Confidently Manage CRS and ICANS: A Practical Guide for Bispecific Antibody Therapy

Cytokine Release Syndrome

Effective CRS management is essential to confidently incorporate bispecific antibody therapy into your practice for appropriate patients.

Cytokine release syndrome (CRS) is characterized by an excessive release of pro-inflammatory cytokines that results in systemic inflammatory symptoms. CD3-based lymphocyte engager therapies carry a universal risk of CRS.[1,2]

Typical Time to Onset..... 1–3 days[2]
Typical Duration..... 7–8 days[2]
Peak Time of Risk..... Cycle 1[2]
Grade of Most Events.Grades 1–2[3]

RISK FACTORS[2]

- High tumor burden
- Rapid tumor progression
- High inflammatory markers (eg, ferritin, CRP)
- Older age or comorbidities
- Rapid CRS onset (<4 hrs from start of infusion)

EARLY CRS SIGNS AND SYMPTOMS[2,4]

- Pyrexia (≥100.4°F/38°C)
- Hypotension
- Hypoxia
- Headache
- Dyspnea
- Tachycardia
- Chills

INITIAL WORKUP[2]

- CBC, CMP, blood cultures
- MRSA, CRP, BNP, ferritin
- Urinalysis, urine culture
- Respiratory virus PCR panel
- Chest X-ray

Management for All Grades[2] *Risks vary by agent; refer to the prescribing information for product-specific dosing and management*

Fever: Oral acetaminophen 650 mg every 4 hrs PRN, cooling blanket, hyperthermia management protocol

Neutropenia: Initiation of empiric broad spectrum antibiotics

Consider providing patients with 1 dose of oral dexamethasone 8–12 mg to take if needed for higher-grade CRS (eg, fever, chills, rigors, difficulty breathing, feeling severely ill) at home prior to travel to Emergency Department, if instructed to do so.

Tocilizumab is available as generic and biosimilar formulation. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

Grade[2]	Definition	Management*
1	Fever ≥38°C only	**Continue or hold treatment** (dependent on bispecific agent)[†] ***CONSIDER:*** • Oral or IV dexamethasone 8–12 mg × 1 dose • IV tocilizumab[‡] for prolonged steroid-refractory CRS (>24–48 hrs) or if high-risk for CRS **Care setting:** Consider inpatient
2	Fever + Hypotension not requiring vasopressors ***and/or*** Hypoxia requiring low-flow nasal cannula[§] or blow-by	**Continue or hold treatment** (dependent on bispecific agent)[†] • Oral or IV dexamethasone 8–12 mg × 1 dose; may repeat every 12 hrs • Oxygen low flow nasal canula ≤6 L/min; IV fluid bolus; cardiac monitoring ***CONSIDER:*** • IV tocilizumab 8 mg/kg × 1 dose[‡] • Alternative cytokine blockers if symptoms persist for >24 hrs **Care setting:** Consider inpatient
3	Fever + Hypotension requiring vasopressor ± vasopressin ***and/or*** Hypoxia requiring high-flow cannula,[§] face mask, non-rebreather mask, or Venturi mask	**Hold treatment**[†] • IV fluid bolus and vasopressors PRN • IV dexamethasone 10 mg × 1 dose; may repeat every 6 hrs • IV tocilizumab 8 mg/kg × 1 dose[‡] • Consider adding alternative cytokine blockers if symptoms persist despite tocilizumab + steroid therapy **Care setting:** ICU
4	Fever + Hypotension requiring multiple vasopressors (excluding vasopressin) ***and/or*** Hypoxia requiring positive pressure ventilation (eg, CPAP, BiPAP, intubation, mechanical ventilation)	**Permanently discontinue treatment**[†] • IV methylprednisolone 1000 mg every 24 hrs × 3 days • IV tocilizumab 8 mg/kg × 1 dose[‡] • Consider adding alternative cytokine blockers if symptoms persist despite tocilizumab + steroid therapy • Multiple vasopressors (excluding vasopressin); positive pressure (eg, CPAP, BiPAP, intubation); echocardiogram **Care setting:** ICU

*All recommendations are NCCN Category 2A unless otherwise noted. [†]The risks associated with each agent vary significantly. Refer to the prescribing information and appropriate clinical trial protocols for guidance on toxicity management after initiation of a specific bispecific agent. [‡]Administer over 1 hr within 2 hrs of onset. Max dose 800 mg; 3 doses in 24 hrs; 4 doses total. If no clinical improvement in oxygenation, hypotension, fever, or other symptoms, dosing may be repeated every 8 hrs. Median time to response after 1st dose: hrs to days (range is generally 1–12 days). [§]Low-flow nasal cannular is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatric. High-flow nasal cannular is defined as oxygen delivered at >6 L/min.

