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

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**INITIAL EVALUATION**

Patient anticipated to receive IEC cell therapy

See Appendix A for Supportive Care and Appendices B and C for Infectious Disease Screening and Prophylaxis Considerations

Patient received IEC cell therapy

Monitoring of patient after cell infusion per protocol to include:
- Vital signs
- Neurological status
- History
- Physical exam
- Lab results
- As clinically indicated: cardiac monitoring, EKG, ECHO and chest x-ray

**MANAGEMENT**

Does patient have either?

- **Yes**
  - Determine if patient has Cytokine Release Syndrome (CRS)\(^1\) and/or immune effector cell-associated neurotoxicity syndrome (ICANS)\(^2\)
  - Determine the grade of CRS\(^3\) and/or ICANS\(^4\)
  - Notify Inpatient Attending

- **No**
  - See Appendix H for Management of CRS
  - See Appendix I for Management of ICANS

---

\(1\) 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
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 CAPD¹ 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 CAPD¹ 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
- Tremors or jerky movements in extremities
- Grade 1 CRS or greater
- Grade 1 ICANS or greater
- New arrhythmia
- Upward trend in liver function tests and/or creatinine
- Oxygen saturation < 92% on room air

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

Continued on next page

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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

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

Continued on next page
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)

<table>
<thead>
<tr>
<th>Required Infectious Disease Screening¹</th>
<th>Optional Infectious Disease Screening (as clinically indicated)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hepatitis B surface antigen (HBsAg)</td>
<td>• Anti-human T-cell lymphotrophic virus (HTLV) antibody (HTLV I/II Ab)</td>
</tr>
<tr>
<td>• Anti-hepatitis B core antibody (HBcAb)</td>
<td>• Rapid Plasma Reagin (RPR) – syphilis</td>
</tr>
<tr>
<td>• Anti-hepatitis C virus antibody (HCVAb)</td>
<td>• Cytomegalovirus (CMV) IgG and IgM</td>
</tr>
<tr>
<td>• Anti-human immunodeficiency virus (HIV) antibody (HIV type 1 / 2 type O Ab)</td>
<td>• West Nile Virus nucleic acid test</td>
</tr>
<tr>
<td>• HIV-1 / HCV / HBV Nucleic Acid Test</td>
<td>• T Cruzi antibody</td>
</tr>
<tr>
<td>• HHV-6 IgG (Herpesvirus 6 Ab panel)</td>
<td>• Strongyloides antibody to assess for previous infection or exposure</td>
</tr>
<tr>
<td>• Cytomegalovirus (CMV) IgG and IgM</td>
<td>• T-spot to assess for exposure or history of tuberculosis</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Preferred Medication</th>
<th>Alternative Medication(s)</th>
<th>Start</th>
<th>Stop</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Viral                | Valacyclovir¹ 15 mg/kg/day  
(maximum 500 mg) PO daily or divided twice daily | Acyclovir¹ 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 | -                                                                       |
| Herpes simplex       |                      |                           |                            |                                           |                                                                         |
| Varicella zoster     |                      |                           |                            |                                           |                                                                         |
| Hepatitis B          | Entecavir¹:  
- 2-15 years old: Consult with Pharmacist for dosing  
- ≥ 16 years old: Entecavir 0.5 mg PO daily | Tenofovir disoproxil fumarate¹  
- ≥ 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. |
| (only for patients who are positive for HBsAg or HBcAb) |                      |                           |                            |                                           |                                                                         |
| Bacterial            | Levofoxacin¹  
- < 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 | Cefpodoxime¹²  
5 mg/kg/dose (maximum 200 mg per dose) PO twice daily  
Or Ciprofloxacin¹  
- 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 |
| (if neutropenia with ANC < 1 K/microliter is expected to last ≥ 7 days) |                      |                           |                            |                                           |                                                                         |

