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 – PEDIATRIC

TABLE OF CONTENTS

Patient Initial Evaluation ............................................................................................................................................................................. Page 2
APPENDIX A: Supportive Care Considerations for Patients Receiving Immune Effector Cells.................................................. Page 3
APPENDIX B: Infection Prophylaxis Considerations............................................................................................................................... Page 4
APPENDIX C: Grading of CRS
APPENDIX D: Definition of High-dose Vaspressors ............................................................................................................................... Page 5
APPENDIX E: CTCAE Grading of Common Organ Toxicities .................................................................................................................. Page 5
APPENDIX F: Management of CRS and Organ Toxicity .......................................................................................................................... Pages 6-7
APPENDIX G: Interleukin-6 (IL-6) Antagonist and Corticosteroid Dosing Tables .................................................................................. Page 8
APPENDIX H: Grading of CRES .............................................................................................................................................................. Page 9
APPENDIX I: CARTOX 10-Point Neurological Assessment
APPENDIX J: Cornell Assessment of Pediatric Delirium (CAPD) ........................................................................................................ Page 10
APPENDIX K: Management of CRES ................................................................................................................................................... Page 11
APPENDIX L: Management of Non-convulsive Status Epilepticus
APPENDIX M: Management of Convulsive Status Epilepticus
APPENDIX N: Management of Convulsive Status Epilepticus
APPENDIX O: Diagnostic Criteria for CAR-Related Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS) ........................................................................................................ Page 12
Suggested Readings.................................................................................................................................................................................. Page 13
Development Credits ................................................................................................................................................................................. Page 14

CTCAE = Common Terminology Criteria for Adverse Events
CRS = Cytokine Release Syndrome

Copyright 2018 The University of Texas MD Anderson Cancer Center

Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 01/30/2018
Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric

**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
- Neurological status
- History
- Physical exam
- Lab results
- Chest x-ray
- Cardiac monitor, EKG, and/or ECHO

**MANAGEMENT**

- Determine if patient has Cytokine Release Syndrome (CRS)\(^1\) and/or CAR-related encephalopathy syndrome (CRES)\(^2\)
- Determine the grade of CRS\(^3\) and/or CRES\(^4\)

Does patient have either?  

Yes
- Notify Inpatient Attending
- See Appendix F for Management of CRS

No

\(^1\)The patient may have CRS if any of the following are present within the first 3 weeks of CAR cell therapy infusion:
- Fever (oral temperature greater than or equal to 38°C)
- Hypotension defined as:
  - Age 1 to 10 years: SBP less than \[70 + (2 \times \text{age in years})\] mmHg
  - Age greater than 10 years: SBP less than 90 mmHg
- Hypoxia (Needing oxygen to maintain oxygen saturation greater than 90%)
- Organ toxicity (See Appendix C for Grading)

\(^2\)The patient may have CRES if the following are present:
- Somnolence
- Confusion
- Encephalopathy
- Dysphasia
- Seizure

\(^3\)See Appendix C for Grading of CRS

\(^4\)See Appendix H for Grading of CRES

Copyright 2018 The University of Texas MD Anderson Cancer Center

Approved by the Executive Committee of the Medical Staff on 01/30/2018
### Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric

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.

**APPENDIX A: Supportive Care Considerations for Patients Receiving Immune Effector Cells**

#### Consults:
- Neurology Team to follow patient starting from day of cell infusion for patients receiving immune effector cells known to cause CRES or first in human products
- Critical Care Team to follow patient prior to day of cell infusion and then 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 10 mg/kg (maximum 500 mg) PO or IV twice daily for 30 days starting on day of cell infusion

