Bristol Myers Squibb®

Management of Patients Receiving CAR T Cell Therapy: CRS and Neurotoxicity

The CAR T Academy Modules are intended to provide a high-level overview of select adverse events and are not meant to be a comprehensive discussion of all adverse events contemplated for CAR T cell therapy.

CAR T Academy: Management of Patients Receiving CAR T Cell Therapy: CRS and Neurotoxicity

01: OVERVIEW

02: CYTOKINE RELEASE SYNDROME (CRS)

03: NEUROTOXICITY

Journey Through the CAR T Cell Therapy Process

Icon indicates areas of collaboration between the non-CAR T and CAR T treatment teams

Manufacturing

Patient identification[1,2]

- Appropriate patients are identified for treatment at qualified treatment sites or referring sites
- Early collaboration may facilitate timely referral and eligibility evaluation
- Once a patient is confirmed as eligible, leukapheresis is scheduled

Apheresis[1-4]

- Before apheresis, patients undergo a washout of prior medications that may affect T cell health to ensure optimal collection
- Physicians, APPs, and nurse coordinators all play a role in ensuring a proper washout occurs before apheresis
- Patients then undergo apheresis, which involves collection of white blood cells
- The collected apheresis product is then sent to the manufacturer

Bridging[1,3]

- Bridging therapy may be given to maintain disease control during CAR T cell manufacturing
- Appropriate bridging therapy should be discussed and coordinated between the referring physicians and those treating with CAR T cell therapy

LDC and infusion[1-3]

- LDC is administered prior to CAR T cell infusion to deplete endogenous T cells and create an environment for CAR T cell expansion
- Infusion will then occur at the qualified treatment center

Monitoring and long-term follow-up[1,2,5]

- After infusion, patients are closely monitored for at least 2 weeks at the CAR T cell therapy treatment site, and side effects are promptly managed
- After at least 2 weeks, patients may be discharged back to the referring physician's care
- Communication continues between the CAR T cell therapy treatment center and the primary hematologist/ oncologist as patients are monitored long-term

APP, advanced practice provider; CAR, chimeric antigen receptor; LDC, lymphodepleting chemotherapy.

References: 1. Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **2.** Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23:27-34. **3.** McGuirk J, et al. *Cytotherapy.* 2017;19(9):1015-1024. **4.** Qayed M, et al. *Cytotherapy.* 2022;S1465-3249(22)00641-7. **5.** FDA Eliminates Risk Evaluation and Mitigation Strategies for Autologous Chimeric Antigen Receptor T cell Immunotherapies. United States Food and Drug Administration. June 26, 2025. Accessed July 14, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor

Severe, Life-Threatening Toxicities Can Arise Following CAR T Cell Infusion

Two of the most serious adverse events (AEs) are **CRS** and **neurotoxicity**[1-8]

Other potentially serious or life-threatening AEs may be prolonged and include:[2-8]

- Serious infections
- Prolonged cytopenias
- Hypogammaglobulinemia
- Hypersensitivity reactions
- Secondary malignancies
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS)
- Increased early mortality

CAR T cell therapy side effects may also affect ability to drive and use machines[8]

Deaths associated with CRS and neurotoxicity have been reported in patients following administration of CAR T cell therapy, underscoring the need for timely assessment and appropriate intervention[9]

The listed AEs do not include all of the side effects that may be associated with CAR T cell therapy.

Treaters should refer to a CAR T cell product's approved prescribing information (or for investigational products, the investigator brochure) for details on the product's AE profile.

References: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **2.** National Institutes of Heath. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed **3.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c 4. National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189 **5.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59 **6.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022 **7.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2 **8.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538 **9.** Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330.

Two Serious Adverse Effects of CAR T Cell Therapy

Cytokine Release Syndrome (CRS)

Severe CRS is primarily managed with tocilizumab and/or corticosteroids

Neurotoxicity

Neurotoxicities are primarily managed with corticosteroids and antiseizure medications

Both of these events require hospitalization

Reference: Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23(2):27-34.

Factors Associated With Severe CRS and Severe Neurologic Toxicity

Several patient-specific factors have been identified that are associated with a higher risk for severe CRS and severe neurotoxicity

- Higher disease burden
- Baseline thrombocytopenia
- Baseline elevations in markers of endothelial activation (eg, angiopoietin-2, von Willebrand factor)
- Elevated CRP after infusion
- Elevated CSF protein after infusion (specific to neurotoxicity)

CRP, C-reactive protein; CSF, cerebrospinal fluid.

Reference: Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55.

CAR T Academy: Management of Patients Receiving CAR T Cell Therapy: CRS and Neurotoxicity

01: OVERVIEW

02: CYTOKINE RELEASE SYNDROME (CRS)

