IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

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CAR = chimeric antigen receptor
CRS = cytokine release syndrome
ICANS = immune effector cell-associated neurotoxicity syndrome
IEC = immune effector cells
GVHD = graft versus host disease

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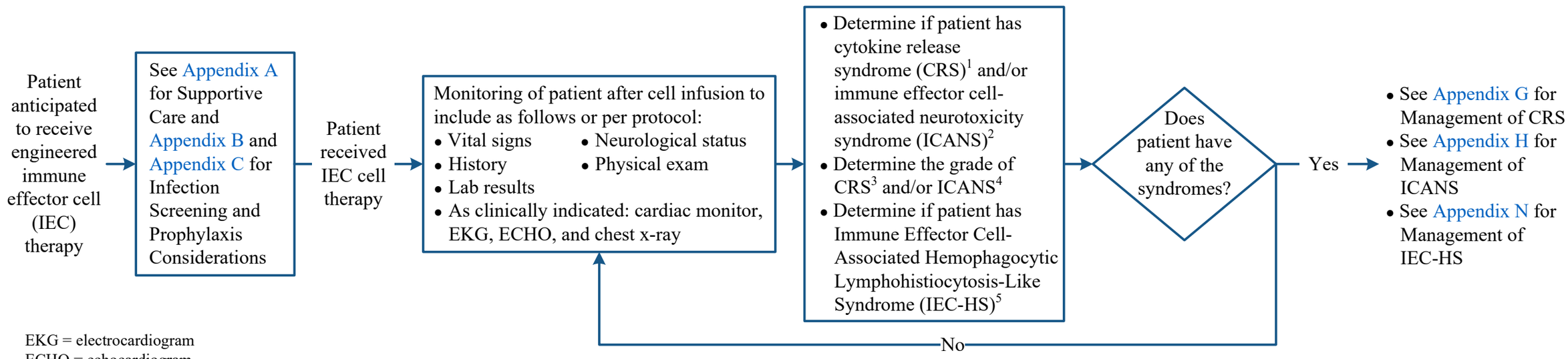
INITIAL EVALUATION

MANAGEMENT



EKG = electrocardiogram
ECHO = echocardiogram

[1] If the subject has fever with or without hypotension or hypoxia within the first 4 weeks of IEC therapy, the subject may have CRS if the symptoms or signs are not attributable to any other cause
- Fever should be present at onset of CRS (temperature ≥ 38°C)
- Hypotension (requiring IV fluids or vasopressors to maintain normal blood pressure)
- Hypoxia (requiring supplemental oxygen to correct a deficit in oxygenation)

[2] If the subject has any of the following within the first 8 weeks of engineered IEC-therapy, the subject may have ICANS if the symptoms or signs are not attributable to any other cause
- IEC-Associated Encephalopathy (ICE) Score of < 10 (Appendix F)
- Depressed level of consciousness
- Convulsive or non-convulsive seizures (can be focal or generalized)
- Motor weakness (can be focal motor weakness, hemiparesis, paraparesis)
- Focal/diffuse cerebral edema on imaging or signs of raised intracranial pressure including decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

[3] See Appendix D for Grading of CRS
[4] See Appendix E for Grading of ICANS
[5] See Appendix N for diagnosis of IEC-HS

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX A: Checklist/Supportive Care Considerations for Managing Patients Receiving IEC Therapy

For Inpatients or Outpatients:

Before and During IEC Infusion (unless otherwise specified by a research protocol)

- Imaging of the brain prior to IEC infusion (preferably MRI with and without contrast but CT without contrast is acceptable if MRI cannot be performed) to rule out any central nervous system (CNS) disease and also to serve as a baseline for comparison in case the patient develops ICANS (within 1 month prior to IEC)
  - For patients with known history of seizures, migraines and/or other CNS disorders including malignant disease, consider Neurology consult prior to IEC infusion
- Central venous access with port-a-cath or double/triple lumen catheter is recommended for IEC infusion as well as for IV fluids and other infusions in case of toxicities
- IEC infusion may be administered either in the ambulatory unit or in the inpatient unit
- If the median time to onset of CRS is expected to be < 48 hours, hospitalization should be considered for IEC infusion
- When hospitalized, recommend admission to an IEC-designated unit with capability for cardiac monitoring by telemetry
- Tumor lysis precautions for patients with high tumor burden, as per standard guidelines (see Tumor Lysis Syndrome (TLS) in Adult Patients algorithm)
- Seizure prophylaxis with levetiracetam 500-750 mg PO every 12 hours for 30 days, starting on the day of infusion for IEC therapies associated with a high incidence of ICANS, and in patients with history of seizures or brain metastases
- Filgrastim or filgrastim biosimilar products may be used if not prohibited by product/protocol if patient is neutropenic and concern for infection (if not already receiving)
  - For the acute lymphocytic leukemia (ALL) indication, may start filgrastim/filgrastim biosimilar Day 14 post IEC if counts have not recovered
- Ensure appropriate documentation in EHR regarding IEC therapy and "conditional" corticosteroid contraindication

Supportive Care for FDA approved CAR T-cell products

	Axicabtagene Ciloleucel and Brexucabtagene Autoleucel	Tisagenlecleucel, Lisocabtagene Maraleucel, Idecabtagene Vicleucel and Ciltacabtagene Autoleucel
Seizure prophylaxis[1]	Levetiracetam **750 mg PO twice daily** from Day 0 to Day +30, then 750 mg PO daily for 3 days, then stop	Levetiracetam **500 mg PO twice daily** from Day 0 to Day +30, then 500 mg PO daily x 3 days, then stop

[1] Levetiracetam may require dose adjustment in renal insufficiency. Dose and stop dates may vary depending on the patient's neurological status. If any seizure activity, involve Neurology for taper.

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APPENDIX A: Checklist / Supportive Care Considerations for Managing Patients Receiving IEC Therapy - continued

For Outpatients:

Patient Monitoring After IEC infusion (unless otherwise specified by a research protocol)

- Monitor for at least 10 to 14 days post IEC infusion
  - For patients with ALL, monitor daily for 14 days if discharged prior to Day 14
- Assess and record vital signs at least once daily in clinic
- Daily weights
- Daily review of patient history and physical examination
- Daily complete blood count with differential and complete metabolic profile
- Coagulation profile at least twice weekly
- Consider monitoring C-reactive protein (CRP) and ferritin levels daily during the phase when CRS is likely to occur and then as needed thereafter
- Consider cytokine panel and CAR T-cell levels if clinically indicated
- Assessment and grading of CRS (document in CARTOX flowsheet) at least daily and if a change in patient status while in clinic
- Assessment and grading for ICANS (document in CARTOX flowsheet) at least daily including 10-point ICE score assessment
- Assessment for IEC-HS until at least Day 30 (or longer if clinically indicated)
- For ciltacabtagene autoleucel, monitor for movement and neurocognitive treatment-emergent adverse events (MNTs), which generally occurs between Days 27 to 100, but may occur earlier (see Appendix M)

Supportive Care

- Encourage oral fluid intake to ensure adequate hydration
- IV fluids as needed

Patient Home Monitoring *(provide patient with a log to document and bring daily to clinic visits; dictate the findings from home log in each clinic note)*

