low protein intake exacerbates the tendency towards malnutrition. Low salt, ward diets are usually adequate.
- Adequate calories/energy.
- Salt restriction, especially while oedematous. Potassium supplementation is sometimes required.
- Fluid restriction is unnecessary (- tendency towards hypovolaemia). Excessive fluid intake must, however be prevented.

C. Oedema/Diuretics:

1. Due to the tendency towards hypovolaemia, aggressive treatment with powerful loop-diuretics such as furosemide (Lasix) is not recommended. Maintenance diuretics: Spironolactone (Aldactone) 3 - 4 mg/kg/day. (Counteracts secondary aldosteronism). Hydrochlorothiazide (Dichlotride) 2 - 3 mg/kg/day can be added.

2. 20% low-salt human albumin intravenously.

   Dose: 4 ml (1 gm)/kg over 2 hours, followed by Lasix 1 mg/kg i.v. stat. (Plasma/serum 20 ml/kg if albumin not available). **NB:** Watch the blood pressure carefully – can cause hypertension and even pulmonary oedema. Do not give an albumin infusion if the plasma albumin level is more than 25 g/l, even if there is oedema present.

   Indications:

   Albumin infusions are not administered according to plasma albumin levels, but according to specific clinical indications. Infusions may be life-saving.

   a) Oedema that causes "discomfort" (Ascites, especially if there is peritonitis present, pleural effusions, scrotal/labial oedema and eyelids that have swollen shut).

   b) Threatening hypovolaemic crisis: Symptoms = Anorexia, abdominal pain and diarrhoea (see also under Clinical Picture).

   NB: Effects of albumin infusions are temporary as well as expensive, and thus should not be administered for moderate oedema.

D. Infections

Secondary infections can result in relapses and should be effectively treated. Early relapses of MCNS can sometimes be reversed with antibiotics.

E. Hypertension and renal failure – Treat if present in cases with nephritic-nephrotic syndrome.

Specific treatment:

1. Corticosteroids: Predominantly limited to children with MCNS (as well as SLE).

   Dose is 2 mg/kg/day in 3 divided doses (maximum 60 mg/day) for 4 - 6 weeks provided that remission occurs (urine is protein-free). Remission usually occurs within ± 10 days. Then decrease dose to 3 mg/kg every second day as a single dose in the morning. The dose is then decreased every 2 weeks, provided the child remains in remission, and then stopped.

   If there is no response after 4 weeks, a biopsy must be performed.

   Response to steroids:

   Group I - good response with no relapses. Minority of cases (< 15%).

   Group II - good response but develop intermittent relapses. Treat as for first episode.

   Group III - good response but develop recurrent relapses (within 1-2 weeks) or become steroid-dependent (± 20%). Try and maintain on low dose steroids (0.6 mg/kg) every second day. If not successful or patient becomes steroid toxic, consider cytostatics.

2. Cytostatics

   Cyclophosphamide (Endoxan) 2.5 mg/kg/day for 12 weeks or Chlorambucil (Leukeran) 0.2 mg/kg/day for 8 weeks. Should be used together with steroids to achieve better remission and also to protect the bone marrow. Although these drugs can result in permanent remission, relapses may sometimes still occur. These drugs have potentially severe side effects and must never be given lightly. Strict supervision is required with 2-weekly white cell counts.

Support to child and parents. Very important. Must be fully informed. Parents must realise that the disease tends to have a chronic course and that relapses will most likely occur.

PROGNOSIS

The prognosis of MCNS is usually eventually good, even if there are recurrent relapses. Progression to renal failure is rare and there is a strong tendency to eventually burn-out during puberty. It is thus important to always be optimistic.

The prognosis of the nephritic-nephrotic syndrome is variable and depends largely on the histology thereof. Selected cases may respond to immunosuppression, but often only supportive therapy can be offered. Progression to chronic end-stage renal failure can occur. Hepatitis B-associated nephropathy in children can remit spontaneously in 30% of cases after 2 years and in 60% after 4 years.

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HENOCH-SCHONLEIN PURPURA/SYNDROME

Also known as Anaphylactoid or allergic purpura.

Henoch-Schonlein purpura (HSP) is characterised by a systemic small vessel vasculitis predominantly affecting a) the skin, b) intestinal tract, c) kidneys and d) joints (any sequence). (Just about any other organ such as the heart, lungs, pancreas and brain can also be affected).

AETIOLOGY AND PATHOGENESIS:

HSP is probably an IgA immune complex disease since IgA deposits are characteristically found in the blood vessel walls of the skin and in the renal mesangium in the acute phase of the disease. Serum IgA levels are often elevated. Although many IgA-stimulating antigens have been blamed, the precise antigen is still not known.

CLINICAL PICTURE:

Peak incidence between 3 - 10 years, but may occur at virtually any age. Gender M:F=3:2. Often follows 1 - 3 weeks after an upper respiratory tract infection. Children often feel ill and may develop a fever up to 38°C.

Skin involvement: Begins as an acute symmetrical erythematous macular rash, initially often limited to the malleoli and then classically spreads to the legs, buttocks and arms. The torso is usually spared. Changes within a few hours to a palpable swollen pink maculopapular rash due to vasculitis. The lesions vary between 0.5 - 2.0 cm in diameter and can later coalesce and become darker. Lesions can occur at various stages and are often precipitated by exercise or pressure on the skin. Lesions usually disappear within 3 - 4 weeks, but may take longer. Two to three repeat episodes even 6 - 18 months later may occur.

Because of the intense inflammatory reaction in the capillary vessels, the vessels break open and give rise to purpura and ecchymoses. The lesions are thus not primarily purpuric. Ischaemia within the lesions may also give rise to skin necrosis, as well as a vesicular rash. The skin and flesh may be extremely tender.

Inflammatory oedema typically occurs on the dorsa of the hands and feet, as well as periorbitally. In children less than 3 years of age, the scalp may also be involved.

Joint involvement: Occurs in 60 - 70% of cases. Affects mainly the ankles and knees, and less frequently the wrists and fingers. Joints are painful and swollen due to periarticular oedema, but are not red or warm. Effusions are rare. No permanent damage occurs.

Gastrointestinal involvement: In 50% of cases. Can precede the skin and joint involvement. Vasculitic lesions may involve any part of the intestinal tract from the stomach to the colon. This results in cramping abdominal pain, melaena, bloody diarrhoea and sometimes haematemesis. An acute abdominal picture may result in laparotomy or appendicectomy. Massive bleeds, intussusseption or protein-losing enteropathy may also occur.

Renal involvement: In 80% or more of cases. Presentation varies between asymptomatic haematuria and proteinuria to the nephrotic syndrome or acute nephritis with renal failure. Chronic renal failure fortunately occurs in the minority of cases.
Renal involvement can present together with the skin rash, or may occur up to a few weeks later.

DIAGNOSIS:

The diagnosis is a clinical diagnosis based on the recognition of the skin rash. 50% of cases have a transitory increase in serum IgA levels. Although the alternative complement pathway is activated, complement fractions C_3 and C_4 are normal. The platelet count is normal.
The condition must be differentiated from other causes of purpura such as meningococcaemia and trombocytopaenia, other causes of arthritis, as well as other causes of nephritis such as SLE, bacterial endocarditis and polyarteritis nodosa.

PROGNOSIS:

The morbidity and mortality are ultimately determined by the degree of renal involvement. Less than 10% of cases develop chronic renal damage. Children with
persistent haematuria or proteinuria must be followed-up long term, as renal failure or hypertension can develop up to 10 years after onset. Most cases burn out after 2 years.

