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

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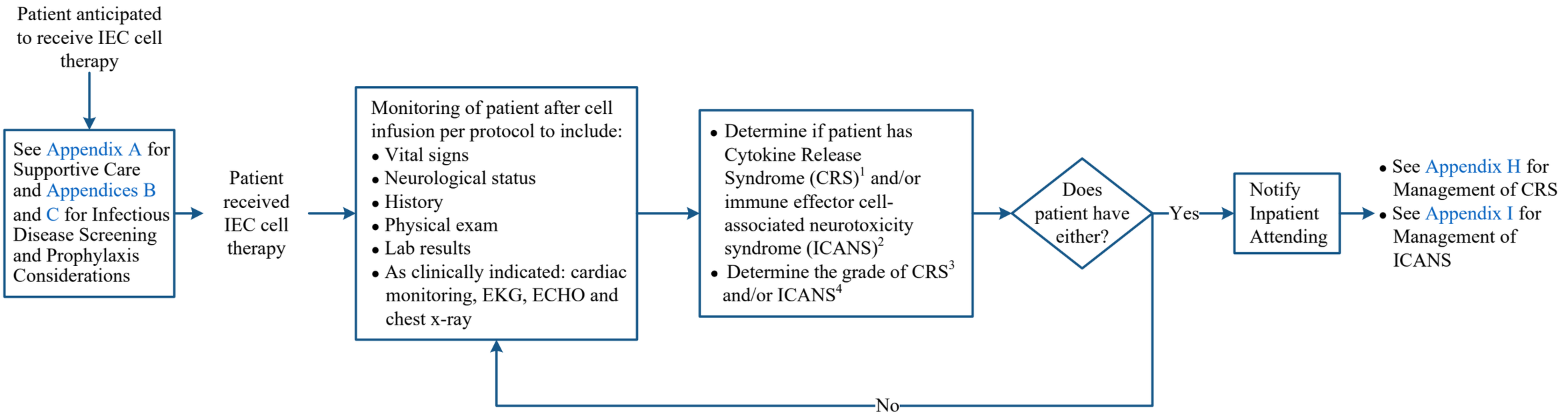
CAR = chimeric antigen receptor
CRS = cytokine release syndrome
ICANS = immune effector cell-associated neurotoxicity syndrome
IEC = immune effector cells
GVHD = graft versus host disease

Department of Clinical Effectiveness V5 Rev
Approved by the Executive Committee of the Medical Staff on 03/23/2021

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

INITIAL EVALUATION

MANAGEMENT



[1] If the subject has fever with or without hypotension or hypoxia within the first 4 weeks of engineered immune effector cell (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 (oral temperature ≥ 38°C)
- Hypotension (requiring IV fluids or vasopressors to maintain normal blood pressure) defined as:
  - Age 1-10 years: SBP < [70 + (2 x age in years)] mmHg
  - Age > 10 years: SBP < 90 mmHg
- 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) and/or Cornell Assessment of Pediatric Delirium (CAPD) Score > 9 (see Appendix G). If CAPD score is increasing from baseline then consider more frequent CAPD monitoring
- 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

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

Before and During IEC Infusion

- 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 disease and also to serve as a baseline for comparison in case the patient develops ICANS
  - For patients with known history of seizures, migraines and/or other CNS disorders including malignant disease, consider Neurology consult prior to IEC infusion
- Baseline ECG/EKG 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, admission to an IEC-designated unit with capability for cardiac monitoring by telemetry is recommended
- Tumor lysis precautions for patients with high tumor burden, as per standard guidelines
- Seizure prophylaxis with levetiracetam 10 mg/kg (maximum 500 mg) PO or IV every 12 hours for 30 days, starting on the day of infusion for IEC therapies associated with a high incidence of ICANS, in patients with history of seizures or brain metastases
- Consider filgrastim products if patient is neutropenic and concern for infection (if not already receiving)
- Ensure appropriate documentation in EHR regarding IEC therapy and "conditional" corticosteroid contraindication