BiPAP=bilevel positive airway pressure; BNP=b-type natriuretic peptide; CBC=complete blood count; CMP=comprehensive metabolic panel; CPAP=continuous positive airway pressure; CRP=C-reactive protein; hrs=hours; ICU=intensive care unit; IV=intravenous; MRSA=methicillin-resistant staphylococcus aureus; NCCN=National Comprehensive Cancer Network; PCR=polymerase chain reaction; PRN=as needed.

Confidently Manage CRS and ICANS: A Practical Guide for Bispecific Antibody Therapy

Immune Effector Cell-associated Neurotoxicity Syndrome

Effective ICANS management is essential to confidently incorporate bispecific antibody therapy into your practice for appropriate patients.

Immune effector cell-associated neurotoxicity syndrome (ICANS) may be caused by pro-inflammatory cytokines that disrupt the blood-brain barrier and is characterized by neurological defects, often concurrently with CRS. It is associated with lymphocyte engager therapy, and early intervention is important to prevent progression to severe ICANS.[2,5]

Typical Time to Onset
Step-up dosing[2]

EARLY ICANS SIGNS AND SYMPTOMS[2,4]

- Aphasia
- Dysgraphia
- Muscle weakness
- Confusion or memory loss
- Lethargy
- Seizures
- Tremors

ICE ASSESSMENT TOOL[2]

Orientation (Year, month, city, hospital)	4 points
Name 3 objects	3 points
Follow simple commands	1 point
Write a standard sentence	1 point
Count backwards from 100 by 10	1 point

Management for All Grades[2] *Risks vary by agent; refer to the prescribing information for product-specific dosing and management*

- Aspiration precautions; withhold oral intake; assess swallow
- Avoid CNS-sedating medications
- Neurology consult if refractory to dexamethasone
- Neuroimaging every 2–3 days if persistent ICANS

ICANS does NOT respond to tocilizumab. Corticosteroids are the cornerstone of treatment.

Grade[2]	Definition	Management*
1 ICE 7–9	Awakens spontaneously	**Continue or hold treatment** (dependent on bispecific agent) • Oral or IV dexamethasone 10 mg × 1 dose; if unresolved or progressing, increase to every 6 hrs • Consider levetiracetam 750 mg every 12 hrs†
2 ICE 3–6	Awakens to voice	**Continue or hold treatment** (dependent on bispecific agent) • IV dexamethasone 10 mg every 6 hrs • Consider levetiracetam 750 mg every 12 hrs†
3 ICE 0-2	Awakens to tactile stimulus only ***or*** Clinical seizure resolving rapidly ***or*** Focal/local edema on neuroimaging	**Hold treatment** • IV methylprednisolone 1000 mg × 1 dose – If refractory, 1000 mg every 12 hrs × 3 days • Levetiracetam 750 mg every 12 hrs† **Care setting:** ICU
4 ICE 0 *Unarousable or unable to perform ICE*	Stupor or coma ***or*** Life-threatening seizure (>5 min) or repetitive seizures without return to baseline ***or*** Deep focal motor weakness ***or*** Diffuse cerebral edema	**Permanently discontinue treatment†** • IV methylprednisolone 1000 mg every 12 hrs • Levetiracetam 750 mg every 12 hrs† **Care setting:** ICU

*All recommendations are NCCN Category 2A unless otherwise noted. †Depending on seizure risk associated with agent used.

CNS=central nervous system; CRS=cytokine release syndrome; EEG=electroencephalogram; hrs=hours; ICE=immune effector cell-associated encephalopathy; ICU=intensive care unit; IV=intravenous; min=minutes; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network.

References: 1. Cosenza M, et al. *Int J Mol Sci.* 2021;22(4):7652. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed April 17, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** Crombie JL, et al. *Blood*. 2024;143(16):1565-1575. **4.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **5.** Rees JH. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). In: Kröger N, et al., ed. *The EBMT/EHA Car-T Cell Handbook*. New York: Springer; 2022:141-145.

Distributed and marketed by Genmab US Inc. 777 Scudders Mill Road, Plainsboro, NJ 08536.
Distributed and marketed by AbbVie Inc. 1 North Waukegan Road, North Chicago, IL 60064.

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