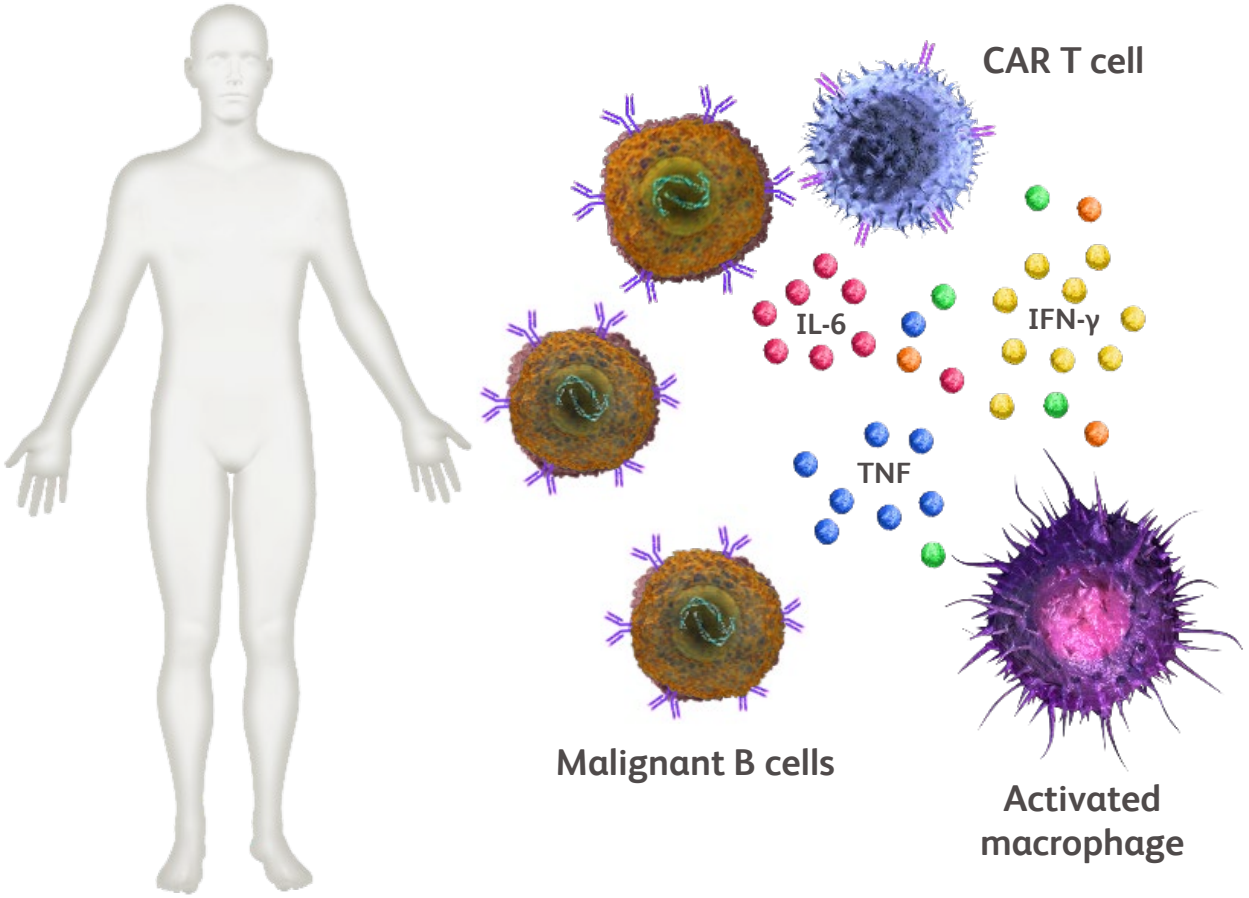
03: NEUROTOXICITY

CRS Pathophysiology

CRS occurs as a result of bulk T-cell activation, which leads to a massive release of inflammatory cytokines produced by CAR T cells or other immune cells[1,2]

The cytokines released include IL-6, most notably, as well as TNF, IFN-g, IL-2, IL-8, and IL-10[2]

CRS Associated With CAR T Cell Therapy[3]



References: 1. Oluwole OO, Davila ML. *J Leukoc Biol.* 2016;100:1265-1272. **2.** Brudno JN, Kochenderfer JN. *Blood.* 2016;127(26):3321-3330. **3.** June CH, et al. *Science.* 2018;359:1361-1365.

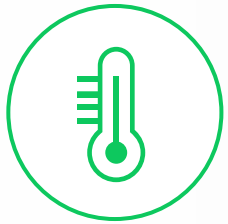
CRS Clinical Presentation

Not all patients will develop CRS, but when it occurs the severity can range from mild to life-threatening or fatal[1]

- Severity may but does not always correlate with disease burden[2]

Typical onset is within 1 to 5 days, but varies[1]

- Time-to-onset can be delayed and can present beyond 14 days[3]



The first symptom is typically fever, which can be high grade (>40°C or >104°F)[1]

- Additional signs and symptoms may include respiratory distress,[1] hypotension,[1] tachycardia[2] and neurologic symptoms[1]
- Although fever is a key indicator of CRS, other AEs, such as infection, should also be assessed and ruled out when fever arises

References: 1. Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265-1272. **2.** June CH, et al. *Science*. 2018;359:1361-1365. **3.** Lee DW, et al. Biol Blood Marrow *Transplant*. 2019;25:625-638.