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

For Outpatients:

Patient Monitoring After IEC infusion (for at least 14 days post-IEC infusion)

- 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 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 and/or CAPD[1] score assessment

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 and 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 and/or CAPD[1] with sentence writing every evening

Considerations for Admission

- Oral temperature ≥ 38°C
- Hypotension defined as:
  - Age 1-10 years: SBP < [70 + (2 x age in years)] mmHg
  - Age > 10 years: SBP < 90 mmHg
- New arrhythmia
- Upward trend in liver function tests and/or creatinine
- Oxygen saturation < 92% on room air
- Tremors or jerky movements in extremities
- Grade 1 CRS or greater
- Grade 1 ICANS or greater

[1] Developmental age should be documented with neurology note with initial assessment

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

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

For Inpatients:

Patient Monitoring After IEC infusion during Inpatient Admission

- 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 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. If a change in status occurs, monitor for CRS every 6 hours or more frequently as indicated.
- Assessment and grading for ICANS (document in CARTOX flowsheet) should be completed at least every 12 hours including the CAPD (if age or developmental age is ≤ 18 years of age) and 10-point ICE score if > 12 years of age. If ≤ 12 years of age, the CAPD should be utilized. Any increase in CAPD score requires monitoring every 6 hours or more frequently as indicated.
- Maintenance IV fluids with normal saline to ensure adequate hydration
- Cardiac monitoring by telemetry is recommended for ≥ Grade 1 CRS and continued 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*

Notifications and contingency orders during Inpatient Admission

- Notify SCT physician on detection of any of the following:

  The baseline blood pressure should be considered to determine monitoring parameters and verified with the physician prior to admission
  - Hypotension defined as:
    - Age 1-10 years: SBP < [70 + (2 x age in years)] mmHg
    - Age > 10 years: SBP < 90 mmHg
  - Heart rate based on age or arrhythmia:
    - Age 1-2 years: > 130 or < 75 beats per minute
    - Age 3-6 years: > 120 or < 70 beats per minute
    - Age 7-12 years: > 110 or < 65 beats per minute
    - Age 13-17 years: > 105 or < 55 beats per minute
  - Respiratory rate based on age:
    - Age 1-2 years: > 40 or < 24 breaths per minute
    - Age 3-6 years: > 34 or < 22 breaths per minute
    - Age 7-12 years: > 30 or < 18 breaths per minute
    - Age 13-17 years: > 16 or < 12 breaths per minute
  - Oxygen saturation < 94% on room air
  - Decreased urine output (< 0.5 mL/kg/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 and/or CAPD score > 9)
  - For oral temperature ≥ 38°C, send blood cultures (central and peripheral) and urine for urinalysis and culture, obtain portable chest x-ray, and notify physician
- 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, and notify physician
- PRN medications
  - Acetaminophen (1st choice) or ibuprofen (2nd choice, if not contraindicated) for fever ≥ 38°C
  - Cooling blanket for fever ≥ 38.3°C
  - Normal saline 10 - 20 mL/kg (maximum 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 > 8 gm/dL
  - Transfuse platelets to maintain > 20 K/microliter; for patients with abnormal brain imaging transfuse platelets to maintain > 50 k/microliter
  - PRN tocilizumab to be activated only on physician order ("ok to give tocilizumab" order should be placed if dose approved by physician)

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 • HHV-6 IgG (Herpesvirus 6 Ab panel) • Cytomegalovirus (CMV) IgG and IgM	• Anti-human T-cell lymphotrophic virus (HTLV) antibody (HTLV I/II Ab) • Rapid Plasma Reagin (RPR) – syphilis • Cytomegalovirus (CMV) IgG and IgM • 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

[1] Primary team should follow up on all testing and order follow up testing 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

