# Tebentafusp-tebn Care Step Pathway - Cytokine Release Syndrome

## Assessment

**Look:**
- Is the patient flushed or sweating?
- Is the patient shivering?
- Does the patient appear to have a headache?
- Is the patient weak or unsteady?
- Does the patient look like they will lose (or have they lost) consciousness?
- Is the patient short of breath?
- Is there abdominal pain?
- Has the patient vomited?
- Is the patient lethargic?
- Is the patient's respiratory rate normal?

**Listen:**
- Is the patient reporting feeling hot or cold or experiencing chills?
- Does the patient report a headache?
- Does the patient report feeling weak or dizzy?
- Is the patient achy?
- Does the patient report feeling like they are going to pass out?
- Is the patient nauseated?
- Does the patient report abdominal pain?
- Does the patient report being short of breath?
- Is the patient wheezing?
- Has the patient reported vomiting?

**Recognize:**
- Fever (any elevation in temperature)
- Respiratory rate
- Altered pulse rate (tachycardia)
- Low blood pressure
- Hypoxia
- Laboratory abnormalities (dehydration, hypovolemia)
- Any baseline issue with hypotension, tachycardia, or hypoxia)

## Grading Toxicity

**CRS**

Definition: An intense inflammatory condition associated with a robust immune response.

**Grade 1 (Mild)**
Temperature ≥100.4 °F (38 °C) but no hypotension or hypoxia

**Grade 2 (Moderate)**
Temperature ≥100.4 °F (38 °C)
(but if fever is actively managed with antipyretic or anticytokine therapy, it is not a requirement for grading)

**PLUS**

Hypotension that responds to fluids

**AND/OR**

Hypoxia requiring low-flow nasal canula (≤6 L/min)

**Grade 3 (Severe)**
Temperature ≥100.4 °F (38 °C)
(but if fever is actively managed with antipyretic or anticytokine therapy, it is not a requirement for grading)

**PLUS**

Hemodynamic instability requiring vasopressor (with or without vasopressin)

**AND/OR**

Worsening hypoxia or respiratory distress requiring high-flow nasal cannula (>6 L/min) or face mask

**Grade 4 (Potentially Life-Threatening)**
Temperature ≥100.4 °F (38 °C)
(but if fever is actively managed with antipyretic or anticytokine therapy, it is not a requirement for grading)

**PLUS**

Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) or high-dose vasopressors

**AND/OR**

Worsening hypoxia or respiratory distress despite oxygen administration, requiring positive pressure ventilation (CPAP, BiPAP,or intubation and mechanical ventilation)

**AND/OR**

Coagulopathy requiring fresh frozen plasma or cryoprecipitate

## Management

**Overall Strategy**
- CRS toxicities with tebentafusp-tebn are generally milder than those seen with some other cellular-based therapies
- Assure adequate hydration/euvolemic status prior to starting tebentafusp-tebn
- Premedication of the first dose is not required, institutional practices vary. Examples of potential premedications include acetaminophen 650 mg PO, ondansetron 8 mg PO, diphenhydramine 25 mg PO, and famotidine 20 mg
- Medications that can be kept for PRN use include methylprednisolone for rash or CRS; saline bolus, meperidine for chills; diphenhydramine IV for rashes and itching, odansetron IV for nausea, and acetaminophen for fevers, chills, and headache
- Fever is generally the first sign of CRS, so once the temperature starts increasing, monitor other vital signs more carefully. Consider active management to prevent CRS from escalating
- Monitor patients during the infusion and for at least 16 hours following the first 3 infusions (induction phase) and then as clinically indicated. For the maintenance phase, patients should be monitored a minimum of 30 minutes after administration
- Monitor temperature, pulse rate, respiratory rate, and blood pressure at least every 4 hours during the induction phase and twice post infusion in the maintenance phase. Increase frequency if patient develops symptoms
- Educate patients and caregivers About the importance of reporting concerning symptoms as soon as possible
- Emphasize that CRS occurs in the vast majority of patients (around 90%) and starts the day of the infusion. But it is manageable—very few patients discontinue because of it

**Grade 1 (Mild)**
- Tebentafusp-tebn therapy to continue
- Provide oral analgesics for discomfort/pain (depending on labs, could be acetaminophen 650 mg PO)
- Corticosteroid management not required
- Provide ondansetron 8 mg IV PRN for nausea
- No requirement for premedication for the next dose
- Next dose can be escalated

**Grade 2 (Moderate)**
**If hypotension or hypoxia lasts < 2 hours:**
- Continue tebentafusp-tebn
- Corticosteroid management is not required
- Premedication for the next dose is not required
- Next dose can be escalated

**If hypotension or hypoxia lasts 2-3 hours or is recurrent:**
- Continue tebentafusp-tebn
- Provide methylprednisolone 2 mg/kg or equivalent PRN
- Corticosteroid premedication for the next dose is required
- Next dose can be escalated

**If hypotension or hypoxia lasts >3 hours & is not responding to therapy:**
- Hold tebentafusp-tebn
- Provide methylprednisolone 2 mg/kor equivalent PRN
- Corticosteroid premedication for the next dose is required
- Next dose cannot be escalated; resume escalation schema once dosages is tolerated
- All Grade 2 events:
  - Saline bolus (500 mL) PRN
  - Administer vasopressin as needed
  - Meperidine 25 mg for chills
  - Ondansetron IV 8 mg IV PRN for nausea
  - Give acetaminophen 650 mg PO PRN for fever/chills/headache
  - Administer low-flow nasal cannula (≤ 6 L/min as needed or blow by oxygen)

**Grade 3 (Severe)**
- Hold tebentafusp-tebn
- Administer vasopressors as required
- Administer corticosteroids (methylprednisolone 2 mg/kg or equivalent PRN)
- Corticosteroid premedication for the next dose is required
- Next dose cannot be escalated; resume escalation schema once dosages is tolerated
- Saline bolus (500 mL) as needed
- Meperidine 25 mg for chills
- Ondansetron IV 8 mg IV PRN for nausea
- Acetaminophen 650 mg PO PRN for fever/chills/headache
- Administer high-flow nasal canula (>6 L/min, as needed, or face mask)

**Grade 4 (Potentially Life-threatening)**
- Permanently discontinue tebentafusp-tebn
- Administer vasopressors, typically multiple
- Provide IV fluids as needed
- Administer corticosteroids (methylprednisolone 2 mg/kg or equivalent)
- If hypotension does not resolve rapidly (within 2-3 hours of onset) with intravenous crystalloid therapy and corticosteroids, tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) can be administered until hypotension resolves
- Provide meperidine 25 mg for chills
- Provide ondansetron IV 8 mg IV PRN for nausea
- Administer positive pressure ventilation (CPAP, BiPAP, or intubation and mechanical ventilation) as required to maintain oxygenation
- Administer analgesia as needed

**RED FLAGS:**
- **Wheezing or shortness of breath**
- **Disorientation or loss of consciousness**