TREATMENT:

Treatment is supportive. Steroids can be used symptomatically for joint pain or abdominal pain, but do not influence the renal involvement. Avoid aspirin. Paracetamol can also be used. High doses of steroids and cytostatics may possibly be of value in severe cases of nephritis, but are not used routinely.

HAEMOLYTIC-URAEMIC SYNDROME

Refer to Paediatrics & Child Health. HM Coovadia + DF Wittenberg. 5th Edition.

Treatment: Treatment and indications for dialysis are essentially the same as for other causes of acute renal failure. Haemodialysis, when available, is preferable to peritoneal dialysis. Platelet transfusions should be avoided, even if the platelet count is very low. Infusions of fresh frozen platelets are probably of no use.

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DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

MBCHB III

ACUTE RENAL FAILURE (ARF) IN CHILDREN

Sudden, severe insufficiency in renal function. Results in life-threatening imbalances in fluid, electrolyte and acid-base balance within a few hours to days.

Because many of the causes in children are reversible, rapid diagnosis and effective treatment are very important in order to prevent permanent damage.

ARF is usually characterised by diminished (oliguria) or absent (anuria) urinary excretion.

Oliguria	< 400ml/1.73 m^2/24 hours	**≤ 1ml/kg/hour in babies** **<0.5ml/kg/hour in children**
Anuria	< 75ml/1.73m^2/24 hours	**< 1ml/kg/24 hours**
(Normal excretion hours)		**1.5 - 2.0 ml/kg/hour** or 35 - 45 ml/kg/24

Total anuria is unusual, except in APSGN, shock, complete post-renal obstruction (particularly in a single kidney) and renovascular occlusion.

A so-called "high turnover renal failure" with normal urine volume, but poor quality urine, may also occur. Examples include partial obstruction, some cases of acute tubular necrosis, especially interstitial nephritis resulting from aminoglycoside toxicity.

ARF is divided into 3 groups pathogenetically:

* Pre-renal: poor renal perfusion
* Renal ("true" renal failure) – renal parenchyma damage/injury
* Post-renal - obstruction of urinary flow

A) PRE-RENAL FAILURE

Mechanism:

Hypotension
Hypovolaemia
→ reduced renal blood flow or effective renal perfusion →

Thus the GFR decreases

Response to reduced perfusion

→ Increased absorption of Na^+ and H_2O as well as ↑ ADH-secretion

→ **Oliguria**

Blood findings: (See later)

Urea increases, often out of proportion (more than twice) to the rise in creatinine.

Urine findings:

* Decreased Na^+ concentration < 20mmol/l because of maximal Na^+ & H_2O reabsorption
* Markedly increased urea concentration
* Increased urine concentration
  Osmolality > 500 mOsm/kg water, SG > 1,020
* Urine/plasma urea ratio > 40

Usually completely reversible once circulation has been restored. If not → renal parenchymal failure. (Acute tubular necrosis)

Causes:

1. Circulatory insufficiency

   * Dehydration - Gastro and DM
   * Shock, hypotension, blood loss, burn wounds, septicaemia, cardiac failure
   * Hypoproteinaemia resulting from nephrotic syndrome, etc.

(2. Renovascular occlusion (arterial) - unusual)

B. RENAL FAILURE

a) **PRIMARY** Failure is primarily due to glomerular, renal parenchymal or vascular conditions.

- Glomerulonephritis (Many causes)
  Acute nephritic syndrome (Most common cause in RSA)
- Haemolytic uraemic syndrome (microangiopathic haemolytic anaemia, thrombocytopaenia and acute renal failure after a diarrhoeal disease, especially Shigella, in a baby)
- Acute pyelonephritis in babies or in already damaged kidneys
- Acute interstitial nephritis (medications and toxins)
- Acute on chronic renal failure e.g. precipitated by dehydration, fever, hypotension and infection.

Mechanism: Inflammatory reaction (infective or non-infective) results especially in glomerular injury. → Inability of glomeruli to excrete K^+, Na^+ and H_2O, as well as other metabolites.

b) **SECONDARY** to extra-renal (systemic) conditions which affect the tubules in particular.

1) **<u>Acute Tubular Necrosis (ATN)</u> (Vasomotor nephropathy)**

Tubules are predominantly affected - Glomeruli spared – Reversible up to 6 weeks after onset.

(a) **Nephrotoxic:**

Various medications.
Especially aminoglycosides. Amphotericin B
Radio-contrast agents. Sangoma medications (Impila).
Bacterial endotoxins (Septicaemia)
Rhabdomyolysis
Ethylene glycol (brake fluid). Heavy metals.
Carbon tetrachloride. Methanol.

(b) **Ischaemic:** Secondary to:

Prolonged pre-renal failure, dehydration or hypotension.
Shock
Severe hypoxia, trauma
Haemolytic conditions
Incompatible blood

Mechanism of ATN (Vasomotor nephropathy)

(a) **Cortical Vasoconstriction:**

Selective, diffuse reduction in cortical blood flow possibly via the Renin-Angiotensin system - secondary to states of shock or as a result of direct actions of toxins.

→ Renal blood flow diminishes to $^1/_3$ normal, but effective GFR decreases to 2-3% normal as a result of "backflow diffusion" (see below)

(b) **Tubular Necrosis:**

In addition to cortical vasoconstriction, there is also tubular damage/necrosis resulting in:

(i) Tubular obstruction
(ii) Backflow diffusion into the renal interstitium (Urea <u>and</u> Creatinine) → Renal failure picture.
(iii) Interstitial oedema. Decreases the effective GFR
(iv) The tubules are unable to conserve salt and water due to
tubular injury and a poor quality urine is often still passed. Some children are anuric however.

A diuresis may develop during recovery.

(2) **<u>Bilateral cortical necrosis</u>**

Both Glomeruli and Tubules affected

Irreversible or results in chronic renal failure

Causes: Essentially the same as ATN, especially ischaemic incidents. Because the aetiology is very much the same as ATN, it is not known why some patients develop ATN and others cortical necrosis. Cortical necrosis is diagnosed when renal function has not normalised within 6 weeks.

NB: The transition from pre-renal failure to ATN is not well defined. Pre-renal failure should be treated actively in order to prevent ATN.

(3) **Renal Medullary/Papillary necrosis**

Rare in children. Not necessarily acute renal failure. Pyelonephritis. DM. Drug-induced (NSAID's). (Can cause obstruction)

(4) **Mechanical or Iatrogenic Damage**

Trauma
Renal angiography

Urine findings in Renal Failure

Urine Na^+ > 60mmol/l
Urine urea only moderately elevated
Osmolality ± 300mOsm/kg (similar to plasma) SG 1,010 → 1,018
Also contain RBC's, WBC's, Cylinders, Protein and tubular cells
Urine/plasma urea ratio < 10 (Urine/plasma ratios can be confusing).

C. POST-RENAL FAILURE

a) Obstruction of urine flow: Congenital obstructive uropathy, e.g. Bilateral pelvi-ureteric obstruction, posterior urethral valve in boys. Stones. Crystalluria - sulphas, uric acid in tumour lysis syndrome.

b) Obstruction of blood flow: Renal venous thrombosis such as in shocked/dehydrated babies or babies of diabetic mothers. Is characterised by palpably enlarged kidney, haematuria and thrombocytopaenia.

BLOOD ABNORMALITIES

* Uraemia.: Usually increases 4-8mmol/l per day. Hypercatabolic state - 15-30mmol/l per day. In pre-renal failure, the urea increases out of proportion to the creatinine.
* Creatinine increases: In oligo-anuria, creatinine can increase by 50-130µmol/l per day – more with muscle breakdown (rhabdomyolysis).
* Salt and water retention
* Hyperkalaemia
* Hyponatraemia – overhydration/haemodilution
* Metabolic acidosis

* Hypocalcaemia

Hyperphosphataemia → As phosphate increases, calcium decreases

* Hypermagnesaemia
* Hyperuricaemia
* Normochromic anaemia
* Bleeding tendencies – platelet dysfunction

SIGNS OF THE URAEMIC SYNDROME

Anorexia, nausea, vomiting - oedema may be "vomited away". (Projectile vomiting and headache as a result of hypertension).

