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CRS = cytokine release syndrome
CTCAE = Common Terminology Criteria for Adverse Events
CRES = CAR-related encephalopathy syndrome
Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult

INITIAL EVALUATION

Patient anticipated to receive CAR cell therapy → See Appendices A and B for Supportive Care and Infection Prophylaxis Considerations → Patient received CAR cell therapy

Monitoring of patient after cell infusion per protocol to include:
- Vital signs
- History
- Lab results
- Cardiac monitor, EKG, and/or ECHO

Determine if patient has cytokine release syndrome (CRS)¹ and/or CAR-related encephalopathy syndrome (CRES)²

Determine the grade of CRS³ and/or CRES⁴

Does patient have either?

Yes → See Appendix F for Management of CRS

No → See Appendix I for Management of CRES

¹The patient may have CRS if any of the following are present within the first 3 weeks of CAR cell therapy infusion:
- Fever (temperature greater than or equal to 38°C)
- Hypotension (SBP less than 90 mmHg)
- Hypoxia (Needing oxygen to maintain oxygen saturation greater than 90%)
- Organ toxicity (See Appendix C for Grading)

²The patient may have CRES if any of the following are present:
- Somnolence
- Encephalopathy
- Seizure
- Agitation
- Dysgraphia
- Cerebral edema

³See Appendix C for Grading of CRS

⁴See Appendix H for Grading of CRES

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Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 10/31/2017
APPENDIX A: Supportive Care Considerations for Patients Receiving Immune Effector Cells

**Consults:**
- Neurology Team to follow patient starting from day of cell infusion and daily for patients receiving immune effector cells known to cause CRES or first in human products
- Critical Care Team will follow patient on an as needed basis
- Infectious disease team will follow patient on an as needed basis
  - Consult should be performed early for patient with positive infectious disease screening

**Seizure Prophylaxis:**
- For patients receiving immune effector cells known to cause CRES or first in human products
- If permitted by protocol, recommended seizure prophylaxis is levetiracetam 500 - 750 mg PO (or IV) twice daily for 30 days starting on day of cell infusion

**Infectious Disease Screening (any time prior to apheresis):**

<table>
<thead>
<tr>
<th><strong>Required Infectious Disease Screening</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>o Hepatitis B surface antigen (HBsAg)</td>
</tr>
<tr>
<td>o Anti-hepatitis B core antibody (HBcAb)</td>
</tr>
<tr>
<td>o Anti-hepatitis C virus antibody (HCVAb)</td>
</tr>
<tr>
<td>o Anti-human immunodeficiency virus (HIV) antibody (HIV type 1 / 2 type O Ab)</td>
</tr>
<tr>
<td>o HIV-1 / HCV / HCB Nucleic Acid Test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Optional Infectious Disease Screening (as clinically indicated)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>o Anti-human T-cell lymphotrophic virus (HTLV) antibody (HTLV I/II Ab)</td>
</tr>
<tr>
<td>o Rapid Plasma Reagin RPR – Syphilis</td>
</tr>
<tr>
<td>o Cytomegalovirus (CMV) IgG and IgM</td>
</tr>
<tr>
<td>o West Nile Virus Nucleic Acid Test</td>
</tr>
<tr>
<td>o T CruzI Antibody</td>
</tr>
<tr>
<td>o T-spot to assess for exposure or history of tuberculosis</td>
</tr>
<tr>
<td>o Strongyloides to assess for previous infection or exposure to strongyloides</td>
</tr>
</tbody>
</table>

**Special Vital Signs (in addition to routine):**
- CARTOX 10-point neurological assessment three times per day (see Appendix H)

**Cardiac Monitoring with Telemetry:**
- For immune effector cells known to cause CRS or first in human products
- Starting on day 0 and until resolution of CRS or discharge from hospital

**Tumor Lysis Precautions:**
- Refer to Tumor Lysis in Adult Patients algorithm for prophylaxis in patients with high tumor burden

**Labs in Addition to Routine Monitoring:**
- Starting on cell infusion day 0 until discharge
  - o C-reactive protein daily
  - o Liver function tests daily
  - o CBC with differential and platelets daily
  - o PT, PTT daily for leukemia patients; twice a week or as indicated for all other patients
- o Ferritin daily
- o Chemistries daily
- o LDH daily