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

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<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Preferred Medication(s)</th>
<th>Alternative Medication(s)</th>
<th>Start</th>
<th>Stop</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jirovecii</td>
<td>Pentamidine inhaled or IV(^1) within 1 week prior to IEC 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)</td>
<td>Pentamidine inhaled ≥ 5 years old: 300 mg flat dose every 28 days</td>
<td>Within 1 week prior to IEC infusion</td>
<td>At least 1 year post IEC infusion; may stop after 1 year if CD4 count &gt; 200 cells/microliter</td>
<td>SMZ/TMP also has activity against toxoplasma and nocardia</td>
</tr>
<tr>
<td></td>
<td>Pentamidine(^1) IV 4 mg/kg (maximum 300 mg per dose) every 21 days</td>
<td>Pentamidine(^1) IV 4 mg/kg (maximum 300 mg per dose) every 21 days</td>
<td>Within 1 week prior to IEC infusion</td>
<td>At least 1 year post IEC infusion; may stop after 1 year if CD4 count &gt; 200 cells/microliter</td>
<td>Albuterol nebulizer premedication encouraged</td>
</tr>
<tr>
<td></td>
<td>Dapsone 2 mg/kg/dose (maximum 100 mg/dose) PO daily</td>
<td>Dapsone 2 mg/kg/dose (maximum 100 mg/dose) PO daily</td>
<td>3-4 weeks post IEC infusion</td>
<td>At least 1 year post IEC infusion; may stop after 1 year if CD4 count &gt; 200 cells/microliter</td>
<td>Can cause pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Atovaquone ● &lt; 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 ● &gt; 24 months-13 years old: 30 mg/kg/day (maximum 1500 mg/day) PO daily ● &gt; 13 years old: 1500 mg PO daily</td>
<td>Atovaquone ● &lt; 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 ● &gt; 24 months-13 years old: 30 mg/kg/day (maximum 1500 mg/day) PO daily ● &gt; 13 years old: 1500 mg PO daily</td>
<td>Within 1 week prior to IEC infusion</td>
<td>At least 1 year post IEC infusion; may stop after 1 year if CD4 count &gt; 200 cells/microliter</td>
<td>Must take with a fatty meal. Also has activity against toxoplasma, but inferior to SMZ/TMP.</td>
</tr>
</tbody>
</table>

\(^1\) Adjust for renal function

1. Adjust for renal function

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APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy - continued

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Preferred Medication</th>
<th>Alternative Medication</th>
<th>Start</th>
<th>Stop</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungal (low risk)</strong></td>
<td>Fluconazole(^1) 12 mg/kg/dose (maximum 400 mg/dose) PO or IV daily</td>
<td>Caspofungin 50 mg/m(^2)/dose IV daily (maximum 50 mg/day)(^2)</td>
<td>IEC infusion day</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Fungal (high risk)(^3)</strong></td>
<td>Posaconazole(^3)</td>
<td>Caspofungin 50 mg/m(^2)/dose IV daily (maximum 50 mg/day)(^2)</td>
<td>IEC infusion day or when high-risk criteria are met</td>
<td>Continue as clinically indicated(^3)</td>
<td>Posaconazole suspension must be taken with a fatty meal. Posaconazole and voriconazole drug-drug interactions via CYP3A4 exist</td>
</tr>
<tr>
<td></td>
<td>• ≤ 12 years old: 4 mg/kg/dose of oral suspension PO three times a day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥ 13 years old: 200 mg PO (oral suspension) three times a day or 300 mg PO (delayed release tablets) or IV daily</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td><em>Tablets preferred in those who can swallow tablets</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2-11 years old or &lt; 50 kg: 9 mg/kg/dose PO every 12 hours (maximum 350 mg/dose) or 8 mg/kg/dose IV every 12 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥ 12 years old and ≥ 50 kg: 200 mg PO every 12 hours or 4 mg/kg/dose IV every 12 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pharmacokinetic monitoring of levels is recommended for both posaconazole and voriconazole</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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, 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. Isaferconazole 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.