#### Infectious Disease Screening (any time prior to apheresis):
- **Required** Infectious Disease Screening
  - Hepatitis B surface antigen (HBsAg)
  - Anti-hepatitis B core antibody (HBcAb)
  - Anti-hepatitis C virus antibody (HCVAb)
  - Anti-human immunodeficiency virus (HIV) antibody (HIV type 1 / 2 type O Ab)
  - HIV-1 / HCV / HCB Nucleic Acid Test
- **Optional Infectious Disease Screening (as clinically indicated)**
  - Anti-human T-cell lymphotropic virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagin RPR – Syphilis
  - CMV IgG and IgM
  - West Nile Virus Nucleic Acid Test
  - T Cruzi Antibody
  - T-spot to assess for exposure or history of tuberculosis
  - Strongyloides to assess for previous infection or exposure to strongyloides

#### Special Vital Signs (in addition to routine):
- For patients greater than 12 years of age, CARTOX 10-point neurological assessment three times per day (see Appendix I)
- For all patients on the Pediatric Service or with developmental age less than 12, CAPD pediatric delirium assessment three times per day (see Appendix J)

#### 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:
- Provide adequate hydration and allopurinol for prophylaxis in patients with high tumor burden and monitor electrolyte abnormalities as clinically indicated
  - Consider rasburicase for one dose if clinically indicated

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

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

---

1. Patients with recent travel out of the country should be considered for some/all of these additional tests.
# 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</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[herpes simplex or varicella zoster]</td>
<td>Valacyclovir 15-20 mg/kg (maximum 500-1,000 mg) &lt;sup&gt;1&lt;/sup&gt; PO daily or Acyclovir 30-45 mg/kg (maximum 800 mg/dose) &lt;sup&gt;1&lt;/sup&gt; PO twice daily</td>
<td>All patients</td>
<td>Start within 7 days of cell infusion, Continue until CD4 greater than 200 cell/mcL, May continue longer if protocol requires</td>
</tr>
<tr>
<td><strong>Pneumocystis carinii/jirovecii</strong></td>
<td>Preferred agent: Sulfamethoxazole/trimethoprim 2.5 mg/kg/trimethoprim (maximum 160 mg) PO twice daily on Mondays, Wednesdays, and Fridays only</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optional dosing for adolescents: Sulfamethoxazole/trimethoprim DS (800 mg/160 mg) PO daily on Mondays, Wednesdays, and Fridays only</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with contraindication or allergy to sulfamethoxazole/trimethoprim may be given pentamidine, atovaquone, or dapsone instead &lt;sup&gt;1&lt;/sup&gt;</td>
<td>All patients</td>
<td>Initiate by day 30, unless otherwise dictated by research protocol, Continue until CD4 greater than 200 cell/mcL, May continue longer if protocol requires</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td>Levofoxacin &lt;ul&gt;&lt;li&gt;Less than 5 years old: 10 mg/kg PO/IV every 12 hours&lt;/li&gt;&lt;li&gt;Greater than or equal to 5 years old: 10 mg/kg (maximum 500 mg) PO/IV every 24 hours&lt;/li&gt;&lt;/ul&gt; or Ciprofloxacin &lt;ul&gt;&lt;li&gt;10 mg/kg (maximum 500 mg) PO twice daily or&lt;/li&gt;&lt;li&gt;10 mg/kg (maximum 400 mg) IV twice daily&lt;/li&gt;&lt;/ul&gt;</td>
<td>Use if neutropenia&lt;sup&gt;2&lt;/sup&gt; expected for greater than 1 week</td>
<td>Start by day of cell infusion, May stop when neutropenia&lt;sup&gt;2&lt;/sup&gt; resolves</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td>Fluconazole 12 mg/kg (maximum 400 mg) PO/IV daily</td>
<td>Use if neutropenia&lt;sup&gt;2&lt;/sup&gt; expected for greater than 2 weeks</td>
<td>Start by day of cell infusion, May stop when neutropenia&lt;sup&gt;2&lt;/sup&gt; resolves</td>
</tr>
</tbody>
</table>

<sup>1</sup>Patients with history of varicella zoster (shingles) may require higher doses