**Imaging at baseline:**
- For patients receiving immune effector cells known to cause CRES or first in human products
  - o CT head without contrast
  - o MRI brain recommended

---

1Patients with recent travel out of the country should be considered for some/all of these additional tests

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### APPENDIX B: Infection Prophylaxis Considerations

Note: Most patients who receive immune effector cells receive a fludarabine-based chemotherapy regimen prior to cell infusion. Fludarabine causes immunosuppression and can increase the risk of opportunistic infections.

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Medication (Doses need to be adjusted for renal dysfunction)</th>
<th>Who Should Receive?</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral (herpes simplex or varicella zoster)</strong></td>
<td>Valacyclovir 500 to 1,000 mg(^1) PO daily or Acyclovir 400 to 800 mg(^1) PO twice daily</td>
<td>All patients</td>
<td>Start within 7 days of cell infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continue until CD4 greater than 200 cell/(\mu)L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May continue longer if protocol requires</td>
</tr>
<tr>
<td><strong>Pneumocystis carinii/jiroveci</strong></td>
<td><strong>Preferred agent:</strong> Sulfamethoxazole/trimethoprim DS (800 mg/160 mg) PO daily on Mondays, Wednesdays, and Fridays only or Sulfamethoxazole/trimethoprim SS (400 mg/80 mg) PO once daily</td>
<td>All patients</td>
<td>Initiate by day 30, unless otherwise dictated by research protocol</td>
</tr>
<tr>
<td></td>
<td>Patients with contraindication or allergy to sulfamethoxazole/trimethoprim may be given pentamidine, atovaquone, or dapsone instead</td>
<td></td>
<td>Continue until CD4 greater than 200 cell/(\mu)L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May continue longer if protocol requires</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td>Levofoxacin 500 mg PO/IV daily or Ciproflacin 500 mg PO or 400 IV twice daily</td>
<td>Use if neutropenia(^2) expected for greater than 1 week</td>
<td>Start by day of cell infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May stop when neutropenia(^2) resolves</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td>Fluconazole 200 to 400 mg PO/IV daily</td>
<td>Use if neutropenia(^2) expected for greater than 2 weeks</td>
<td>Start by day of cell infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May stop when neutropenia(^2) resolves</td>
</tr>
</tbody>
</table>

\(^1\) Patients with history of varicella zoster (shingles) may require higher doses
\(^2\) Neutropenia defined as absolute neutrophil count (ANC) of 0.5 K/\(\mu\)L or less
APPENDIX C: Grading of 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>Category</th>
<th>Sign/Symptom</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>Vital signs</td>
<td>Temperature greater than or equal to 38°C</td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>SBP less than 90 mmHg</td>
<td>No</td>
<td>Responds to IV fluids or low-dose vasopressor</td>
<td>Requires high-dose or multiple vasopressors(^3)</td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>Needing oxygen to maintain (O_2) saturation greater than 90%</td>
<td>No</td>
<td>(\text{FiO}_2) less than 40%</td>
<td>(\text{FiO}_2) greater than or equal to 40% and/or requiring BiPAP</td>
<td>Requires ventilator support</td>
</tr>
<tr>
<td>Organ Toxicity</td>
<td>See Appendix E</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3 or grade 4 transaminitis</td>
<td>Grade 4 except grade 4 transaminitis</td>
</tr>
</tbody>
</table>

\(^1\)Grade 1 CRS may manifest as fever and/or grade 1 organ toxicity

\(^2\)For grades 2, 3, or 4 CRS: any one of the criteria other than temperature is sufficient

\(^3\)See Appendix D for definition of high-dose vasopressors

\(\text{FiO}_2\) = fraction of inspired oxygen

\(\text{BiPAP}\) = bilevel positive airway pressure

APPENDIX D: Definition of High-dose Vasopressors (all doses are required for greater than or equal to 3 hours)

