# Immune-Related Adverse Event Management Algorithm – CRS

| Grading of CRS | Action | Follow-up |
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| **Grade 1**<br>• Temperature ≥ 38°C<br>• No hypotension or hypoxia | **Investigations**<br>• Bloods, cultures, rule out other infections, ECG<br>**Management**<br>• For Fever, diagnose and treat for any concomitant infection<br>• Antipyretics – paracetamol 1g QDS. Consider ibuprofen 400mg TDS if needed and appropriate | **If worsens:**<br>• Treat as G2 /3. |
| **Grade 2**<br>• Temperature ≥ 38°C<br>• Hypotension that responds to fluids and does not require vasopressors.<br>• Oxygen requirement includes low flow nasal cannulae (delivery of oxygen ≤ 6L/min) | **Investigations**<br>• Inform registrar/consultant<br>• Vitals every 30 mints with continuous pulse oximetry<br>**Hypoxia or drop Sp02:**<br>- < 6L/min O2 via nasal cannula - Auscultation, exclude bronchoconstriction, if applicable inhalation with bronchodilator - If >6L/min O2, inform consultant and move to ITU (Grade 3) - Administer Tocilizumab (confirm with consultant/ registrar)<br>***Hypotension (if systolic BP is ≥ 20mmHg lower than baseline average)***<br>Intravenous fluids – Compound Sodium Lactate (Hartmann's solution) or sodium chloride 0.9% - 1000ml/hr or increase if needed - If after 2000-3000ml if asymptomatic but not orthostatic, provide IV fluids until hypotension resolves | ***Hypotension resistant to therapy with IV fluids (not resolving within 2-3 hours treat as grade 3)***<br>- Administer high dose intravenous corticosteroid (methylprednisolone 2mg/kg) - Consider administering tocilizumab (to be confirmed with consultant or registrar)<br>Tocilizumab 8mg/kg (max 800mg) IV STAT PRN for Grade 2 or 3 CRS on instruction of the consultant/ registrar<br>For Grade 2 CRS that is persistent (lasting 2-3 hours) or recurrent (occurrence of ≥ Grade 2 CRS with more than one dose), consider administering corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose – discuss with consultant. |
| **Grade 3**<br>• Temperature ≥ 38°C<br>• Requires vasopressors to treat hypotension<br>• Requires high-flow nasal cannula (delivery of oxygen >6L/min), face mask / non-rebreather mask or Venturi mask | Arrange urgent transfer to ICU<br>Symptom management as Grade 2<br>**Persistent hypotension**<br>Administer vasopressive therapy according to ICU consultant | • For Grade 3 CRS, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose |
| **Grade 4**<br>• Temperature ≥ 38°C<br>• Requires multiple vasopressors<br>• Requiring positive pressure ventilation (e.g. CPAP / BiPAP / intubation and mechanical ventilation | Arrange urgent transfer to ICU<br>Symptom management as Grade 2<br>1. **Hypotension**- Vasoactive therapy with several vasopressors<br>2. **Hypoxia**- Consider O2 supply via positive pressure<br>3. **Persistent/ recurrent symptoms**- Consider further immunosuppressive treatment | Permanently discontinue tebentafusp |

**Additional information:**

Cytokine release syndrome Cytokine release syndrome occurred in 89 % of tebentafusp-treated patients in the IMCgp100-202 trial. The overall incidence of CRS included 12 % Grade 1, 76 % Grade 2 and 0.8 % Grade 3 events. The majority (84 %) of episodes of CRS started the day of infusion. The median time to resolution of CRS was 2 days. CRS rarely (1.2 %) led to treatment discontinuation. All CRS symptoms were reversible and were managed with intravenous fluids, antipyretics, or a single dose of corticosteroid. Two patients (0.8 %) received tocilizumab.

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