ASCO® Guidelines

Management of Immune-Related Adverse Events in Patients Treated with Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline	
Cytokine Release Syndrome Recommendations	
Workup and Evaluation and Supportive Care Recommendations (all grades): • CBC, CMP, magnesium, phosphorus, CRP, LDH, uric acid, fibrinogen, PT/PTT, and ferritin • Assess for infection with blood and urine cultures, and a chest radiograph if fever is present • If patient is neutropenic, follow institutional neutropenic fever guidelines • Patients who experience grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. • Perform cardiac monitoring in patients who experience at least G2 CRS, clinically significant arrhythmia, and additionally as clinically indicated • Consider screening for CMV and EBV • Consider chest/abdominal CT imaging, brain MRI, and/or lumbar puncture.	
Grading (on the basis of ASTCT consensus grading)[1]	**Management**
G1: **Fever[a]:** temperature ≥38°C not attributable to any other cause **Hypotension:** none **Hypoxia:** none	• Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms. • May consider empiric broad-spectrum antibiotics and granulocyte colony-stimulating factor (G-CSF) if neutropenic. Note: GM-CSF is not recommended. • In patients with persistent (> 3 days) or refractory fever, consider managing as per G2.
G2: **Fever[a]:** temperature ≥38°C not attributable to any other cause ***Plus*** **Hypotension:** not requiring vasopressors ***And/or*** **Hypoxia:** Requiring low-flow nasal cannula (i.e. oxygen delivered at ≤ 6 L/min) or blowby	• Continue supportive care as per G1 and include IV fluid bolus and/or supplemental oxygen as needed. • Administer tocilizumab[2-4] 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of 3 doses in a 24-hour period, with a maximum of 4 doses total. • In patients with hypotension that persists after 2 fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to two doses and then reassess. • Manage per G3 if no improvement within 24 hours of starting tocilizumab.

G3: **Fever[a]:** temperature ≥ 38°C not attributable to any other cause ***Plus*** **Hypotension:** requiring a vasopressor with or without vasopressin ***And/or*** **Hypoxia:** Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	• Continue supportive care as per G2 and include vasopressors as needed. • Admit patient to ICU. • If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring. • Tocilizumab as per G2 if maximum dose not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve. • If refractory, manage as per G4.
G4: **Fever[a]:** temperature ≥ 38°C not attributable to any other cause ***Plus*** **Hypotension:** requiring multiple vasopressors (excluding vasopressin) ***And/or*** **Hypoxia:** Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	• Continue supportive care as per G3 plus mechanical ventilation as needed. • Administer tocilizumab as per G2 if maximum dose not reached within 24-hour period. • Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to G1. • If not improving, consider methylprednisolone 1000 mg IV 2 times a day or alternate therapy.[b]

Additional Considerations:

- Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
- CRS may be associated with cardiac, hepatic, and/or renal dysfunction.
- Earlier steroid use appears to reduce the rate of CAR T-cell treatment-related CRS and neurologic events and is recommended for some products (axicabtagene ciloleucel or bexucabtagene autoleucel).[5-7]
- Strongly consider antifungal prophylaxis in patients receiving steroids for the treatment of CRS and/or ICANS.

ICANS Recommendations

Workup/Evaluation and Supportive Care Recommendations (all grades):

- Routine neurological evaluation including the Immune ICE score for cognitive assessment and assessment of motor weakness conducted at least two times a day.
- Continually reassess for improvement or deterioration and escalate or de-escalate treatment and monitoring accordingly.
- Serial monitoring of laboratory tests including CRP, ferritin, CBC, CMP, fibrinogen, and PT/PTT.
- Consider seizure prophylaxis for CAR T-cell products known to be associated with ICANS or in patients at higher risk of seizure, such as those with prior seizure history, CNS disease, concerning EEG findings, or neoplastic brain lesions.[8-10]
- Initiate neurology consultation in patients with signs of neurotoxicity.
- Aspiration precautions, elevated head of bed.
- Neuroimaging of the brain (MRI with and without contrast or CT if MRI is not available/feasible) for ≥ G2 neurotoxicity. For persistent grade ≥ 3 neurotoxicity, consider repeat neuroimaging (MRI or CT) every 2-3 days.
- Lumbar puncture for ≥ G3 neurotoxicity and may consider for G2.
- EEG evaluation for unexplained altered mental status to assess seizure activity or for ≥ G2 neurotoxicity.
- Monitor and correct severe hyponatremia.