<table>
<thead>
<tr>
<th>Vasopressor</th>
<th>Definition of High-dose Vasopressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine monotherapy</td>
<td>Greater than or equal to 20 mcg/minute</td>
</tr>
<tr>
<td>Dopamine monotherapy</td>
<td>Greater than or equal to 10 mcg/kg/minute</td>
</tr>
<tr>
<td>Phenylephrine monotherapy</td>
<td>Greater than or equal to 200 mcg/minute</td>
</tr>
<tr>
<td>Epinephrine monotherapy</td>
<td>Greater than or equal to 10 mcg/minute</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Vasopressin + norepinephrine equivalent of greater than or equal to 10 mcg/minute(^4)</td>
</tr>
<tr>
<td>Combination vasopressors</td>
<td>Norepinephrine equivalent of greater than or equal to 20 mcg/minute(^5)</td>
</tr>
</tbody>
</table>

\(^4\)VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = \left[\text{norepinephrine (mcg/minute)}\right] + \left[\text{dopamine (mcg/kg/minute)} / 2\right] + \left[\text{epinephrine (mcg/minute)}\right] + \left[\text{phenylephrine (mcg/minute)} / 10\right]

\(^5\)Combination vasopressors (not including vasopressin)
APPENDIX E: CTCAE Grading of Common Organ Toxicities

**Note:** For toxicities not listed here, refer to CTCAE, version 4 for grading

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Sinus tachycardia</td>
<td>Asymptomatic; No intervention needed</td>
<td>Symptomatic, non-urgent intervention indicated</td>
<td>Urgent intervention indicated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia or heart block</td>
<td>Asymptomatic; No intervention needed</td>
<td>Symptomatic, non-urgent intervention indicated</td>
<td>Urgent intervention indicated</td>
<td>Life-threatening</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction(^1) decreased</td>
<td>-</td>
<td>EF 40-50% or 10-19% drop from baseline</td>
<td>EF 20-39% or greater than or equal to 20% drop from baseline</td>
<td>EF less than 20%</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pleural effusion</td>
<td>Asymptomatic; No intervention needed</td>
<td>Symptomatic, intervention indicated (diuretics or thoracentesis)</td>
<td>Symptomatic with respiratory distress; needs surgical intervention (chest tube or pleurodesis)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pulmonary edema</td>
<td>Minimal dyspnea on exertion</td>
<td>Moderate dyspnea on exertion; medical intervention indicated; limits instrumental ADL</td>
<td>Dyspnea at rest; oxygen indicated; limits self-care ADL</td>
<td>Life-threatening; urgent intervention or ventilatory support indicated</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>Loss of appetite without alteration in eating habits</td>
<td>Oral intake decreased without dehydration or weight loss</td>
<td>Inadequate oral caloric or fluid intake; receiving tube feeding or TPN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1-2 episodes / 24 hours</td>
<td>3-5 episodes / 24 hours</td>
<td>Greater than 6 episodes / 24 hours; receiving tube feeding or TPN</td>
<td>Life-threatening</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Increase of 1-3 stools/day over baseline</td>
<td>Increase of 4-6 stools/day over baseline</td>
<td>Increase of greater than 6 stools/day over baseline; limits self-care ADL</td>
<td>Life-threatening</td>
<td>-</td>
</tr>
</tbody>
</table>

CTCAE= Common Terminology Criteria for Adverse Events  
EF = ejection fraction  
ADL = activities of daily living  
\(^1\)Ejection fraction may be increased with CRS, but is not graded

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Continued on next page
### APPENDIX E: CTCAE Grading of Common Organ Toxicities - continued