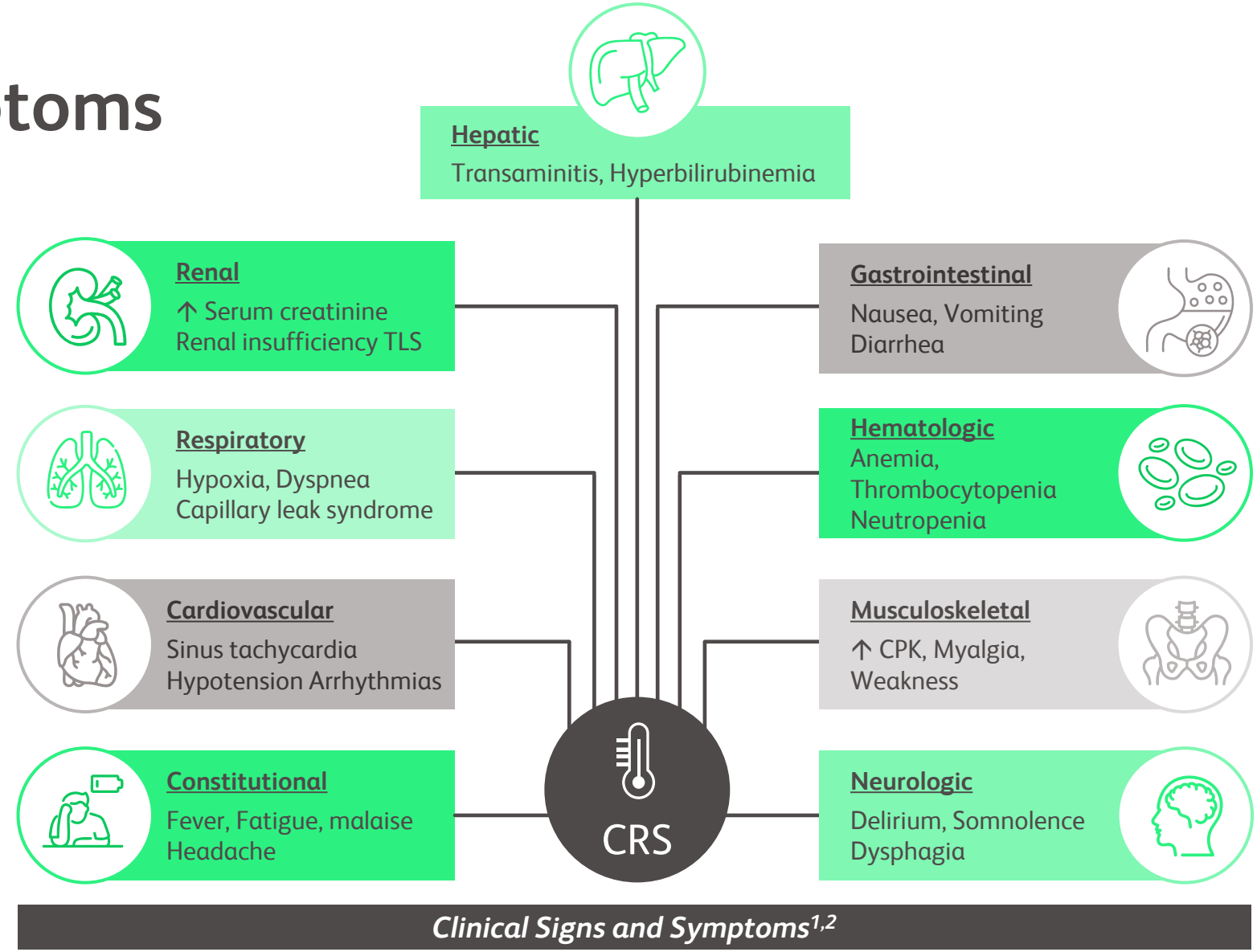
CRS Signs and Symptoms

Common signs and symptoms of CRS include high fever, sinus tachycardia, hypotension, depressed cardiac function, dyspnea, and hypoxia[1]

Additional constitutional symptoms may include fatigue, headache, and myalgia[1]

CAR T–associated CRS can cause many end-organ toxicities. However, many of these are reversible[1]

CRS can be fatal[2]



CPK, creatine phosphokinase; TLS, tumor lysis syndrome.

References: 1. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. **2.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55.

CRS Recognition

The importance of timely recognition of CRS cannot be overstated given the potential for mortality. Note that CRS and neurotoxicity can occur simultaneously[1,2]

Routine Monitoring

Vital signs including temperature, O_2 saturation, etc[1]

Review of systems and physical exam[1]

- Focus on cardiovascular, pulmonary, and neurologic systems
- Survey for occult infection

Laboratory monitoring of inflammatory markers[1,2]

- CRP
- Cytokines*
- Ferritin
- LDH

Focused Assessment Based on Symptoms

Fever[1]

- Blood and urine culture
- Targeted imaging to assess for potential sources of infection

Tachycardia[1]

- Electrocardiogram to assess for arrhythmia

Hypotension/persistent tachycardia[1]

- Echocardiogram to assess for decreased ejection fraction

*May be sent out for testing.
CRP, C-reactive protein; LDH, lactate dehydrogenase.
References: 1. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55. **2.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

CRS Management

Several supportive care interventions may be utilized, depending on the severity of symptoms[1]

Intervention	When used for CRS management
Antipyretics (eg, acetaminophen)	To control fever
Supplemental oxygen	For hypoxia
Anti-infective agents	For patients with infections, febrile neutropenia, and/or who are hemodynamically unstable
IV fluids and vasopressors	As needed for hypotension

CRS Management continued on next slide.

Reference: Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55.

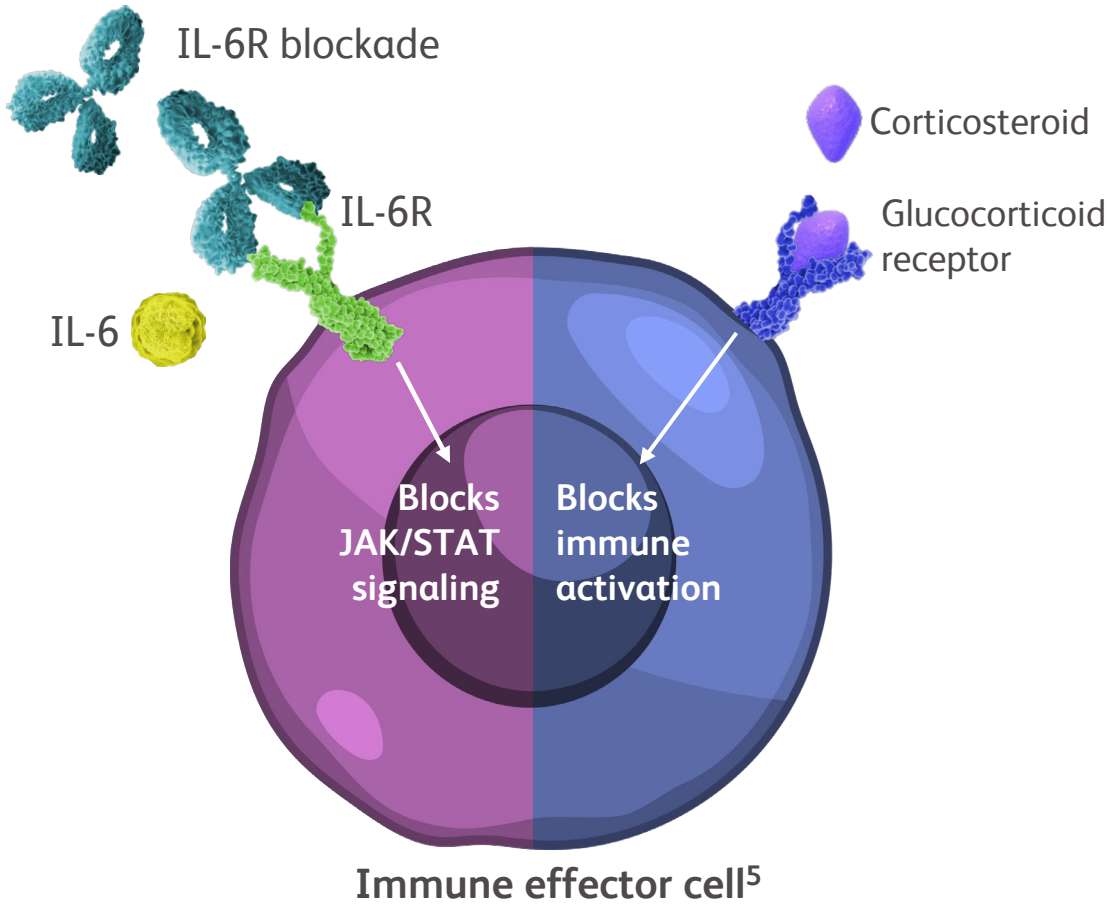
CRS Management (cont.)