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-cells 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] 15 mg/kg/day (maximum 500 mg) PO daily or divided twice daily	Acyclovir[1] 30-45 mg/kg/dose (maximum 800 mg/dose) PO twice daily or 5 mg/kg IV every 8 hours	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]: • 2-15 years old: Consult with Pharmacist for dosing • ≥ 16 years old: Entecavir 0.5 mg PO daily	Tenofovir disoproxil fumarate[1] ≥ 2 years old and ≥ 10 kg and adolescents: 8 mg/kg/dose (maximum 300 mg/day) 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] • < 5 years old: 10 mg/kg/dose (maximum 250 mg/dose) PO/IV every 12 hours • ≥ 5 years old: 10 mg/kg/dose (maximum 500 mg/dose) PO/IV every 24 hours	Cefpodoxime[1,2] 5 mg/kg/dose (maximum 200 mg per dose) PO twice daily **Or** Ciprofloxacin[1] • 10 mg/kg/dose (maximum 500 mg per dose) PO twice daily • 10 mg/kg/dose (maximum 400 mg per dose) IV 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 (whichever is longer)	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-cells are at increased risk of infection due to B-cell aplasia.

Prophylaxis	Preferred Medication(s)	Alternative Medication(s)	Start	Stop	Comment
Pneumocystis jirovecii	Pentamidine inhaled or IV[1] within 1 week prior to EIC infusion and then transition to Sulfamethoxazole/trimethoprim (SMZ/TMP; preferred post-IEC infusion) by 3-4 weeks if counts have recovered: 2.5 – 5 mg/kg/dose trimethoprim (maximum 160 mg) PO twice daily given three days per week on consecutive days (i.e. Fri, Sat, Sun) or on alternating days (i.e. Mon, Wed, Fri) Optional dosing for adolescents: SMZ/TMP 1 double strength tab (800/160 mg) PO daily given three days per week on consecutive days (i.e. Fri, Sat, Sun) or on alternating days (i.e. Mon, Wed, Fri)	-	Within 1 week prior to IEC infusion	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
		Pentamidine inhaled ≥ 5 years old: 300 mg flat dose every 28 days	Within 1 week prior to IEC infusion	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	Albuterol nebulizer premedication encouraged
		Pentamidine[1] IV 4 mg/kg (maximum 300 mg per dose) every 21 days	Within 1 week prior to IEC infusion	At least 1 year post IEC infusion; may stop after 1 year if CD4 count > 200 cells/microliter	Can cause pancreatitis
		Dapsone 2 mg/kg/dose (maximum 100 mg/dose) PO daily	3-4 weeks post IEC infusion	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
		Atovaquone • < 4 months old: 30 mg/kg/day (maximum of 1500 mg/day) PO daily • 4-24 months old: 45 mg/kg/day (maximum of 1500 mg/day) PO daily • > 24 months-13 years old: 30 mg/kg/day (maximum 1500 mg/day) PO daily • > 13 years old: 1500 mg PO daily	Within 1 week prior to IEC infusion	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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APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy - *continued*

Prophylaxis	Preferred Medication	Alternative Medication	Start	Stop	Comment
Fungal (low risk)	Fluconazole[1] 12 mg/kg/dose (maximum 400 mg/dose) PO or IV daily	Caspofungin 50 mg/m^2/dose IV daily (maximum 50 mg/day)[2]	IEC infusion day	Continue until ANC > 0.5 K/microliter for 3 consecutive days without growth factor support	-
Fungal (high risk)[3]	Posaconazole[3] • ≤ 12 years old: 4 mg/kg/dose of oral suspension PO three times a day • ≥ 13 years old: 200 mg PO (oral suspension) three times a day or 300 mg PO (delayed release tablets) or IV daily **Tablets preferred in those who can swallow tablets** Voriconazole[3] • 2-11 years old **or** < 50 kg: 9 mg/kg/dose PO every 12 hours (maximum 350 mg/dose) or 8 mg/kg/dose IV every 12 hours • ≥ 12 years old **and** ≥ 50 kg: 200 mg PO every 12 hours or 4mg/kg/dose IV every 12 hours **Pharmacokinetic monitoring of levels is recommended for both posaconazole and voriconazole**	Caspofungin 50 mg/m^2/dose IV daily (maximum 50 mg/day)[2]	IEC infusion day or when high-risk criteria are met	Continue as clinically indicated[3]	Posaconazole suspension must be taken with a fatty meal Posaconazole and voriconazole drug-drug interactions via CYP3A4 exist

[1] Adjust for renal function

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[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, those who receive ≥ 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 or voriconazole prophylaxis if ANC < 1 K/microliter. Isavuconazole may be used if the patient had previously been taking it or if posaconazole is not covered by insurance. In the event posaconazole, voriconazole, 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.

APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy - *continued*

Prophylaxis	Comment
Human Immunodeficiency Virus (HIV)	Antiretroviral Therapy (ART) and monitoring per ID recommendations. Obtain an ID consult on any patient with HIV.
Herpesvirus 6 (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	Routine CMV prophylaxis is not required but CMV monitoring by PCR is recommended 1-2 times a week 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 hemophagocytic lymphohistiocytosis (HLH)[1]. CMV monitoring is recommended for at least 30 days after 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 (< 500 mg/dL)
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 with filgrastim 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[1], or infection.

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

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

APPENDIX D: 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 tocilizumab or corticosteroids, 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 ≤ 5 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 5 liters/minute and may vary based on the size of the pediatric patient. The definition of low-flow and high-flow nasal canula for pediatric patients may differ from the published ASTCT consensus grading guideline

From "ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells" by Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J.,. . . Neelapu, S. S., 2019, *Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation,* 25(4), 625–638. https://doi.org/10.1016/j.bbmt.2018.12.758

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

APPENDIX E: ASTCT Grading of ICANS[1]

Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment (ICE) Score[2]	7-9	3-6	0[3]-2	0[3] (patient is unarousable and unable to perform ICE)
CAPD[4] score	1-8	1-8	≥ 9	Unable to perform CAPD
Depressed level of consciousness[5]	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[6]	-	-	-	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure[7] / cerebral edema	-	-	Focal/local edema on neuroimaging[8]	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

CAPD = Cornell Assessment of Pediatric Delirium EEG = electroencephalogram

[1] ICANS grade is determined by the most severe event (CAPD and/or ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause). For example, a patient with a 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 for patients > 12 years of age

[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] CAPD is intended for patients on Pediatric Service who are ≤ 12 years of age and/or for children > 12 years of age for whom this is developmentally appropriate (see Appendix G)

[5] Depressed level of consciousness should not be attributable to any other cause (e.g., sedating medication)

[6] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading

[7] Ophthalmology may be consulted to assess for papilledema if concern for elevated ICP, but otherwise not needed for all patients

[8] 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

From "ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells" by Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J.,. . . Neelapu, S. S., 2019, *Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation,* 25(4), 625–638. https://doi.org/10.1016/j.bbmt.2018.12.758

APPENDIX F: Immune Effector Cell-associated Encephalopathy (ICE) Score - for patients > 12 years of age

- **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

From "ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells" by Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J.,. . . Neelapu, S. S., 2019, *Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation,* 25(4), 625–638. https://doi.org/10.1016/j.bbmt.2018.12.758

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APPENDIX G: Cornell Assessment of Pediatric Delirium (CAPD)[1] score (for children ≤ 12 years of age and/or for children > 12 years of age for whom this is developmentally appropriate)

RASS Score[2] (if -4 or -5, do not proceed)
Answer the following questions based on your interactions with the patient over the course of your shift[3]

	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0		Never 0	Rarely 1	Sometimes 2	Often 3	Always 4
1. Does the child make eye contact with the caregiver?						5. Is the child restless?					
2. Are the child's actions purposeful?						6. Is the child inconsolable?					
3. Is the child aware of his/her surroundings?						7. Is the child underactive – very little movement while awake?					
4. Does the child communicate needs and wants?						8. Does it take the child a long time to respond to interactions?					

[1] An increasing CAPD score (even if less than 9) may indicate concern for delirium and warrants more frequent monitoring.

