Cytokine Release Syndrome (CRS)

Excessive and rapid release of cytokines into the blood stream can result in cytokine release syndrome (CRS). CRS is an acute systemic inflammatory response, characterised by fever and in severe events can lead to multiple organ dysfunction. Severity of CRS ranges from mild to life-threatening, and when severe, is considered an oncological emergency.

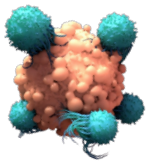
Causes of CRS

CRS may be triggered by treatments which involve, simulate or engage the immune system for example:

- CAR T-cell therapy
- haploidentical haematopoietic stem cell transplant (HSCT)
- monoclonal antibodies (e.g. rituximab) and immune checkpoint inhibitors
- bi-specific antibodies (e.g. blinatumumab)

Risk factors

- **Type of disease**
- **High disease burden**
- **Dose of the active agent**



Clinical presentation

Symptoms of CRS can be progressive over days or even weeks dependant on causative agent.

30 -120 minutes	With monoclonal antibodies and immune checkpoint inhibitors
1 -3 days	With haploidentical haematopoietic stem cell transplants
1 -14 days	With CAR T-cell therapy

A fever of ≥38^{0}C must be present at onset of symptoms for diagnosis of CRS to be made.

MILD

Fever may be accompanied by:

- fatigue
- headache
- rash
- diarrhoea
- arthralgia
- myalgia.

SEVERE

Fever may be accompanied by:

- hypotension and uncontrolled SIRS with circulatory collapse
- vascular leakage
- peripheral and/or pulmonary edema
- renal failure
- cardiac dysfunction
- multiorgan system failure.

Nursing assessment and immediate interventions

Grading of CRS severity will differ depending on the cause, however both grading systems consider both the presence of fever, hypoxia and hypotension. Therefore, the assessment of a patient with suspected CRS should include:

- medical history, including current and recent treatments
- clinical patient assessment, including vital signs

Many features of CRS mimic infection/sepsis. Health care practitioners must exclude other causes of fever, hypotension, haemodynamic instability and/or respiratory distress.

Grading

For CRS related to CAR T-cell therapy, the American society for transplant and cellular therapy (ASTCT) provides a consensus grading scale.

CRS Paremeter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature > 38°C	Temperature > 38°C	Temperature > 38°C	Temperature > 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And / or				
Hypoxia	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Grading of CRS related to monoclonal antibodies, immune checkpoint inhibitors, bispecific antibodies and haploidentical bone marrow transplant are commonly graded according to the Common Terminology Criteria for Adverse Events (CTCAE) grading criteria.

Grade 1	Grade 2	Grade 3	Grade 4
Fever, with or without constitutional symptoms.	Hypotension responding to fluids. Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention required.

Cytokine Release Syndrome (CRS)

Investigations and diagnosis

Blood results

- Full blood examination
- Septic screen
- Elevated interleukin-6 (IL6)
- Elevated tumour necrosis factor-alpha (TNF-α)
- Elevated Lactate dehydrogenase (LDH)
- Elevated liver enzymes
- Elevated creatinine
- Elevated Human C-reactive protein (CRP)
- Deranged coagulation factors
- Decreased lymphocytes
- Decreased platelets

Imaging

- **Chest X-ray** – bilateral opacities
- **Cardiac ultrasound** – decreased ejection fraction

Management

Management of CRS related to CAR T-cell therapy depends on the grade and may include anti-IL-6 therapy, corticosteroids or additional supportive care.

Management of CRS related to monoclonal antibodies depends on the grade and may include includes symptomatic management with supportive treatments, corticosteroids and vasopressors.

For more detail on the management of CRS related to CAR T-cell therapy, please refer to the eviQ clinical resource.

Management of CRS related to monoclonal antibodies

Mild **Grade 1 and grade 2**	• May not require interruption of the infusion* • May include symptomatic management with supportive treatments, including oxygen, antihistamines, antipyretics, intravenous fluids, and close monitoring as ordered by medical officer (MO) or nurse practitioner (NP). • For mild CRS that progresses or deteriorates while receiving symptomatic treatment, treat as grade 3 or 4.
Moderate to severe **Grade 3 and grade 4**	Management may include: • interruption of the infusion • supportive treatments such as oxygen • corticosteroids** • vasopressors or cytokine blocking agents*** as ordered and directed by MO or NP. If symptoms resolve consult with MO or NP regarding instruction on recommencing infusion.

*For Mild CRS, the balance of benefit and toxicity with symptomatic treatment is more favorable than with high dose glucocorticoids, tocilizumab, or interruption of the infusion.

**There is some initial evidence that treatment with corticosteroids, while effective in minimising CRS, can decrease efficiency of treatment with bispecific antibodies, whereas tocilizumab does not appear to have a negative effect on efficacy. As such a risk verse benefit assessment must be considered when choosing the treatment for CRS.

***Tocilizumab and siltuximab block IL-6 and etanercept and infliximab block TNF-α, which can interrupt and slow the cytokine storm process, improving symptoms of CRS.

t +61 (0)2 8374 5600 f +61 (0)2 8374 3600 e cinsw-information@health.nsw.gov.au