Varying levels of consciousness, confusion, fatigue, sleepiness, depression, and coma.

Tremor or flap

Bleeding tendencies - epistaxis, melaena – as a result of platelet dysfunction

Uraemic pericarditis (Rub)

Uraemic "snow" on forehead/face

APPROACH TO DIAGNOSIS AND INVESTIGATION

Must <u>first</u> decide whether pre-renal, renal or post-renal.

(History – points to contributory causes)

General examination: Anaemia - ? degree (Obvious anaemia more in favour of blood loss or chronic renal failure). Anaemia can develop very rapidly with the Haemolytic uraemic syndrome. Skin lesions such as impetigo or vasculitis.

Circulatory state:

* Dehydration/fluid overload (oedema) – Often difficult to assess, especially in fat babies. There must be a 10% increase in interstitial fluid volume before oedema is clinically detectable.
* Blood pressure, Pulse rate, Weight
* Respiratory rate - ? Acidosis, ? Pulmonary oedema

Abdominal examination:

* Palpable kidneys - Obstructive hydronephrosis, renal venous thrombosis, polycystic kidneys.
* Palpable bladder/poor stream - obstruction e.g. posterior urethral valve, stone.

Urine:

* Blood (red/dark brown)

* Protein, sugar
* Microscopy: RBC, WBC, casts (type)
  Organisms – do culture

SPECIAL INVESTIGATIONS

1. **Blood chemistry:**

   Electrolytes (K^+), acid-base (acidosis)
   Urea + creatinine (Degree/type of renal failure)
   Calcium and phosphate
   Albumin and cholesterol (nephritic-nephrotic syndrome can clinically mimic ARF. Albumin less than 25g/l can cause pre-renal renal failure).
   Blood sugar
   Liver functions - systemic diseases/septicaemia. CK for rhabdomyolysis.
   Immuno-electrophoresis (Immunocomplex diseases - IgG ↑)

2. **Haematology:**

   Anaemia – degree/type. Infection (Uraemia can cause leukocytosis)
   Haemolysis. Clotting profile if DIC is suspected.

3. **Ultrasound (Sonar): NB**

   Very useful non-invasive investigation. (Obstruction/hydronephrosis, renal size, stones).
   NB: Always do if cause of ARF not obvious.

4. **X-rays:**

   Chest – pulmonary oedema, cardiac size
   Abdomen – stones, kidney size
   Micturating cystogram - urethral obstruction, reflux
   IVP (High dose) – To detect structural abnormalities. Never done in acute phase or if fluid overloaded! Poor image if creatinine more than double normal and then of little value.

5. **Serology:**

   ASOT and complement fractions (Acute Post-Streptococcal Glomerulonephritis),
   ANF (Immune complex and collagen diseases)

6. **Blood culture**

TREATMENT

Treatment should be aimed at the type of renal failure present, e.g. if obstructive uropathy is present, effect drainage (nephrostomy or bladder catheter depending on site of obstruction).
Do not prescribe diuretics (Lasix) in the presence of an obstruction.
First correct pre-renal failure before prescribing diuretics.

Pay careful attention to the maintenance of fluid and electrolyte balance, acid-base equilibrium and nutritional status.

Monitor intake/output, blood pressure, pulse, weight, fever, as well as the clinical signs of oedema and cardiac failure or dehydration.

FLUID THERAPY/BALANCE: Formulae only provide useful guidelines. Repeated clinical re-assessment is essential.

1. Circulatory insufficiency (As in pre-renal failure)

(a) Hypovolaemic shock.

i) Dehydration as a result of gastroenteritis.

- Colloid-volume expander (SHS-Stabilised Human Serum) at 20 ml/kg over ½ to 1 hour.
- Crystalloid (Plasmalyte B or normal Saline).

ii) Blood loss - blood.

(b) Dehydration <u>without shock</u> as a result of gastroenteritis.

Estimate % dehydration and rehydrate over 6-12 hours according to the degree.

(50 ml/kg for 5% dehydration and 100 ml/kg for 10% dehydration).

(i) If K^+ & Na^+ are normal: ½ Darrows in 5% Dextrose water. **(This fluid must <u>only</u> be used for gastroenteritis as it contains potassium).**

(ii) If K^+ is high: 0.45% NaCl and 5% Dextrose.

(iii) If $Na^+ \leq 120$ mmol/l, cerebral oedema may be present. First give 0.9% NaCl (Normal Saline) until the Na^+ is 125 - 130 mmol/l, then use ½ Darrows.

(iv) If Na^+ is increased (> 160 mmol/l) , brain shrinkage may be present. ½ Darrows is then suitable.

After rehydration, the normal maintenance fluid (e.g. 150 ml/kg for babies under 3 months) is given over the next 18 - 24 hour.

(c) Nephrotic syndrome with hypovolaemic shock - 20% human albumin (4 ml/kg over 2-3 hours) followed by furosemide (Lasix) 1 mg/kg.

* Add: $NaHCO_3$ and Ca gluconate as necessary.
Must <u>not</u> overhydrate. Evaluate hourly.

* If anuria persists after rehydration: give Lasix 1-2mg/kg slowly intravenously. Repeat 6 hourly as necessary.

2. <u>Normal</u> maintenance with normal hydration:

* Insensible loss (5% Dextrose) + previous 24 hour excretion (0.2-0.45% NaCl) (+ GIT loss)

* Insensible loss =

(a) 10-25ml/kg/24 hours.
(Newborns = 25ml/kg/24 hours,
5-year olds = 15ml/kg/24 hours and
10-year olds = 10ml/kg/24 hours

(b) 400ml/m^2/24 hours

NB: Avoid all potassium-containing fluids in renal failure

3. Fluid overload: (As in renal failure)

Do not perpetuate the oedema. GFR cannot be forced by means of fluid overloading.

Avoid intravenous fluid. Thirst is no indication of the fluid requirements.

* Oedema without cardiac failure - Gives only insensible loss.

* Cardiac failure/pulmonary oedema - No fluid - strict salt and water restriction. Oxygen ? Digitalise with care.

  - Effect diuresis:

    Furosemide (Lasix) 1 to 5mg/kg slowly intravenously. Can be repeated 6 hourly if necessary. (Oral diuretics are poorly absorbed with fluid overload).

4. Post-renal failure/Obstruction:

Do not initiate diuresis in the presence of post-renal failure. Catheterise if low obstruction. Percutaneous nephrostomy if high obstruction. Beware of post-obstructive diuresis.

ELECTROLYTE AND ACID-BASE DISTURBANCES

a) Hyperkalaemia:

K^+ > 8,0mmmol/l or 7,0mmol/l + ECG changes require immediate treatment. Use ECG monitor. Causes a slow, irregular pulse.

– Impending hyperkalaemia: $K^+ \geq 6.0$ mmol/l or ≥ 6.5 in babies less than 1 year old.

  Act prophylactically:

  - Eliminate all K^+ intake.
  - Kayexalate (exchange resin) P.R. as a retention enema (½ - 1 gm/kg in 5% Dextrose). Eliminates potassium from body and begins working within 30 - 60 minutes.
  - 4% or 8% $NaHCO_3$ (2 mg/kg) slowly I.V. stat if acidotic. Shifts K^+ into cells.
  - Effect diuresis with furosemide (Lasix).