- Provide patient with self-care instructions and team contact information
- Provide patient with guidance for when to report to the Acute Cancer Care Center
- Oral temperature every evening
- ICE-score with sentence writing every evening

Considerations for Admission

- Temperature ≥ 38°C
- SBP < 90 mmHg
- New arrhythmia
- Upward trend in liver function tests and/or creatinine
- Oxygen saturation < 92% on room air and/or shortness of breath
- Tremors or jerky movements in extremities
- Grade 1 CRS or greater
- Grade 1 ICANS or greater
- Signs of IEC-HS

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APPENDIX A: Checklist / Supportive Care Considerations for Managing Patients Receiving IEC Therapy - continued

For Inpatients:

Patient Monitoring After IEC infusion (unless otherwise specified by a research protocol)

- Assess vital signs every 4 hours (inpatient encounter)
- Strict monitoring of oral and IV fluid input and output (including urine and stool)
- Daily measurement of body weight
- Daily review of patient history and physical examination
- Daily complete blood count with differential and complete metabolic profile
- Coagulation profile at least twice weekly or more frequently if clinically indicated
- Consider monitoring C-reactive protein (CRP) and ferritin levels daily during the phase when CRS is likely to occur and continue to monitor until CRS and/or ICANS resolves (if present). Monitor as needed thereafter.
- Consider cytokine panel and CAR T-cell levels if clinically indicated
- Assessment and grading of CRS (document in CARTOX flowsheet) should be completed at least every 12 hours and whenever there is a change in patient's status
- Assessment and grading for ICANS (document in CARTOX flowsheet) should be completed at least every 12 hours including the 10-point ICE score assessment while awake
- Maintenance IV fluids with normal saline to ensure adequate hydration
- Cardiac monitoring by telemetry is recommended as follows:
  - Upfront (Day 0) for patient > 70 years old or significant cardiac history (*e.g.,* arrythmia, pacemaker, cardiac involvement of tumor, pericardial effusion, *etc*.)
  - Otherwise, start telemetry if ≥ Grade 1 CRS and continue until CRS resolves
- For post-IEC infusion headache that is unresponsive to analgesics, consider brain imaging and lumbar puncture
- Neurology consult recommended for patients who develop Grade 1 or higher ICANS
- Critical Care and/or MERIT team will follow patients on an as-needed basis
- Infectious Diseases team will follow patients on an as-needed basis
  - Consult should be performed early for patients with positive infectious disease screening or for persistent fevers

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APPENDIX A: Checklist / Supportive Care Considerations for Managing Patients Receiving IEC Therapy - continued

For Inpatients - continued:

Notifications and contingency orders

- Notify primary physician on detection of any of the following:
  - SBP > 140 or < 90 mmHg
  - Heart rate > 120 or < 60 beats per minute or arrhythmia
  - Respiratory rate > 25 or < 12 breaths per minute
  - Oxygen saturation < 92% on room air
  - Urine output < 1,500 mL/24 hours or 60 mL/hour
  - Upward trends in creatinine or liver function tests
  - Tremors or jerky movements in extremities
  - Change in mental status (alertness, orientation, speech, ability to write a sentence, or ICE score of < 10)
- For temperature ≥ 38.3°C, send blood cultures (central and peripheral) and urine for urinalysis and culture, obtain portable chest x-ray, and notify provider
  - If temperature ≥ 38°C, notify provider
- For patients with neutropenia and fever, start empiric broad-spectrum antibiotics
- Do not administer corticosteroids unless approved by physician
- If patient develops ICANS, withhold oral intake of food, fluids, and medicines, elevate head of bed 30 degrees, and notify physician
- PRN medications
  - Acetaminophen (1st choice) or ibuprofen (2nd choice, if not contraindicated) for fever ≥ 38.3°C
  - Cooling blanket for fever ≥ 38.3°C
  - Crystalloid fluids (normal saline, Lactated Ringer's, or Plasma-Lyte) 500-1,000 mL bolus PRN for hypotension; may repeat once if patient remains hypotensive after 1st bolus
  - Transfuse packed red blood cells (PRBC) to maintain hemoglobin at least > 7 gm/dL
  - Transfuse platelets to maintain > 10 K/microliter; for patients with abnormal brain imaging, see recommendations as in Grades 3 and 4 ICANS
  - PRN tocilizumab to be activated only on physician order ("ok to give tocilizumab" order should be placed if dose approved by physician)

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX B: Infectious Disease Screening (within 30 days prior to apheresis is recommended)

Required Infectious Disease Screening[1]	Optional Infectious Disease Screening (as clinically indicated)[2]
• Hepatitis B surface antigen (HBsAg) • Anti-hepatitis B core antibody (HBcAb) • Anti-hepatitis C virus antibody (HCVAb) • Anti-human immunodeficiency virus (HIV) antibody (HIV type 1 / 2 type O Ab) • HIV-1 / HCV / HBV Nucleic Acid Test • Cytomegalovirus (CMV) IgG and IgM	• Anti-human T-cell lymphotrophic virus (HTLV) antibody (HTLV I/II Ab) • Rapid Plasma Reagin (RPR) – syphilis • West Nile Virus nucleic acid test • T Cruzi antibody • Strongyloides antibody to assess for previous infection or exposure • T-spot to assess for exposure or history of tuberculosis • Herpesvirus 6 Ab panel[3] (HHV-6 IgG)

[1] Primary team should follow up on all testing and order follow up testing (*e.g.*, PCR, titer for positive screening) and consults as indicated prior to proceeding to IEC therapy
[2] Patients with recent travel out of the country should be considered for some/all of these additional tests
[3] Recommended for patients with hematologic malignancies prior to the start of lymphodepletion

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy

Most patients who receive immune effector cells receive a fludarabine-based chemotherapy regimen prior to IEC infusion. Fludarabine causes immunosuppression and can increase the risk of opportunistic infections. Additionally, patients who receive IEC therapies targeting B-cell are at increased risk of infection due to B-cell aplasia.

Prophylaxis	Preferred Medication	Alternative Medication(s)	Start	Stop	Comment
Viral • Herpes simplex • Varicella zoster	Valacyclovir[1] 500-1,000 mg PO daily	Acyclovir[1] 400-800 mg PO twice daily	IEC infusion day	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	-
Hepatitis B (only for patients who are positive for HBsAg or HBcAb)	Entecavir[1] 0.5 mg PO daily	Tenofovir alafenamide 25 mg PO daily **or** Tenofovir disoproxil fumarate[1] 300 mg PO daily	2 weeks before IEC	12-24 months post IEC	• Consider Infectious Disease and/or Hepatology consult if not already following • Monitor HBV DNA PCR once a month while on prophylaxis and for a year after stopping • Consult Infectious Diseases if entecavir cannot be used or if DNA PCR detectable
Bacterial (if neutropenia with ANC < 1 K/microliter is expected to last ≥ 7 days)	Levofloxacin[1] 500 mg PO or IV daily	Cefpodoxime[1,2] 200 mg PO twice daily **or** Ciprofloxacin[1] 500 mg PO twice daily	IEC infusion day or when ANC ≤ 0.5 K/microliter	Continue until ANC > 0.5 K/microliter for 3 consecutive days without growth factor support	Consult Infectious Diseases if patient is allergic to quinolones and cephalosporins

ANC = absolute neutrophil count
[1] Adjust for renal function
[2] Cefpodoxime does not cover *Pseudomonas*

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APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy - continued

Most patients who receive immune effector cells receive a fludarabine-based chemotherapy regimen prior to IEC infusion. Fludarabine causes immunosuppression and can increase the risk of opportunistic infections. Additionally, patients who receive IEC therapies targeting B-cell are at increased risk of infection due to B-cell aplasia.