[2]Richmond Agitation Sedation Scale (RASS):
+4 Combative - Overly combative, violent, immediate danger to staff
+3 Very Agitated – Pulls or removes tube(s) or catheter(s); aggressive
+2 Agitated – Frequent non-purposeful movement, fights ventilator
+1 Restless – Anxious, but movements not aggressive or vigorous
0 Alert and Calm
-1 Drowsy – Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (≥ 10 seconds)
-2 Light sedation – Briefly awakens with eye contact to voice (< 10 seconds)
-3 Moderate sedation – Movement
-4 Deep sedation – No response to voice, but movement or eye opening to physical stimulation
-5 Unarousable

[3]For patients age 1-2 years, the following serve as guidelines to the corresponding questions (1-8):
1. Holds gaze. Prefers primary parent. Looks at speaker.
2. Reaches and manipulates objects, tries to change position, if mobile may try to get up
3. Prefers primary parent, upset when separated from preferred caregivers. Comforted by familiar objects (*i.e.,* blanket or stuffed animal)
4. Uses single words or signs
5. No sustained calm state
6. Not soothed by usual comforting actions, for example, singing, holding, talking, and reading
7. Little if any play, efforts to sit up, pull up, and if mobile crawl or walk around
8. Not following simple directions. If verbal, not engaging in simple dialogue with words or jargon

From "Cornell Assessment of Pediatric Delirium: A Valid, Rapid, Observational Tool for Screening Delirium in the PICU*" by Traube, C., Silver, G., Kearney, J., Patel, A., Atkinson, T. M., . . . Greenwald, B, 2014, *Critical care medicine,* 42(3), 656–663. Copyright 2014 by Wolters Kluwer Health, Inc. Reprinted with permission

APPENDIX H: 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 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 10 mg/kg (maximum 500 mg) PO or IV twice daily	Consider tocilizumab[1] for 1 dose for persistent fever lasting greater than 3 days
Grade 2	**Hypotension**[2]	• Cardiac telemetry • Fever work-up if not previously performed ◦ Assess for infection with blood and urine cultures, and chest radiography	• Consider transfer to PICU • IV fluid bolus ◦ 10-20 mL/kg (maximum 1,000 mL) normal saline ◦ Repeat once as needed to maintain normal BP • If hypotension persists after IV fluids, tocilizumab, and hydrocortisone, start vasopressors, transfer to PICU, 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 after second IV fluid bolus • If possible adrenal insufficiency, consider stress dose hydrocortisone 12.5- – 25 mg/m^2/day divided every 6 hours • If hydrocortisone not used, consider methylprednisolone 1 – 2 mg/kg for one dose [or dexamethasone 0.15 - 0.5 mg/kg/dose (maximum 10 mg) IV for 1 dose] 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
	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	• Administer tocilizumab[1] for 1 dose **and** consider methylprednisolone 1 – 2 mg/kg for one dose [or dexamethasone 0.5 mg/kg/dose (maximum 10 mg) IV for 1 dose] 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

PICU = Pediatric Intensive Care Unit

[1]See Appendix J for Interleukin-6 Antagonist and Alternative Agents

[2]Hypotension defined as:
- Age 1-10 years: SBP < [70 + (2 x age in years)] mmHg
- Age > 10 years: SBP < 90 mmHg

Continued on next page

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

APPENDIX H: Management of CRS - *continued*

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**

Grade 3	**Hypotension**[1]	• 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 PICU
			• 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[2] 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 stress dose hydrocortisone 12.5-25 mg/m^2/day divided every 6 hours if not already given
				• If still hypotensive on vasopressor and hydrocortisone then consider methylprednisolone or dexamethasone as follows:
				  ◦ If on one vasopressor: methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours [or dexamethasone 0.5 mg/kg/dose (maximum 10 mg) IV every 6 hours]
				  ◦ If on two vasopressors: methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours (or dexamethasone 1 mg/kg/dose [maximum 20 mg] IV every 6 hours)
				• If vasopressin and norepinephrine equivalent[3] 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[2] and methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours (or dexamethasone 0.5 mg/kg/dose [maximum 10 mg] IV every 6 hours) if not a administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • 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, methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours [or dexamethasone 1 mg/kg/dose (maximum 20 mg) IV every 6 hours] • Once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation

[1]Consider stress-dose hydrocortisone for patients with vasopressor-resistant hypotension attributed to adrenal insufficiency
[2] See Appendix J for Dosing of IL-6 Antagonists and Alternative Agents
[3] 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 H: 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 PICU
			• 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 stress dose hydrocortisone 12.5 – 25 mg/m^2/day divided every 6 hours if not already given
				• If still hypotensive on vasopressor and hydrocortisone then consider methylprednisolone as follows:
				  ◦ Methylprednisolone 30 mg/kg/day (maximum 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 J) 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 PICU • 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 • Methylprednisolone 30 mg/kg/day (maximum 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 J) including activation of safety switches if applicable

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

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

APPENDIX I: 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 and/or CAPD 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 [0.02 mg/kg/dose (maximum 0.5 mg) IV every 8 hours] or haloperidol [0.01 mg/kg/dose (maximum 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	• If associated with concurrent CRS, add tocilizumab[1] • If no response to tocilizumab or for isolated ICANS, start dexamethasone 0.5 mg/kg/dose (maximum 10 mg) IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated
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 0.5 mg/kg/dose (maximum 10 mg) IV every 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

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

Continued on next page

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

APPENDIX I: 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 PICU transfer • If there are new abnormal findings on brain imaging[1] not related to primary malignancy, control hypertension with the goal of 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 0.5 mg/kg/dose (maximum 10 mg) IV every 6 hours (or methylprednisolone equivalent) ◦ If associated with concurrent CRS, add tocilizumab[2] • If Grade 3 encephalopathy is persistent for > 24 hours, increase dexamethasone to 1 mg/kg/dose (maximum 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 PICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive seizures, or non-convulsive seizures, treat as per Appendix K	• Dexamethasone 1 mg/kg/dose (maximum 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
	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 PICU • Supportive care as in Grade 1 ICANS	• If focal edema is in brain stem or thalamus, methylprednisolone 30 mg/kg/day (maximum 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[2] • If focal edema is in other areas of brain, methylprednisolone 30 mg/kg/day (maximum 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[2]

[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 J for Dosing of IL-6 Antagonists and Alternative Agents

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

APPENDIX I: 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 PICU • 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 30 mg/kg/day (maximum 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] • Continue corticosteroids until improvement to less than or equal 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 J) 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 PICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive or non-convulsive seizure or convulsive status epilepticus, treat as in Appendix K • For convulsive status epilepticus, treat as in Appendix L	• Methylprednisolone 30 mg/kg/day (maximum 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] • If Grade 4 ICANS is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix J) 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 PICU • Supportive care as in Grade 1 ICANS	• Methylprednisolone 30 mg/kg/day (maximum 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] • If Grade 4 ICANS is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix J) including activation of safety switches if applicable
	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 PICU • Supportive care as in Grade 1 ICANS • For diffuse cerebral edema or signs of raised intracranial pressure, treat as in Appendix M	• Methylprednisolone 30 mg/kg/day (maximum 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] • If Grade 4 ICANS is refractory for > 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix J) including activation of safety switches if applicable

[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 J for Dosing of IL-6 Antagonists and Alternative Agents