– $K^+ > 6.5 - 7.0$ mmol/l

  Act as above **PLUS**

  - 10% Ca^{++} gluconate 0.5 - 1.0 ml/kg very slowly intravenously. Protects the heart from the toxic effects of K^+.

    If response is not satisfactory:
  - Salbutamol given slowly intravenously (4 µg/kg) or nebulisation (2.5 - 5.0 mg) promotes K^+ entry into the cells.
  - 50% Dextrose water 1 - 2 ml (0.5 - 1 gm)/kg over 30 minutes ± soluble insulin 0.1 U/kg. Promotes K^+ entry into cells. (Seldom actually necessary unless persistent anuria and no response to furosemide).

    Monitor blood sugar levels.

- Dialyse if this is not effective.
  NB: Dialysis take time to get going.

b) Metabolic acidosis:

Hypocalcaemia is often present in renal failure. Increasing the pH by the administration of $NaHCO_3$, results in the decrease in the ionised Ca^+ fraction, and may aggravate the hypocalcaemia and cause tetany.

Thus: - If the Ca^{++} is decreased, give 10% Ca Gluconate 0,5-1,0ml/kg slowly intravenously before beginning to correct the acidosis. (Keep an eye on the pulse → Bradycardia – must not decrease by more than 20 beats/minute.)

- Never correct the acidosis completely. (pH of 7,2 and CO_2 content of 15mmol/l is acceptable in acute renal failure).
- Formulae 0,6 x weight in kg x BE = ml. 4% $NaHCO_3$.
  Use $^1/_3$-$^1/_2$ of the requirement.

  Oral maintenance with bicarbonate is frequently necessary.

c) Hypocalcaemia and hyperphosphataemia:

As the phosphate increases, the calcium decreases.
Aluminium hydroxide (Amphojel) p.o. with meals or Calcium carbonate (Titralac) binds phosphate in the intestinal tract and allows Ca^{++} absorption. 10% Calcium gluconate slowly I.V. is sometimes necessary if the hypocalcaemia is severe.
NB: Avoid aluminium hydroxide in chronic renal failure.

d) Hyponatraemia:

With oedema: Usually as a result of a haemodilution effect - overhydration or water retention. Thus: Limit fluid intake, administer diuretics or dialyse. Administration of hypertonic salt solutions may be dangerous.

With dehydration: Requires NaCl infusion if Na^+ is below 120 mmol/l.

e) Hypernatraemia:

Seldom a problem, except in hypertonic dehydration as a result of gastroenteritis.

DIETARY AND CALORIC REQUIREMENTS:

Difficult to maintain. May lose 1-2% weight/day.

- Give high calorie or carbohydrate intake (CHO 2-3 gm/kg/day)
  This limits endogenous protein catabolism (Protein sparing effect)
  Use Hycal or Caloreen. Glucose sweets.
  (Minimum calorie requirements 400kcal/m^2/day or 1600kJ/m^2/day)
  1-3 years old: 100Kcal/kg
  4-6 years old: 90Kcal/kg
  7-10 years old: 80 Kcal/kg (1Kcal = 4.2 kJ)

- Fat is poorly tolerated but 1-2 gm/kg/day will increase caloric intake.

- Protein – Limit intake to "normal" requirements, i.e. ± 1,5g/kg/day
  (NB: "Normal" ward diet is a high protein diet)
  - Low Na^+ humanised milk in babies (NAN, S26 give ± 1,5g/prot/100ml
  - Limit salt intake
  - Potassium restriction also often necessary
  - Vitamins

Anaemia:

Blood loss. Blood dilution. Decreased half-life and decreased erythropoeisis. Unless there is shock present as a result of blood loss, transfusion is not necessary unless the Hb < 6,0g/dl. Give packed cells 5-10ml/kg slowly. Beware of overloading. Urea may increase further. Easier to give during dialysis.

Infection:

Big danger → death. Uraemia suppresses the response to infections.

Prevention: strict asepsis. If catheterised, do repeated urine cultures. Physiotherapy - lungs, etc.

Antibiotics:

"Safe"- Penicillin, Ampicillin, Amoxil, Augmentin, Cloxacillin, Erythromycin, Chloro, Doxycycline, Cephtriaxone (if liver function is normal), Clindamycin.

Other antibiotics must be modified or avoided (Aminoglycosides). Various medications are nephrotoxic.

Convulsions:

Determine cause and treat where possible. Often associated with hypertension, electrolyte disturbances (hypocalcaemia) or hypoglycaemia.

Short-acting phenobarb (Sodium gardenal), Valium, Epanutin.

Hypertension:

See Acute nephritis lecture - medications

Salt and water restrictions. Take care with blood transfusions. Diuretics and dialysis may help.

DIALYSIS

Besides the uraemic syndrome, there is no other direct specific indications for dialysis. The entire clinical picture and progress of the individual must be considered.

Guidelines:

- Uraemic syndrome (Pericarditis/bleeding tendencies)
- Urea > 40-50mmol/l
- Creatinine > 400-900µmol/l
- Phosphate > 3,0 mmol/l

- Hyperkalaemia > 7,0 mmol/l that is not responding to conservative treatment.
- Severe uncontrolled acidosis
- Severe hypovolaemia and overload - pulmonary oedema (Can be ventilated)
- Hypernatraemia/hyponatraemia
- No response to high dose diuretics - anuria
- Poisoning with dialyzable medications

SUMMARY

Make the diagnosis of renal failure:

- High index of suspicion – Do routine urea/creatinine determinations in a child presenting with an unexplainable picture.
- Try to determine the cause or type of renal failure - further action is highly dependant on this (Examine abdomen. Ultrasound of kidneys is a very useful investigation)
- Identify and treat the danger signs, e.g. Hyperkalaemia/hypocalcaemia, acidosis, fluid overload/pulmonary oedema, hypertension, uraemic pericarditis.
- Administer fluid extremely conservatively. Avoid all potassium-containing fluid. (Indications for intravenous fluid are very limited). Once fluid has been infused, it is very difficult to "remove" it from the anuric patient.
- Try and effect diuresis, except in post-renal failure. Continue with this until the fluid overload/oedema is resolved.
- Eliminate pre-renal failure quickly and effectively so as to prevent secondary damage (ATN).

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Fact

DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

MBCHB III

URINARY TRACT INFECTIONS (UTIs) IN CHILDREN

- Second most common infection after (upper) respiratory tract infections.
- Most common disease of the urinary tract (includes acute pyelonephritis, acute cystitis and asymptomatic or covert bacteriuria).

NB: Do not confuse acute pyelonephritis with glomerulonephritis!

INCIDENCE

Overall incidence (all ages): 2-3% (Up to 5% in girls and 1-2% in boys).
Highest frequency of anatomical abnormalities: 1 month to 2 years. (Anatomical anomalies, especially hydronephrosis, are now frequently detected by antenatal sonar).
Gender distribution:

First month	F:M - 0,4:1
2-6 months	F:M - 1,5:1
2 years and older	F:M - 10:1

Thus, UTIs are predominantly a disease of girls, except in the neonatal period.

Importance of urinary tract infections

In young children (especially less than 2 years of age) with UTI, approximately 1 out of 3 girls and 1 out of 2 boys have underlying urinary tract anomalies. The most common anomaly is congenital vesico-ureteric reflux (VUR), followed by congenital obstructive lesions.

The danger of acute renal parenchymal infection (acute pyelonephritis) is "renal (cortical) scarring". This used to be referred to as Chronic Pyelonephritis , but histologically could not be differentiated from other causes of Interstitial nephritis.