Prophylaxis	Prior to Count Recovery	Start 3 to 4 Weeks After IEC	Stop	Comment
Pneumocystis jiroveci	Pentamidine inhaled or IV[1] within one week (before or after) IEC infusion	**Preferred:** Sulfamethoxazole/trimethoprim (SMZ/TMP): • 1 double strength tablet PO every Monday, Wednesday, Friday **or** • 1 single strength tablet PO daily	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	SMZ/TMP also has activity against *Toxoplasma* and *Nocardia*
		Alternative: Pentamidine inhaled 300 mg flat dose every 28 days	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	Albuterol nebulizer premedication encouraged
		Alternative: Pentamidine[1] IV 4 mg/kg (max 300 mg) every 21 days	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	Can cause pancreatitis
		Alternative: Dapsone 100 mg PO daily or 50 mg PO every 12 hours	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	• Check G6PD level • Use caution if patient has sulfa allergy • Can cause hemolytic anemia
		Alternative: Atovaquone 1,500 mg PO daily	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	• Must take with a fatty meal • Also has activity against *Toxoplasma*, but inferior to SMZ/TMP

[1] Adjust for renal function

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IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy - continued

Prophylaxis	Preferred Medication	Alternative Medication	Start	Stop
Fungal (low risk)	Fluconazole[1,2] 200-400 mg PO or IV daily	Caspofungin[2] 50 mg IV daily	IEC infusion day or when ANC ≤ 0.5 K/microliter	Continue until ANC > 0.5 K/microliter for 3 consecutive days without growth factor support
Fungal (high risk)[3]	Posaconazole[2] 300 mg PO (as tablets) or IV daily	Caspofungin[2] 50 mg IV daily	IEC infusion day or when high-risk criteria are met	Continue as clinically indicated[3]
HIV	Antiretroviral Therapy (ART) and monitoring per Infectious Diseases (ID) recommendations. Obtain an ID consult on any patient with HIV.			
HHV-6	Monitor HHV-6 by quantitative PCR from blood plasma once weekly if neutropenia lasts ≥ 14 days, if patient experiences Grade 3 or 4 CRS/ICANS, if patient receives ≥ 3 days of corticosteroids, or if patient develops HLH[4]. HHV-6 monitoring is recommended for at least 30 days after completion of corticosteroids.			
CMV	**CMV prophylaxis:** Routine CMV prophylaxis is not recommended. **Pre-emptive CMV monitoring**: • CMV PCR once weekly through at least Day +30 is recommended in all CMV IgG seropositive patients • CMV PCR once weekly through at least Day +30 is recommended in all multiple myeloma patients regardless of CMV serostatus • Continued once weekly CMV PCR monitoring is recommended for the following patients: CMV IgG seropositive or multiple myeloma, lymphoma, and leukemia patients who received ≥ 3 days of corticosteroids for CRS, ICANS, or IEC-HS. Patients should continue CMV PCR weekly for at least 30 days after the completion of corticosteroids.			
Immunoglobulin replacement therapy	Hypogammaglobulinemia may be observed after IEC therapies that target B-cells and IgG levels should be checked in such patients when they develop respiratory infections. Immunoglobulin replacement therapy and/or prophylaxis is only indicated for patients who develop hypogammaglobulinemia and recurrent infections, with the exception of multiple myeloma patients who may receive routine prophylaxis.			
Prolonged cytopenias	Grade 3 or 4 cytopenias lasting beyond Day 30 have been reported in approximately 30% of patients after IEC therapies. Cytopenias may be managed, when not prohibited, with filgrastim/pegfilgrastim or filgrastim/pegfilgrastim biosimilar products; monitor blood counts at least weekly. Continue appropriate prophylactic antimicrobials as described above. Diagnostic bone marrow may be performed to rule out other causes such as myelodysplasia, malignancy, HLH[4], or infection.			

HHV-6 = Herpesvirus 6 HIV = Human Immunodeficiency Virus HLH = hemophagocytic lymphohistiocytosis

[1] Adjust for renal function

[2] Loading dose of antifungals is not needed if it is being used for prophylaxis

[3] Posaconazole prophylaxis is recommended for HIGH RISK patients with leukemia, recent allogenic stem cell transplant, prior history of mold infection, neutropenia lasting ≥ 14 days, Grade 3 or 4 CRS/ICANS and receives ≥ 3 days of corticosteroids, or those who develop hemophagocytic lymphohistiocytosis (HLH) (see Appendix N). If corticosteroids are given, continue posaconazole for at least 1 month AFTER COMPLETION of corticosteroids. Do not stop posaconazole prophylaxis if ANC < 1 K/microliter. Voriconazole or isavuconazole may be used if the patient had previously been taking them or if posaconazole is not covered by insurance. In the event posaconazole, voriconazole, isavuconazole, or an echinocandin are contraindicated or pose affordability/access issues, then use fluconazole for prophylaxis and consider aspergillus antigen testing at least once a week DURING corticosteroids and for at least a month AFTER completion of corticosteroids. Patients not meeting high risk definitions will be considered to be at LOW RISK for fungal infections and receive prophylaxis as detailed above.

[4] See Appendix N for Diagnostic Criteria for IEC-associated Fulminant Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS)

APPENDIX D: American Society for Transplantation and Cellular Therapy (ASTCT) Grading for CRS[1]

(Note: CRS grade should be determined at least twice daily and any time there is a change in patient's status)

CRS Parameter	CRS Grade 1	CRS Grade 2	CRS Grade 3	CRS Grade 4
Fever[2]	Yes	Yes	Yes	Yes
		With		
Hypotension[3]	No	Requiring IV fluids but not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/Or		
Hypoxia[3]	No	Requiring low-flow O_2 via nasal cannula[4] or blow-by	Requiring O_2 via high-flow nasal cannula[4], facemask, non-rebreather mask, or Venturi mask	Requiring O_2 via positive pressure (*e.g.,* CPAP, BiPAP, and mechanical ventilation)

CPAP = continuous positive airway pressure
BiPAP = bilevel positive airway pressure

[1] Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading
[2] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as anakinra, tocilizumab or corticosteroids within 24 hours, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[3] 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 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.
[4] Low-flow nasal cannula is defined as oxygen (O_2) delivered at ≤ 6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics.
High-flow nasal cannula is defined as oxygen delivered at > 6 liters/minute.

