

CAR.6.1. Appendix 1. Cytokine Release Syndrome [CRS] assessment and management^

[Link to main protocol \[CAR.6.1\]](#) ^For clinical trials – please refer to the relevant clinical trial protocol

CRS assessment – ASTCT Consensus CRS Grading*

CRS	Grade 1	Grade 2	Grade 3	Grade 4
Fever**	Temperature $\geq 38^{\circ}\text{C}$			
		And		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or***		
Hypoxia	None	Requiring low-flow**** oxygen by nasal cannula on blow-by	Requiring high flow**** oxygen by nasal canula, facemask, nonrebreather mask, or Venturi mask	Requiring oxygen by positive pressure (for example, CPAP, BiPAP, intubation and mechanical ventilation)

*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading. Individual organ toxicities presumed to be related to the CAR cells should be documented in the patient's medical records. Grade 5 CRS is defined as death due to CRS in which another cause is not the principal factor leading to this outcome.

** Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS and then receive antipyretic or anti-cytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

*** CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

**** Low-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L/minute}$. Low flow also includes blow-by oxygen delivery, sometimes used in paediatrics. High-flow nasal cannula is defined as oxygen delivered at $> 6\text{L/minute}$.

CRS assessment – Summary of investigations

- **Observations [minimum 4-hourly*]:** temperature, pulse, BP, respiratory rate O₂ Sats, A/VBG, GCS [***more frequent when CRS is suspected**]
 - FBC, U&Es, LFTs, Mg, uric acid, Ca/PO₄, LDH, CRP: minimum daily
 - Coagulation screen, fibrinogen: once a week or daily if CRS suspected
 - Ferritin: 3 times a week or daily if CRS suspected
 - BNP and Troponin (at baseline and as clinically indicated)
 - Urine dip
 - CXR (urgent mobile) and microbiological studies: blood cultures, urine, line swabs, sputum (if present)
 - Physical examination
 - Check for neurological symptoms – refer to [CAR.6.1. Appendix 2](#).
 - Check for signs of tumour lysis syndrome – refer to [TLS protocol \[H.8\]](#)

CRS management – SYMPTOMATIC MEASURES – Notify attending/on-call Consultant of any CRS development

CRS	Grade 1	Grade 2	Grade 3	Grade 4
ITU	Consider alerting ICU	Alert ICU, consider transfer	Transfer to ICU (Intensive Care Unit)	
Antibiotics	Start pre-emptive broad-spectrum antibiotics following the infective screen +/- CXR [refer to OUH Antimicrobial guidelines [Link]			
Hydration	IV fluids when appropriate (for example, when oral intake insufficient)			
Fever	Paracetamol IV (avoid NSAIDs - consider potentially increased risk of renal impairment/anti-platelet effect/bleeding)			
Hypoxia	N/A	Oxygen: low flow (nasal cannula or blow-by)	Oxygen: high flow (e.g., facemask, nonrebreather mask, Venturi mask)	Oxygen requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)
Hypotension	N/A	Sodium chloride 0.9% IV bolus 500mL (2 x 500mL if SBP remains < 90mHg). Avoid repeated fluid resuscitation as capillary leak, pulmonary oedema and pleural effusions can precipitate a life-threatening CRS. Consider echocardiogram (ECHO), if hypotension persists despite fluid resuscitation and tocilizumab.		
Vasopressors	N/A	Not required	Vasopressor required +/- vasopressin	Multiple vasopressors required (excluding vasopressin)

CRS management - TOCILIZUMAB +/- STEROIDS – Only prescribe on advice of the Consultant

CRS	1 st line	2 nd line ¹
Grade 1	Consider Tocilizumab ^{2,3} – Steroids not required	Consider Tocilizumab ^{2,3} – Steroids not required
Grade 2	Tocilizumab³ + Consider Steroids ⁴	Continue Tocilizumab³ (up to max. 4 doses) + Dexamethasone 10mg IV ^{5,6} QDS (6-hourly) for 1-3 days
Grade 3	Tocilizumab³ + Dexamethasone 10mg IV ^{5,6} QDS (6-hourly) for 1-3 days	Continue Tocilizumab³ (up to max. 4 doses) + Dexamethasone dose increased to 20mg IV ^{6,7} QDS (6-hourly) for 3 days, followed by progressive tapering within 3–7 days
Grade 4	Tocilizumab³ + Dexamethasone 20mg IV ^{6,7} QDS (6-hourly) for 3 days, followed by progressive tapering within 3–7 days	Continue Tocilizumab³ (up to max. 4 doses) + Switch steroid to Methylprednisolone 1000mg IV OD for 3 days, then 250mg IV BD 2 days, then 125mg IV BD for 2 days, then 60mg IV BD for 2 days, then once Grade ≤ 1, continue tapering to stop over 3 days

¹ In presence of deterioration, absence of improvement after 12 hours or persistence of symptoms.

² Grade 1 CRS – consider tocilizumab in patients with prolonged fever (≥ 3 days), or in presence of significant symptoms, co-morbidities, and/or age > 65 years.

³ **Tocilizumab dosing:** according to patient's actual (not adjusted) body weight: ≥ 30kg: 8mg/kg; < 30kg: 12mg/kg; [**max. 800mg/dose**]; dose can be repeated **every 8 hours, if required, for up to max. 4 doses**. Refer to [Tocilizumab for CRS \[H.126\]](#).

⁴ Grade 2 CRS – consider steroids 1st line in patients at high-risk of severe CRS or if hypotension persists after 1–2 doses of tocilizumab – consider dexamethasone 10mg and reassess in 6 hours. For further doses as appropriate.

⁵ Dexamethasone 10mg IV = 8.25mg dexamethasone base [2.5mL x 3.3mg/mL] – prescribe on inpatient prescription as dexamethasone base injection.

⁶ As alternative to dexamethasone – methylprednisolone at equivalent dose can be considered.

⁷ Dexamethasone 20mg IV = 16.5mg dexamethasone base [5.0mL x 3.3mg/mL] – prescribe on inpatient prescription as dexamethasone base injection.

3rd line

For CRS grade 3 or 4, refractory to tocilizumab and steroids, alternative treatments should be considered, for example, ▪ **anakinra** 200mg SC* OD, increased if necessary up to 8mg/kg/day, continued until clinical response (*IV route is unlicensed - when used in critical illness, it should be switched back to SC route as soon as patient's condition improved and is clinically stable), or ▪ **siltuximab** IVI 11mg/kg (single dose) - discuss with ACT Consultant and Pharmacist (note off-label use of both anakinra and siltuximab – clinical governance framework and local approvals for funding must be ensured).