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

APPENDIX J: 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]	Less than 30 kg: 12 mg/kg IV for up to three doses in a 24-hour period 30 kg and greater: 8 mg/kg IV for up to three doses in a 24-hour period	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]	11 mg/kg IV once	No more than 1 dose in a 3-week period	Binds to both soluble and membrane bound IL-6 Neutralizes IL-6	• Recommended primarily for patients who are intolerant to tocilizumab • No more than 1 dose in a 3 week period
Anakinra[3]	Children ≥ 2 years and Adolescents: 1 mg/kg (maximum 100 mg) subcutaneously daily for 7 days	-	IL-1 receptor antagonist	• Renal dose adjustment may be needed for creatinine clearance < 30 mL/minute
Cyclophosphamide	1,500 mg/m^2 IV for one dose	-	Alkylating agent	• Give with mesna 1500 mg/m^2 IV over 24 hours for one dose
Anti-thymocyte globulin (rabbit)	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.,* iCaspase-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

[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] Not on MD Anderson formulary; use at MD Anderson is based on internal data in patients with tocilizumab and/or siltuximab failure

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

APPENDIX K: Management of Focal or Generalized Convulsive or Non-Convulsive Seizures

- Assess CAB / consider airway protection / check blood glucose
- Consult Neurology
- For focal and generalized convulsive seizures, lorazepam 0.05 mg/kg (maximum 1 mg) IV; repeat dose every 5 minutes (to a maximum 4 doses) to control electrographical seizures
- Levetiracetam 40 mg/kg (maximum 2,500 mg) IV bolus (in addition to maintenance dose)
- Replete with magnesium as needed to maintain magnesium level > 2 mg/dL
- Thiamine 100 mg IV every 8 hours for 5 days
- If non-convulsive seizures persist, transfer to PICU and add phenobarbital loading dose of 10-20 mg/kg (maximum 1,000 mg) IV (monitor for respiratory depression, bradycardia and hypotension)
- Maintenance doses after resolution of non-convulsive status epilepticus
  - Lorazepam 0.05 mg/kg (maximum 1 mg) IV every 8 hours for 3 doses
  - Levetiracetam 15 mg/kg (maximum 1,500 mg) IV every 12 hours
  - Phenobarbital 1-3 mg/kg IV every 12 hours
    - Monitor for respiratory depression, bradycardia and hypotension
    - Assess for drug-drug interactions (*i.e.*, 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

APPENDIX L: Management of Convulsive Status Epilepticus

- Assess CAB / airway protection / high flow O_2, check blood glucose
- Transfer to PICU
- Consult Neurology
- Lorazepam 0.1 mg/kg (maximum 4 mg) IV; repeat dose after at least 1 minute (to a maximum of 2 doses) to control seizures
- Levetiracetam 40 mg/kg (maximum 2,500 mg) IV bolus (in addition to maintenance dose)
- Replete with magnesium as needed to maintain magnesium level > 2 mg/dL
- Thiamine 100 mg IV every 8 hours for 5 days
- If seizures persist, add phenobarbital at a loading dose 10-20 mg/kg (maximum 1,000 mg) IV (monitor for respiratory depression, bradycardia and hypotension)
- If refractory, consider additional therapies (see Appendix J) including activation of safety switches if applicable
- Maintenance doses after resolution of status epilepticus
  - Lorazepam 0.05 mg/kg (maximum 1 mg) IV every 8 hours for 3 doses
  - Levetiracetam 30 mg/kg (maximum 1,500 mg) IV every 12 hours or increase the current dose by 10 mg/kg IV every 12 hours
  - Phenobarbital 1-3 mg/kg IV every 12 hours
    - Monitor for respiratory depression, bradycardia and hypotension
    - Assess for drug-drug interactions (*i.e.*, 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 if seizures are refractory to treatment

CAB = circulation, airway, breathing

APPENDIX M: Management of Diffuse Cerebral Edema and/or Raised Intracranial Pressure