APPENDIX E: American Society for Transplantation and Cellular Therapy (ASTCT) Grading of ICANS[1]

Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[2]	7-9	3-6	0[3]-2	0[3] (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[4]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	-	-	Any clinical seizure (focal or generalized) that resolves rapidly (< 5 minutes) or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (≥ 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[5]		-	-	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure[6] / cerebral edema			Focal/local edema on neuroimaging[7]	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

EEG = electroencephalogram

[1] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause). For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.
[2] See Appendix F for Immune Effector Cell-associated Encephalopathy (ICE) Score
[3] A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia or Grade 4 ICANS if the patient is unarousable
[4] Depressed level of consciousness should not be attributable to any other cause (*e.g.,* sedating medication)
[5] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading
[6] Ophthalmology may be consulted to assess for papilledema if concern for elevated intracranial pressure (ICP), but otherwise not needed for all patients
[7] 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.

APPENDIX F: Immune Effector Cell-associated Encephalopathy (ICE) Score

- **Orientation:** Orientation to year, month, city, hospital: 4 points (1 point each)
- **Naming:** Name 3 objects (*e.g.,* clock, pen, button): 3 points (1 point each)
- **Following commands:** (*e.g.,* Show me 2 fingers or close your eyes and stick out your tongue): 1 point
- **Writing:** Ability to write a standard sentence (*e.g.,* Our national bird is the bald eagle): 1 point
- **Attention:** Count backwards from 100 by 10: 1 point

Score 10: No impairment
Score 7-9: Grade 1 ICANS
Score 3-6: Grade 2 ICANS
Score 0-2: Grade 3[1] ICANS
Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

[1] A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia or may be classified as having Grade 4 ICANS if the patient is unarousable

APPENDIX G: Management of CRS

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 1	**Fever**	• Assess for infection with blood and urine cultures, and chest radiography • Cardiac telemetry and pulse oximetry	• Acetaminophen and hypothermia blanket as needed for the treatment of fever • Ibuprofen if fever is not controlled with above; use with caution or avoid with thrombocytopenia or renal dysfunction • Empiric broad-spectrum antibiotics and consider filgrastim or filgrastim biosimilar products if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines • If not on seizure prophylaxis, initiate levetiracetam[1] 500 mg-750 mg PO twice daily • Cardiac monitoring, if not already in place	Consider tocilizumab[2] for 1 dose for persistent fever lasting > 1 (for high risk[3] disease) to 3 days

[1] Levetiracetam may require dose adjustment in renal insufficiency
[2] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents
[3] High risk = high tumor burden and/or high baseline inflammatory markers

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APPENDIX G: Management of CRS - continued

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 2	**Hypotension**	• Cardiac telemetry • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• IV fluid bolus of 500-1,000 mL crystalloid fluids (normal saline, Lactated Ringer's, or Plasma-Lyte); repeat once as needed to maintain normal BP • If hypotension persists after IV fluids, tocilizumab, and dexamethasone, start vasopressors, transfer patient to ICU, obtain ECHO, and refer to further management as in Grade 3 or 4 CRS • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Administer tocilizumab[1] for 1 dose **and** consider dexamethasone 4-10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated ◦ Tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period ◦ If a second dose of tocilizumab is needed, it is necessary to give dexamethasone 4-10 mg IV for 1 dose • Consider anakinra for patients who are refractory to anti-IL-6 therapy and corticosteroids (defined as ongoing grade 2-4 CRS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.*, psychosis)
	Hypoxia	• Pulse oximetry • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• Use supplemental oxygen as needed • If hypoxia persists after above interventions, but oxygen requirement is stable with low-flow nasal cannula, continue close monitoring. If oxygen requirement increases to high-flow nasal cannula, face mask, or positive pressure ventilation, refer to further management as in Grade 3 or 4 CRS • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	

[1] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

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APPENDIX G: Management of CRS - continued

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 3	**Hypotension**	• Obtain ECHO if not performed already • Cardiac telemetry • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• Transfer patient to ICU • IV fluid boluses as needed as in Grade 2 CRS • Use vasopressors as needed • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 CRS if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Consider anakinra for patients who are refractory to anti-IL-6 therapy and corticosteroids (defined as ongoing grade 2-4 CRS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.*, psychosis) • If on one vasopressor: tocilizumab as in Grade 2 CRS and dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) • If on two vasopressors: tocilizumab as in Grade 2 CRS and dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) • If vasopressin and norepinephrine equivalent[2] is ≥ 15 mcg/minute, follow as in Grade 4 CRS • Once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Hypoxia	• Pulse oximetry • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• Supplemental oxygen including high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask as needed • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] and dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Consider anakinra for patients who are refractory to anti-IL-6 therapy and corticosteroids (defined as ongoing grade 2-4 CRS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.*, psychosis) • If there is no improvement in hypoxia within 24 hours or there is rapid progression of pulmonary infiltrates or sharp increase in FiO_2 requirements, increase dexamethasone to 20 mg IV every 6 hours (or methylprednisolone equivalent) • Once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation

[1] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

[2] VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (mcg/minute)] + [dopamine (mcg/kg/minute) / 2] + [epinephrine (mcg/minute)] + [phenylephrine (mcg/minute) / 10]

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APPENDIX G: Management of CRS - continued

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 4	**Hypotension**	• Obtain ECHO if not performed already • Cardiac telemetry • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• Transfer patient to ICU • IV fluid boluses as needed as in Grade 2 CRS • Vasopressors as in Grade 3 CRS • Use vasopressors as needed • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 CRS if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Consider anakinra for patients who are refractory to anti-IL-6 therapy and corticosteroids (defined as ongoing grade 2-4 CRS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.*, psychosis) • Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by rapid taper as per clinical situation • If hypotension is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix I) including activation of safety switches if applicable
	Hypoxia	• Monitor oxygen saturation while on mechanical ventilation • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• Transfer patient to ICU • Positive pressure ventilation including CPAP, BiPAP, mechanical ventilation • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 CRS if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Consider anakinra for patients who are refractory to anti-IL-6 therapy and corticosteroids (defined as ongoing grade 2-4 CRS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.*, psychosis) • Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by rapid taper as per clinical situation • If hypoxia is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix I) including activation of safety switches if applicable

[1] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

APPENDIX H: Management of ICANS

ICANS Grade	Sign or symptom	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 1	Encephalopathy and/or depressed level of consciousness	• MRI imaging of the brain with and without contrast; CT of brain without contrast may be performed if MRI is not feasible; MRI spine if focal deficits are noted • Neurology consultation • ICE Score assessment every 6 hours or more frequently if clinically indicated • EEG • Consider diagnostic lumbar puncture if other causes of encephalopathy are suspected (*e.g.,* infections, autoimmune, leptomeningeal disease) ◦ Add a meningitis-encephalitis panel from CSF in patients with neurologic symptoms that persist or worsen after ICANS therapy and/or if symptoms start after corticosteroids	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food/medications/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 after EEG is performed (0.25-0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) may be used with careful monitoring for agitated patients • If no seizures on EEG, continue prophylactic levetiracetam • If EEG shows focal or generalized convulsive or non-convulsive seizure or convulsive status epilepticus, refer to further management as in Grade 3 or 4 ICANS	• Consider dexamethasone 4-10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated ◦ If associated with concurrent CRS, add tocilizumab[1]