<sup>2</sup>Neutropenia defined as absolute neutrophil count (ANC) of 0.5 K/microliter 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>Hypotension¹</td>
<td>No</td>
<td>Responds to IV fluids or low-dose vasopressor</td>
<td>Requires high-dose or multiple vasopressors³</td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>Needing Oxygen to maintain O₂ saturation greater than 90%</td>
<td>No</td>
<td>FiO₂ less than 40%</td>
<td>FiO₂ 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>

¹Grade 1 CRS may manifest as fever and/or grade 1 organ toxicity
²For grades 2, 3, or 4 CRS: any one of the criteria other than temperature is sufficient
³Hypotension defined as:
   - Age 1 to 10 years: SBP less than [70 + (2 x age in years)] mmHg
   - Age greater than 10 years: SBP less than 90 mmHg
⁴See Appendix D for definition of high-dose vasopressors

**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 0.3 mcg/kg/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 0.3 mcg/kg/minute</td>
</tr>
<tr>
<td>Epinephrine monotherapy</td>
<td>Greater than or equal to 0.3 mcg/kg/minute</td>
</tr>
<tr>
<td>Vasopressin monotherapy</td>
<td>Greater than or equal to 0.03 units/kg/hour⁶</td>
</tr>
<tr>
<td>Combination vasopressors (not including vasopressin)</td>
<td>Norepinephrine equivalent of greater than or equal to 0.5 mcg/kg/minute⁵</td>
</tr>
</tbody>
</table>

⁵VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (mcg/kg/minute)] + [dopamine (mcg/kg/minute) / 2] + [epinephrine (mcg/kg/minute)] + [phenylephrine (mcg/kg/minute) / 10]
### APPENDIX E: CTCAE Grading of Common Organ Toxicities

<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>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>
</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>
</tr>
<tr>
<td></td>
<td>Ejection fraction&lt;sup&gt;1&lt;/sup&gt; 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>
</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</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>
</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 calorific or fluid intake; receiving tube feeding or TPN</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>
</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>
</tr>
</tbody>
</table>

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

---

CTCAE = Common Terminology Criteria for Adverse Events

EF = ejection fraction

ADL = activities of daily living

<sup>1</sup>Ejection fraction may be increased with CRS, but is not graded

Continued on next page

---

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.
### 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 1 mL/kg/hour over 8 hours)</td>
<td>Anuria (less than 0.5 mL/kg/hour over 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</td>
<td>Life-threatening; dialysis indicated</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Disseminated Intravascular Coagulation (DIC)</td>
<td></td>
<td></td>
<td>Laboratory findings with no bleeding</td>
<td>Laboratory findings with bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Life-threatening; urgent intervention indicated</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash acmeiform</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>
</tr>
<tr>
<td></td>
<td>Rash maculo-papular</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>
</tr>
</tbody>
</table>

Note: For toxicities not listed here, please 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>
<tbody>
<tr>
<td>Grade 1</td>
<td>Fever or Grade 1 organ toxicity</td>
<td>- Acetaminophen and hypothermia blanket as needed for fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Assess for infection with blood and urine cultures, and chest x-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Consider antibiotics and filgrastim (if neutropenic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- IV fluids as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Symptomatic management of constitutional symptoms and organ toxicities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Consider IL-6 antagonist(^1) for persistent (greater than 3 days) or refractory fever</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hypotension(^2)</td>
<td>- IV fluid bolus of 10 – 20 mL/kg (maximum 1,000 mL) normal saline; repeat as necessary to correct hypotension(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Consider IL-6 antagonist(^1) for hypotension refractory to fluid boluses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If hypotension(^2) persists after two fluid boluses and IL-6 antagonist(^1), start vaspressors, transfer patient to PICS, and obtain ECHO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- In patients at high-risk for CRS(^3), if hypotension persists after IL-6 antagonist(^1), if there are signs of hypoperfusion(^4) or if there is rapid deterioration in the opinion of the clinician, may use dexamethasone 0.5 mg/kg/dose (maximum 10 mg/dose) IV every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Manage fever and constitutional symptoms as in Grade 1 CRS</td>
</tr>
<tr>
<td>Grade 2 organ toxicity</td>
<td>Hypoxia</td>
<td>- Use supplemental oxygen as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Use IL-6 antagonist(^1) with or without corticosteroids as in hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Manage fever and constitutional symptoms as in Grade 1 CRS</td>
</tr>
</tbody>
</table>

