Emergencies

CONTENTS

TUMOUR LYSIS SYNDROME (TLS)

Tumour Lysis Syndrome is an acute metabolic derangement caused by tumour cell destruction that is usually as a result of chemotherapy but occasionally may occur before chemotherapy starts.

Aetiology and pathophysiology

When tumour cells lyse, nucleic acids (purines) and phosphate are released into the blood. Purines are converted to hypoxanthine, xanthine and uric acid, and phosphate complexes with calcium forming $Ca_3(PO_4)_2$; all these substances may precipitate in the renal tubules resulting in impaired renal function.

Uric acid and xanthine precipitate at acid pH whereas calcium phosphate and hypoxanthine precipitate at alkaline pH. Therefore, alkalinisation of urine is **not** routinely advised particularly if urate oxidase is used in high-risk cases.

The complexing of phosphate with calcium may lead to hypocalcaemia.

Drugs work as follows:

- Allopurinol- inhibits xanthine oxidase and therefore breakdown of xanthine and hypoxanthine to uric acid
- Urate oxidase (rasburicase)- permits enzymatic oxidation of uric acid into allantoin which is at least 5 times more soluble than uric acid

Purine catabolism

⇓ ⇓

guanine adenine

⇓ ⇓

xanthine ⇐ hypoxanthine

⇓ **X** xanthine oxidase (allopurinol works here) X

uric acid

⇓ √ urate oxidase (not present in humans – rasburicase works here)

allantoin

Tumour cell lysis may be present prior to treatment or may develop up to 5 days after starting chemotherapy. However, most cases are recognised within 6-24 hours after starting chemotherapy. TLS is most common in malignancies with a large tumour cell burden and a high growth fraction:

- B-cell lymphomas and anaplastic large cell lymphomas

particularly those with

- Bulky abdominal disease
- Renal infiltration by lymphoma
- Adenopathy causing renal outflow obstruction
- Ascites and/or pleural effusions in whom maintaining a sensible fluid balance is a nightmare

➢ Acute leukaemia and T-cell NHL, particularly

- High white cell counts
- Bulky liver, spleen and/or anterior mediastinal mass
- Renal infiltration by leukaemia
- Infants

But any patient with leukaemia or bulky non-Hodgkin's lymphoma is at risk – TLS can strike "out of the blue" so be wary.

Tumour lysis is more common when the patient has oliguria or dehydration so establishing adequate diuresis prior to starting treatment is vital.

A high urate and phosphate before starting treatment is particularly ominous.

In almost all cases, biochemical evidence of TLS is either not present or minimal at presentation. It is most unusual for a patient to be *symptomatic* from TLS at presentation. The usual sequence of events is:

$\uparrow PO_4$ $\uparrow$ hypoxanthine, xanthine, uric acid

$\Downarrow$ $\Downarrow$

low Ca $\Leftarrow Ca_3(PO)_2$ $\Rightarrow$ $\uparrow$ urea and creatinine $\Rightarrow$ fluid overload

$\Downarrow$

tetany, seizures but $\Downarrow$ $\Downarrow$

unusual with [Ca] > 1.2mmol/l

unless patient alkalinised $\uparrow$ K $\uparrow$ BP and oedema

$\Downarrow$

arrythmias

cardiac arrest

Invariably the first evidence for TLS is hyperphosphataemia not hyperkalaemia

Therapeutic goals

1. Prevention
2. If evidence of TLS occurs, controlling the metabolic and fluid derangement so the patient is not endangered. The major risks for the patient are:
    - Renal failure
    - Hyperkalaemia – arrythmias, cardiac arrest
    - Hypocalcaemia – tetany, seizures although these are rare because the patient is usually acidotic
    - Hypertensive encephalopathy – occurs due to fluid overload and often with only moderate hypertension.
    - May cause the posterior leucoencephalopathy syndrome – sudden onset of obtundation, seizures and blindness. Dramatic but usually recovers!