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>AST or ALT increased</td>
<td>Greater than ULN to 3 x ULN</td>
<td>Greater than 3 x ULN to 5 x ULN</td>
<td>Greater than 5 x ULN to 20 x ULN</td>
<td>Greater than 20 x ULN</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin increased</td>
<td>Greater than ULN to 1.5 x ULN</td>
<td>Greater than 1.5 x ULN to 3 x ULN</td>
<td>Greater than 3 x ULN to 10 x ULN</td>
<td>Greater than 10 x ULN</td>
</tr>
<tr>
<td>Renal</td>
<td>Urine output decreased</td>
<td>-</td>
<td>-</td>
<td>Oliguria (less than 80 mL / 8 hours)</td>
<td>Anuria (less than 240 mL / 24 hours)</td>
</tr>
<tr>
<td></td>
<td>Acute kidney injury</td>
<td>Creatinine 1.5-2 x above baseline</td>
<td>Creatinine 2-3 x above baseline</td>
<td>Creatinine greater than 3 x baseline or greater than 4 mg/dL.</td>
<td>Life-threatening; dialysis indicated</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Disseminated Intravascular Coagulation (DIC)</td>
<td>-</td>
<td>Laboratory findings with no bleeding</td>
<td>Laboratory findings with bleeding</td>
<td>Life-threatening; urgent intervention indicated</td>
</tr>
<tr>
<td>Rash aceneiform</td>
<td>Papules and/or pustules covering less than 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL</td>
<td>Papules and/or pustules covering greater than 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any percent BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Macules/papules covering less than 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)</td>
<td>Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL</td>
<td>Macules/papules covering greater than 30% BSA with or without associated symptoms; limiting self-care ADL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ULN = upper limit of normal  
BSA = body surface area

Note: For toxicities not listed here, refer to CTCAE, version 4 for grading.
### APPENDIX F: Management of CRS and Organ Toxicity

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Sign/Symptom</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Grade 1** | Fever or Grade 1 organ toxicity | - Acetaminophen and hypothermia blanket as needed for fever  
- Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic  
- Assess for infection with blood and urine cultures, and chest x-ray  
- Consider antibiotics and filgrastim (if neutropenic)  
- IV fluids as needed  
- Symptomatic management of constitutional symptoms and organ toxicities  
- Consider IL-6 antagonist\(^1\) for persistent (greater than 3 days) or refractory fever |
| **Grade 2** | Hypotension | - IV fluid bolus of 500 – 1,000 mL normal saline; repeat as necessary to maintain SBP greater than 90 mmHg  
- Consider IL-6 antagonist\(^1\) for hypotension refractory to fluid boluses  
- If hypotension persists after two fluid boluses and IL-6 antagonist\(^1\), start vasopressors, transfer patient to ICU, and obtain ECHO  
- In patients at high-risk for severe CRS\(^2\), if hypotension persists after IL-6 antagonist\(^1\), if there are signs of hypoperfusion\(^3\) or if there is rapid deterioration in the opinion of the clinician, may use dexamethasone 10 mg IV every 6 hours  
- Manage fever and constitutional symptoms as in Grade 1 CRS |
| **Grade 2** | Hypoxia | - Use supplemental oxygen as needed  
- Use IL-6 antagonist\(^1\) with or without corticosteroids as in hypotension  
- Manage fever and constitutional symptoms as in Grade 1 CRS |

<table>
<thead>
<tr>
<th>Grade 2 organ toxicity</th>
<th>Management</th>
</tr>
</thead>
</table>
| - Manage organ toxicity as per standard guidelines  
- Use IL-6 antagonist\(^1\) with or without corticosteroids as in hypotension  
- Manage fever and constitutional symptoms as in Grade 1 CRS |

\(^1\)See Appendix G for Interleukin-6 Antagonist and Corticosteroid Dosing Tables  
\(^2\)High risk for CRS includes any of the following:  
- High tumor burden  
- Early onset CRS (less than 3 days from cell infusion)  
- Co-morbidities (a score of 3 or greater using the Hematopoietic Cell Transplantation Comorbidity Index; for solid tumor patients – prior solid tumor will not be counted)  
\(^3\)Signs of hypoperfusion include:  
- Decreased urine output (less than 0.5 mL/kg/hour)  
- Lactate greater than or equal to 4 mmol/L, rising lactate, and/or poor lactate clearance (less than 10%) despite adequate fluid resuscitation

continued on next page
APPENDIX F: Management of CRS and Organ Toxicity - continued