In case of more severe CRS symptoms:

Immunosuppressive therapy

- Approved first-line agent: IL-6R blockade (tocilizumab)[1]
- Systemic corticosteroids[1]
- Other agents are under investigation including agents that target:[2,3]
  - IL-1, TNFα, JAK/STAT, ITK, GM-CSF

Extreme cases of CRS may require intubation and mechanical ventilation[4]



GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; ITK, IL-2 Inducible T cell Kinase; JAK, Janus Kinase; STAT, Signal Transducer and Activator of Transcription; TNF, Tumor Necrosis Factor.

References: 1. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. **2.** Siegler EL, et al. *Front Immunol*. 2020 Aug 28;11:1973 **3.** Kenderian SS, et al. *Blood*. 2020;136 (Supplement 1):6–7. **4.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **5.** Bonifant CL, et al. *Molecular Therapy—Oncolytics*. 2016;3(16011).

CRS Grading Systems

There are multiple systems that have been developed for grading CRS associated with CAR T cell therapy[1,2]

Systems For Grading CRS Associated with CAR T Cell Therapy[1,2]

- ASTCT
- Lee Criteria (Lee, et al. 2014)
- Penn Grading Scale
- CARTOX

CRS grading and treatment recommendations may differ by scale and by product. Treating healthcare providers should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

ASTCT, American Society for Transplantation and Cellular Therapy; CARTOX, CAR T cell therapy associated toxicity; CTCAE, Common Terminology Criteria for Adverse Events.

References: 1. Schuster SJ, et al. *Blood Adv*. 2020;4(7):1432-1439. **2.** Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

CRS Grading Scales: Lee, ASTCT, Penn, and CARTOX

Grade	Lee Criteria[1]	ASTCT Criteria[2]	Penn Criteria[3]	CARTOX Criteria[4]
1	Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgias, malaise)	Fever (≥ 38°C)[b]	• Mild reaction: treated with supportive care such as antipyretics, antiemetics	• Temperature ≥38 °C and/or grade 1 organ toxicity[d]
2	Symptoms require and respond to moderate intervention: • O_2 requirement <40% FiO_2, **OR** • Hypotension responsive to IV fluids or low dose of one vasopressor, **OR** • Grade 2 organ toxicity[a]	Fever (≥ 38°C)[b], not requiring vasopressors, and/or[c] requiring low-flow nasal cannula or blow-by	• Moderate reaction: Some signs of organ dysfunction (eg, grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition • Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for IV therapies (not including fluid resuscitation for hypotension)	• Hypotension responds to IV fluids or low-dose vasopressors • Hypoxia requiring FiO_2 <40% • Grade 2 organ toxicity[d]
3	Symptoms require and respond to aggressive intervention: • O_2 requirement ≥40% FiO_2, **OR** • Hypotension requiring high dose or multiple vasopressors, **OR** • Grade 3 organ toxicity[a] or grade 4 transaminitis	Fever (≥ 38°C)[b], requiring vasopressor with or without vasopressin, and/or[c] requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	• More severe reaction: hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition • Hypotension treated with multiple fluid boluses or low-dose vasopressors • Coagulopathy requiring FFP, cryoprecipitate, or fibrinogen concentrate • Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	• Hypotension needing high-dose or multiple vasopressors • Hypoxia requiring FiO_2 ≥40% • Grade 3 organ toxicity[d] or grade 4 transaminitis
4	Life-threatening symptoms: • Requirement for ventilator support, **OR** • Grade 4 organ toxicity[a] (excluding transaminitis)	Fever (≥ 38°C)[b], requiring multiple vasopressors (excluding vasopressin), and/or[c] requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	• Life-threatening complications such as hypotension requiring high-dose vasopressors • Hypoxia requiring mechanical ventilation	• Life-threatening hypotension • Needing ventilator support • Grade 4 organ toxicity[d] except grade 4 transaminitis
5	Death	Death	Death	Death

[a]As per CTCAE Version 4.0.[b]Not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. [c]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. [d]Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum ALT, AST, or bilirubin levels), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatological (rash), and coagulopathy (disseminated intravascular coagulation), as per CTCAE Version 4.03.
BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FFP, fresh frozen plasma; FiO_2, fraction of inspired oxygen; IV, intravenous; LFT, liver function test.

References: **1.** Lee DW, et al. *Blood*. 2014;124:188–195. **2.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **3.** Porter D, et al. *J Hematol Oncol*. 2018;11:35. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47–62.