Clinical approach to tumour lysis syndrome

Assess risk

(a) Clinical examination - assess disease bulk, palpable kidneys, BP, ascites, pleural effusion, oedema etc

(b) FBC - white cell count

(c) Biochemistry - Na, K, urea, urate, creatinine, Ca, PO_4, LDH

(d) CXR (PA + lateral) - large mediastinal mass, pleural effusions etc

(e) Ultrasound abdomen - disease bulk, ascites, urinary tract obstruction, renal infiltration. Malignant infiltration of the kidneys usually shows as:

- Leukaemia - symmetrically enlarged kidneys with normal parenchymal echo pattern. At the time of presentation of a new leukaemic, the kidneys are frequently bright - this represents uric acid nephropathy and **not** malignant infiltration.
- Lymphoma – particularly B-cell presents with “lumpy” infiltration

Risk Stratification

Patients may then be divided into:

- High risk
    - ALL or AML with presenting white cell count > 100 x 10^9/litre
    - Lymphoma with large anterior mediastinal mass, hepatosplenomegaly, bulky abdominal disease
    - evidence of renal infiltration or outflow obstruction

- Infant with leukaemia

- Standard risk – all other cases of leukaemia and non-Hodgkin's lymphoma.

Management

Commence measures (as detailed below) to institute diuresis and correction of metabolic imbalances *but never delay commencement of anti-cancer treatment > 24 hours.*

Accurate observations

- 4 hourly pulse, BP (stipulate 95th percentile systolic and diastolic limits for age and sex– see Symptom Care chapter - Hypertension), respiratory rate. If concerned, increase frequency of monitoring.
- accurate fluid balance
- twice daily weight

Standard risk

(a) hyperhydrate with 0.18% saline in 4% dextrose (**no added K^+**) at 125mls/m^2/hour and ensure urine output $\geq$ 100mls/m^2/hour. A mild degree of hypokalaemia is permissable. If urine output inadequate over first 6 hours, increase volume to 4 litres/m^2/day

(b) allopurinol 100mg/m^2/dose PO 8 hourly

(c) monitor biochemistry 12 hourly – including Ca, PO_4, urate

Start these measures 12-24 hours before commencing induction chemotherapy.

High risk

(a) start measures as for low-risk patients but monitor biochemistry 6 hourly

(b) consider judicious introduction of chemotherapy - prednisone or prednisolone alone at a starting dose of 0.2 – 0.5mg/kg/day

Complications of tumour lysis syndrome

Hyperkalaemia

Get an urgent ECG – look for broad QRS, high T waves. If abnormal, treat as for REAL hyperkalaemia. If normal, then distinguish between:

1) SPURIOUS hyperkakaemia - occurs with ultra-high count leukaemia when blasts lyse and release K^+ during aspiration, transport and spin down. If the K^+ comes back raised and you suspect spurious hyperkalaemia:
    - Aspirate blood slowly through large-bore needle, transport quickly to lab (not through Lansom tube!) and ensure an atraumatic, slow spin-down (discuss with lab).
2) REAL hyperkalaemia – for patients who are intravascularly depleted at diagnosis, give fluids! For acute reduction of real hyperkalaemia the following measures can be taken:
    - IV calcium gluconate 0.5ml/kg over 20 min (with ECG monitoring)
    - IV 50% dextrose (1g dextrose/kg) with 1 unit Actrapid insulin/ml
    - Calcium resonium 0.5-1g/kg can be given orally or even better rectally). This causes a less immediate but more sustained drop in the potassium level.

Hyperphosphataemia

Phosphate may rise above normal despite hyperhydration and allopurinol:

- increase fluids to 4 – 5 l/m^2/day
- monitor biochemistry 6 hourly

A PO_4 > 3mmol/l will inevitably result in some renal dysfunction; a level > 4mmol/l is an indication for haemodialysis.

Hypocalcaemia

Avoid adding calcium to fluids (if at all possible) whilst the phosphate level is rising or peaks because calcium phosphate will complex out in the kidneys and renal damage will worsen. Also, try and avoid frusemide as this can cause a precipitous drop in calcium levels. Calcium can be added when the phosphate level starts to drop:

- infuse 10% Ca-gluconate 1 mmol/kg/day (approximately 4 ml/kg) initially, increase if necessary.
- with seizures, 0.1 mmol/kg/dose of 10% Ca-gluconate IV stat. (approximately 0.5 ml/kg/dose).
- Check magnesium concentration as well
- Avoid $CaCl_2$ as it may cause local vein toxicity and late ulceration.

