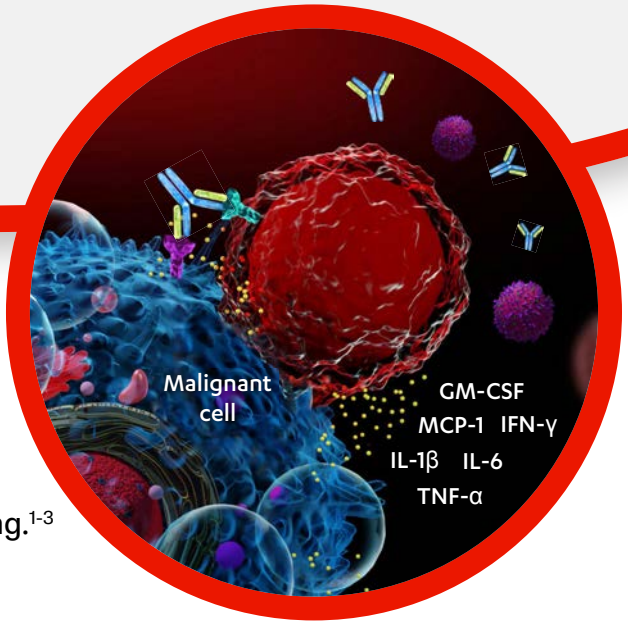
Johnson&Johnson

The intent of this handout is to provide background information regarding CRS and grading system management guidelines. This handout is not intended to provide treatment guidance for patients.

Cytokine Release Syndrome



CRS is characterized by elevated levels of proinflammatory cytokines and a supraphysiologic response to infection (eg, COVID-19), disorders (eg, HLH), or T-cell–engaging therapy (eg, bispecific antibodies, CAR-T). CRS is a life-threatening adverse event that can be effectively managed in the clinical setting.[1-3]

Symptoms[1,2,4]

Flu-like symptoms[1,2,4]

- Fever ≥100.4°F (≥38°C)
- Fatigue
- Headache
- Rash
- Diarrhea
- Arthralgia
- Myalgia

Severe life-threatening manifestations

- **Hypotension**
- **Hypoxia**
- **Seizures**
- **Disseminated intravascular coagulation**
- **Multiorgan dysfunction**
- **Fatality**

Uncontrolled systemic inflammatory response

Clinical factors associated with the severity of CRS[5]

Patient-related

Age | Comorbidities
Preexisting inflammation
Thrombocytopenia prior to lymphodepletion (eg, with CAR-T)

Therapy-related

Immune therapy modality construct
Administration dose and schedule
Strength of T-cell activation
Degree of T-cell expansion

Disease-related

Disease type
High tumor burden

Conditions associated with CRS[1]

CRS has clinical signs similar to those of HLH/MAS and sepsis. Appropriate differential diagnosis should be considered for CRS diagnosis and management.

Possible risk associated with CRS: neurotoxicity – ICANS[4]

Pathologic outcome involving the central nervous system with T-cell–engaging therapies. Symptoms may include tremor, encephalopathy, aphasia, seizure, cerebral edema, and others.

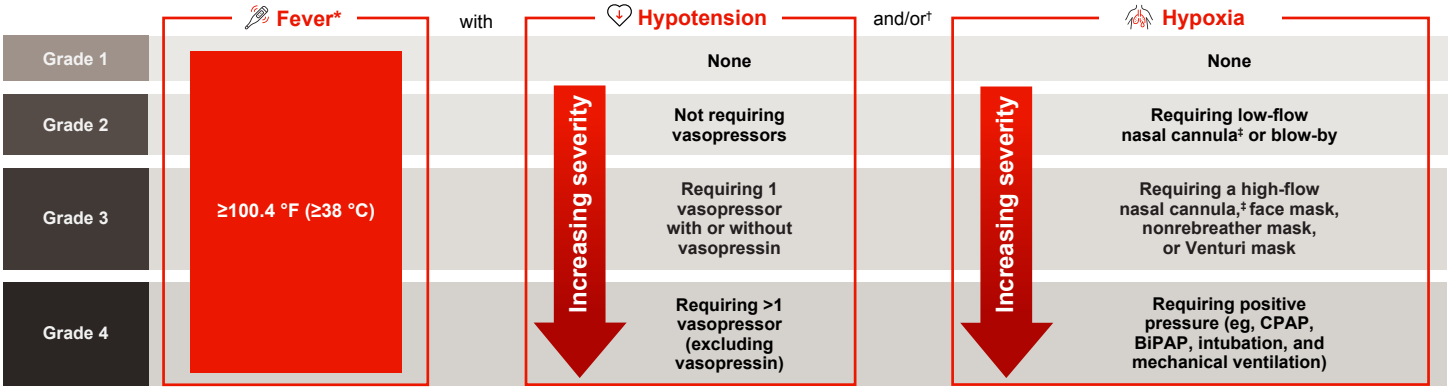
CAR-T, chimeric antigen receptor T cells; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell–associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; MAS, macrophage activation syndrome; MCP-1, monocyte chemoattractant protein-1; TLS, tumor lysis syndrome; TNF, tumor necrosis factor.

1. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. *J Immunother Cancer*. 2018;6:56. **2.** Wang Z, Han W. *Biomarker Res*. 2018;6:4. **3.** Fajgenbaum DC, June CH. *N Engl J Med*. 2020;383:2255-2273. **4.** Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **5.** Acharya UH, Dhawale T, Yun S, et al. *Expert Rev Hematol*. 2019;12:195-205.

Cytokine Release Syndrome

CRS grading systems

Multiple grading criteria have been defined, including CTCAE,[1] CARTOX,[2] and MSKCC[3] guidelines. ASTCT (shown below) is a broadly used grading system that harmonizes other guidelines into a consensus framework.[4]



*Fever is defined as 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 anti–IL-6R 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 temperature of 103.1 °F (39.5 °C), hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as having grade 3 CRS. ‡Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; IL-6R, interleukin-6 receptor.

Figure modified from Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Operational considerations for therapy modalities[5,6]

1. Potential requirement of **clinical interventions** (eg, inpatient monitoring, anti–IL-6R availability, and ICU availability) and **specific site training** on CRS
2. Implementation of a **dedicated clinical and safety monitoring plan** for outpatient and inpatient setting
3. **Logistical considerations for the transition of care:** outpatient to inpatient and inpatient to outpatient
4. **Patient and caregiver education** on signs and symptoms of CRS

Mitigation[5-12]

For prevention of CRS associated with therapy, clinical trials include the following medications for consideration as per therapy modality:

- Corticosteroids
- Antipyretics
- Antihistamines
- Anti–IL-6R (ie, tocilizumab)*

Administration of bispecific therapies should be avoided during active infections as infections could precipitate severe CRS

Monitoring[5,13]

Monitor for early signs and symptoms indicative of CRS, including clinical assessment and laboratory testing for:

- Fever
- Disseminated intravascular coagulation
- Hematology parameters
- Pulmonary, cardiac, renal, and hepatic function

Management[3,5,7,11-19]

Shown below are select pharmacological management strategies for CRS from established guidelines.

Established CRS management guidelines are available for immunotherapies (ie, bispecifics, CAR-T). For more comprehensive guidance on supportive care related to CRS management, refer to your institutional guidelines and established guidelines (eg, **ASCO**,[14] **CARTOX**,[15] **IMWG**,[12] **mSMART**,[16] **National Comprehensive Cancer Network® [NCCN®],**[17] and **SITC**[18]).

Consider administration of:

- Anti–IL-6R (ie, tocilizumab)
- Acetaminophen
- Intravenous fluids
- Corticosteroids
- Oxygen
- Antibiotics†

*The NCCN® states that prophylactic tocilizumab may be considered to reduce the risk of CRS[17]; IMWG guidelines state that prophylactic tocilizumab use is considered investigational but note the increasing body of evidence for its use in the real-world setting.[12] †In patients with neutropenia, concomitant infection, or other predisposing risk factors for infection.[19]

ASCO, American Society of Clinical Oncology; ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CAR-T, chimeric antigen receptor T cells; CARTOX, CAR-T cell therapy–associated toxicity; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; ICU, intensive care unit; IL-6R, interleukin 6 receptor; IMWG, International Myeloma Working Group; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer.

1. National Cancer Institute. Accessed November 20, 2025. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf. **2.** Neelapu SS, Tummala S, Kebriaei P, et al. *Nat Rev Clin Oncol*. 2018;15:47-62. **3.** Park JH, Rivière I, Gonen M, et al. *N Engl J Med*. 2018;378:449-459. **4.** Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **5.** Stewart MD, McCall B, Pasquini M, et al. *Cytotherapy*. 2022;S1465-324900023-8. **6.** Using Bispecific Antibodies in Community Practice: Challenge and Opportunities. Accessed November 20, 2025. https://www.accc-cancer.org/docs/projects/bispecific-antibodies/checklist-for-bispecific-antibodies-jan-2022.pdf ?sfvrsn=ad2f3ee4_2. **7.** Acharya UH, Dhawale T, Yun S, et al. *Expert Rev Hematol*. 2019;12:195-205. **8.** Brudno JN, Kochenderfer JN. *Blood*. 2016;127:3321-3330. **9.** Maude SL, Laetsch TW, Buechner J, et al. *N Engl J Med*. 2018;378:439-448. **10.** Topp MS, Gökbuget N, Stein AS, et al. *Lancet Oncol*. 2015;16:57-66. **11.** Moreau P, Garfall AL, van de Donk NWCJ, et al. *N Engl J Med*. 2022;387:495-505. **12.** Rodriguez-Otero P, Usmani S, Cohen AD, et al *Lancet Oncol*. 2024;25:E205-E216. **13.** Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. *J Immunother Cancer*. 2018;6:56. **14.** Santomasso BD, Nastoupil LJ, Adkins S, et al. *J Clin Oncol*. 2021;39:3978-3992. **15.** University of Texas MD Anderson Cancer Center. Accessed November 20, 2025. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf. **16.** Mayo Clinic. mSMART. Accessed November 20, 2025. https://www.msmart.org/mm-treatment-guidelines. **17.** 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. 2025. All rights reserved. Accessed [December 11, 2025]. 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. **18.** Maus MV, Alexander S, Bishop MR, et al. *J Immunother Cancer*. 2020;8:e001511. **19.** Rodriguez-Otero P, et al. *Lancet Oncol*. 2024;25(5):Suppl.