In the 1970's, it was found that UTI + VUR + IRR = RN - Reflux Nephropathy (renal scarring) (IRR = Intra-renal reflux). The term Reflux nephropathy thus replaced the term chronic pyelonephritis, and was regarded as just about the only cause of renal scarring.

It is now obvious that any acute renal parenchymal infection, with or without VUR, can cause Renal scarring.

Renal scarring can lead to hypertension, proteinuria and, in severe cases, chronic renal failure.

NB: Renal scarring can often be prevented or diminished by the early diagnosis and treatment of acute pyelonephritis.

Factors which predispose to renal scarring include:

- VUR causing renal dysplasia *in utero*
- Congenital obstructive uropathy (structural or neurogenic)
- Young age with acute pyelonephritis, especially <1-2 years of age. Older children are still at risk.
- Delay in antibiotic therapy for acute pyelonephritis
- Severe VUR (Grade III-V)
- Recurrent acute pyelonephritis

DIAGNOSIS

UTI's have the (dubious) reputation of being one of the most misdiagnosed diseases of children.

Urine culture (in other words, the demonstration of significant bacteriuria) is the only "reliable" method of diagnosis, and must be done with care. Many doctors use only Dipsticks or symptoms to make a diagnosis.

Consequences of incorrect diagnosis include:

a) Poorly documented diagnosis results in unnecessary treatment, radiological and urological investigations.
b) Bearing in mind the danger of renal scarring as well as obstruction, a missed diagnosis could result in unnecessary/premature chronic renal failure.

Pitfalls:

a) A low index of suspicion and neglect to culture urine (see under symptoms).
b) Incorrect collection and processing of urine.
c) Reliance on side-room investigations alone.
d) The "treatment" of symptoms that may mimic UTI's without examining the urine.

Criteria/Requirements

Ideal: A freshly collected, early morning, midstream urine sample that is cultured immediately is necessary for the accurate diagnosis of a UTI.

Culture

Significant: $\geq 100\ 000\ (10^5)$ organisms/ml. Two successive cultures of the same organism are preferable in order to obtain a confidence level of ± 100%. Nonetheless, a single specimen in a symptomatic patient is usually sufficient. (Any growth from a suprapubic specimen is significant.)

Negative: $< 10\ 000\ (10^4)$ organisms/ml have a 98% probability that there is no infection.

Doubtful cultures should be repeated (10^4-10^5 organisms/ml) before treatment is given.

Side-room investigations

Dipsticks (Dipstix, Labstix)

a) Blood/protein: Presence is non-specific; many other causes. (Haematuria occurs in 10-15% cases of UTI).
b) Leukocyte esterase test: Sensitive for leukocytes but not specific for UTI's – especially in girls. Reliable if negative
c) Nitrite test for bacteria: (Bacterial reduction of nitrate to nitrite in the urine within the bladder takes 3-4 hours). Very reliable (99%) if positive, but gives a false negative result in ± 50%.
d) pH: Very alkaline urine may be indicative of Proteus infection. Very acidic or diluted urine can result in false negative cultures.

- Urine with any positive parameters should be cultured
- Negative screening tests are still valuable in children without clinical UTI's, but infections will still be missed.

  Be aware of limitations.

Microscopy

Very useful for the rapid evaluation of urine for infection, but may also be subjected to errors of judgement.

a) Bacteria: 2-3 moving organisms/h.p.f. (uncentrifuged) or 15-20 organisms/h.p.f (centrifuged) correlate well with a bacterial count of 100 000 organisms/ml. Bacteria are not always easy to visualise, especially in a bright light. Amorphous phosphates which undergo "Brownian"-movements may resemble cocci.
b) White blood cells: Traditional, but may also give false positive and false negative results.
   Centrifuged: (2000 rpm for 3 minutes)
   < 5 WBC/h.p.f = negative
   > 5-10 WBC/h.p.f. = suggestive
   Uncentrifuged:
   < 4000 WBC/ml

Bacteriuria without pyuria

Bacteriuria may be present in the absence of white blood cells. The absence of pyuria thus does not exclude a UTI.

Covert or asymptomatic bacteriuria occurs most commonly in girls of school-going age (1.1-2.8%). 20-35% of them have VUR of which 20% have reflux nephropathy. Symptoms are frequently vague or absent.

Recurrent infections, especially within 1 month of symptomatic infection, frequently start (± 50%) with asymptomatic bacteriuria and bacteriuria may sometimes be the only sign of acute pyelonephritis. (Steroid therapy can also mask symptoms of pyelonephritis).

Sterile pyuria without a UTI

Fever
Acute systemic/virus infections
Dehydration
Vulvovaginitis & urine reflux in vagina. (Contamination from female genitalia.) Balanitis
The glomerulonephritides, interstitial nephritis
Half treated UTI's (Antibiotic)
Appendicitis
Tuberculosis (Relatively uncommon in children)
Kidney stones (Usually infective in children)
Cystic diseases of the kidneys
After polio vaccination

* **CONCLUSION:** White blood cells may thus be present in the absence of infection, or may be absent in the presence of infection. Demonstration of a significant bacteriuria, by means of a culture of fresh cleanly collected midstream urine specimen, gives the most trustworthy result.

COLLECTION OF URINE

Careful attention to detail must be given to the correct collection of urine, otherwise false positive cultures or contamination will result.

Can be divided into 3 groups:

1. **Suprapubic puncture** - Urine collected in this manner should be sterile; in other words, any culture should be regarded as positive. Most reliable method and one that is both simple and safe - provided the bladder is palpable. (The bladder is an extra-pelvic organ in babies). Suitable for all ages, but especially babies.

   If this method is not used, then we have to deal with:

2. Babies that **do not micturate on command** – biggest problem. Either the "bag"-method or the "catch"-method can be used. Although the "bag"-method is rejected by many authors, it is still commonly used; attention to detail diminishes false positive results.

   a) **"Bag"-method**:

   * Rinse genitalia (Sterile water is sufficient. If antiseptics are used, they must be rinsed off with sterile water.)
   * First cover the perineum with bag.
   * Leave the bag open between the legs – this can easily be monitored. (Do not cover the bag with nappy/blankets).
   * Give small feeds – this helps to stimulate micturition and keeps the baby happy.
   * Massage the bladder or place some ice over it.
   * Perform the Perez-reflex on the baby.
   * Remove immediately after micturition. (Repeat the procedure if the baby has not micturated after 45 minutes).
   * Aspirate the urine out of the bag with a sterile syringe. Send immediately for culture or store in refrigerator (see later).

b) **"Catch"-method**:

The same procedure is followed and the urine is caught in a sterile container upon micturation.

c) **Catheter specimen** – Acceptable if antibiotics are to be used.

3. Older children that can **micturate on command** – clean the genitalia with sterile water.

* Midstream urine is collected in a sterile container.

PROCESSING OF URINE

Urine at room temperature is an excellent culture medium; the bacterial count (E.coli) doubles every ± 20 minutes → a false positive culture can be obtained within 1-1½ hours.

Thus: Place immediately on culture medium or let the child micturate in the laboratory. If this is not possible, keep in refrigerator at 4°C and/or transport to the laboratory on ice. Urine can be kept in the refrigerator for 24 hours without affecting the bacterial count. There is **no** excuse for urine lying around, or not collecting for culture, irrespective of the time, day or night.

SOURCE OF INFECTION

- Haematogenous spread - only neonates/young babies
- Ascending UTI - most infections

    - Source - Faecal bacteria

      Bacteria must be able to adhere to and colonise the gut → adhere to the perineum and vagina or prepuce → urethra → bladder → ureter → kidneys

      Bacteria possess a variety of virulence factors that protect them against lysis and phagocytosis, as well as fimbriae (adhesins) which facilitates adhesion to urothelial cells.