Management of Grade 1 and 2 CRS According to Different CRS Grading Scales

Grade	Lee[1]	ASTCT[2]	Penn[3]	CARTOX[4]
1	• Vigilant supportive care • Assess for infection • Treat fever and neutropenia if present • Monitor fluid balance • Antipyretics, analgesics as needed	• Antipyretics and IV hydration • Diagnostic work-up to exclude infection • Growth factors and antibiotics if neutropenic (optional)	• Treated with supportive care such as antipyretics, antiemetics	• Acetaminophen and hypothermia blanket for the treatment of fever • Ibuprofen can be used as second treatment option for fever, if not contraindicated • Assess for infection using blood and urine cultures, and chest radiography • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab or siltuximab[a] for persistent (lasting >3 days) and refractory fever
2	• Vigilant supportive care • IV fluids or one low dose pressor for hypotension • Oxygen for hypoxia • For patients without extensive comorbidities or younger pts: monitor cardiac and other organ function closely • For older pts or pts with extensive comorbidities: tocilizumab ± corticosteroids	• Supportive care as for grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab ± dexamethasone (or methylprednisolone equivalent)	• IV therapies • Hospitalization to manage CRS-related symptoms including fevers with associated neutropenia	• Supportive care – Manage fever and constitutional symptoms as in grade 1 – Supplemental oxygen – One or more IV fluid bolus of normal saline • Tocilizumab or siltuximab[a] for the treatment of hypotension that is refractory to fluid boluses – Vasopressors if hypotension persists after 2 fluid boluses and anti-IL-6 therapy, consider transfer to ICU, obtain echocardiogram, and initiate other methods of hemodynamic monitoring • Dexamethasone for high-risk pts or pts with persistent hypotension • Tocilizumab or siltuximab[a] ± corticosteroids and supportive care, as recommended for the management of hypotension, for hypoxia, and/or organ toxicity • Symptomatic management of organ toxicities, as per standard guidelines

[a]Siltuximab is not currently indicated for treatment of CRS for CAR T cell therapy.
ICU, intensive care unit.
References: 1. Lee DW, et al. Blood. 2014;124(2):188-195. **2.** Neelapu SS. *Hematol Oncol.* 2019;37(S1):48-52. **3.** Porter DL, et al. *Sci Transl Med.* 2015;7(303):303ra139. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

Management of Grade 3 and 4 CRS According to Different CRS Grading Scales

Grade	Lee[1]	ASTCT[2]	Penn[3]	CARTOX[4]
3	• Vigilant supportive care • Multiple pressors or high dose pressors for hypotension • Supplemental oxygen if needed • Tocilizumab ± corticosteroids	• Supportive care as in grade 1 • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10-20 mg IV q6h (or methylprednisolone equivalent) • Consider ICU monitoring (optional)	• Hospitalization to manage symptoms related to organ dysfunction • Manage hypotension with IV fluids or low-dose vasopressors • Fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate for coagulopathy • Supplemental oxygen	• Supportive care – Manage fever and constitutional symptoms as in grade 1 – IV fluids as recommended for grade 2 – Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab or siltuximab[a] ± corticosteroids as per grade 2, if not administered previously • Dexamethasone • Vasopressors as needed • ICU transfer, obtain echocardiogram, and haemodynamic monitoring as in grade 2 • Symptomatic management of organ toxicities as per standard guidelines
4	• Vigilant supportive care • Mechanical ventilation if needed • Tocilizumab ± corticosteroids	• Supportive care as in grade 1 • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/day • ICU monitoring	• High-dose vasopressors • Mechanical ventilation	• Supportive care – Manage fever and constitutional symptoms as in grade 1 – IV fluids • Tocilizumab or siltuximab[a] ± corticosteroids as per grade 3 • Vasopressors and haemodynamic monitoring as per grade 3 • Methylprednisolone for hypotension • Mechanical ventilation • Symptomatic management of organ toxicities as per standard guidelines

[a]Siltuximab is not currently indicated for treatment of CRS for CAR T cell therapy.

References: 1. Lee DW, et al. Blood. 2014;124(2):188-195. **2.** Neelapu SS. *Hematol Oncol.* 2019;37(S1):48-52. **3.** Porter DL, et al. *Sci Transl Med.* 2015;7(303):303ra139. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

Macrophage Activation Syndrome (MAS)

Macrophage activation syndrome (MAS), also referred to as hemophagocytic lymphohistiocytosis (HLH), is closely associated with severe CRS[1,2]

- Caused by excessive activation and multiplication of T cells and macrophages[1]
- Pathogenesis is very similar to CRS, and may be a complication of severe CRS[1]
- Reliable indicators in patients treated with CAR T cell therapy may include hemophagocytosis, hypofibrinogenemia, and hypertriglyceridemia[2]
- May occur in ~1-6% of CAR T cell-treated patients[2-7]
- Although HLH/MAS can be fatal, symptoms are resolved with the resolution of CRS in the majority of patients[1,3]

References: 1. Leukemia & Lymphoma Society. Chimeric Antigen Receptor (CAR) T-Cell Therapy. https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy. Accessed October 5, 2021. **2.** Titov A, et al. *Cell Death Dis.* 2018;9(9):897. **3.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **3.** National Institutes of Heath. DailyMed. Accessed July 14, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **4.** National Institutes of Heath. DailyMed. Accessed July 14, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022. **5.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2. **6.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538. **7.** National Institutes of Health. DailyMed. Accessed July 15, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189

Diagnosis and Management of HLH/MAS per CARTOX

Diagnostic considerations:[1]

Following CAR T cell therapy, patients may have HLH/MAS if they have CRS plus a peak serum ferritin level > 10,000 ng/mL and subsequently develop any two of the following:

- Grade ≥ 3 increase in serum bilirubin, AST, or ALT levels[a]
- Grade ≥ 3 oliguria or increase in serum creatinine levels[a]
- Grade ≥ 3 pulmonary edema[a]
- Presence of hemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

Management of HLH/MAS may involve:[1]

Management of grade ≥ 3 organ toxicity with anti-IL-6 therapy + corticosteroids

Monitoring of blood ferritin, LDH, fibrinogen, transaminases, bilirubin, creatine levels

- If no improvement after 48 hours, then consider adding etoposide to treatment and/or intrathecal cytarabine for neurotoxicity
- If improving after 48 hours, continue management per CRS algorithm

Based on a survey of 114 treatment centers that had cases of HLH/MAS from 2016-2018, there is a lack of consensus on how to best diagnosis and manage HLH/MAS[2]

[a]Grading as per CTCAE version 4.03

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HLH, hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome.