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

\(^2\)Hypotension defined as:
- Age 1 to 10 years: SBP less than \([70 + (2 \times \text{age in years})] \text{ mmHg}\)
- Age greater than 10 years: SBP less than 90 mmHg

\(^3\)High risk for CRS includes any of the following:
- High tumor burden
- 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

\(^4\)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

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 – Pediatric

Copyright 2018 The University of Texas MD Anderson Cancer Center

Approved by the Executive Committee of the Medical Staff on 01/30/2018
### 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 PICS and obtain ECHO if not done already
- Start dexamethasone 0.5 mg/kg/dose (maximum 10 mg/dose) IV every 6 hours; increase to 1 mg/kg (maximum 20 mg) IV every 6 hours if refractory
- Manage fever and constitutional symptoms as in Grade 1 CRS

### Hypoxia
- Use supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation
- Start high flow nasal cannula or BiPAP for FiO² needs greater than 40% and SpO²/FiO² ratio greater than 190 or PaO₂/FiO² ratio greater than 200
- Use IL-6 antagonist¹, corticosteroids as above and supportive care

### 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

### 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

### Hypoxia
- Mechanical ventilation
- Use IL-6 antagonist¹, high-dose methylprednisolone¹ and supportive care

### 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
- Mechanical ventilation for SpO₂/FiO² ratio less than 190, PaO₂/FiO² ratio less than 200, OSI 5-7.5 or OI 4.8²

---

¹See Appendix G for Interleukin-6 Antagonist and Corticosteroid Dosing Tables
²Oxygen Saturation Index (OSI) = (FiO₂ x mean airway pressure x 100)/SpO₂
Oxygenation Index (OI) = (FiO₂ x mean airway pressure x 100)/PaO₂
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>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>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 4 doses total</td>
<td>Maximum 800 mg per dose</td>
<td>IL-6 receptor antagonist</td>
<td>First line agent; Doses can be given 8 hours apart</td>
</tr>
<tr>
<td>Siltuximab</td>
<td>11 mg/kg IV once</td>
<td>No more than 1 dose in a 3-week period</td>
<td>Binds to both soluble and membrane bound IL-6</td>
<td>Consider in patients who fail to respond to 1-2 doses of tocilizumab</td>
</tr>
</tbody>
</table>

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>0.5-1 mg/kg (maximum 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 6 hours</td>
<td>May be used in place of dexamethasone for CRES</td>
</tr>
<tr>
<td>High-dose Methylprednisolone</td>
<td>15 mg/kg (maximum 500 mg) IV every 12 hours for 3 days, followed by 7.5 mg/kg (maximum 250 mg) IV every 12 hours for 2 days, then 2 mg/kg (maximum 125 mg) IV every 12 hours for 2 days, then 1 mg/kg (maximum 60 mg) IV every 12 hours until CRS or CRES improvement to Grade 1 and then taper over 2 weeks</td>
<td>For patients with improvement to Grade 1 within one week or less, the corticosteroids can be stopped without tapering</td>
</tr>
</tbody>
</table>
**APPENDIX H: Grading of CRES**