Predisposing factors to infection

* Stasis of urine (incomplete voiding)

    - Mechanical/structural:

      Congenital obstructive lesions of the ureters (various)
      Posterior urethral valve (boys)
      Vesico-ureteric reflux (especially Grade III-V)
      Phimosis (Recurrent infections is a medical indication for circumcision)
      "Prune-belly"-syndrome

    - Functional:

sterile container

NB: Incomplete voiding as a result of **constipation**
Bladder dysfunction syndrome
Neurogenic bladder (➔ Obstruction)

- Other kidney conditions:

  Nephrotic syndrome
  Polycystic kidneys, horse-shoe kidneys, etc.

* Local factors:

- Short female urethra opens in to contaminated area

  Poor hygiene, dirty nappies, etc.

- Local irritants

  Foam baths etc.
  Pin worms (Enterobius vermicularis)

- Catheterisation and foreign objects

* Systemic diseases:

  Malnutrition (Kwashiorkor)
  Diabetes mellitus
  Immune deficiency diseases and immunosuppression (steroids)

Protective factors against infection

a) Regular and complete voiding of the bladder with free drainage of the entire urinary tract: Intact voiding mechanism probably the most important factor.
b) Urine acidity: Bacteria multiply slowly in acidic urine.
c) Normal vaginal and perineal flora normally compete with faecal bacteria (Can be disrupted by antibiotics).
d) Mucous membrane defence mechanism: Urothelial cells have a bactericidal activity. Bacteria coming into direct contact with the bladder mucous membrane are normally destroyed within minutes by secretory IgA, lysozyme and IgG antibodies. (Chronic infections disrupt this mechanism for a protracted time).

BACTERIOLOGY

Gram-negative bacilli, of which Escherichia Coli is the most common (± 80%). Klebsiella spp, Enterococci (Enterococcus faecalis) as well as Proteus spp in boys (urine is alkaline), Pseudomonas and Serratia. Candida albicans occurs especially in premature babies and neonates and may present with an obstructive picture due to the Candida-balls.

Adenoviruses may cause a haemorrhagic cystitis; Chlamydia and Mycoplasma are implicated in the urethral syndrome.

PATHOLOGY

Acute: (Acute pyelonephritis)

Wedge-shaped lesion of acute inflammation through the cortex which is particularly affects the interstitial tissue and tubules. (Poles especially involved). Cortical vasoconstriction, interstitial oedema, arteriolar and capillary obstruction by granulocytes ➔ Focal ischaemia which occurs early. Visible on DMSA renal scintigram on day 3.

Chronic:

Renal scarring as a result of acute parenchymal infection. Irregular kidney. Calyceal-system blunted and close to the kidney surface. Occurs as a result of release of superoxide, oxygen radicals and toxic enzymes such as lysozymes. Results in bacterial and tubular cell death and interstitial fibrosis. Lesion on DMSA renal scintigram 6 months post- infection is permanent.

CLINICAL PICTURE

Very varied. High index of suspicion often necessary. Symptoms of UTI in babies often not related to urinary tract. Recurrent episodes of fever are often attributed to upper respiratory tract infections. (NB: Urine investigation is essential in any child with undiagnosed disease/fever, even if there are no tell-tale symptoms of a UTI).

Newborn and infants:

Often a picture of septicaemia. Prolonged neonatal jaundice. Renal failure. Hypo- or hyperthermia. Apathy or irritability. Convulsions. Poor feeding or development. Diarrhoea, vomiting. Acidosis. Poor urine stream in boys. (Posterior urethral valve).

Older children:

a) Upper urinary tract (Pyelonephritis) – mostly systemic signs. Fever above 38°C. Rigors/convulsions. Vomiting. Dehydration. Abdominal pain. Tender renal angles. Sometimes dysuria.
b) Lower urinary tract (Cystitis) - few systemic signs. Minimal or no fever. Lower abdominal/bladder tenderness. Dysuria and frequency. Malodourous urine – sometimes bloody. Crying on micturition. Chronic nappy rash. Secondary enuresis.

The difference between upper and lower urinary tract infections is sometimes not clear cut. Children with proven urinary tract infections with high fevers (sedimentation & CRP) **must** be considered to be, and treated for acute pyelonephritis. Chronic recurrent abdominal pain and abnormal micturition patterns may be secondary to a UTI. Chronic constipation predisposes to UTI's.

SYMPTOMS MIMICKING UTI's

Urethral or Sham syndrome

- Frequency, urgency and dysuria are **not** synonymous with infection.
- Symptoms of UTI should disappear within 48 hours. If not, consider the following:

  Organism may be resistant to antibiotics
  Underlying uropathy (obstruction)
  No infection! NB

Causes:

a) During development of bladder control/sensation during the day, especially in 2-3 year olds. The uninhibited bladder. Too busy playing. Often associated with nappy dermatitis.
b) Local irritants
   Foam baths, detergents, soap, chlorine, pin worm, foreign bodies, tight clothes and nylon panties, nappy dermatitis, (ammonia, monilia) injury and meatal ulceration.
c) Vulvitis as a result of a relative oestrogen deficiency. Frequently associated with a discharge. Treat with Premarin cream nightly for 7 days. Antibiotic if the culture is positive.
d) Emotional problems with or without secondary enuresis. Often attention-seeking or adaptation problem.
e) Constipation
f) After acute nephritis/hospitalisation – self-limiting.
g) Unusual organisms. Chlamydia & mycoplasma

TREATMENT

Early treatment can prevent or diminish renal damage. Bedrest if acutely ill. CRP & FBC. Blood culture, especially in neonates. Renal function tests (Acute pyelonephritis does not usually result in renal failure, except in the neonate or when there is already underlying renal damage). High fluid intake and regular voiding. Antipyrexial medications. Adjust antibiotic dosage in renal failure.

Neonate/baby: Danger of Gram negative septicaemia - use parenteral antibiotics for 7-10 days.

a) Cephalosporins e.g. Cefuroxime (Zinacef), Ceftriaxone (Rocephin), Cefotaxime (Claforan)
b) Aminoglycosides e.g. Amikacin (Amikin), Gentamycin - monitor blood levels - avoid in renal failure!

Older child:

* Acutely ill child with systemic signs and vomiting: Intravenous antibiotics for ±48 hours & then oral, e.g. Cephalosporins (E.Coli, Klebsiella, Proteus). I.V. especially when there is obstruction. Aminoglycosides, Piperacillin (especially for Pseudomonas). (**NB:** Ampicillin, Amoxycillin and Co-trimoxazole are of little value due to high resistance).

* Without systemic signs: Oral antibiotics (see below). Nitrofurantoin (Furadantin suspension/Macrodantin capsules) or Nalidixic acid (Winlomylon) for cystitis. **NB:** Nitrofurantoin & Nalidixic acid are urinary antiseptics and do not penetrate the renal parenchyma. Should therefore not be used in acute pyelonephritis or in babies under 2 months.

* Oral Antibiotics: Amoxycillin/clavulinic acid (Augmentin), Cefuroxime (Zinnat). Cefaclor (Ceclor) and Cefadroxil (Cefadrox) are effective oral antibiotics.

Duration of treatment is 7-10 days. 10-14 days with obstruction. Urine should be sterile within 48 hours unless there are resistant organisms or underlying obstruction. Follow-up cultures should be performed 2-3 days after starting and completing therapy. Also repeat after 1 month. (High incidence of re-infection).