Continued on next page

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APPENDIX C: Infection Prophylaxis Considerations for IEC Therapy - continued

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Immunodeficiency Virus (HIV)</td>
<td>Antiretroviral Therapy (ART) and monitoring per ID recommendations. Obtain an ID consult on any patient with HIV.</td>
</tr>
<tr>
<td>Herpesvirus 6 (HHV-6)</td>
<td>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&lt;sup&gt;1&lt;/sup&gt;. HHV-6 monitoring is recommended for at least 30 days after completion of corticosteroids.</td>
</tr>
<tr>
<td>CMV</td>
<td>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 Grades 3 or 4 CRS/ICANS, if patient receives ≥ 3 days of corticosteroids, or if patient develops hemophagocytic lymphohistiocytosis (HLH)&lt;sup&gt;1&lt;/sup&gt;. CMV monitoring is recommended for at least 30 days after completion of corticosteroids.</td>
</tr>
<tr>
<td>Immunoglobulin replacement therapy</td>
<td>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 (&lt; 500 mg/dL)</td>
</tr>
<tr>
<td>Prolonged cytopenias</td>
<td>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&lt;sup&gt;1&lt;/sup&gt;, or infection.</td>
</tr>
</tbody>
</table>

<sup>1</sup> See Appendix N for Diagnostic Criteria for IEC-associated Fulminant Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS)
### APPENDIX D: ASTCT Grading for CRS

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

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>CRS Grade 1</th>
<th>CRS Grade 2</th>
<th>CRS Grade 3</th>
<th>CRS Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever²</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypotension³</td>
<td>No</td>
<td>Requiring IV fluids but not requiring vasopressors</td>
<td>Requiring one vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia³</td>
<td>No</td>
<td>Requiring low-flow O₂ via nasal cannula⁴ or blow-by</td>
<td>Requiring O₂ via high-flow nasal cannula⁴, facemask, non-rebreather mask, or Venturi mask</td>
<td>Requiring O₂ via positive pressure (e.g., CPAP, BiPAP, and mechanical ventilation)</td>
</tr>
</tbody>
</table>

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 (O₂) 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 cannula for pediatric patients may differ from the published ASTCT consensus grading guideline.

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

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APPENDIX E: ASTCT Grading of ICANS

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological assessment</td>
<td>7-9</td>
<td>3-6</td>
<td>0(^4)2</td>
<td>0(^1) (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>(ICE) Score</td>
<td></td>
<td></td>
<td></td>
<td>Unable to perform CAPD</td>
</tr>
<tr>
<td>CAPD(^4) score</td>
<td>1-8</td>
<td>1-8</td>
<td>≥ 9</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma</td>
</tr>
<tr>
<td>Depressed level of</td>
<td>Awakens</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Life-threatening prolonged seizure (≥ 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>consciousness(^5)</td>
<td>spontaneously</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>-</td>
<td>-</td>
<td>Any clinical seizure (focal or generalized) that resolves rapidly (&lt; 5 minutes) or non-convulsive seizures on EEG that resolve with intervention</td>
<td></td>
</tr>
<tr>
<td>Motor findings(^6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Raised intracranial</td>
<td>-</td>
<td>-</td>
<td>Focal/local edema on neuroimaging(^8)</td>
<td>Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad</td>
</tr>
<tr>
<td>pressure(^7) / cerebral edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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 an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

\(^2\) A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma.

\(^3\) 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).

\(^4\) 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.

\(^6\) 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.