Fluid overload and hypertension

Try and avoid frusemide as this worsens the hypocalcaemia. In TLS, a degree of fluid overload is inevitable so do not try to be exact about intake and output in the face of increasing hyperphosphataemia. However, use frusemide and accept the consequences if patient becomes hypertensive. Patients with TLS are particularly prone to hypertensive encephalopathy. Set 95th percentile systolic and diastolic limits for age and sex for BP (see Hypertension in Symptom Care chapter)

When to stop hyperhydration and allopurinol

Continue hyperhydration for *at least* 48 hours after initiation of anti-cancer therapy and until:

- White cell count <2 x 10^9/litre
- Tumour masses from B-cell NHL impalpable
- No biochemical evidence of TLS
- Child drinking well

Continue allopurinol for *at least* 48 hours after hyperhydration has stopped and only discontinue when urate normal

HYPERLEUCOCYTOSIS

Pathophysiology

A very raised presenting white cell count (> 100 x 10^9/litre) is seen in ~ 10% of patients with ALL, 15% with AML (particularly M4/M5). The potential problems with hyperleucocytosis are:

- tumour lysis syndrome (particularly ALL)
- hyperviscosity and stasis (particularly AML)

Hyperleucocytosis increases blood viscosity which is dependent on:

- packed red cell volume and
- packed white cell volume

In addition, blasts are not easily deformed. The net result is cell trapping in the microvasculature with microthrombi leading to poor tissue perfusion and acidosis.

The potential consequences with hyperviscosity and stasis are:

- CNS – confusion, blurred vision, ↓ LOC
- Lung – dyspnoea, hypoxia, acidosis
- GIT – haemorrhage
- Priapism

Management

- Follow Tumour Lysis Syndrome guidelines
- Avoid transfusion unless:
  1. Patient clearly symptomatic from anaemia (this may be difficult to judge because of dyspnoea etc related to hyperleucocytosis). In any event, never raise the Hb > 80g/litre
  2. If patient has CNS symptoms, keep platelets above 20 x 10^9/litre otherwise follow usual criteria for platelet transfusion (platelets do not substantially contribute to blood viscosity)
- Avoid LP in patient with CNS symptoms/signs until blast cell count substantially reduced
- Start anti-leukaemic therapy as soon as safely possible ie. once diagnosis established (this can be done on peripheral blood if there is a substantial risk from GA), allopurinol commenced and adequate urine output.

SUPERIOR MEDIASTINAL COMPRESSION (SMC) SYNDROME

Background

About 10% of tumours that occur in the anterior-superior mediastinum compress the superior vena cava (SVC) and/or the trachea. This represents an acute emergency. The tumours that may produce the SMC syndrome are:

- T-cell NHL - by far the most common cause
- Hodgkins disease
- and then far less commonly
  - neuroblastoma
  - Ewings sarcoma
  - Rhabdomyosarcoma
  - germ cell tumour
  - thymoma (particularly rare in childhood)

Symptoms and signs

SVC obstruction

- duskiness/plethora of the face, swelling and venous congestion in the SVC distribution and collaterals over the chest wall.
- there may also be suffusion and oedema of the conjunctiva.

- drowsiness, confusion, headache, distorted vision and/or syncope are particularly worrying developments.

Tracheal compression

- produces dyspnoea particularly on lying down, cough and hoarseness, stridor, chest pain
- agitation.
- cyanosis is a very late (and perturbing!) sign of upper airway obstruction so do not be mislead by normal SaO_2

Clinical approach

The airway is compressed at a level well below the cricothyroid membrane so that tracheostomy will not reverse the obstruction. Avoid sedation of any kind even if the patient is restless - it can tip the patient into complete upper airways obstruction; when this occurs, very little can be done to recover the airway.

1. Clinical examination for signs of SMC syndrome as described above. Search for evidence of disease outside the chest, in particular supraclavicular lymph nodes, which can be easily missed on cursory examination.