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence¹</td>
<td>Mild drowsiness / sleepiness</td>
<td>Moderate somnolence, limiting instrumental ADL</td>
<td>Obtundation or stupor</td>
<td>Life-threatening needing urgent intervention or mechanical ventilation</td>
</tr>
<tr>
<td>Confusion¹</td>
<td>Mild disorientation / confusion</td>
<td>Moderate disorientation, limiting instrumental ADL</td>
<td>Severe disorientation, limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td>Encephalopathy¹</td>
<td>Mild limiting of ADL</td>
<td>Limiting instrumental ADL</td>
<td>Limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td>Dysphasia¹</td>
<td>Dysphasia not impairing ability to communicate</td>
<td>Dysphasia with moderate impairment in ability to communicate spontaneously</td>
<td>Severe receptive or expressive dysphasia, impairing ability to read, write or communicate intelligibly</td>
<td>-</td>
</tr>
<tr>
<td>Seizure¹</td>
<td>Brief partial seizure; no loss of consciousness</td>
<td>Brief generalized seizure</td>
<td>Multiple seizures despite medical intervention</td>
<td>Life-threatening; prolonged repetitive seizures</td>
</tr>
<tr>
<td>Incontinence or motor weakness³</td>
<td>-</td>
<td>-</td>
<td>Bowl / bladder incontinence; Weakness limiting self-care ADL, disabling</td>
<td>-</td>
</tr>
<tr>
<td>Tremor¹</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>-</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>-</td>
<td>-</td>
<td>Stage 1 or 2 papilledema² with CSF OP less than 20 mmHg</td>
<td>Stage 3, 4, or 5 papilledema² or CSF OP greater than or equal to 20 mmHg or cerebral edema</td>
</tr>
<tr>
<td>Neurological assessment score³</td>
<td>Mild (7-9)</td>
<td>Moderate (3-6)</td>
<td>Severe (0-2)</td>
<td>Critical (obtunded; convulsive status epilepticus; motor weakness; papilledema; CSF OP greater than or equal to 20 mmHg; cerebral edema)</td>
</tr>
<tr>
<td>Cornell Assessment of Pediatric Delirium (CAPD)⁴</td>
<td>-</td>
<td>Score 7-9</td>
<td>Score greater than 9</td>
<td>Critical (obtunded; convulsive status epilepticus; motor weakness; papilledema; CSF OP greater than or equal to 20 mmHg; cerebral edema)</td>
</tr>
</tbody>
</table>

*ADL = activities of daily living
*OP = opening pressure

¹Grading per CTCAE, version 4
²Papilledema grading is performed according to Modified Frisén scale
³For patients greater than 12 years of age; see Appendix I for CARTOX 10-point Neurological Assessment
⁴For all patients on Pediatric Service; see Appendix J for CAPD

Note: For toxicities not listed here, refer to CTCAE, version 4 for grading.
APPENDIX I: CARTOX 10-Point Neurological Assessment

- 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., National bird is the bald eagle): 1 point
- Count backwards from 100 by tens: 1 point

APPENDIX J: Cornell Assessment of Pediatric Delirium (CAPD)

RASS Score\(^1\) ______ (if -4 or -5, do not proceed)

| Answer the following based on your interactions with the patient over the course of the shift\(^2\) |
|---------------------------------|-------|------|------|------|------|-------|-------|------|------|
| 1. Does the child make eye contact with the caregiver? | Never | Rarely | Sometimes | Often | Always | Never | Rarely | Sometimes | Often | Always |
| 2. Are the child’s actions purposeful? |         |       |          |       |        |       |       |          |       |        |
| 3. Is the child aware of his/her surroundings? |         |       |          |       |        |       |       |          |       |        |
| 4. Does the child communicate needs and wants? |         |       |          |       |        |       |       |          |       |        |
| 5. Is the child restless? |        |       |          |       |        |       |       |          |       |        |
| 6. Is the child inconsolable? |        |       |          |       |        |       |       |          |       |        |
| 7. Is the child undertactive – very little movement while awake? |        |       |          |       |        |       |       |          |       |        |
| 8. Does it take the child a long time to respond to interactions? |        |       |          |       |        |       |       |          |       |        |