CSF = cerebrospinal fluid

[1] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

Continued on next page

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX H: Management of ICANS - continued

ICANS Grade	Sign or symptom	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 2	Encephalopathy and/or depressed level of consciousness	Neurological work-up as in Grade 1 ICANS	Supportive care as in Grade 1 ICANS	• Dexamethasone 4-10 mg IV every 6 to 12 hours (or methylprednisolone equivalent) ◦ If associated with concurrent CRS, add tocilizumab[1] • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation • Consider anakinra for patients who are refractory to corticosteroids (defined as ongoing grade 2-4 ICANS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.,* psychosis)

[1] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

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APPENDIX H: Management of ICANS - continued

ICANS Grade	Sign or symptom	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 3	Encephalopathy and/or depressed level of consciousness	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging (CT or MRI) every 2-3 days for persistent ≥ Grade 3 encephalopathy • Consider diagnostic lumbar puncture if Grade 3 encephalopathy persists ≥ 2 days or earlier if other causes are suspected (*e.g.,* infections, autoimmune, leptomeningeal disease) ◦ Add a meningitis-encephalitis panel from CSF in patients with neurologic symptoms that persist or worsen after ICANS therapy and/or if symptoms start after corticosteroids	• Supportive care as in Grade 1 ICANS • Consider ICU transfer • If there are new abnormal findings on brain imaging[1] not related to primary malignancy, control hypertension with the goal of maintaining mean arterial pressure (MAP) within 20-25 mmHg of baseline MAP; correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets > 20-50 K/microliter, fibrinogen > 200 mg/dL and INR < 1.5)	• Dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) ◦ If associated with concurrent CRS, add tocilizumab[2] • Consider anakinra for patients who are refractory to corticosteroids (defined as ongoing grade 2-4 ICANS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.,* psychosis) • If Grade 3 encephalopathy is persistent for > 24 hours, increase dexamethasone to 20 mg IV every 6 hours (or methylprednisolone equivalent) • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Seizure	• Neurological work-up as in Grade 1 ICANS • EEG if clinically indicated (*e.g.,* ongoing seizures, depressed level of consciousness) • Rule out other potential causes of seizure (*i.e.*, beta-lactams, *etc*.)	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive seizures, or non-convulsive seizures, treat as per Appendix J	• Consider anakinra for patients who are refractory to corticosteroids (defined as ongoing grade 2-4 ICANS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.,* psychosis) • Dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) ◦ If associated with concurrent CRS, add tocilizumab[2] • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation

CSF = cerebrospinal fluid

[1] Abnormal findings on imaging where correction of hypertension, uremia, and/or coagulopathy should be performed include changes suggestive of typical or atypical posterior reversible encephalopathy syndrome (PRES), temporal lobe and limbic system encephalitis (autoimmune or infection), acute disseminated encephalomyelitis, emboli, vasculitis, strokes, and/or seizure-related changes

[2] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

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APPENDIX H: Management of ICANS - continued

ICANS Grade	Sign or symptom	Management		
		Diagnostic Work-up	**Supportive Care**	**Anti-IEC Therapies**
Grade 3	Focal cerebral edema	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging (CT or MRI) every 24 hours until edema resolves or more frequently if clinically indicated	• Transfer to ICU • Supportive care as in Grade 1 ICANS	• If focal edema is in brain stem or thalamus, methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper depending on clinical situation ◦ If associated with concurrent CRS, add tocilizumab[1] • Consider anakinra for patients who are refractory to corticosteroids (defined as ongoing grade 2-4 ICANS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.,* psychosis) • If focal edema is in other areas of brain, methylprednisolone 1,000 mg/day in divided doses IV for 1 day; assess daily and continue or taper depending on clinical situation ◦ If associated with concurrent CRS, add tocilizumab[1]

[1] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

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APPENDIX H: Management of ICANS - continued

ICANS Grade	Sign or symptom	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 4	Encephalopathy and/or depressed level of consciousness	• Neurological work-up as in Grade 1 ICANS • Repeat neuro-imaging and lumbar puncture as in Grade 3 ICANS	• Transfer to ICU • Supportive care as in Grade 1 ICANS • Consider mechanical ventilation for airway protection • If there are new abnormal findings on brain imaging[1] not related to primary malignancy, control hypertension with the goal of maintaining MAP within 20-25 mmHg of baseline MAP; correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets > 20 - 50 K/microliter, fibrinogen > 200 mg/dL and INR < 1.5)	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab[2] • Consider anakinra for patients who are refractory to corticosteroids (defined as ongoing grade 2-4 ICANS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.,* psychosis) • Continue corticosteroids until improvement to ≤ to Grade 1 ICANS and then taper and stop corticosteroids depending on clinical situation • If Grade 4 ICANS is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix I) including activation of safety switches if applicable
	Seizure	• Neurological work-up as in Grade 1 ICANS • Rule out other potential causes of seizure (*i.e.*, beta-lactams, *etc.*)	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive or non-convulsive seizure or convulsive status epilepticus, treat as in Appendix J • For convulsive status epilepticus, treat as in Appendix K	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab[2] • Consider anakinra for patients who are refractory to corticosteroids (defined as ongoing grade 2-4 ICANS 6 hours after initiation of corticosteroids), dependent on corticosteroids (relapse while tapering off), and/or intolerant to corticosteroids (*e.g.,* psychosis) • If Grade 4 ICANS is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix I) including activation of safety switches if applicable
	Motor Weakness	• Neurological work-up as in Grade 1 ICANS • MRI with and without contrast of the spine	• Transfer to ICU • Supportive care as in Grade 1 ICANS	
	Diffuse cerebral edema or raised intracranial pressure	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging as in focal cerebral edema from Grade 3 ICANS	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For diffuse cerebral edema or signs of raised intracranial pressure, treat as in Appendix L	

[1] Abnormal findings on imaging where correction of hypertension, uremia, and/or coagulopathy should be performed include changes suggestive of typical or atypical posterior reversible encephalopathy syndrome (PRES), temporal lobe and limbic system encephalitis (autoimmune or infection), acute disseminated encephalomyelitis, emboli, vasculitis, strokes, and/or seizure-related changes

[2] See Appendix I for Dosing of IL-6 Antagonists and Alternative Agents

APPENDIX I: Recommendations for Use of IL-6 Antagonists and Alternative Agents for Management of CRS and ICANS