2. CXR (PA + lateral). In addition to confirmation of the mediastinal mass, the degree of posterior deviation and narrowing of the trachea can be assessed. Often, the trachea is compressed against the vertebral column so that it appears only a few millimetres wide.
3. Start hyperhydration and allopurinol. **Do not:**
    - insert IV cannula into a vein draining into SVC ie. put into foot vein or greater saphenous**.**

If at all possible give hyperhydration for at least 6 hours before starting chemotherapy but if the situation is critical this rule can be ignored.

4. Try to establish the diagnosis **but without** resorting to sedation or a general anaesthetic:
    - FBC. If blast cells are present on the FBC, these can be stained and typed without resorting to an initial bone marrow aspirate. In T-cell disease, the bone marrow is unlikely to be involved without diffuse lymphadenopathy and hepatosplenomegaly
    - Fine needle aspirate of palpable, pathological lymph node

INVOLVEMENT OF INFERIOR VENA CAVA BY WILMS TUMOUR

Background

Renal vein involvement by Wilms tumour is found in 11% of cases. Further extension into the IVC is seen in 4% and right atrial extension in ~0.7%. It is very unusual for IVC/atrial involvement to be symptomatic but sometimes it produces tricuspid incompetence. It is crucial to demonstrate vascular involvement because primary resection under these circumstances is contraindicated as it may result in substantially increased morbidity.

Investigations

- X-ray - massive IVC involvement is occasionally missed radiologically so one has to be on the lookout
  - US with Doppler flow study of IVC
  - CT with IV contrast should be routinely performed on all cases of suspected Wilms tumour.

Treatment and Management

Discuss with treatment centre in NZ

EXTRAVASATION OF CHEMOTHERAPEUTIC AGENTS

BACKGROUND

Several anti-cancer drugs can cause **irritation** to the vein into which they are infused. This shows as erythema or dark discolouration along the blood vessel often with aching and a sensation of tightness. Irritation can be minimised by further diluting the drug or slow intermittent injection into a continuous IV crystalloid infusion.

A **flare** is a local allergic reaction causing red blotches along the vein usually with itching.

Irritation and flare must be distinguished from **extravasation** in which the injected drug leaks into tissues surrounding the vein. Under these conditions, some drugs (vesicants) may cause substantial tissue necrosis, full thickness ulceration, and subsequent scarring and chronic contractures. Inflammation and skin breakdown may progress gradually over a number of weeks.

Anti-cancer drugs may be divided into 5 categories:

Vesicants (Group A)

Capable of causing pain, inflammation and blistering of the local skin, underlyng flesh and structures, leading to tissue death and necrosis:

- anthracyclines and related drugs - **daunorubicin**, **doxorubicin**,
- vinca alkaloids - **vincristine, vinblastine,**
- some antitumour antibiotics - **actinomycin D**

Exfoliants (Group B)

Capable of causing inflammation and shedding of skin, but less likely to cause tissue death:

- **cisplatin**

Irritants (Group C)

Capable of causing inflammation and irritation, rarely proceeding to breakdown of the tissue:

- **carboplatin**

epipodophyllotoxins - **etoposide** (VP16)

Inflammatory agents (Group D)

Capable of causing mild to moderate inflammation and flare in local tissues:

- **methotrexate**

Non-vesicants (Group E)

Very rarely associated with local tissue necrosis

- **asparaginase**
- some alkylating agents – **cyclophosphamide**, **ifosfamide**
- **bleomycin**
- **cytarabine**

PREVENTION

Peripheral venous cannula

Acceptable for the **bolus injection** of vesicant drugs:

1. use a well-secured, freshly-inserted cannula, *not* a butterfly needle
2. check patency of vein using a saline flush before injection of chemotherapy
3. ensure that there is backflow of blood. **If there is no backflow, do not proceed - resite cannula. However, backflow does not, in itself, guarantee that the bevel is entirely in the vein.**
4. site tip of cannula away from joint. Extravasation over a joint can cause contractures with major functional consequences.
5. avoid the cubital fossa. Extravasation here is difficult to detect early and it is over a joint.
6. use dilute injections of chemotherapy eg. vincristine 1mg/ml. The larger volume makes extravasation easier to detect and greater dilution means potentially less vesicant effect.
7. observe injection site constantly for signs of infiltration during infusion
8. vein should be irrigated with saline after the drug is infused in order to flush the vein and avoid leakage of drug on withdrawal of the catheter

Recognition of Extravasation

- Burning /stinging pain around the injection or infusion site. NB. Ask patients to report symptoms. Younger patients may become distressed or inconsolable.
- A change at the infusion site:

- Swelling
- "solid" redness ie. a bit like sudden cellulitis
- blanching
- fluid leakage out of injection site

- Resistance while giving drug

TREATMENT

An extravasation kit should contain "instant" hot and cold packs and topical corticosteroid.