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Sign/Symptom</th>
<th>Management</th>
</tr>
</thead>
</table>
| Grade 3   | Hypotension  | - IV fluid boluses as needed as in Grade 2 CRS  
- IL-6 antagonist¹ as in Grade 2 if not administered previously  
- Use vasopressors as needed  
- Transfer patient to ICU and obtain ECHO if not performed already  
- Start dexamethasone 10 mg IV every 6 hours; increase to 20 mg IV every 6 hours if refractory  
- Manage fever and constitutional symptoms as in Grade 1 CRS  
Grade 3 organ toxicity or  
Grade 4 transaminitis  
- Manage organ toxicity as per standard guidelines  
- Use IL-6 antagonist¹, corticosteroids as above and supportive care  
- Manage fever and constitutional symptoms as in Grade 1 CRS  |
| Grade 4   | Hypotension  | - IV fluids, IL-6 antagonist¹, vasopressors, and hemodynamic monitoring as in Grade 3  
- High-dose methylprednisolone¹  
- Manage fever and constitutional symptoms as in Grade 1  
Grade 4 organ toxicity  
excluding transaminitis  
- Symptomatic management of organ toxicity as per standard guidelines  
- Use IL-6 antagonist¹, high-dose methylprednisolone¹ and supportive care  |
|           | Hypoxia      | - Use supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation  
- Use IL-6 antagonist¹, corticosteroids as above and supportive care  |

¹See Appendix G for Interleukin-6 Antagonist and Corticosteroid Dosing Tables
## APPENDIX G: Interleukin-6 (IL-6) Antagonist and Corticosteroid Dosing Tables

### IL-6 Antagonist Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose for CRS and/or CRES</th>
<th>Maximum Dose</th>
<th>Mechanism of Action</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Tocilizumab1    | 8 mg/kg IV for up to three doses in a 24-hour period (Maximum 4 doses total) | Maximum 800 mg per dose | IL-6 receptor antagonist | First line agent  
Doses can be given 8 hours apart |
| 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 | Consider in patients who fail to respond to 1-2 doses of tocilizumab  
Requires chemotherapy consent |

1. Formulary restricted for use in CRS/CRES and for use in hemophagocytic lymphohistiocytosis (HLH)
2. Formulary restricted for use in CRS/CRES

### Corticosteroid Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose for CRS and/or CRES</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>10 to 20 mg IV either as a one-time dose or every 6 hours</td>
<td>Frequency of dosing depends on severity of symptoms and response</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>1 mg/kg IV every 12 hours</td>
<td>May be used in place of dexamethasone for CRES</td>
</tr>
</tbody>
</table>
| High-dose Methylprednisolone | 500 mg IV every 12 hours for 3 days, followed by  
+ 250 mg IV every 12 hours for 2 days, then  
+ 125 mg IV every 12 hours for 2 days, then  
+ 60 mg IV every 12 hours until CRS or CRES improvement to Grade 1 and then taper over 2 weeks | For patients with improvement to Grade 1 within one week or less, the corticosteroids can be stopped without tapering |
APPENDIX H: Grading of CRES

<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 score (see below)</td>
<td>Mild (7-9)</td>
<td>Moderate (3-6)</td>
<td>Severe (0-2)</td>
<td>Critical / obtunded</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>-</td>
<td>-</td>
<td>Stage 1 or 2 papilledema with CSF opening pressure less than 20 mmHg</td>
<td>Stage 3, 4, or 5 papilledema or CSF opening pressure greater than or equal to 20 mmHg or cerebral edema</td>
</tr>
<tr>
<td>Seizures or motor weaknesses</td>
<td>-</td>
<td>-</td>
<td>Partial seizure or non-convulsive seizures on EEG responding to benzodiazepine</td>
<td>Generalized seizures or convulsive or non-convulsive status epilepticus or new motor weakness</td>
</tr>
</tbody>
</table>

**CARTOX 10-point neurological assessment**
(Assign one point for each task performed correctly; score of 10 = normal)
- Orientation to year, month, city, hospital, President: 5 points
- Name 3 objects (point to clock, pen, button): 3 points
- Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- Count backwards from 100 by ten: 1 point

1Papilledema grading is performed according to Modified Frisén scale

CSF = cerebrospinal fluid  
EEG = electroencephalogram  
CARTOX = CAR T-cell therapy-associated TOXicity
### APPENDIX I: Management of CRES

