Management of Cytokine Release Syndrome (CRS) due to Solid Tumour or Haematooncology Treatments

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Introduction

This document has been developed to assist management of Cytokine Release Syndrome (CRS).

It is primarily intended for patients receiving tebentafusp, tarlatamab and alternative T-cell engaging bispecific antibody therapy or chimeric antigen receptor T-cell therapy.

It should also be followed for CRS suspected in patients receiving treatment for haematological conditions with glofitamab, epcoritamab, teclistamab.

Bispecific antibodies have two binding sites, one targets an antigen expressed on the malignant cell surface, and one targets a T-cell surface marker (CD3). This interaction enhances host cytotoxic T-cell activity against malignant cells. Specific toxicities related to this mode of action are seen, including CRS. Bispecific antibodies are also associated with immune cell associated neurotoxicity syndrome (ICANS), for which there is a separate LSC Alliance guideline. https://www.healthierlsc.co.uk/application/files/1217/4050/9775/ICANS_guideline_LSC_version_1_Dec_24.pdf

Drug specific guidelines should also be followed and referred to as there may be specific complications for individual agents that require alternative management.

Cytokine release syndrome (CRS)

CRS is a systemic inflammatory response that can occur following the administration of a range of systemic anti-cancer therapies [1]. The severity of CRS can range from a mild flu-like illness to multi-organ failure. It can present similarly to severe sepsis or tumour lysis syndrome, and these should be kept in the differentials when CRS is suspected [2]. Reactions will usually occur during or shortly after intravenous infusions or within 24 hours if causative medication is delivered subcutaneously. However, it can occur up to 7 days after drug administration. Higher volume disease increases the likelihood of CRS developing [2].

Features of mild CRS can include fevers/chills, tachycardia, mild hypertension or hypotension, sweating, flushing, tachypnoea, nausea and vomiting, headache, myalgia, rash and dizziness [1]. These mild features can be treated symptomatically with anti-pyretics, antihistamines and analgesics as indicated. Symptoms are typically less severe with subsequent treatments [2].

Severe CRS can cause profound hypotension, tachycardia, dyspnoea and chest pain. This can be difficult to differentiate from an infusion related or anaphylactic reaction [2]. Patients who show signs of severe CRS should be resuscitated promptly and treated aggressively as described below. Early involvement of ICU/critical care may be necessary.

Life threatening complications that can occur from CRS include renal failure, hepatic failure, cardiac failure, acute respiratory distress syndrome (ARDS), neurological toxicity and disseminated intravascular coagulation (DIC) [1]. CRS can also be associated with Haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) [1]. These are life-threatening hyper-inflammatory syndromes characterised by an uncontrolled immune response.

Pre-admission preparation

Ensure the following arrangements are made for patients admitted for treatment with a known precipitator of CRS.

- Ensure drug specific protocols are printed and available at the patient's bedside for easy access, along with the CRS management protocol.

Notify the following teams of the patient's admission:

- Oncology registrar and consultant on call.
- Critical care outreach team.
- Clinical night team and medical team on call.

Confirm that the ward has sufficient stock of:

- IV methylprednisolone (in case of infusion reactions).
- Tocilizumab (available in the pharmacy).

Ensure the following medications are prescribed and available on the ward:

- Chlorphenamine (Piriton): 10mg IV qds/prn.
- Hydroxyzine hydrochloride (Atarax): 25mg PO qds/prn.
- Paracetamol: 1g PO/IV qds/prn.
- Ibuprofen: 400mg PO tds/prn (if no contraindications).
- Epimax/E45 cream: PRN for skin irritation.
- Hydrocortisone: 200mg IV in case of infusion reaction.

Physical Examination and Monitoring:

- Perform a full physical examination before each treatment to ensure the patient is well enough to proceed, including an assessment of fluid status.
- Temperature and Blood Pressure: Pay particular attention to the patient's temperature and blood pressure. A rise in body temperature, typically 3-4 hours post-infusion, should trigger suspicion of CRS.