Vesicant Drug (group A)

If extravasation of a vesicant drug is suspected:

1. stop injection immediately. **Do not remove the cannula/needle at this stage.**
2. detach syringe or line containing remaining chemotherapy
3. attach new syringe and aspirate as much fluid and blood as possible from the subcutaneous space
4. remove cannula/needle
5. <u>vincristine/vinblastine</u> <u>all other vesicants</u>
   apply a warm pack apply a cold pack to site
6. elevate limb
7. keep patient nil by mouth
8. administer analgesia IV as required
9. Notify the Paediatrician/medical staff.
10. prescribe Augmentin IV/PO if indicated

Exfoliant and Irritant Drugs (group B and C)

If extravasation of a irritant drug is suspected:

1. stop injection immediately. **Do not remove the cannula/needle at this stage.**
2. detach syringe or line containing remaining chemotherapy
3. attach new syringe and aspirate as much fluid and blood as possible from the subcutaneous space
4. remove cannula/needle
5. inform medical staff

6. give pain relief
7. elevate limb and encourage movement
8. cover with ice pack/cold compress for 1 hour and then observe site
9. after 1 hour, if erythema present then send home with topical corticosteroid dressing to be changed daily with regular review
10. If blistering/ulceration occurs, discuss with plastic surgeons.

GUIDELINES FOR THE MANAGEMENT OF STEROID DEFICIENT (ADDISONIAN) CRISES

Oncology patients who have recently received steroids and become septic are at particular risk of Addisonian crisis.

This may present as:

- hypotension and poor tissue perfusion,
- but isolated hyponatraemia is a common presentation .

Beware the child recently off steroids who presents with malaise, perhaps a low temperature and hyponatraemia – admit this patient!

It is important to treat these crises early to avoid severe morbidity and mortality. Boluses of Hydrocortisone are insufficient treatment and allow potentially dangerous trough levels in children with severe illness.

Deaths have also occurred with bolus iv hydrocortisone as the trough levels can be dangerously low, even when given 4 hourly.

1. Admit to Hospital.

2. IV Hydrocortisone treatment, infusion of 2mg/m^2/hour (50mg/m^2/day).

NB. This calculation is not appropriate for children weighing less than 10 kg.

Chart on hydrocortisone infusion chart (see below)

Perioperative management: Children undergoing surgery requiring a general anaesthetic should receive iv hydrocortisione infusion as per the moderate to severe illness guideline. Normal steroid usage can resume 24-48 hours later depending on recovery.

References:

Instructions from Drs Wayne Cutfield and Paul Hofman (Paediatric Endocrinology, Starship)

PAEDIATRIC **HYDROCORTISONE** **INFUSION**	NAME ..... PATIENT No. ..... SEX ..... DOB ..... AGE ..... WARD..... **Surface Area (m^2)** (Fix label or fill in)

PRESCRIPTION: Date: _____ Time: _____ (hours)

1. Take hydrocortisone, 100mg vial, and make up to 2 mls as per package directions (50mg/ml solution).
2. Take 1 ml of this solution and make up to 50mls with normal saline (1mg/ml solution).

Surface Area = $\sqrt{\left[\frac{\text{height (cm) x weight (kg)}}{3600}\right.}$

-square root of the [product of (height and weight) divided by 3600]

Run at 2mls/m^2/hour = 2x surface area (m^2) mls/hour (= 2mg/m^2/hour)

= _____ mls/hour

Other Instructions

1. Prescription must be checked by separate nurse and paediatric registrar.
2. Use syringe driver pump to administer infusion.
3. Change solution every 24 hours.

Medical Nursing

Signature _____ Signature _____