Management of Immune-Related Adverse Events in Patients Treated with Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline	
Grading (on the basis of ASTCT consensus grading)[1c]	**Management**
G1: **ICE score[d]:** 7-9 with no depressed level of consciousness	**No Concurrent CRS** • Offer supportive care with IV hydration and aspiration precautions. **With Concurrent CRS** • Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of four doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose.
G2: **ICE score[d]:** 3-6 ***And/or*** Mild somnolence awaking to voice	**No Concurrent CRS** • Offer supportive care as per G1. • For high-risk products or patients consider dexamethasone 10 mg IV × two doses (or equivalent) and reassess. Repeat every 6-12 hours if no improvement.[e] Rapidly taper steroids as clinically appropriate once symptoms improve to G1.[f] **With Concurrent CRS** • Consider ICU transfer if ICANS associated with ≥ G2 CRS. • Administer tocilizumab as per G1. • If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[e]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement togGrade 1, then rapidly taper as clinically appropriate.[f]
G3: **ICE score[d]:** 0-2 ***And/or*** Depressed level of consciousness awakening only to tactile stimulus ***And/or*** Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention ***And/or*** Focal/local edema on neuroimaging	**All G3 patients:** • Transfer patient to ICU. **No Concurrent CRS** • Administer dexamethasone (10 mg IV every 6-12 hours[e]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). **With Concurrent CRS** • Administer tocilizumab as per grade 1. • If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours [e]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, then rapidly taper as clinically appropriate.[f]

G4: **ICE score[d]:** 0 (patient is unarousable and unable to perform ICE) ***And/or*** Stupor or coma ***And/or*** Life-threatening prolonged seizure (> 5 min) or repetitive clinical or electrical seizures without return to baseline in between ***And/or*** Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, or papilledema, cranial nerve VI palsy, or Cushing's triad	**All G4 patients:** • Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection. **No Concurrent CRS** • Administer high-dose methylprednisolone IV 1000 mg one to two times per day for 3 days. • If not improving, consider 1000 mg of methylprednisolone two to three times per day or alternate therapy.[g] • Continue corticosteroids until improvement to grade 1, then taper as clinically appropriate.[f] • Status epilepticus to be treated as per institutional guidelines **With Concurrent CRS** • Administer tocilizumab as per Grade 1 in addition to methylprednisolone 1000 mg IV one to two times per day for 3 days • If not improving, consider 1000 mg of methylprednisolone IV two to three times a day or alternate therapy.[g] • Continue corticosteroids until improvement to grade 1, then taper as clinically appropriate.[f]

Notes:[1]

- Other signs and symptoms such as headache, tremor, myoclonus, asterixis, parkinsonism, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in the grading scale, careful attention and directed therapy may be warranted.
- A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
- Decreased level of consciousness should be attributable to no other cause (eg, no sedating medication).
- In cases of ICANS with concurrent CRS, tocilizumab use is directed at the concurrent CRS as tocilizumab has not been shown to mitigate neurologic toxicity.
- Because of the possibility that tocilizumab may worsen ICANS, the management of ICANS may take precedence over the management of low-grade CRS when the two occur simultaneously. For example, a patient with grade 2 ICANS and fever alone (grade 1 CRS) should be given steroids.

Management of Immune-Related Adverse Events in Patients Treated with Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

Hemophagocytic Lymphohistiocytosis (HLH) Recommendations

Workup and Evaluation: [11]

- CBC with differential and coagulation studies (PT, aPTT, fibrinogen, D-dimer)
- Liver function tests (ALT, AST, GGT, total bilirubin, albumin, and lactate dehydrogenase)
- Serum triglycerides (fasting) and serum ferritin
- Soluble IL-2 receptor alpha (sCD25 or sIL-2R), and/or CXCL9
- The following testing should be performed in all patients, based on the signs and symptoms of specific organ involvement and/or the degree of suspicion for the presence of HLH:[11]
  - Cultures of blood, bone marrow, urine, and cerebrospinal fluid (CSF); and viral titers and quantitative PCR testing for EBV, CMV, adenovirus, and other suspected viruses. Follow levels of any identified virus during treatment with the appropriate antiviral therapy.
  - Bone marrow aspirate and biopsy.
  - Electrocardiograph, chest radiography, and echocardiogram.
  - Lumbar puncture with CSF analysis.
  - Brain MRI scan, with and without contrast. Imaging of the CNS may show parameningeal infiltrations, subdural effusions, necrosis, and other abnormalities.

Grading	Management[12-14]
All Grades	• Offer supportive care. • Use corticosteroids if patient is deteriorating or unstable. • While data are insufficient to recommend a transfusion threshold, replacement of fibrinogen should be considered in patients with a fibrinogen level below 150 mg/dL. • Manage ≥G3 organ toxicity with IL-6 antagonist plus corticosteroids. • If insufficient response after 48 hours, consider adding anakinra.[15-17] • Etoposide could be considered in severe, refractory cases, although there is a lack of data in this setting and concern for effect on lymphocytes.[18-19] Intrathecal cytarabine, with or without hydrocortisone, may also be considered for patients with HLH-associated neurotoxicity.

Cytopenias Recommendations

Workup and Evaluation:

- CBC with differential, peripheral blood smear, reticulocyte count. If abnormalities are detected and further investigation is necessary for a diagnosis, proceed with bone marrow evaluation.

