[Clinic or Hospital Logo]		
	SOP #	[Number]
	Effective	[Date]
	Approved	[Date]
	Next Review	[Date]
	Owner	[Name]
	Department	[Name]
	Tags	[Tags]
	Applicability	[Name of sites]

Management of Cytokine Release Syndrome Associated with Bispecific T-Cell Engagers

(Example 1)

Where Did This Resource Come From?	
Clinic/Hospital Type	Mid-sized, rural, community cancer center
What's Unique?	• This clinic administers step-up dosing in the outpatient setting. • CRS management guidance is based on the proposals by Crombie and colleagues (2024); however, this clinic has applied it to all BTCEs, not just those used for lymphoma. • Offers guidance on managing Grade 1 at home and in the outpatient clinic or emergency department (ED).

1. Purpose

To provide a framework for the monitoring and management of Cytokine Release Syndrome (CRS) in patients receiving bispecific T-cell engager (BTCE) therapy.

2. Scope

This policy is applicable to all clinical staff at [site name].

3. Definitions

- **Bispecific T-Cell Engager (BTCE)**: Synthetic proteins that bind two distinct antigens: one targets the CD3 protein on T cells, and the other targets a specific cancer antigen, redirecting T cells to activate an antitumor immune response.
- **Step-Up Dose**: A dosing strategy that starts with a lower dose and gradually increases it to effectively prime the immune system while minimizing adverse effects.
- **Cytokine Release Syndrome (CRS)**: A potentially severe inflammatory response that occurs when immune effector cell therapy leads to the release of cytokines into the bloodstream. This syndrome causes symptoms such as fever, hypotension, hypoxia, chills, tachycardia, dyspnea, nausea, rash, headache, and myalgia.

4. Workup

- Workup and Evaluation
    - Pertinent history and physical examination, including vital sign evaluation and evaluation of respiratory symptoms
    - Review medications, including BTCE therapy received, last dose of antipyretic therapy, steroids, or anticytokine administration
    - Assess for concurrent symptoms of neurotoxicity
    - Assess for an alternate diagnosis, including infection (including neutropenic fever), venous thromboembolism, respiratory infection (including COVID-19 and influenza), volume overload or dehydration, and exacerbation of the underlying cardiopulmonary condition. Treat as appropriate.
    - For duration of symptoms over 1 week, consider excluding hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).
- Monitoring
    - Consider monitoring patient for 1-2 h after infusion if outpatient administration of bispecific T-cell engager on day of step-up dosing.
- Grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥100.4°F (38°C)	Temperature ≥100.4°F (38°C)	Temperature ≥100.4°F (38°C)	Temperature ≥100.4°F (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, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure

* Fever is defined as a temperature ≥100.4 °F (38°C) not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine 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 a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring a low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

5. Management

Grade	Management
1	Home: • Acetaminophen 650-1000 mg by mouth, can repeat, if recurrent fever, ≥6-8 h later if clinically stable • Recommend aggressive oral hydration • Continue to check temperature every 1-2 h and other vitals if able. Patients should recontact the clinic urgently or present to ED if blood pressure goes <10 mm Hg below baseline AND <90 mm Hg systolic, new orthostatic symptoms, weakness, confusion, dizziness, or new hypoxia (<90%). Home vs outpatient/ED evaluation: • If refractory or recurrent fever (<6-8 h) consider dexamethasone 10 mg once. Home management may be appropriate if vital signs remain stable and no other concerning symptoms. Otherwise, patients should be evaluated in a health care facility. • Consider earlier administration of steroids and immediate in-person evaluation for patients with multiple disease risk factors or comorbidities • Consider daily dexamethasone with persistent symptoms Additional management: • Consider anticytokine therapy (e.g., tocilizumab) in cases of protracted fever (e.g., >48 h despite corticosteroids) • Early tocilizumab after trial of dexamethasone should be considered for patients with multiple medical risk factors (e.g., comorbidities)
2	• All patients should be urgently evaluated in person. Recommend inpatient management for most cases of grade 2 CRS unless qualified outpatient day hospital/infusion center and no hypoxia. • If after hours without access to appropriate outpatient treatment area or if clinical scenario dictates, recommend ED evaluation • Acetaminophen 650-1000 mg by mouth as needed, up to 3-4 times daily • Dexamethasone 10 mg by mouth every 12 h • Administer IV fluids/supplemental oxygen as appropriate • Administer tocilizumab† if symptoms persist despite IV fluids and dexamethasone (~4-6 h after dosing) or if clinically unstable • Consider alternative agent (e.g., anakinra or siltuximab) if persistent symptoms despite maximal dosing
3	• Emergent inpatient admission (floor or ICU) for hemodynamic monitoring, IV fluids, oxygen therapy, and vasopressors • Acetaminophen 1000 mg IV as needed up to 3-4 times daily when safe • Dexamethasone (e.g., 10 mg IV Q 6 h), until resolution to grade ≤1, followed by dexamethasone taper • Evaluate for sepsis and consider empiric antibiotics • Administer tocilizumab† and consider alternative agent (e.g., anakinra or siltuximab) if persistent grade 3 CRS despite maximal dosing

	• If refractory hypotension/hypoxia, admit to ICU
4	• Inpatient admission to ICU for hemodynamic monitoring, IV fluids, oxygen therapy, and vasopressors • Acetaminophen1000 mg IV as needed up to 3-4 times daily when safe • Dexamethasone (e.g., 20 mg IV every 6 h), until resolution to grade ≤1, followed by dexamethasone taper • Administer tocilizumab and if repeated doses of tocilizumab have been used, consider alternative agent (e.g., anakinra or siltuximab) if persistent grade 4 CRS despite maximal dosing of first agent

Abbreviations: BP, blood pressure; ED; emergency department; ICU, intensive care unit; MAS, macrophage activation syndrome.

[†]Tocilizumab dosing: 8 mg/kg IV. Tocilizumab should not be administered more than twice per CRS event (at least 8 hours apart) or 3 times within a 6-week period.

6. References

1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.
2. Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. *Blood*. 2024;143(16):1565-1575. doi:10.1182/blood.2023022432.

7. Revision History

Version #	Date	Description of Changes	Reviewed / Approved By