Drug	Recommended Dose for CRS and/or ICANS	Maximum Dose	Mechanism of Action	Comments
Tocilizumab[1]	8 mg/kg IV	Maximum 800 mg per dose	IL-6 receptor antagonist	• Maximum of 4 doses total over the entire course of CRS and ICANS • Dose may be repeated every 8 hours for up to three doses in a 24-hour period
Siltuximab[2,3]	11 mg/kg IV once	-	IL-6 antibody	• Recommended primarily for patients who are intolerant to tocilizumab or if tocilizumab is not available • No more than 1 dose in a 3 week period
Anakinra	100 mg subcutaneously or IV twice daily for 7 days	-	IL-1 receptor antagonist	In case of high grade ICANS or not responsive to initial dose, consider increase to 200 mg every 8 hours and change to IV, for up to 10 days
Cyclophosphamide[3]	1,500 mg/m^2 IV for one dose	-	Alkylating agent	Give with mesna 1,500 mg/m^2 IV over 24 hours for one dose
Anti-thymocyte globulin (rabbit)[3]	1-2 mg/kg IV daily for 3 days	-	Immunosuppressant	• Hypersensitivity reactions can occur; premedicate with diphenhydramine and scheduled dose of corticosteroid • Infuse over a minimum of 6 hours
Safety switches	-	-	-	If the IEC product contains a safety switch (*e.g.,* iCapsase-9 or EGFRt-positive), the corresponding drug to eliminate those cells can be considered in doses according to manufacturer. Examples include rimiducid to eliminate iCaspase-9 or cetuximab to eliminate EGFRt-positive cells.
Dasatinib[3]	100 mg PO daily for 7 days	-	Tyrosine kinase inhibitor	CYP3A4 substrate, assess for drug interactions and consider QTc monitoring if strong CYP inhibitor
Methylprednisolone	Consider dose increase to a maximum of 3 grams per day	Maximum 3 grams per day	Immunosuppressant	Consider if progression of symptoms or no response after being on 1 gram per day for 24 to 48 hours

[1] MD Anderson formulary restricted for use in CRS/ICANS and for use in hemophagocytic lymphohistiocytosis (HLH), see Appendix N
[2] MD Anderson formulary restricted for use in CRS/ICANS
[3] Informed consent is required

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX J: Management of Focal or Generalized Convulsive or Non-Convulsive/Electrographic Seizures

- Assess CAB / consider airway protection / check blood glucose
- Consult Neurology
- For focal and generalized convulsive seizures, lorazepam 1-2 mg IV and repeat as needed (to a maximum cumulative dose of 4 mg)
- For electrographical seizures, including non-convulsive status epilepticus, lorazepam 0.5 mg IV and repeat every 5 minutes as needed (to a maximum cumulative dose of 2 mg)
- Levetiracetam 500-1,500 mg IV bolus, followed by an increased maintenance dose of 1,000-1,500 mg every 12 hours
- Replete with magnesium as needed to maintain magnesium level > 2 mg/dL
- Thiamine 300 mg IV daily for 5 days
- If non-convulsive seizures persist, transfer to ICU and add an additional agent:
  - If clinically indicated, consider lorazepam 0.5 mg IV every 8 hours for 3 doses
  - If no cardiac abnormalities are seen, lacosamide 100-200 mg IV over at least 15 minutes, followed by 100-200 mg IV every 12 hours (monitor for cardiac arrhythmia) **or**
  - Phenobarbital 60 mg IV once, followed by 30 mg IV every 12 hours (~0.5 mg/kg every 12 hours)
    - Monitor for respiratory depression, bradycardia and hypotension
    - Assess for drug-drug interactions (*e.g*, may induce metabolism of azole antifungals or other CYP3A4 substrates) and consider alternative therapy if drug interactions are significant

CAB = circulation, airway, breathing

APPENDIX K: Management of Convulsive Status Epilepticus

- Assess CAB / consider airway protection / check blood glucose
- Transfer to ICU
- Consult Neurology
- Lorazepam 0.1 mg/kg (maximum 4 mg/dose) given at a maximum rate of 2 mg/minute; may repeat in 5 to 10 minutes
- Levetiracetam 40-60 mg/kg (max 4,500 mg) IV bolus, followed by an increased maintenance dose to 1,000-1,500 mg IV every 12 hours
- Replete with magnesium as needed to maintain magnesium > 2 mg/dL
- Thiamine 300 mg IV daily for 10 days
- If seizures persist, add an additional agent:
  - Lacosamide 5 mg/kg (max 400 mg) IV over 30 minutes followed by maintenance dose 100-200 mg IV every 12 hours (monitor for cardiac arrhythmia) **or**
  - Phenobarbital loading dose of 15 mg/kg IV followed by maintenance dose 0.5 mg/kg IV every 12 hours
    - Monitor for respiratory depression, bradycardia and hypotension
    - Assess for drug-drug interactions (*e.g.*, may induce metabolism of azole antifungals or other CYP3A4 substrates) and consider alternative therapy if drug interactions are significant
    - Target serum trough levels 15-40 mcg/mL
- Continuous EEG monitoring if seizures are refractory to treatment
- If refractory, consider additional therapies (see Appendix I) including activation of safety switches if applicable

CAB = circulation, airway, breathing

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX L: Management of Diffuse Cerebral Edema, Raised Intracranial Pressure

For papilledema without diffuse cerebral edema or other signs of raised intracranial pressure	• Acetazolamide 1,000 mg IV followed by 250-1,000 mg IV every 12 hours (monitor renal function and acid/base balance once or twice daily and adjust dose accordingly) • Dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) and start taper after resolution of papilledema
For diffuse cerebral edema on neuroimaging or signs of raised intracranial pressure such as decerebrate or decorticate posturing, cranial nerve VI palsy, or Cushing's triad	• Methylprednisolone 1,000-3,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated • Elevate head end of patient's bed to an angle of 30 degrees • Hyperventilation to achieve target $PaCO_2$ of 28-30 mmHg, but maintained for no longer than 24 hours • Hyperosmolar therapy with either mannitol (20 g/dL solution) **or** hypertonic saline (3% or 23.4% as detailed below) ◦ Mannitol: initial dose 0.5-1 g/kg IV; maintenance dose 0.25-1 g/kg IV every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours; withhold mannitol if serum osmolality is ≥ 320 mOsm/kg or osmolality gap is ≥ 40 ◦ Hypertonic 3% saline: initial dose 250 mL IV over 15 minutes, maintenance dose of 50-75 mL/hour IV while monitoring electrolytes every 4 hours; withhold infusion if serum sodium levels reach ≥ 155 mEq/L) ◦ Hypertonic 23.4% saline (for patients with imminent herniation): dose to be administered by physician; initial dose of 30 mL IV; repeat after 15 minutes, if needed • If patient has ommaya reservoir, drain CSF to target the opening pressure < 20 mmHg • Control hypertension with the goal of maintaining mean arterial pressure (MAP) within 20-25 mmHg of baseline MAP; correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets > 20-50 K/microliter, fibrinogen > 200 mg/dL and INR < 1.5) • Consider neurosurgery consultation and IV anesthetics for burst-suppression pattern on EEG; transfuse to keep platelets ≥ 100 K/microliter if possible and correct coagulopathy in case of surgical intervention • Consider additional therapies (see Appendix I) including activation of safety switches if applicable • Metabolic profile every 6 hours and daily CT head without contrast, with adjustments in usage of aforementioned medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia and hypotension

CSF = cerebrospinal fluid

APPENDIX M: Movement and Neurocognitive Treatment-Emergent Adverse Events (MNTs)