References: 1. Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62. **2.** Sandler RD, et al. *Front Immunol.* 2020;11:524.

CAR T Academy: Management of Patients Receiving CAR T Cell Therapy: CRS and Neurotoxicity

01: OVERVIEW

02: CYTOKINE RELEASE SYNDROME (CRS)

03: NEUROTOXICITY

Pathophysiology of Neurotoxicity

Neurotoxicity can occur in the absence of CRS, concurrent with CRS, or more commonly, after CRS[1,2]

Considered to be a distinct process from CRS, based on their timing and the treatments to which they respond[1]

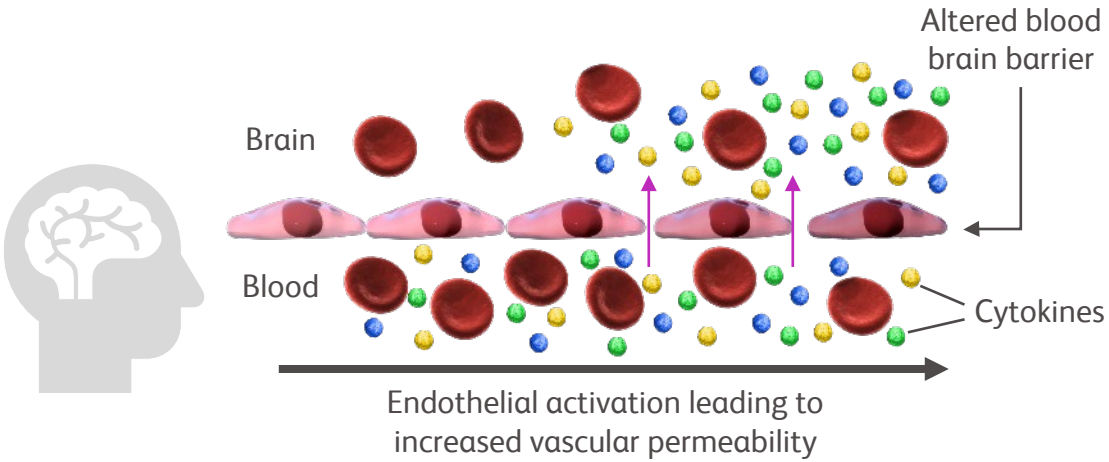
The exact mechanism of CAR T cell–associated neurotoxicity is not known. Presence of CAR T cells in the CNS may be directly or indirectly involved[3]

- Endothelial injury possibly resulting from pro-inflammatory cytokines may contribute[4]

Onset can vary widely. Median time to onset of neurotoxicity is generally 2-10 days (range: 1-301 days)[5-11]

Toxicities tend to be self-limited and reversible, but can be life-threatening or fatal in some cases[12]

Development of Neurotoxicity Associated With CAR T Cell Therapy[4]



Neurotoxicities associated with CAR T cell therapy are sometimes referred to as immune effector cell-associated neurotoxicity syndrome (ICANS)[1]