Pre-Treatment Blood Pressure Protocol:

- Seat the patient for at least 20 minutes before measuring blood pressure.
- Measure BP twice, 5 minutes apart, using the same upper limb if possible.
- Calculate the average systolic BP by adding both readings and dividing by two.
- Record the baseline systolic BP clearly and legibly for future reference.

Management of CRS

Grading of the severity of CRS is based on the American Society for Transplantation and Cellular Therapy (ASTCT). Management should be based on this grading as described below.

Table 1. ASTCT consensus grading of CRS [3].

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	>38°C	>38°C	>38°C	>38°C
Hypotension			***With***	***With***
	None	No vasopressor requirement	Single vasopressor requirement with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or	***And/or***	***And/or***
Hypoxia	None	Oxygen requirement - ≤6L/min delivered by low flow nasal cannula	Oxygen requirement - >6L/min delivered by high flow nasal cannula, face mask, Venturi mask or non-rebreather mask	Oxygen requirement – positive pressure via CPAP, BiPAP or intubation and mechanical ventilation

Table 2. CRS management guidance

CRS Grade	Management
1	• Hourly observations until resolution of grade 1 toxicity • Provide antipyretic as per guidelines • Bloods including magnesium and phosphate – replace any deficiencies intravenously
2	• Manage any hypotension with IV fluid challenge (see below). • Manage hypoxia with supplemental O2 to maintain oxygen saturation above 94% • Repeat observations after fluid challenge and/or 02 supplementation. • Discuss with the on-call Oncology/Medical SpR if BP/02 saturations not improving to baseline levels with above treatments • Inform CCOT • Consider IV methylprednisolone (1mg/kg) or tocilizumab (8mg/kg and not exceeding 800mg dose).
3	• Management as for grade 2 CRS, but patient must be escalated to ITU team for consideration of vasopressors and high flow oxygen as indicated. ITU referral should involve Oncology/Medical SpR.
4	• As per grade 3 but for consideration of ventilator support. • May require additional immunosuppressives such as MMF or infliximab.

For guidance on resumption/continuation of the precipitating medication, please see drug specific guidelines and discuss with treating consultant.

Specific Management of Symptoms

General supportive management of CRS

- If sepsis is suspected patients should have a sepsis 6 bundle completed (blood culture, urine output measurement, serum lactate, IV fluids, antibiotics, supplementary oxygen) as required. Consider antibiotics as per trust guidelines.
- Hourly monitoring of vital signs and an accurate fluid balance chart must be completed.
- The blood glucose should be monitored.
- Check magnesium and phosphate - if less than lower limit of normal then give IV replacement.
- CRS investigations: Specific additional tests to consider:
    - Ferritin, triglycerides, and AST - to facilitate the potential diagnosis of haemophagocytic lymphohistiocytosis and/or macrophage activation syndrome.
    - Troponin +/- transthoracic echocardiogram - to diagnose associated cardiac toxicity with CRS
    - Uric acid (& U+Es, calcium, phosphate, ABG) if tumour lysis syndrome is suspected.
    - Cytokine profile

Fevers/rigors:

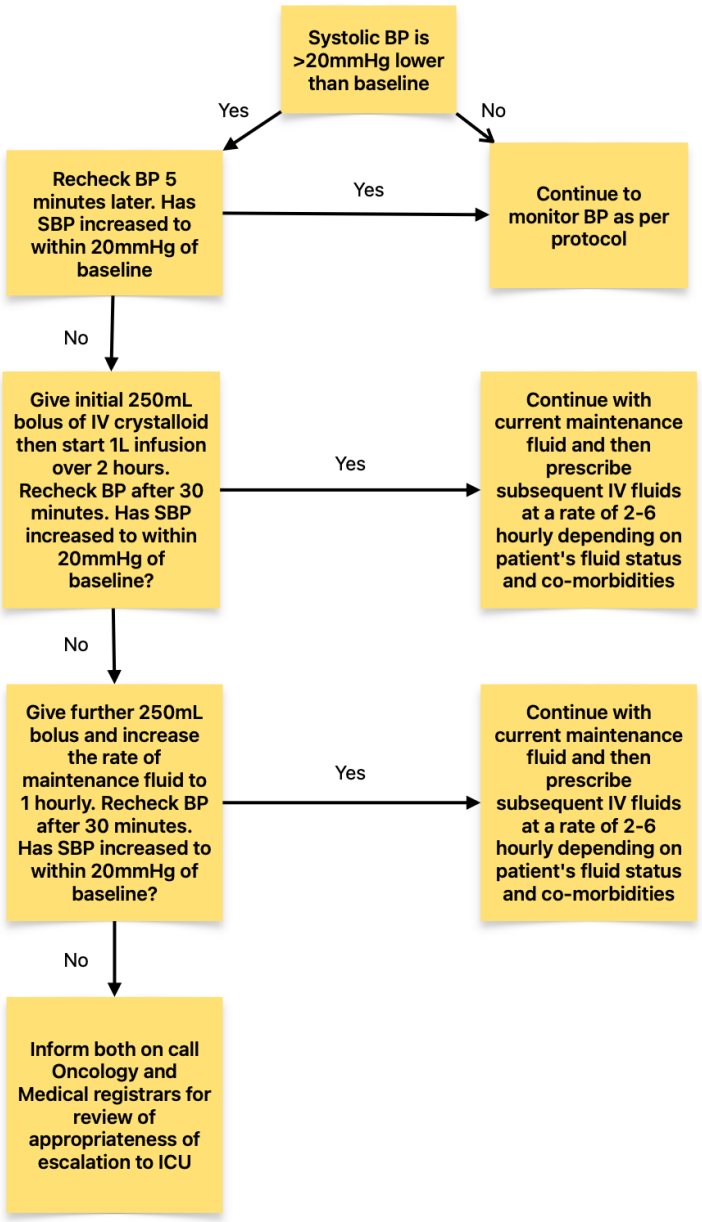
If the patient develops rigors or a temperature over 38°C:

- Monitor with more frequent observations (hourly) until resolution.
- Provide an antipyretic. Give paracetamol 1g and recheck temperature in 30 minutes. If temperature remains >38°C, give ibuprofen 400mg if patient has no contraindications to NSAIDs and escalate to the medical team. Recheck temperature in 30 minutes. If temperature remains >38°C, consider stat dose hydrocortisone 200mg.
- If rigors, consider pethidine 25mg slow IV.

Hypotension:

- Measure the BP 2 hourly with the patient seated. If they are ambulant around the ward or bed space, lying down in bed and/or asleep then ensure they are sat up for at least five minutes before measuring BP.
- If the systolic BP is more than 20mmHg lower than the baseline average, repeat BP 5 minutes later. If systolic BP is confirmed <20mmHg below baseline average, then inform the doctor and start IV fluids according to schedule below. If the BP recovers but then falls again, repeat the fluid challenge and iv schedule below
- If BP continues to fall below the 20mmHg from baseline threshold or patient remains/becomes symptomatic or develops hypovolemic shock, then seek advice from critical care outreach.
- Record accurate fluid balance throughout admission
- See flowchart below for step-by-step guidance.

Hypotension Flowchart:



Hypoxia:

- Administration of supplemental O2 is required if oxygen saturation drops (<94%) or patient becomes dyspnoeic (RR>20).
- Repeat observations hourly. If patient is requiring oxygen delivered by high-flow nasal cannula (> 6L/min), facemask, nonrebreather mask, or Venturi mask to maintain saturations >94% and/or has hypotension then inform oncology registrar (on call if out of hours and medical reg) and call critical care outreach.

References

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2. Roselló, S. et al. (2017) ‘Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines’, Annals of Oncology, 28, pp. iv100–iv118. doi:10.1093/annonc/mdx216.
3. Lee, D.W. et al. (2019) ‘ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells’, Biology of Blood and Marrow Transplantation, 25(4), pp. 625–638. doi:10.1016/j.bbmt.2018.12.758.