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. This may occur spontaneously, but more usually in response to chemotherapy.
- 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 cause further renal damage. Hyperkalaemia can cause cardiac arrhythmias.

Presentation:
- TLS is most commonly seen in B-cell NHL, T-cell NHL or high count leukaemia.
- Patients at high risk of developing TLS:
  - B-NHL
  - Bulky abdominal/mediastinal NHL disease being particularly at risk.
  - ALL with white cell count >100x 10⁹/L
  - Co – existent renal dysfunction, renal infiltration

- In these patients white cell count or tumour size may double in 24 hours and treatment is urgent. Partial exchange or leukopheresis may be considered if counts are greater than 500 x 10⁹/L or in the case of severe symptoms.

Features of tumour lysis syndrome are:
- Falling urine output
- High potassium (beware of problems with haemolysed/difficult to obtain samples taken through small cannulas, see below)
- High phosphate (again this level can be affected if the sample is haemolysed)
- High urate
- Low calcium
Prevention and Management:
For all patients ensure:
- Pre – treatment weight is recorded
- Good IV access i.e. at least two IV cannula
- Accurate fluid input and output – aim for at least 3ml/kg/hour urine output or at least 75% input over a 4 hourly period, whichever is the larger volume. Use Furosemide if required to drive urine output.
- Baseline bloods:
  - Urate, U&Es, creatinine, bicarbonate, calcium, phosphate and magnesium.
  - FBC

Suggested guideline for frequency of TLS bloods:

<table>
<thead>
<tr>
<th>TLS risk group</th>
<th>Before starting treatment</th>
<th>After starting treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>8 hourly</td>
<td>4 to 6 hourly</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>12 to 24 hourly</td>
<td>6 to 8 hourly</td>
</tr>
<tr>
<td>Low risk</td>
<td>24 hourly</td>
<td>8 to 12 hourly</td>
</tr>
</tbody>
</table>

- Blood results must be looked up and acted upon as soon as they are available. If electrolyte problems become apparent, monitoring may need to be more intense and samples should be both sent to the lab and be put through the gas machine (see pseudohyperkalaemia below). Inform Consultant if you have concerns.

**TABLE: OVERVIEW OF INITIAL TLS PREVENTATIVE STRATEGIES:**

<table>
<thead>
<tr>
<th>Low count ALL &lt;20 Normal bulky NHL Normal renal fxn</th>
<th>WCC 20 -100 Normal renal fxn</th>
<th>WCC &gt;100 B NHL with abd mass Significant liver/spleen Renal infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid volume</td>
<td>1.5L/m²/day</td>
<td>2 – 3L/m²/day</td>
</tr>
<tr>
<td>Fluid volume</td>
<td>2 – 3L/m²/day</td>
<td>3L/m²/day</td>
</tr>
<tr>
<td>Fluid volume</td>
<td>Infants: 200ml/kg/day</td>
<td></td>
</tr>
<tr>
<td>Fluid type</td>
<td>2.5% dextrose/0.45% sodium chloride with No added potassium</td>
<td></td>
</tr>
<tr>
<td>Urine criteria</td>
<td>75 – 80% of input over 4 hours</td>
<td>75 – 80% of input over 4 hours</td>
</tr>
<tr>
<td>Blood tests</td>
<td>q12 - 24hrly</td>
<td>q8 – 12hrly</td>
</tr>
<tr>
<td>Uric acid prevention</td>
<td>Allopurinol</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Uric acid prevention</td>
<td>Rasburicase</td>
<td></td>
</tr>
</tbody>
</table>
Prevention and Management of TLS:

**Fluids:**
- Do not use potassium containing fluid without discussion with senior staff members
- Discuss fluid volumes for the following patients with senior staff members:
  - young patients (< 1 years)
  - concurrent low haemoglobin levels (Hb ≤ 5g%)
  - pre-existing cardiac conditions
  - if not passing ≥75% input despite furosemide support (may need PICU)
- Increasing phosphate >1.8mmol/L despite 3L/m$^2$/day
  - May need to increase to 4L/m$^2$/day if no signs of fluid overload