For papilledema without diffuse cerebral edema or other signs of raised intracranial pressure	• Acetazolamide 15 mg/kg (maximum 1,000 mg) IV followed by 8-12 mg/kg (maximum 1,000 mg) IV every 12 hours (monitor renal function and acid/base balance once or twice daily and adjust dose accordingly) • Dexamethasone 1 mg/kg/dose (maximum 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 30 mg/kg/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% **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; and withhold mannitol infusion if serum osmolality is ≥ 320 mOsm/kg or osmolality gap is ≥ 40) ◦ Hypertonic 3% saline: initial dose 5 mL/kg IV over 15 minutes, maintenance dose of 1 mL/kg/hour IV to reach a target sodium level of 150-155 mEq/L (monitor electrolytes every 4 hours; hold infusion if serum sodium levels reach > 155 mEq/L) ◦ Hypertonic 23.4% saline (for patients with imminent herniation): 0.5 – 1 mL/kg. Dose to be administered by physician; repeat after 15 minutes, if needed • If patient has ommaya reservoir, drain CSF to target OP < 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 J) including activation of safety switches if applicable • Metabolic profile every 6 hours and daily CT scans of head without contrast, with adjustments in usage of aforementioned medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia and hypotension

OP = opening pressure

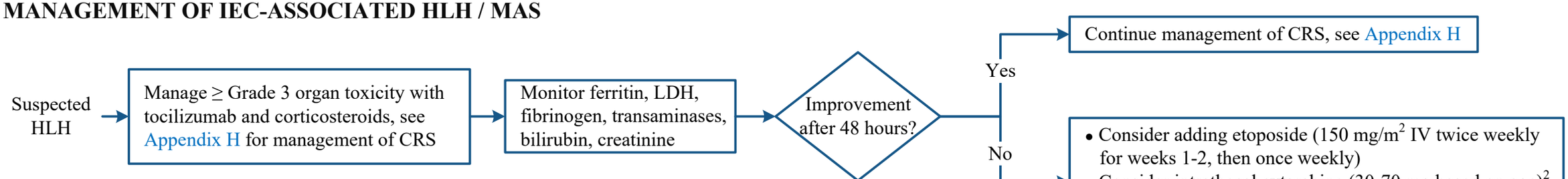
IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – Pediatric

APPENDIX N: Diagnostic Criteria for IEC-Related Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS)

- Consider HLH/MAS if a patient has a peak ferritin > 10,000 ng/mL during the CRS phase and develops any two of the following organ toxicities after IEC therapy
  - ≥ Grade 3 increase in bilirubin, aspartate transaminase, or alanine transaminase[1]
  - ≥ Grade 3 oliguria or increase in creatinine[1]
  - ≥ Grade 3 pulmonary edema[1]
  - Presence of hemophagocytosis by morphology and/or CD68 immunohistochemistry in bone marrow or organs
- If HLH/MAS is suspected, obtain baseline fasting triglyceride level and serum soluble IL-2 receptor

[1]Grading as per Common Terminology Criteria for Adverse Events, version 5

MANAGEMENT OF IEC-ASSOCIATED HLH / MAS



[2] Intrathecal cytarabine
- 1 – 1.99 years: 30 mg
- 2 – 2.99 years: 50 mg
- At least 3 years old: 70 mg

[3] Intrathecal hydrocortisone
- 1 – 1.99 years: 15 mg
- 2 – 2.99 years: 25 mg
- At least 3 years old: 50 mg

APPENDIX O: Determine if the Subject Has Allogeneic IEC-associated Acute Graft-Versus-Host Disease (GVHD)

If a subject has any of the following symptoms or signs within the first 3 months after allogeneic IEC therapy, the subject may have acute GVHD if the symptoms or signs are not attributable to any other cause.

1. Skin rash
2. Diarrhea (may also be associated with nausea, vomiting, and/or anorexia due to upper GI GVHD)[1]
3. Total bilirubin ≥ 2 mg/dL

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

APPENDIX P: 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	< 10 mL/kg/day or < 4 episodes/day
1	Maculopapular rash < 25% BSA	2 - 3 mg/dL	10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1 - 6 mg/dL	20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash > 50% BSA	6.1 - 15 mg/dL	> 30 mL/kg/day or > 10 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)

BSA = body surface area

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[2], or lower GI involvement
II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI[2] 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[2]
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI[2]

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

APPENDIX Q: 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 > 10 mL/kg/day	• 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

SUGGESTED READINGS

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