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Grade 1** | - Vigilant supportive care: aspiration precautions; IV hydration  
- Withhold oral intake of food/medicines/fluids and assess swallowing  
- Convert all oral medications and/or nutrition to IV if swallowing is impaired  
- Avoid medications that cause CNS depression  
- Low doses of lorazepam (0.25-0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) may be used for agitated patients with careful monitoring  
- Neurology consultation  
- Daily CÁRTOX 10-point neurological assessment as in Appendix H  
- Fundoscopic exam to assess for papilledema  
- MRI brain with and without contrast; diagnostic lumbar puncture with OP; RMI spine if focal signs exist; CT of brain may be performed if MRI brain is not feasible  
- Daily 30-minute EEG; if no seizures detected on EEG, continue levetiracetam  
- If EEG shows non-convulsive status epilepticus, treat as per algorithm in Appendix J  
- Consider IL-6 antagonist\(^1\), if associated with concurrent CRS |
| **Grade 2** | - Supportive care and neurological workup as per Grade 1  
- IL-6 antagonist\(^1\), if associated with concurrent CRS  
- Dexamethasone or methylprednisolone\(^2\) for CRES not associated with concurrent CRS, or if refractory to IL-6 antagonist therapy when it is administered  
- Consider ICU transfer if associated with Grade 2 or greater CRS |
| **Grade 3** | - Supportive care and neurological workup as per Grade 1  
- ICU transfer is recommended  
- IL-6 antagonist\(^1\), if associated with concurrent CRS and if not administered previously  
- Dexamethasone or methylprednisolone around the clock\(^2\), if symptoms worsen despite IL-6 antagonist therapy or for CRES without concurrent CRS. Continue corticosteroids until improvement to Grade 1 and then taper or stop.  
- Low grade (Stage 1 or 2) papilledema with CSF OP less than 20 mmHg, see Appendix K  
- Consider repeat neuro-imaging (CT or MRI) every 2-3 days if persistent CRES greater than or equal to Grade 3 |
| **Grade 4** | - Supportive care and neurological workup as per Grade 1  
- ICU monitoring; consider mechanical ventilation for airway protection  
- IL-6 antagonist\(^1\) and repeat neuro-imaging as per Grade 3  
- High dose methylprednisolone\(^1\)  
- For convulsive status epilepticus, treat as per Appendix L  
- For high grade (Stage 3, 4, or 5) papilledema, CSF OP greater than or equal to 20 mmHg, or cerebral edema, see Appendix K |

\(^1\)See Appendix G for Interleukin-6 Antagonist Dosing and Corticosteroid Dosing Tables

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This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.
Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult

APPENDIX J: Management of Non-Convulsive Status Epilepticus

- Assess CAB / airway protection / high flow O₂, check blood glucose
- Lorazepam 0.5 mg IV x 1 with additional 0.5 mg IV every 5 minutes (to a maximum cumulative dose of 2 mg) to control electrographical seizures
- Levetiracetam 500 mg IV bolus (in addition to maintenance dose)
- If seizures persist, transfer to ICU and add a second agent phenobarbital at a loading dose of 60 mg IV
- Maintenance doses after resolution of status epilepticus
  - Lorazepam 0.5 mg IV every 8 hours x 3 doses
  - Increase levetiracetam to 1,000 mg IV every 12 hours
  - Phenobarbital 30 mg IV every 12 hours

APPENDIX K: Management of Raised Intracranial Pressure with or without Cerebral Edema