**Prevention of hyperuricaemia:**
- To prevent hyperuricaemia all patients need to be started on Allopurinol or Rasburicase at least 12 hours, or as soon as possible, prior to induction chemotherapy and this should be continued for 3-7 days after chemotherapy is started.
- **Allopurinol dose 100mg/m$^2$/dose orally tds (round up to nearest 50mg).**
  (1 month – 15 years max. 400mg daily; 15 – 18 years max. 900mg daily). Allopurinol reduces uric acid production but will not reduce pre-existing hyperuricaemia

- **Rasburicase dose 0.2mg/kg/day once daily** as 30 minute infusion in 50 ml 0.9% sodium chloride for 5-7 days (infusion volume can be reduced if needed in younger children). **Contraindicated in G6PD deficiency.** Rasburicase converts uric acid into allantoin which is water soluble and therefore lowers plasma uric acid levels very quickly, normalising values within 4 hours. Once Rasburicase is started repeat uric acid measurements are not required. The use of Rasburicase should be discussed with the Consultant in all cases as it is a very expensive drug.
Electrolyte problems associated with Tumour Lysis Syndrome (TLS)

- Bloods are to be taken 4 hourly if baseline electrolytes are abnormal and risks of TLS high. Otherwise 8-12 hourly may be sufficient.

See full guidance

Hyperkalaemia (beware pseudohyperkalaemia see below)
Hyperkalaemia tends to be a relatively short-term problem. Provided urine output is maintained the kidneys will excrete potassium. If urine output fails then filtration may be required.

If potassium is rising ensure ECG monitoring and follow the guidelines below:

If potassium rising but less than 5.5mmol/L:
- Hydration should be increased to 4L/m²/day
- Furosemide 1mg/kg to increase urine output
- Assess VBG for acidosis
- Change fluids to 0.9% sodium chloride/10% dextrose (see recipe below) to ensure sufficient sodium in tubules to exchange for potassium.

If potassium above 5.5mmol/L:
- Salbutamol nebulised
  - <2.5 yrs: 2.5mg
  - >2.5 yrs: 5mg
- Discuss with senior staff member to consider half correction of acidosis
  - See specific metabolic problems policy - section E. Hyperkalemia
  - 0.5 – 1 mmol/kg Sodium Bicarbonate slow infusion

If potassium above 6mmol/L or ECG changes associated with hyperkalaemia:
- Inform Consultant as the child may need PICU support
- Salbutamol nebulised
- Correct acidosis
- Insulin and dextrose infusion: 25 units Human Actrapid insulin added to 1 litre 10% dextrose and infuse at 0.1units/kg/hour i.e. 4ml/kg/hour. Check blood glucose (BM) every 30 minutes. Check potassium after 1 hour of infusion and repeat as necessary. Insulin/glucose is only a temporary solution; it will not increase excretion of potassium.
- If urine output is poor and not responding to fluids and Furosemide the patient will need to be assessed by PICU as they may well require haemofiltration
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 haemolysed 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.

**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.

**Hypocalcaemia**

Usually a phenomenon secondary to hyperphosphataemia – see metabolic problem section on page 30.

**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.

**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

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Sheila Lane, Paed Oncology Consultant</td>
<td>New doc</td>
<td>June 2011</td>
<td>1.0</td>
<td>June 2013</td>
</tr>
<tr>
<td>Dr Sheila Lane, Paed Oncology Consultant</td>
<td>Not recorded</td>
<td>June 2013</td>
<td>2.0</td>
<td>June 2015</td>
</tr>
<tr>
<td>Dr Shaun Wilson, Paed Oncology Consultant</td>
<td>WBC levels changed</td>
<td>Sept 2015</td>
<td>2.1</td>
<td>Sept 2017</td>
</tr>
<tr>
<td></td>
<td>Format changed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor wording changes / additions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>