Patients at risk

- Ciltacabtagene autoleucel patients with at least 2 of the following:
  - High tumor burden and/or high baseline inflammatory markers pre-IEC
  - Grade ≥ 2 CRS or any grade ICANS
  - High CAR T-cell expansion/persistence

Prevention/Mitigation

- Enhanced bridging therapy to decrease tumor burden if IEC is known to cause MNTs
- Neuroimaging baseline for patients with preexisting neurologic conditions (MRI and EEG)
- Early and aggressive treatment of CRS and/or ICANS
  - Tocilizumab for any grade ICANS with concurrent CRS and/or
  - Dexamethasone (grade 1 to 3) or methylprednisolone (grade 4)
  - Consider use of anakinra in ICANS not responding to tocilizumab or corticosteroids
- Use of prophylactic antimicrobials (viral/pneumocystis carinii) for up to 12 months after IEC

Monitoring

- All patients who receive ciltacabtagene autoleucel should be monitored for at least 1-year post IEC infusion for MNTs
  - For other agents knows to cause MNTs, patient should be monitored for at least 1-year post IEC unless otherwise indicated by research protocol
- Neurologic exam with onset of any sign/symptoms listed below
- Routine monitoring with regular handwriting assessments for early detection of micrographia, dysgraphia, or agraphia

Signs and Symptoms

Category	Signs and Symptoms
Movement Disorder	Symptoms to be elicited from patient/caregivers: changes in handwriting, new onset tremors, new onset movements, smiles inappropriately, difficulty in ambulation, imbalance, falls. Signs: micrographia, reduced facial expression, bradykinesia, cogwheel rigidity, dysgraphia, dyskinesia, dysmetria, essential tremor, resting tremor, stereotypy, myoclonus, impaired hand-eye coordination, new abnormal posture, new ataxia.
Personality Changes & Cognitive Impairment	Symptoms to be elicited from patient/caregivers: personality changes, memory difficulty, sleep disturbances, unusual behavior. Signs: amnesia, apraxia, bradyphrenia, cognitive disorder, disturbance in attention, psychomotor retardation, memory impairment, mini mental status examination and/or Montreal cognitive assessment.
Nerve Changes	Symptoms to be elicited from patient/caregivers: difficulty in swallowing, double vision, facial droop, increasing numbness in legs, progressive weakness in legs and arms, progressive balance difficulty, progressive difficulty in getting up from chair and bathroom commode, progressive difficulty getting in and out of car, progressive difficulty in buttoning shirts and use of utensils, worsening hand weak grip. Signs: new motor and sensory changes, new gait imbalance and gait changes, new cranial nerve findings, new positive Romberg's.

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APPENDIX M: Movement and Neurocognitive Treatment-Emergent Adverse Events (MNTs) - continued

Diagnostic workup of suspected MNTs from ciltacabtagene autoleucel (or other IECs known to cause MNTs)

Consider the following work-up:

- Infection workup for Human Herpesvirus 6 (HHV6), plasma John Cunningham Virus (JC virus) (change from baseline) or other infections (metagenomic CSF analysis) known to cause neurologic disorders
- Karius test (multipathogen detection test from blood)
- Neurofilament light chain assay[1]
- Paraneoplastic panel
- Dopamine Transporter Scan (DaTscan) – performed by nuclear medicine
- Movement Disorder Autoimmune/Paraneoplastic Evaluation, serum (serum MDS2) - if Parkinsonian symptoms[1]
- MRI Brain with and without contrast
- MRI spine with and without contrast for new onset weakness
- Lumbar puncture (if feasible and safe) to evaluate for:
  - Infection
  - Flow cytometry for IECs and malignancy
  - Paraneoplastic autoantibody
  - Oligoclonal bands
  - Meningitis/encephalitis panel
  - CSF metagenomic analysis
  - CSF JC virus
- Electromyography (EMG)
- Myelin associated glycoprotein (MAG), Ganglioside antibodies (if Guillain Barre symptoms)

Management (may include any of the modalities below or all of them)

- Treat infection if applicable
- PT/OT consult
- Consult neurology
- Vitamin C 1,000 mg PO daily
- Vitamin E 400 units PO daily
- Sinemet 25/100 mg PO three times daily (trial and maintenance)
- Amantadine 100 mg PO twice or three times daily (trial and maintenance)
- Guillain Barre (GBS)/GBS variants/Chronic inflammatory demyelinating polyneuropathy (CIDP) (IVIG, therapeutic plasma exchange, pulse steroids)

CSF = cerebrospinal fluid

[1]Mayo send out lab

APPENDIX N: Diagnosis and Management of Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS)

Definition: IEC-HS is a hyperinflammatory syndrome, independent from CRS and ICANS that:

- Presents with features of macrophage activation/HLH
- Is attributed to IEC therapy
- Is associated with progression or new onset cytopenias, hyperferritinemia, coagulopathy with hypofibrogenemia, and/or transaminitis

Diagnostic Work-up for Suspected IEC-HS

- CBC with differential, complete metabolic profile, ferritin, CRP, LDH, uric acid, gamma-glutamyl transferase (GGT), cytokine panel 12
- PT, aPTT, D-dimer, fibrinogen, triglycerides (fasting), soluble CD25
- Bone marrow aspirate and biopsy to assess for hemophagocytosis
- Infectious work-up: chest x-ray or CT chest, blood cultures, urine culture, viral PCR for CMV, HHV6, Epstein–Barr virus (EBV), Herpes Simplex virus (HSV), other viruses and fungal infections as clinically indicated, and other imaging if clinically indicated
- In patients with neurological symptoms/signs: Imaging of the brain (MRI preferred) and CSF analysis including work-up for CNS infection and flow cytometry for IECs and malignancy when feasible

Diagnostic Criteria for IEC-HS: ***Diagnosis is made only when not attributable to alternative etiologies, including CRS, infection and/or disease progression****

Diagnostic Criteria
Required[1]: • Rapidly rising ferritin to a minimum level of 10,000 ng/mL • Rapidly rising hepatic transaminases to a minimum level of 5 x ULN (if baseline was normal) or > 5 x baseline (if baseline was abnormal) • New onset, worsening or refractory cytopenias, with at least 1 lineage being grade 4 (platelets, neutrophils, or hemoglobin)
Other common manifestations[1]: • Onset with resolving CRS or worsening inflammatory response after initial improvement with CRS-directed therapy • Hypofibrinogenemia (< 150 mg/dL or < lower limit of normal) • Hemophagocytosis in bone marrow or other tissue

CSF = cerebrospinal fluid

[1] Required and common manifestations typically occur simultaneously (all within 72 hours)

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APPENDIX N: Diagnosis and Management of Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS) - continued

Other manifestations that may be present:

- Lactate dehydrogenase elevations (> ULN)
- Other coagulation abnormalities (elevated PT/PTT)
- Hyperbilirubinemia (direct bilirubin)
- New-onset splenomegaly
- Fever – new or persistent
- Neurotoxicity
- Pulmonary (hypoxia, pulmonary infiltrates, pulmonary edema)
- Renal insufficiency – new onset
- Hypertriglyceridemia – fasting > ULN