\(^8\) Cushing’s triad

\(^9\) EEG = electroencephalogram
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 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


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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)

<table>
<thead>
<tr>
<th>RASS Score² (if -4 or -5, do not proceed)</th>
<th>Answer the following questions based on your interactions with the patient over the course of your shift³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never</strong></td>
<td><strong>Rarely</strong></td>
</tr>
<tr>
<td>1. Does the child make eye contact with the caregiver?</td>
<td>4</td>
</tr>
<tr>
<td>2. Are the child’s actions purposeful?</td>
<td>0</td>
</tr>
<tr>
<td>3. Is the child aware of his/her surroundings?</td>
<td>0</td>
</tr>
<tr>
<td>4. Does the child communicate needs and wants?</td>
<td>0</td>
</tr>
<tr>
<td>5. Is the child restless?</td>
<td>0</td>
</tr>
<tr>
<td>6. Is the child inconsolable?</td>
<td>0</td>
</tr>
<tr>
<td>7. Is the child underactive – very little movement while awake?</td>
<td>0</td>
</tr>
<tr>
<td>8. Does it take the child a long time to respond to interactions?</td>
<td>0</td>
</tr>
</tbody>
</table>

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

²Richmond Agitation Sedation Scale (RASS):
-4 Combatant - Overly combative, violent, immediate danger to self
-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 – Brief awakenings with eye contact to voice (< 10 seconds)
-3 Moderate sedation – Movement
-4 Deep sedation – No response to voice, but movement or opening to physical stimulation
-5 Unarousable

³For patients age 1-2 years, the following serve as guidelines to the corresponding questions (1-8):
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

## APPENDIX H: Management of CRS

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>CRS Parameter</th>
<th>Diagnostic Work-Up</th>
<th>Supportive Care</th>
<th>Anti-IEC Therapies</th>
</tr>
</thead>
</table>
| 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 |

\(^1\)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
### APPENDIX H: Management of CRS - continued

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>CRS Parameter</th>
<th>Diagnostic Work-Up</th>
<th>Supportive Care</th>
<th>Management</th>
<th>Anti-IEC Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>● Obtain ECHO if not performed already</td>
<td>● Transfer patient to PICU</td>
<td>● Tocilizumab&lt;sup&gt;2&lt;/sup&gt; 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</td>
<td>● Consider stress dose hydrocortisone 12.5-25 mg/m&lt;sup&gt;2&lt;/sup&gt;/day divided every 6 hours if not already given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Cardiac telemetry</td>
<td>● IV fluid boluses as needed as in Grade 2 CRS</td>
<td></td>
<td>● If still hypotensive on vasopressor and hydrocortisone then consider methylprednisolone or dexamethasone as follows:</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>● Fever work-up if not previously performed</td>
<td>● Use vasopressors as needed</td>
<td></td>
<td>○ 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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Assess for infection with blood and urine cultures, and chest radiography</td>
<td>● Symptomatic management of fever as in Grade 1 CRS</td>
<td></td>
<td>○ 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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines</td>
<td></td>
<td>● If vasopressin and norepinephrine equivalent&lt;sup&gt;3&lt;/sup&gt; is ≥ 15 mcg/minute, follow as in Grade 4 CRS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>● Once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation</td>
</tr>
<tr>
<td><strong>Hypoxia</strong></td>
<td></td>
<td>● Pulse oximetry</td>
<td>● Supplemental oxygen including high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask as needed</td>
<td>● Tocilizumab&lt;sup&gt;2&lt;/sup&gt; 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 administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period</td>
<td>● If there is no improvement in hypoxia within 24 hours or there is rapid progression of pulmonary infiltrates or sharp increase in FiO&lt;sub&gt;2&lt;/sub&gt; 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]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Fever work-up if not previously performed</td>
<td>● Symptomatic management of fever as in Grade 1 CRS</td>
<td></td>
<td>● Once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Assess for infection with blood and urine cultures, and chest radiography</td>
<td>● Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Consider stress-dose hydrocortisone for patients with vasopressor-resistant hypotension attributed to adrenal insufficiency