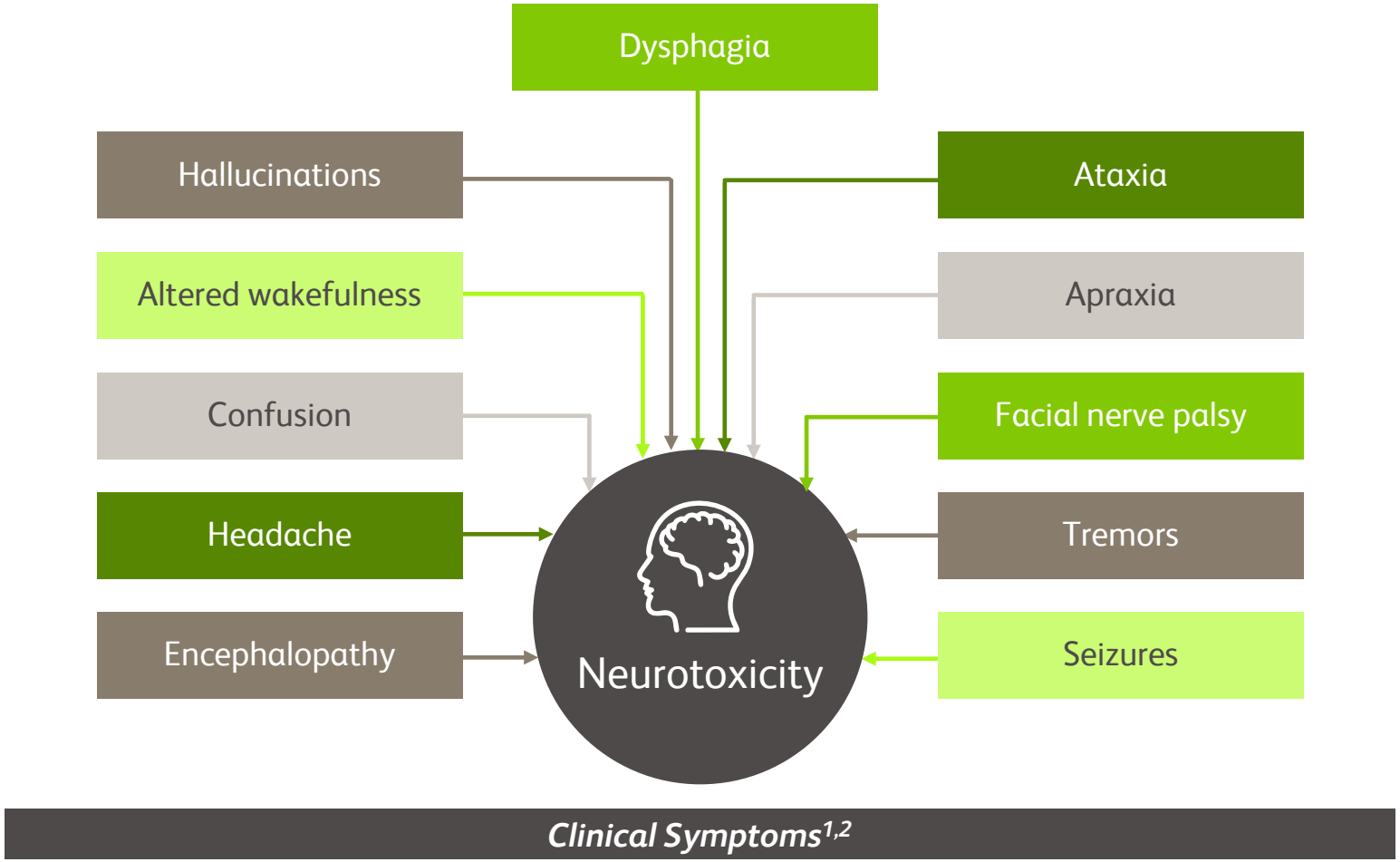
CNS, central nervous system

References: 1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **2.** Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. **3.** Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265-1272. **4.** June CH et al. *Science*. 2018;359:1361-1365. **5.** National Institutes of Heath. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **6.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **7.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022. **8.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. **9.** National Institutes of Health. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. **10.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2. **11.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538. **12.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45-55.

Neurotoxicity Symptoms

Neurotoxicities caused by CAR T cells are diverse and do not localize to one region of the neuroanatomy[1]

Some of the earliest manifestations of neurotoxicity associated with CAR T cell therapy include tremors, dysphagia, impaired attention, apraxia, and mild lethargy[2]



References: 1. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. **2.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Neurotoxicity Recognition and Monitoring

Routine Monitoring and Follow-up

Periodic review of the neurologic system and full neurologic exam in accord with institutional tools and guidelines[1]

- If evidence of neurotoxicity, neurologic exam every 8 hours[2]

If neurotoxicity is detected, urgent imaging is warranted (head CT and MRI, when feasible)[1]

Lumbar puncture may be warranted to identify infectious pathogens or other neurologic etiologies, cytokine levels, and CAR T cell levels in the CNS, when feasible[2]

Neurology consultation[2]

Before discharge from certified CAR T cell treatment center's care, it is important to educate patients and their caregivers about the symptoms of neurotoxicity, the need to monitor for these symptoms, and the importance of seeking immediate medical attention should symptoms arise, particularly those related to encephalopathy[1]

CT, computed tomography; MRI, magnetic resonance imaging

References: 1. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55. **2.** Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330.

Neurotoxicity Management

The primary treatment used to manage neurotoxicity associated with CAR T cell therapy is systemic corticosteroids[1]

- Continued until resolution of life-threatening toxicities and independent patient function restored

Antiepileptics may be used for patients with seizures[2]

Extreme cases may require intubation and mechanical ventilation for airway protection[2]

If a patient is experiencing both neurotoxicity and CRS, tocilizumab, corticosteroids, and antiepileptic medications may be needed[3-8]

References: 1. Brudno JN, Kochenderfer JN. *Blood* Rev. 2019;34:45-55. **2.** Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. **3.** National Institutes of Heath. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **4.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **5.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022. **6.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. **7.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2. **8.** National Institutes of Health. DailyMed. Accessed July 14, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189.

Neurotoxicity Grading Systems

There are multiple systems that can be used for grading neurotoxicity associated with CAR T cell therapy[1]

Systems For Grading Neurotoxicity Associated with CAR T Cell Therapy[1]

CTCAE | **CARTOX** | **ASTCT ICANS**

- ASTCT and CARTOX systems utilize screening tools to assess cognitive function:
  - ASTCT system uses a screening tool called the Immune Effector Cell-Associated Encephalopathy (ICE) screening tool[2]
  - CARTOX system uses a screening tool called CARTOX-10[3]

Neurotoxicity grading and treatment recommendations may differ by scale and by product. Treating healthcare providers should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

CARTOX-10, CARTOX 10-point neurological assessment

References: 1. Maziarz RT, et al. *Blood Adv*. 2020;4(7):1440-1447. 2. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. 3. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.

ICE Scoring Is Used in the ASTCT Consensus Grading for Neurologic Toxicity

Using the 10-point Immune Effector Cell-Associated Encephalopathy (ICE) Screening Tool, cognitive function is assessed across 5 domains for a maximum possible score of 10 points

Domain	Definition	Points
Orientation	Orientation to: year, month, city, hospital	4 total (1 point for each item)
Naming	Ability to name 3 objects (eg, point to clock, pen, button)	3 total (1 point for each item)
Following commands	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1
Writing	Ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1
Attention	Ability to count backwards from 100 by 10	1

ICE, Immune Effector Cell-Associated Encephalopathy

Reference: Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

CARTOX-10 Scoring Is Used in the CARTOX Grading for Neurotoxicity

CARTOX-10 uses a 10-point scale to assess alterations in concentration, speech, and writing ability that are associated with CAR T-cell-related encephalopathy syndrome (CRES)

Task	Points
Orientation to: year, month, city, hospital, and President/Prime Minister of country of residence	5 total (1 point for each item)
Ability to name 3 objects (e.g., point to clock, pen, button)	3 maximum points
Ability to write a standard sentence (e.g., “Our national bird is the bald eagle”)	1
Ability to count backwards from 100 by 10	1

CRES, CAR T-cell-related encephalopathy syndrome.

Reference: Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47–62.