<table>
<thead>
<tr>
<th>Stage 1 and 2 papilledema with CSF OP less than 20 mmHg without cerebral edema</th>
<th>Acetazolamide 1,000 mg IV followed by 250-1,000 mg IV every 12 hours (monitor renal function and acid/base balance once or twice daily and adjust dose accordingly)</th>
</tr>
</thead>
</table>
| Stage 3, 4, and 5 papilledema, any cerebral edema on imaging studies, or CSF OP greater than or equal to 20 mmHg | - Use high-dose corticosteroids as per Grade 4 CRES along with the following measures for management of cerebral edema
  - Elevate head of bed to 30 degrees
  - Hyperventilation to achieve target PaCO₂ of 28-30 mmHg for no more than 24 hours
  - Hyperosmolar therapy with either mannitol 20% or hypertonic saline (3% or 23.4%)
    - Mannitol: initial dose 0.5-1 g/kg; maintenance dose 0.25-1 g/kg every 6 hours (metabolic profile and serum osmolality every 6 hours; hold mannitol if serum osmolality greater than or equal to 320 mOsm/kg or osmolol gap greater than or equal to 40)
    - Hypertonic 3% saline: initial dose 250 mL IV over 15 minutes, maintenance dose 50-75 mL/hour IV (electrolytes every 4 hours; hold infusion if serum sodium greater than or equal to 155 mEq/L)
  - Hypertonic 3% saline: initial dose 250 mL IV over 15 minutes, maintenance dose 50-75 mL/hour IV (electrolytes every 4 hours; hold infusion if serum sodium greater than or equal to 155 mEq/L)
  - Mannitol: initial dose 0.5-1 g/kg; maintenance dose 0.25-1 g/kg every 6 hours (metabolic profile and serum osmolality every 6 hours; hold mannitol if serum osmolality greater than or equal to 320 mOsm/kg or osmolol gap greater than or equal to 40)
  - Hypertonic 3% saline: initial dose 250 mL IV over 15 minutes, maintenance dose 50-75 mL/hour IV (electrolytes every 4 hours; hold infusion if serum sodium greater than or equal to 155 mEq/L)
  - If patient has ommaya reservoir, drain CSF to target OP less than 20 mmHg
  - Consider neurosurgery consultation, IV anesthetics for burst-suppression EEG
  - Metabolic profile every 6 hours; CT head daily; and adjust above medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia and hypotension.

CAB = circulation, airway, breathing
APPENDIX M: Diagnostic Criteria for CAR-Related Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS)

- If a patient that had a peak ferritin greater than 10,000 ng/mL during the cytokine release syndrome phase and developed any two of the following organ toxicities after CAR T-cell therapy, the patient may have HLH/MAS.
  - Greater than or equal to Grade 3 increase in bilirubin, aspartate transaminase, or alanine transaminase
  - Greater than or equal to Grade 3 oliguria or increase in creatinine
  - Greater than or equal to Grade 3 pulmonary edema
  - Presence of hemophagocytosis by morphology and/or CD68 immunohistochemistry in bone marrow or organs

Obtain baseline fasting triglyceride level and soluble IL-2

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APPENDIX L: Management of Convulsive Status Epilepticus

- Assess CAB / airway protection / high flow O₂, check blood glucose
- Transfer to ICU
- Lorazepam 2 mg IV × 1 with additional 2 mg IV after at least 1 minute to a total of 4 mg to control seizures
- Levetiracetam 500 mg IV bolus (in addition to maintenance dose)
- If seizures persist, and add a second agent phenobarbital at a loading dose 15 mg/kg IV
- Maintenance doses after resolution of status epilepticus
  - Lorazepam 0.5 mg IV every 8 hours × 3 doses
  - Increase levetiracetam to 1,000 mg IV every 12 hours
  - Phenobarbital 1-3 mg/kg IV every 12 hours
  - Continuous EEG if seizures are refractory

- Manage greater than or equal to Grade 3 organ toxicity with tocilizumab and corticosteroids as per CRS algorithm, see Appendix F

- Monitor ferritin, LDH, fibrinogen, transaminases, bilirubin, creatinine

- Improvement after 48 hours?
  - Yes
    - Continue management of CRS, see Appendix F
  - No
    - Consider adding etoposide (75-100 mg/m² IV every 4-7 days)
    - Consider intrathecal cytarabine (100 mg) with or without intrathecal hydrocortisone (50-100 mg) for CRES

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- Consider intrathecal cytarabine (100 mg) with or without intrathecal hydrocortisone (50-100 mg) for CRES
Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult

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SUGGESTED READINGS


This practice consensus algorithm is based on majority expert opinion of the CAR Cell Therapy Toxicity Assessment and Management work group at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following providers:

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