Tumour Lysis Syndrome (TLS)

Overview:
- Tumour lysis syndrome refers to a number of metabolic disturbances (hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia) that occur as the result of rapid cell lysis in patients with leukaemia and lymphoma. This may occur spontaneously, but more usually once treatment starts.
- Potassium and phosphate are released from the dying cells (leukaemic cells contain 4x more phosphate than normal cells)
- Uric acid is produced from the breakdown of nucleic acid.
- Hypocalcaemia occurs as a secondary response to hyperphosphataemia and renal failure.
- Hyperuricaemia, hyperphosphataemia and hypocalcaemia can cause renal damage and hyperkalaemia can cause cardiac arrhythmias.

Presentation:
- Patients at high risk of developing TLS:
  - B-NHL - Bulky abdominal/mediastinal NHL disease being particularly at risk.
  - High count acute leukaemia (ALL, AML) with white cell count >50x $10^9/L$ or very bulky disease.
  - Co – existent renal dysfunction, e.g. renal infiltration by leukaemia/lymphoma

Features of tumour lysis syndrome are:
MOST Important
- High or rapidly rising normal phosphate (NB: if the sample is haemolysed or wbc high can get spurious results – repeat sample on blood gas)
- High or rapidly rising urate levels BOTH need to be controlled asap prior to and during treatment, to prevent renal failure, and less commonly;
- High potassium (beware of problems with haemolysed/difficult to obtain samples taken through small cannulas, also spurious from high wbc) NB: AML M4 (monoblastic leukemias) can have very low K+ secondary to lysozyme activity in the blasts.
- Low calcium

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Review date: 03/02/2018
Prevention and Management:

Summary: To avoid renal failure requires

1. IV hydration (management of hyperphosphataemia)
2. Management of hyperuricaemia
3. Start both 1 & 2 prior to starting treatment by at least 12hrs if possible

For all patients ensure:

**HYDRATION:**
- Pre – treatment weight is recorded and weigh daily once hydration starts (b.d. if nec)
- TLS bloods: U&Es, creatinine, urate and phosphate & calcium
- If signs of established intrinsic (rather than pre-) renal failure before starting treatment – will need to make the renal dialysis team aware. If looks like post renal – urgent US abdo required – may need stenting/draining.
- Good IV access – to give fluids (2.5% dextrose/0.45% sodium chloride with **No added potassium**) and to check 6-8hrly bloods
  - If U & E, Phos, Urate normal – start hydration at 2.5L/m² increasing according to changing results.
  - If U & E, Phos, Urate show **sign of tumour lysis** start at 3L/m² and increase to 3.5, 4, 5L/m² as necessary to control Phos & Urate
  - Accurate fluid input and output – aim for at least 3ml/kg/hour urine output. Use Furosemide if required to drive urine output.

**MANAGEMENT OF HYPERURICAEMIA:**
- Start/continue Allopurinol (100mg/m² orally tds (round up to nearest 50mg) if urate normal or coming down with hydration alone.
- Give one dose of Rasburicase (**0.2mg/kg/day**) if urate is raised and rising despite hydration – check G6PD status first or ideally asap. Can start allopurinol and change to Rasburicase as required. No need to keep checking urate levels once Rasburicase administered.

**MANAGEMENT OF TLS**
- **IF CONCERNED: DISCUSS WITH CONSULTANT ON – CALL**
- If TLS bloods normal before treatment, repeat 6hrs after treatment starts and adjust fluids accordingly (as above).
- If phosphate rising, even if still within the normal range i.e. 1.5mmol/l to 1.8 mmol/l increase fluids, i.e. if on 3L/m² increase to 3.5L/m², then 4L/m² if not improving up to 5L/m² (NB: watch Na+ and if signs of hyponatraemia change fluids to 0.9% normal saline).
• If TLS is identified, then continue 6hrly checks, increasing fluids to bring phosphate under control, if coming under control then 8hrly until lysis settling, and wean down fluids back to previous level i.e. from 4L/m² back to 3.5L/m², then b.d. then daily bloods as lysis finishes. Be guided by your consultant.
• If unable to control rising phosphate and levels ≥2.5mmol/l and not reducing with increased fluids then start planning for haemofiltration/haemodialysis (alert PICU/PHDU early).
• Likewise if signs of renal failure developing i.e. creatinine/urea not coming down with hydration (renal failure could be secondary to infiltration of the kidneys by leukaemia/lymphoma) discuss with PICU re: dialysis.
• If problems with pseudohyperkalaemia then samples can be run through blood gas machine (wbc have less time to lyse in bottle that is processed quickly).

Refer to Management of electrolyte imbalance protocols p. 30

**Additional educational notes:**

a) Beware *"pseudohyperkalaemia"* - with a very high WCC, in vitro haemolysis can occur leading to a falsely high potassium result from the lab. The sample will not appear obviously lysed, as it is the white cells that have lysed rather than the red cells. Under these circumstances repeat sample urgently but also send blood for analysis in the PICU gas machine. If there is a discrepancy, it will be the whole blood potassium (i.e. blood gas result), which will be the true one.

b) **Hyperphosphataemia**
Acute high levels of phosphate can only be reduced by renal excretion. Other measures only temporarily lower plasma phosphate by shifting it back into cells. If the phosphate is rising rapidly and or above the upper end of normal values
- Hydration should be increased to 4L/m²/day: use furosemide as above to maintain urine output over 75% input. Increase to 5L/m² as required.
- Phosphate binders may be used to bind any phosphate already present in the gut, **calcium carbonate**:
  - 1 month – 1 year: 120mg calcium carbonate 3-4 times a day with feed.
  - 1 – 6 years: 300mg calcium carbonate 3-4 times a day prior to food.
  - 6 - 12 years: 600mg calcium carbonate 3-4 times a day prior to food.
  - 12 – 18 years: 1.25g calcium carbonate 3-4 times a day prior to food.
• Do not alkalinise urine and avoid giving IV calcium unless patient is markedly symptomatic i.e. showing signs of severe hypocalcaemia.
• Watch potassium levels during this phase. Hyperkalaemia is short lived, hyperphosphataemia may last several days and measures taken to treat the latter may have an effect on the former. See section on hypokalaemia.

c) **Hypocalcaemia**
Usually a phenomenon secondary to hyperphosphataemia – see metabolic problem section on page 30.

d) **General points**
The period of maximal risk of tumour lysis is 8-24 hours after starting chemotherapy. If tumour lysis has not occurred in this time it is unlikely to occur at all: it is then possible to start reducing hydration fluids and the frequency of blood tests over the next 48 hours. If tumour lysis has occurred, once the tumour bulk has been satisfactorily reduced and renal function and electrolytes have normalised, start reducing fluid intake and other measures. Hyperphosphataemia is more prolonged than hyperkalaemia and may last for several days.

e) **Hypokalaemia**
This is not usually a problem in the early phase of tumour lysis but if hyperhydration is continued for a number of days it can occur. Monitor carefully with daily U&E measurements. **Potassium should not be added to the IV fluids during the first 24 hours of chemotherapy** without specific discussion with the managing Consultant. If replacement is necessary follow guidelines in section on electrolyte problems.

### Review

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Dr Shaun Wilson, Paed Oncology Consultant & Dr Georgina Hall, Paed Haematology Consultant | Complete revision/Major reductions in text making document more directive and concise | Feb 2016 | 3.0 | Feb 2018