Neurotoxicity[a] Grading Scales: ASTCT, CARTOX, CTCAE

CTCAE criteria are graded for each neurotoxicity domain (encephalopathy, seizure, dysphasia, tremor, headache, confusion, depressed level of consciousness, cerebral edema)

Grade	ASTCT Criteria[1,b]	CARTOX Criteria[2]	CTCAE, Version 5.0[3]
1	• ICE score: 7-9 • Awakens spontaneously	• CARTOX-10 score: 7-9 (mild impairment)	• Mild symptoms of encephalopathy or tremor • Brief partial seizure and no loss of consciousness • Awareness of receptive or expressive characteristics • Not impairing ability to communicate • Mild headache, mild disorientation, decreased level of alertness
2	• ICE score: 3-6 • Awakens to voice	• CARTOX-10 score: 3-6 (moderate impairment)	• Moderate encephalopathy, tremor, and/or pain symptoms limiting instrumental ADL • Brief generalized seizure • Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously • Moderate disorientation and/or slow response to stimuli limiting instrumental ADL; sedation
3	• ICE score: 0-2 • Awakens only to tactile stimulus • Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention • Focal/local edema on neuroimaging[c]	• CARTOX-10 score: 0-2 (severe impairment) • Stage 1-2 papilledema[d] or CSF opening pressure <20 mmHg • Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	• Severe encephalopathy, tremor, pain, or disorientation symptoms limiting self-care ADL • New-onset seizures (partial or generalized) • Multiple seizures despite medical intervention • Severe receptive or expressive characteristics, impairing ability to read, write or communicate intelligibly • Difficult to arouse • New onset cerebral edema/worsening from baseline
4	• ICE score: 0 (unarousable and unable to perform ICE) • Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between • Deep focal motor weakness such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	• Critical condition, and/or obtunded and cannot perform assessment of CARTOX-10 tasks • Stage 3-5 papilledema[d] or CSF opening pressure ≥20 mmHg, or cerebral edema • Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness	• Life-threatening consequences from encephalopathy, seizure, confusion, depressed level of consciousness and/or cerebral edema; coma; prolonged repetitive seizures • Urgent intervention indicated
5	• Death	• Death	• Death

[a]ASTCT guidelines refer to neurotoxicity as immune effector cell-associated neurotoxicity syndrome (ICANS); CARTOX guidelines refer to neurotoxicity as CAR T cell-related encephalopathy syndrome (CRES). [b]Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication). Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. [c]Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0. [d]Papilledema grading is performed according to the Modified Frisén scale.

References: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **2.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47–62. **3.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). V5.0. Accessed Aug 5, 2021. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. 4. Frisen L. *J. Neurol. Neurosurg. Psychiatry.* 1982;45:13–18.

Management of Neurotoxicity[a,b]: ASTCT and CARTOX

Grade	ASTCT [1]	CARTOX[2]
1	• Aspiration precautions and IV hydration • Seizure prophylaxis w/ levetiracetam • EEG • Brain imaging • Consider tocilizumab if there is concurrent CRS	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing; convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam or haloperidol can be used, with careful monitoring, for agitated patients • Neurology consultation; fundoscopic exam to assess for papilledema • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if patient has focal peripheral neurological deficits; CT scan can be performed if MRI is not feasible • Daily 30 min EEG until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam; if EEG shows non-convulsive status epilepticus, treat as per CARTOX recommendations • Consider anti-IL-6 therapy with tocilizumab or siltuximab, if CRES is associated with concurrent CRS
2	• Supportive care as in grade 1 • Consider dexamethasone or methylprednisolone equivalent	• Supportive care and neurological work-up as described for grade 1 CRES • Tocilizumab or siltuximab if associated with concurrent CRS • Dexamethasone or methylprednisolone if refractory to anti-IL-6 therapy, or for CRES without concurrent CRS • Consider transferring patient to ICU if CRES associated with grade ≥2 CRS
3	• Supportive care as in grade 1 • Dexamethasone (or methylprednisolone equivalent) • Seizure control with benzodiazepines (short-term) and levetiracetam ± phenobarbital and/or lacosamide • High-dose methylprednisolone for focal/local edema	• Supportive care and neurological work-up as indicated for grade 1 CRES; ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS, as described for grade 2 CRES and if not administered previously • Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy, or for CRES without concurrent CRS; continue corticosteroids until improvement to grade 1 CRES and then taper • Stage 1 or 2 papilledema with CSF opening pressure <20 mmHg should be treated as CARTOX recommendations • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 CRES
4	• Supportive care as in grade 1 • High-dose methylprednisolone • Seizure control as per grade 3 • Spine imaging for focal motor weakness • Lower intracranial pressure by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema	• Supportive care and neurological work-up as outlined for grade 1 CRES • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 CRES • High-dose corticosteroids continued until improvement to grade 1 CRES and then taper • For convulsive status epilepticus or stage ≥3 papilledema, with a CSF opening pressure ≥20 mmHg or cerebral edema, treat as per CARTOX recommendations

[a]CTCAE guidelines do not provide management strategies for neurotoxicities; [b]ASTCT guidelines refer to neurotoxicity as immune effector cell-associated neurotoxicity syndrome (ICANS); CARTOX guidelines refer to neurotoxicity as CAR T cell-related encephalopathy syndrome (CRES).
CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.
References: 1. Neelapu SS. *Hematol Oncol.* 2019;37 Suppl 1:48-52. **2.** Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47–62.

Summary

Serious life-threatening reactions that may lead to death are known to occur with CAR T cell therapies

Two of the most serious adverse events are CRS and neurotoxicity

CRS and neurologic toxicity are largely treatable and reversible

Current management strategies involve:

- Careful monitoring
- Early recognition
- Prompt intervention with:
  - Supportive care for low-grade toxicities
  - Tocilizumab and/or corticosteroids for severe CRS
  - Corticosteroids and antiseizure medications for neurologic toxicities

Thank you for completing this module of CAR T Academy

We hope you found it informative and educational

Follow this link to download a printable acknowledgment of completion:

- **https://www.car-t-academy.com/pdf/car-t-academy-crs-and-neurotoxicity-acknowledgment.pdf**
- NOTE: Completion of CAR T Academy modules does not qualify as CME or any other type of accreditation

For more information and access to other CAR T Academy modules, please visit: https://www.car-t-academy.com/