IEC-HS Grading:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic or mild symptoms; requires observation and/or clinical and diagnostic evaluation. Intervention not indicated.	Mild to moderate symptoms, with intervention indicated (*e.g.*, immunosuppressive agents directed at IEC-HS, transfusions for asymptomatic hypofibrinogenemia)	Severe or medically significant but not immediately life- threatening (*e.g.*, coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress)	Life-threatening consequences: urgent intervention indicated (*e.g.*, life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury)	Death

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Monitoring During Treatment:
Check the following HLH parameters daily until ferritin is <50% of peak, and then twice a week until resolution of HLH as per treating team:
ferritin, LDH, triglycerides, LFTs, CRP, fibrinogen, cytokine-3 panel, soluble IL-2, interferon gamma

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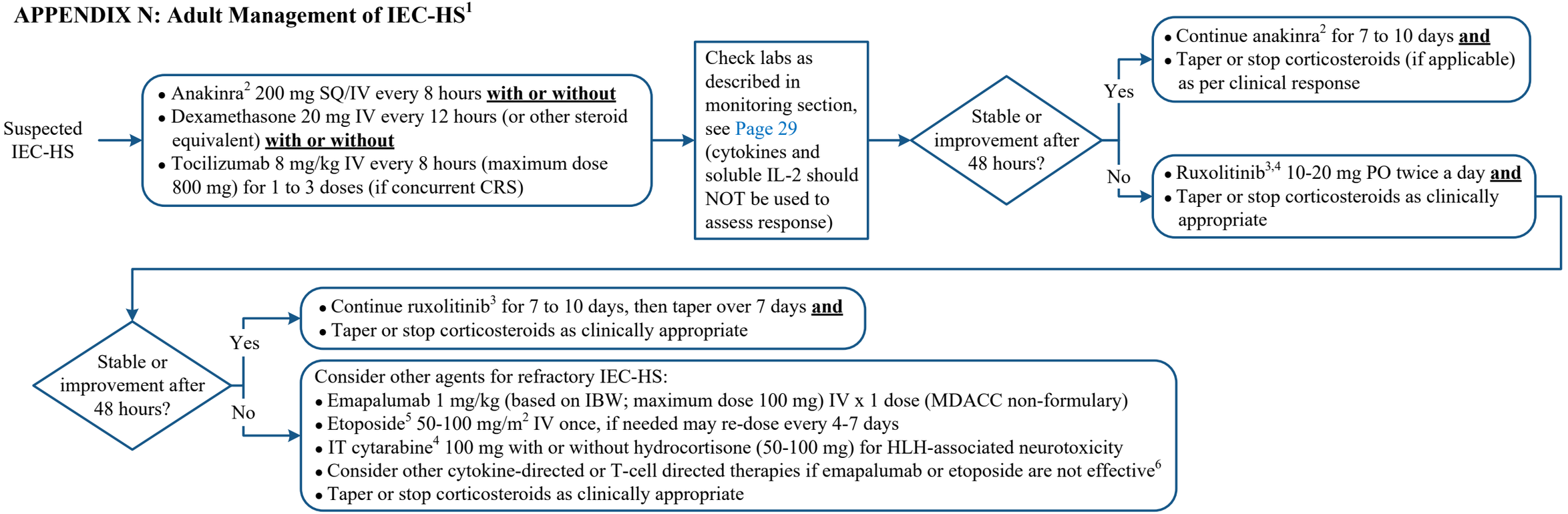
IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX N: Adult Management of IEC-HS[1]



[1] This management algorithm is meant for patients with suspected or documented IEC-HS. If the diagnostic work-up reveals that alternative causes such as infection or malignant disease progression may be the reason for the laboratory abnormalities, the management strategy should be reconsidered.

[2] Consider dose adjustment for anakinra in patients with renal dysfunction (do not exceed anakinra 100 mg SQ/IV every 8 hours if creatinine clearance < 30 mL/minute). Cases needing doses > 200 mg every 8 hours should be discussed with the CARTOX committee.

[3] Dose adjustments to ruxolitinib are not required upfront for renal or hepatic dysfunction or for drug-drug interactions given the benefit vs risk in managing IEC-HS. Dose may be adjusted based on clinical response and/or toxicity (*i.e.* thrombocytopenia).

[4] Consent is required for ruxolitinib, etoposide, IT cytarabine

[5] Dose adjustment may be needed for renal or hepatic dysfunction

[6] Alternative/salvage agents: Cytokine directed – canakinumab, siltuximab, tadekinig alfa, etanercept; T-cell directed – alemtuzumab, basiliximab, anti-thymocyte globulin, cyclosporine (note that many agents are not on the MDACC formulary)

APPENDIX O: Determine the Grade of IEC-associated Acute GVHD

GVHD Target Organ Staging

Stage	Skin	Liver (bilirubin)	Lower GI (stool output/day)
0	No active (erythymatous) GVHD rash	< 2 mg/dL	< 500 mL/day or < 3 episodes/day
1	Maculopapular rash < 25% BSA	2 - 3 mg/dL	500-999 mL/day or 3-4 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1 - 6 mg/dL	1,000-1,500 mL/day or 5-7 episodes/day
3	Maculopapular rash > 50% BSA	6.1 - 15 mg/dL	> 1,500 mL/day or > 7 episodes/day
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% BSA	> 15 mg/dL	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Overall Clinical Grade (based on most severe organ involvement)

Grade	Comment
0	No stage 1-4 of any organ
I	Stage 1-2 skin without liver, upper GI[1], or lower GI involvement
II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI[1] and/or stage 1 lower GI
III	Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI[1]
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI[1]

BSA = body surface area

[1] Isolated upper GI GVHD with nausea, vomiting, and/or anorexia is uncommon following allogeneic lymphocyte infusion

IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Adult

APPENDIX P: Manage IEC-associated Acute GVHD

Grade	Sign or Symptom	Management
Grade I	Skin rash	• Skin biopsy, preferably non-sun exposed site • Hydrocortisone cream 1% twice daily to face • Triamcinolone cream 0.1% three times daily to affected body area • If patient fails triamcinolone, may consider clobetasol cream 0.05% twice daily to body; limit use to no longer than 1-2 weeks • All corticosteroid creams should be followed by an emollient such as CeraVe®, Aquaphor®or Eucerin® (creams not lotions) 20-40 minutes after application of corticosteroid
Grade II-IV	• Skin rash > 50% BSA and/or • Total bilirubin > 2 mg/dL and/or • Diarrhea > 500 mL/day	• At onset of symptoms that are grade II or higher, consult Stem Cell Transplant team for GVHD workup and management • Skin biopsy as above for rash • Gastrointestinal consult for flexible sigmoidoscopy with or without upper GI endoscopy with duodenal biopsy[1] • DO NOT give GI prep (GoLytely®, *etc*.) unless full colonoscopy ordered • Stool culture for *C. difficile* and GI multiplex panel • DO NOT wait for completion of these procedures to start systemic therapy • Start prednisone 2 mg/kg/day orally or methylprednisolone equivalent in divided doses

BSA = body surface area

[1] Upper GI endoscopy may be considered if patient has nausea, vomiting, and/or anorexia and upper GI GVHD is suspected

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