Grading	Management
G1: Anemia: LLN – 10.0 g/dL; neutropenia: > 1,500 per mm^3; thrombocytopenia: > 75,000 per mm^3	• Offer supportive care.
G2: Anemia: < 10.0-8.0 g/dL; neutropenia: >1,000 per mm^3; thrombocytopenia: > 50,000 per mm^3	• Offer supportive care and/or consider corticosteroids. • If improved to ≤ G1, taper steroids over 4-6 weeks

G3: Anemia: < 8.0/dL; neutropenia: > 500 per mm^3; thrombocytopenia: > 25,000 per mm^3 **G4:** Anemia:life-threatening; neutropenia: < 500 per mm^3; thrombocytopenia: < 25,000 per mm^3	• Critical care support. • Use high-dose methylprednisolone. • Consider growth factor support for neutrophil recovery, per institutional guidelines.
B-Cell Aplasia Recommendations	
Workup and Evaluation: • Full blood count	
Grading	**Management**[9, 20-22]
All Grades	• Recommend influenza and COVID vaccination of patients and family members. • Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until CD4 cell count is > 200 cells/μL. • Antifungal agents should be considered for high-risk patients including any patient receiving corticosteroids for management of CRS or ICANS. • G-CSF should be considered in patients after CRS with > 7 days of neutropenia.
G1: Asymptomatic, no intervention needed	• Offer supportive care
G2: Symptomatic (i.e. recurrent infections), non-urgent intervention indicated	• Consider treatment with IVIG replacement therapy at IgG levels < 400.
G3: Urgent intervention indicated **G4:** Life-threatening	• Consider treatment with IVIG replacement therapy at IgG levels < 400.
Disseminated Intravascular Coagulation (DIC) Recommendations	
Workup/Evaluation: Full blood count to assess platelet number, fibrinogen, PT, PTT, d-dimer. A test scoring system developed by the ISTH may be used to help determine if DIC is present.[63] The higher the score, the more likely it is that DIC is present.	
Grading	**Management**
G1: –	• Offer supportive care.
G2: Laboratory findings with no bleeding	• Use IL-6 antagonist with or without corticosteroids. • If improved to ≤ G1, taper steroids over 4-6 weeks.
G3: Laboratory findings with bleeding **G4:** Life-threatening; urgent intervention indicated	• Critical care support. • Use IL-6 antagonist and methylprednisolone IV 1,000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. • Consider replacement of fibrinogen in patients with a fibrinogen level below 150 mg/dL.

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Infections Recommendations	
Workup and Evaluation: • History and physical exam • Full blood count • Bacterial cultures and evaluation for other infection (fungal and viral)	
Grading	**Management**[9,20-22]
All Grades	• Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until CD4 cell count is > 200 cells/μL. • Antifungal agents should be considered for high-risk patients. • G-CSF should be considered in patients after CRS with > 7 days of neutropenia.
G1: Mild infection only	• Offer supportive care. • Empiric antimicrobials (antibiotics such as levofloxacin or ciprofloxacin, antifungals such as fluconazole or antivirals such as valacyclovir or acyclovir) should be considered upon onset of fever.
G2: Mild infection; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	• Start course of oral antimicrobials.
G3: Severe infection; IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	• Start IV antimicrobials.
G4: Life-threatening consequences; urgent intervention indicated	• Critical care support.

Footnotes:

[a]Fever is not required to grade subsequent CRS severity in patients who receive antipyretics or anticytokine therapy (steroids or tocilizumab). Instead, CRS grading is driven by hypotension and/or hypoxia.[1]

[b]Noting limited experience with other agents, alternate options may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, and ATG. [6,15,23]

[c]For children age <12 years, the CAPD is recommended to aid in the overall grading of ICANS. [24-26] A CAPD score of ≥ 9 is suggestive of delirium and should be considered grade 3 ICANS. The CAPD score also may be used in patients age >12 years with baseline developmental delay as it has been validated up to age 21 years.

[d]**Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool:**[1]

- Orientation: orientation to year, month, city, hospital: 4 points
- Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
- Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- Attention: ability to count backwards from 100 by 10: 1 point

[e]For some products that may be associated with more neurotoxicity (axicabtagene ciloleucel or bexucabtagene autoleucel) earlier administration of steroids starting at G1 ICANS and use of high dose steroids at G3 may be an option.[5-7]

[f]ICANS flares have been reported with rapid steroid taper.[27] Close monitoring for ICANS relapse is encouraged during steroid taper.[27]

[g]Noting limited experience with other agents, alternate options for persistent or worsening ICANS may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, ATG, or intrathecal hydrocortisone (50 mg) plus methotrexate (12 mg). [6,16]

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ASTCT, American Society of Transplantation and Cellular Therapy; ATG, antithymocyte globulin; BiPAP, bilevel positive airway pressure; CAPD, Cornell Assessment of Pediatric Delirium; CAR T, chimeric antigen receptor; CBC, complete blood count; CD4, cluster of differentiation; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CNS, central nervous system; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; EEG, electroencephalogram; G, grade; G-CSF, granulocyte-colony stimulating factor; GGT, gamma-glutamyl transferase; GM-CSF, granulocyte-macrophage colony-stimulating factor; h, hours; HLH,

hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune Effector Cell-Associated Encephalopathy; ICU, intensive care unit; IgG, immunoglobulin G; IL, interleukin; ISTH, International Society on Thrombosis and Haemostasis; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LLN, lower limit of normal; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia; PT, prothrombin time; PTT, partial thromboplastin time

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