<sup>2</sup>See Appendix J for Dosing of IL-6 Antagonists and Alternative Agents

<sup>3</sup>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

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>CRS Parameter</th>
<th>Diagnostic Work-Up</th>
<th>Supportive Care</th>
<th>Management</th>
<th>Anti-IEC Therapies</th>
</tr>
</thead>
</table>
| 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 |}\(^1\) See Appendix J for Dosing of IL-6 Antagonists and Alternative Agents  

| Grade 4   | 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 |
# APPENDIX I: Management of ICANS

<table>
<thead>
<tr>
<th>ICANS Grade</th>
<th>Sign or symptom</th>
<th>Diagnostic Work-up</th>
<th>Supportive Care</th>
<th>Anti-IEC Therapies</th>
</tr>
</thead>
</table>
| **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/liquids 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 tocilizumab¹  
  ● 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 tocilizumab¹  
  ● 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
### APPENDIX 1: Management of ICANS - continued

<table>
<thead>
<tr>
<th>ICANS Grade</th>
<th>Sign or symptom</th>
<th>Diagnostic Work-up</th>
<th>Management</th>
<th>Anti-IEC Therapies</th>
</tr>
</thead>
</table>
| 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)  
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 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\(^2\)  | 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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Continued on next page
## APPENDIX I: Management of ICANS - continued

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<th>ICANS Grade</th>
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<th>Supportive Care</th>
<th>Management</th>
<th>Anti-IEC Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy and/or depressed level of consciousness</td>
<td>Neurological work-up as in Grade 1 ICANS</td>
<td>• Transfer to PICU</td>
<td>• Supportive care as in Grade 1 ICANS</td>
<td>• 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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat neuro-imaging and lumbar puncture as in Grade 3 ICANS</td>
<td>• Consider mechanical ventilation for airway protection</td>
<td>• 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 &gt; 20 - 50 K/microliter, fibrinogen &gt; 200 mg/dL and INR &lt; 1.5)</td>
<td>• Continue corticosteroids until improvement to less than or equal to Grade 1 ICANS and then taper and stop corticosteroids depending on clinical situation</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>Neurological work-up as in Grade 1 ICANS</td>
<td>• Transfer to PICU</td>
<td>• Supportive care as in Grade 1 ICANS</td>
<td>• If Grade 4 ICANS is refractory for &gt; 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix J) including activation of safety switches if applicable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rule out other potential causes of seizure (i.e., beta-lactams, etc.)</td>
<td>• For focal or generalized convulsive or non-convulsive seizure or convulsive status epilepticus, treat as in Appendix K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Weakness</td>
<td>Neurological work-up as in Grade 1 ICANS</td>
<td>• Transfer to PICU</td>
<td>• Supportive care as in Grade 1 ICANS</td>
<td>• 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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI with and without contrast of the spine</td>
<td>• For convulsive status epilepticus, treat as in Appendix L</td>
<td></td>
<td>• If Grade 4 ICANS is refractory for &gt; 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix J) including activation of safety switches if applicable</td>
<td></td>
</tr>
<tr>
<td>Diffuse cerebral edema or raised intracranial pressure</td>
<td>Neurological work-up as in Grade 1 ICANS</td>
<td>• Transfer to PICU</td>
<td>• Supportive care as in Grade 1 ICANS</td>
<td>• 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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider repeat neuro-imaging as in focal cerebral edema from Grade 3 ICANS</td>
<td>• For diffuse cerebral edema or signs of raised intracranial pressure, treat as in Appendix M</td>
<td></td>
<td>• If Grade 4 ICANS is refractory for &gt; 24 hours or if patient is deteriorating rapidly, consider additional therapies (see Appendix J) including activation of safety switches if applicable</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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
# APPENDIX J: Recommendations for Use of IL-6 Antagonists and Alternative Agents for Management of CRS and ICANS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose for CRS and/or ICANS</th>
<th>Maximum Dose</th>
<th>Mechanism of Action</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Tocilizumab¹        | 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 |
| Siltuximab²         | 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 |
| Anakinra³           | 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/m² IV for one dose            | - | Alkylating agent  
|                     |                                         |                           | • Give with mesna 1500 mg/m² 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
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 electrographic 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
-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 O₂, 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