Prophylactic chemotherapy

Indications:

1. Recurrent or "chronic" cystitis in girls: Keep on prophylaxis for 6-9 months so that normal mucous membrane defence mechanisms can repair. Exclude predisposing factors (especially constipation).
2. Obstruction – until surgically corrected.
3. Vesico-ureteric reflux. (See later)

Prophylactic medications:

$^1/_3$ to $^1/_2$ normal dosage given at night. Nitrofurantoin, Nalidixic acid. Rotate medications every ± 6 weeks.

Further treatment

In well-documented UTI's, up to $^1/_3$ of girls en $^1/_2$ of boys have urinary tract abnormalities. Vesico-ureteric reflux (± 35%) is the most common, followed by obstruction. Identifying these cases is important.

Imaging investigations

Sonar

Valuable non-invasive investigation, especially in acutely ill patients when abnormalities are suspected. Done in all children with first infection. Reliability is, nevertheless, operator dependent and has thus not precluded the use of conventional radiology. Good for obstruction (hydronephrosis), stones and gross damage. Poor for scarring.

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enal

Intravenous pyelogram (IVP)

Outstanding visualisation of calyces, pelvis and renal tract, except in renal failure. Used when sonar findings are uncertain. Reasonably sensitive for scarring (long-term).

Micturition cysto-urethragram (MCUG)

Best method for diagnosing VUR and imaging the ureters & calyces in reflux. All children under 2 years of age. Normal sonar or IVP does not exclude reflux, and danger of reflux nephropathy is greatest in this age group. Also performed to diagnose posterior urethral valves, ureterocoele, bladder diverticuli etc.

Also done with:

- Recurrent infections
- Abnormal sonar and
- Family history of VUR (sibbe)

Diuresis Renogram (DTPA, MAG_3) (Functional investigation)

Investigation of hydronephrosis and defining possible obstruction
Differentiates between multicystic dysplasia, which is not functional, and obstruction
Differential renal function (e.g. Pre- & Post-operatively for hydronephrosis).

DMSA (Dimercoptosuccinic acid) Cortical scintigram

On 3rd day of infection: Diagnostic for acute pyelonephritic ischaemia

- Identify children at risk for scarring
- Repeat after 6 months - >50% normalise

Acute pyelonephritis is nevertheless, a clinical diagnosis and it is thus not necessary to perform routine DMSA at this stage.

After 6 months or more post-infection: Diagnostic for scarring

- After VUR & obstruction are corrected
- ? All children with acute febrile pyelonephritis
  - Can be discharged if no scarring

Cystoscopy

Not a routine investigation! Usually only indicated pre-operatively e.g. before re-implantation. Bladder neck stenosis exceptionally rare in children and bladder neck dilatation is thus unnecessary.

Grad
Repea

FOLLOW-UP

All children should be followed-up after 1 month as the incidence of relapse, especially in girls, is high. (Recurrent infections often begin asymptomatically. 50% of children will have another infection within 2 years). The prognosis is good if the urinary tract is normal.

If there is a structural abnormality, the child should be started on prophylaxis and followed up every 1-2 months in order to detect breakthrough infections in good time. Follow-ups should take place until the underlying problem has been rectified. The prognosis depends on the degree of renal damage present and the prevention of further damage and infections.

Vesico-ureteric reflux (VUR)

VUR means the retrograde flow of urine out of the bladder and into the ureters and kidneys. VUR is the most common congenital abnormality of the urinary tract. VUR together with infection can result in renal scarring - reflux nephropathy – which is an important cause of hypertension in children and young adults. Chronic renal failure can develop in severe cases.

VUR can be primary or secondary:

Primary reflux: Congenital dysfunction of the vesico-ureteric junction as a result of inadequate intravesical length of the ureter which can be compressed during micturition. This abnormality is already present in the foetus.

Secondary reflux: Secondary to:

* Congenital paraureteric diverticulum
* Infravesical obstruction - posterior urethral valve
* Ectopic ureter or duplication of the ureters
* "Prune belly" syndrome
* Neurogenic bladder (Obstructive effect)

Incidence: ± 30% (20-50%) of children (especially babies) with well documented urinary tract infection have reflux. (Less common in black children).

Importance of VUR, especially Grade III to V: Intrarenal reflux plus urinary tract infection can result in renal scarring in rapidly growing kidneys and thus especially in children younger than 2 years. $^{2}/_{3}$ of children with reflux are at risk of developing scarring if they acquire an infection. The scarring is inclined to develop in the kidney poles.

Because irreversible scarring can occur within 7 days after an infection, it is important to diagnose and treat urinary tract infections early in order to try and prevent scarring.

Grading of VUR:

*	Grade I	Only up into the ureter, but not up into the calyces
*	Grade II	Up to the calyces, with no dilatation of the ureter or calyces
*	Grade III	Early dilatation of the ureter and calyces
*	Grade IV	Moderate dilatation of the ureter and blunting of the calyces
*	Grade V	Severe dilatation of the ureter and calyces. Ureter often tortuous.

Treatment of vesico-ureteric reflux: TBH policy

Grade I-II reflux: Prophylactic chemotherapy changing every ± 6 weeks until it resolves. Repeat MCUG after ± 18 months. Chance of spontaneous resolution is good.

Grade III: Grey area. Treat on merits.

Grade IV-V: Prophylaxis and repair surgically (re-implantation of the ureter/s). Chance of spontaneous resolution is poor.

Perform:

* MCUG and diuresis renogram 3 months after re-implantation if this was necessary.
* Perform DMSA renal scintigram later to exclude scarring.
* Check blood pressure and renal function yearly if scarring present. More frequently if patient already has chronic renal failure.

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Revised 2004

DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

MBChB III

CHRONIC RENAL FAILURE (CRF) IN CHILDREN

Chronic renal failure is always irreversible (incurable). – Damaged nephrons/glomeruli cannot be regenerated.

If both kidneys are involved in the disease process, the following occurs:

a) Gradual tendency of progression towards end-stage renal failure especially if GFR is <50%.
b) As the renal function deteriorates, a number of metabolic and clinical abnormalities (including growth retardation) develop.

Treatment of chronic renal failure is two-fold:

a) Reduction in the progression of chronic renal failure.
b) Support and treatment of the metabolic abnormalities that occur and optimal nutrition in order to try and promote growth.

- 40% of children with the end-stage renal failure are below the 3rd percentile for length.
- The younger the child at the onset of renal failure, the more pronounced the growth retardation and the older he becomes, the less his growth potential.

Thus it is important to diagnose renal failure at any early age and start on optimum treatment. (Growth retardation does not correlate well with the degree of renal failure).

Causes of CRF in children

1. Congenital abnormalities:
   Bilateral obstructive uropathy.
   Bilateral dysplastic hypoplastic kidneys.
   Prune-belly syndrome. [A triad of a) Cryptorchidism, b) Defective or absent abdominal muscles, and c) Urological abnormalities such as hydronephrosis, megaureters and megacystis with poor peristaltic function].

2. Chronic bilateral renal scarring secondary to pyelonephritis/reflux nephropathy.

3. Chronic glomerulonephritis: a variety of causes including Haemolytic-uraemic syndrome.

4. Hereditary kidney conditions:
   Autosomal recessive Polycystic kidney disease. Always associated with hepatic fibrosis, portal hypertension and hypersplenism.
   Renal Fanconi syndrome and Cystinosis. Always associated with metabolic bone disease (rickets) and growth retardation.

Important aspects in the treatment of children with CRF

1. Factors that impede residual renal function must be eliminated, for example urinary tract infection and obstruction.

2. Hypertension.
Must be controlled as this can result in further renal damage which aggravates hypertension. Good B.P. control reduces headaches and improves appetite and well being.