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.
### 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 \( \geq 320 \text{ mOsm/kg} \) or osmolality gap is \( \geq 40 \)  
  ○ 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
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
  - ≥ Grade 3 oliguria or increase in creatinine
  - ≥ Grade 3 pulmonary edema
  - 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

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

MANAGEMENT OF IEC-ASSOCIATED HLH / MAS

Suspected HLH → Manage ≥ Grade 3 organ toxicity with tocilizumab and corticosteroids, see Appendix H for management of CRS → Monitor ferritin, LDH, fibrinogen, transaminases, bilirubin, creatinine → Improvement after 48 hours?

- Yes → Continue management of CRS, see Appendix H
- No → Consider adding etoposide (150 mg/m² IV twice weekly for weeks 1-2, then once weekly)
  - Consider intrathecal cytarabine (30-70 mg based on age) with or without intrathecal hydrocortisone (15-50 mg based on age) for ICANS

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

^2 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

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

GVHD Target Organ Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (bilirubin)</th>
<th>Lower GI (stool output/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No active (erythematous) GVHD rash</td>
<td>&lt; 2 mg/dL</td>
<td>&lt; 10 mL/kg/day or &lt; 4 episodes/day</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash &lt; 25% BSA</td>
<td>2 - 3 mg/dL</td>
<td>10-19.9 mL/kg/day or 4-6 episodes/day</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25 – 50% BSA</td>
<td>3.1 - 6 mg/dL</td>
<td>20-30 mL/kg/day or 7-10 episodes/day</td>
</tr>
<tr>
<td>3</td>
<td>Maculopapular rash &gt; 50% BSA</td>
<td>6.1 - 15 mg/dL</td>
<td>&gt; 30 mL/kg/day or &gt; 10 episodes/day</td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythroderma (&gt; 50% BSA) plus bullous formation and desquamation &gt; 5% BSA</td>
<td>&gt; 15 mg/dL</td>
<td>Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)</td>
</tr>
</tbody>
</table>

Overall Clinical Grade (based on most severe organ involvement)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stage 1-4 of any organ</td>
</tr>
<tr>
<td>I</td>
<td>Stage 1-2 skin without liver, upper GI², or lower GI involvement</td>
</tr>
<tr>
<td>II</td>
<td>Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI² and/or stage 1 lower GI</td>
</tr>
<tr>
<td>III</td>
<td>Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI²</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI²</td>
</tr>
</tbody>
</table>

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

² Isolated upper GI GVHD with nausea, vomiting, and/or anorexia is uncommon following allogeneic lymphocyte infusion
## APPENDIX Q: Manage IEC-associated Acute GVHD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sign or Symptom</th>
<th>Management</th>
</tr>
</thead>
</table>
| 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


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

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DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Pediatric IEC Therapy Toxicity Assessment and Management experts at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

Core Development Team Leads

- Alison Gulbis, PharmD (Pharmacy Clinical Programs)
- Sajad Khazal, MD (Pediatrics – Patient Care)
- Kris M. Mahadeo, MD (Pediatrics – Patient Care)
- Rodrigo Mejia, MD (Pediatrics – Patient Care)
- Maria Estela Mireles, PharmD (Pharmacy Clinical Programs)
- Demetrios Petropoulos, MD (Pediatrics – Patient Care)
- Shehla Razvi, MD (Pediatrics – Patient Care)
- Basirat Shoberu, PharmD (Pediatrics – Patient Care)

Workgroup Members

- Linette J. Ewing, MD (Pediatrics – Patient Care)
- Christina Perez*
- Elizabeth Shpall, MD (Stem Cell Transplantation)
- John Slopis, MD (Neuro-Oncology)
- Milena Zhang, PharmD*

* Clinical Effectiveness Development Team