3. Electrolyte, water and acid-base balance

- Potassium

Usually not a problem until end-stage CRF. If hyperkalaemia exists, it is usually due to excessive dietary intake (bananas, oranges, potatoes, "chips", K^+-containing salt, etc.) dehydration, or metabolic acidosis. ACE inhibitors can also cause hyperkalaemia.

- Sodium

* Some patients with chronic renal failure lose salt → lose ECF → ↓ GFR, thus worsening the renal failure. (Na^+ is required for growth – especially connective tissue and cartilage).

Salt restriction is often unnecessary unless oedema, cardiac failure or hypertension is present. Nevertheless, no "extra" salt is permitted. (Excessive salt intake is usually poorly tolerated - measure 24 hour Na^+ loss to determine the exact requirements, if necessary).

- Water

Many patients with CRF, e.g. after relieving congenital obstructive uropathy, have poor urinary concentrating abilities, due to tubular damage, resulting in ongoing polyuria. Fluid requirements may thus be normal to elevated.
Unnecessary fluid restriction can thus result in dehydration and worsening of renal failure.

- Acid-base balance/Chronic metabolic acidosis

Bicarbonate reabsorption and generation, as well as H^+ ion excretion in the kidneys may be defective. H^+ ions are then buffered by bone calcium carbonate base, resulting in the loss of calcium from bone and bone demineralisation.
Chronic metabolic acidosis also causes protein and muscle breakdown.
Treatment: Keep serum bicarbonate levels ≥ 20mmol/l with oral supplementation.

4. Trace elements (various abnormalities)

Zn Deficiency may result in growth retardation.
Administration thereof may improve the sense of taste in some patients, and consequently the appetite.

Anaemia Normochromic, normocytic anaemia, as a result of erythropoietin deficiency, decreased red blood cell production and red cell survival, is present in the majority of children with less than $^1/_3$ of their renal function. Although anaemia "per se" does not cause growth retardation, the elimination of anaemia can also contribute to the child's general welfare (and appetite).

Treatment: Administration of recombinant erythropoietin is effective but expensive. Use thereof also increases Fe requirements.

Iron Episodic iron deficiency anaemia may exist - especially as a result of chronic low-grade intestinal bleeding, due to platelet dysfunction in CRF, and excessive phlebotomy for various tests. Monitor serum ferritin and iron levels and treat only when levels are low – there is a danger of iron overload. (There is also a danger of iron overload as well as antibody formation, Hepatitis B & HIV, with excessive/unnecessary blood transfusions). An Hb of 6gm/dl or more is acceptable, but recombinant erythroproietin should be administered if possible.

Folic acid Supplementation with 1mg per day is recommended.

5. Hormonal factors (various)

(a) Although growth hormone is usually increased, growth hormone receptors are decreased. Growth hormone administration is effective, but prohibitively expensive.

(b) Corticosteroids: High, normal and elevated fasting cortisol levels are found. Adrenal hypertrophy is also found. (Long-standing ↑ cortisol levels probably inhibit growth).

NB: Steroid administration, for the treatment of an underlying renal disease or following renal transplant, suppresses growth and can also result in osteopaenia.

(c) Hiperinsulinism: (degradation is abnormal). There is glucose intolerance due to insulin resistance.

Insulin is important for cellular growth. Uraemia may suppress the metabolism of insulin, as well as the peripheral action thereof → inefficient energy metabolism in muscle and fat cells.

(d) Increased Parathyroid hormone (P.T.H.) → Osteodystrophy (see under Bone metabolism).

6. Bone metabolism

(a) Bone age is retarded and growth potential decreased. As a result of the delayed maturation of bone age, children can grow for a longer period of time, but end up shorter due to the decreased growth potential. The younger the child at the onset of CRF, the more severe the growth retardation.

(b) Renal osteodystrophy: Much higher incidence in children than in adults due to the fact that bone turnover is much higher during growth.

(Bone remodelling/turnover: - Adults - 3-5% per year
- Children - 50% per year)

* Mechanism of Renal osteodystrophy:

a) Secondary hyperparathyroidism: As soon as the serum PO_4 begins to rise, with advancing renal failure, the serum Ca^{++} decreases. This stimulates parathyroid hormone (P.T.H.) secretion (secondary hyperparathyroidism) which enhances increased phosphate excretion (phosphaturia) to normalise phosphate levels, but, unfortunately, also causes Ca^{++} withdrawal from the bone in order to "normalise" serum calcium levels.

When renal function (G.F.R.) drops below ± 30% of normal, increased P.T.H. secretion cannot facilitate adequate phosphaturia and serum phosphate levels become elevated. Serum calcium levels tend to decrease or remain "normal" due to excessive P.T.H. secretion.

b) Deficiency of active vitamin D as a result of defective hydroxylation in the kidneys. Results in poor intestinal absorption of Ca^{++}, hypocalcaemia and poor bone mineralisation.

(N.B. Chronic metabolic acidosis also aggravates bone demineralisation.)

* Treatment: Maintain serum PO_4 below 2,0mmol/l with diet and phosphate binders such as calcium carbonate. Active form of Vitamin D according to individual requirements. Beware of overtreatment, hypercalcaemia and (Ca^{++} x PO_4) product above 6 → Results in metastatic calcification and nephrocalcinosis.

7. Protein-energy malnutrition

(a) Energy –Necessary **firstly** for:

* Basal metabolism - higher in child

(Baby – body mass is more brain, heart, liver and kidneys
Adults – more fat and muscles)
and then for,

* Physical activity,

and only then for,

* Growth

For example:

- Babies grow 25cm in their first year – will never again grow so rapidly. (Brain size doubles in the first 2 years of life). Must first supply basic requirements before growth can occur.
- Energy intake of a 14kg 3-year old child = ½ energy intake of a 70kg man.
- A 14kg child eats 2300Kcal/m^2/day; a 70kg man eats 1 600Kcal/m^2/day.

In addition to the fact that a child thus requires more energy for growth, the appetite is frequently suppressed in CRF → eats less energy → growth retardation and muscle atrophy. Adequate calories also restrict endogenous protein catabolism.

Thus: Provide extra calories (CHO)

Hycal □ various recipes
Caloreen/Polycose □
Glucose sweets

Babies require at least 120 kilocals/kg/day, children 80-100 kilocals/kg/day and adults 40 kilocals/kg/per day.

(b) Protein intake (more complex)

* Some amino acids are increased / normal / decreased] in renal failure

* Children require more protein for growth than adults.

* Too much protein in CRF can cause further renal damage. A careful balance must be maintained.
  Too little - malnutrition
  Too much - uraemic toxicity →
  loss of appetite → ↓ energy intake →
  growth retardation and renal damage

  If renal function falls below 50% of normal, protein must be restricted to the basic requirements: 1.5gm/kg/day for children, up to 2.0gm/kg/day for babies. 50% of the protein must be of higher biological value.

(c) Protein and energy together: - For any given level of protein intake, the nitrogen balance can be improved by addition of energy – will eventually be restricted by the protein level in the diet. In other words, maintain an optimum balance between protein and energy intake. Work closely with a dietician.

Aims:

1. Maintain satisfactory nutrition in terms of nitrogen, calories, minerals and vitamins: Good co-operation between the child, parent, dietician and doctor is essential in order to individually adapt the diet of every child.
   Do not force a child to eat→ may refuse totally. Identify factors that may suppress the appetite. Monitor the weight.

2. Maintain bone metabolism: Monitor growth (height), X-rays including bone age, serum PTH, Ca^{++}, PO_4 en alkaline phosphatase as well as acid-base balance regularly.

3. Retain residual renal function as long as possible: Monitor renal function regularly and identify factors that may impede renal function, such as infections (especially urinary tract), hypertension, sodium depletion and urinary tract obstruction.

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