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

\(^2\) For 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 K: 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 [0.05 mg/kg (maximum 1 mg) IV every 8 hours] or haloperidol [0.05 mg/kg (maximum 1 mg) IV every 6 hours] may be used for agitated patients with careful monitoring  
  ● Neurology consultation  
  ● CARTOX 10-point Neurological Assessment and/or CAPD Pediatric Delirium Assessment as in Appendix I and J  
  ● Fundoscopic exam to assess for papilledema  
  ● MRI brain with and without contrast; diagnostic lumbar puncture with OP; MRI 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 L  
  ● Consider IL-6 antagonist¹, if associated with concurrent CRS  |
| **Grade 2** | ● Supportive care and neurological workup as per Grade 1  
  ● IL-6 antagonist¹, if associated with concurrent CRS  
  ● Dexamethasone or methylprednisolone¹ for CRES not associated with concurrent CRS, or if refractory to IL-6 antagonist therapy when it is administered  
  ● Consider PICS transfer if associated with Grade 2 or greater CRS  |
| **Grade 3** | ● Supportive care and neurological workup as per Grade 1  
  ● PICS transfer is recommended  
  ● IL-6 antagonist¹, if associated with concurrent CRS and if not administered previously  
  ● Dexamethasone or methylprednisolone around the clock¹, 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 M  
  ● 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  
  ● PICS monitoring; consider mechanical ventilation for airway protection  
  ● IL-6 antagonist¹ and repeat neuro-imaging as per Grade 3  
  ● High dose methylprednisolone¹  
  ● For convulsive status epilepticus, treat as per Appendix N  
  ● For high grade (Stage 3, 4, or 5) papilledema, CSF OP greater than or equal to 20 mmHg, or cerebral edema, see Appendix M  |

OP = opening pressure
APPENDIX L: Management of Non-convulsive Status Epilepticus

- Assess CAB / airway protection / high flow O₂, check blood glucose
- Lorazepam 0.05 mg/kg (maximum 1 mg) IV; repeat dose every 5 minutes (to a maximum of 4 doses) to control electrographical seizures
- Levitiracetam 40 mg/kg (maximum 2,500 mg) IV bolus (in addition to maintenance dose)
- If seizures persist, transfer to PICS and add phenobarbital at a loading dose of 10 – 20 mg/kg (maximum 1,000 mg) IV
- Maintenance doses after resolution of status epilepticus
  - Lorazepam 0.05 mg/kg (maximum 1 mg) IV every 8 hours × 3 doses
  - Levitiracetam 15 mg/kg (maximum 1,500 mg) IV every 12 hours
  - Phenobarbital 1 – 3 mg/kg IV every 12 hours

CAB = circulation, airway, breathing

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

| Stage 1 and 2 papilledema with CSF OP less than 20 mmHg without cerebral edema | 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) |
| Stage 3, 4, and 5 papilledema, any cerebral edema on imaging studies, or CSF OP greater than or equal to 20 mmHg | 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) |

- 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%)  
  - 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 5 mL/kg IV over 15 minutes, maintenance dose 1 mL/kg/hour IV to reach a target sodium level of 150-155 mEq/L (electrolytes every 4 hours; hold infusion if serum sodium greater than 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

OP = opening pressure
Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric

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.

APPENDIX N: Management of Convulsive Status Epileptics

- Assess CAB / airway protection / high flow O₂, check blood glucose
- Transfer to PICS
- Lorazepam 0.1 mg/kg (maximum 2 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)
- If seizures persist, transfer to PICS and add phenobarbital at a loading dose 10 – 20 mg/kg (maximum 1,000 mg) IV
- Maintenance doses after resolution of status epilepticus
  - Lorazepam 0.05 mg/kg (maximum 1 mg) IV every 8 hours × 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
  - Continuous EEG if seizures are refractory

APPENDIX O: 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

1Grading as per Common Terminology Criteria for Adverse Events, version 4

MANAGEMENT OF CAR-RELATED HLH / MAS

Suspected HLH

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 (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 CRES

Intrathecal cytarabine

1. 1 – 1.99 years: 30 mg
2. 2 – 2.99 years: 50 mg
3. At least 3 years old: 70 mg

Intrathecal hydrocortisone

1. 1 – 1.99 years: 15 mg
2. 2 – 2.99 years: 25 mg
3. At least 3 years old: 50 mg

2Graded specifically for use in children

Copyright 2018 The University of Texas MD Anderson Cancer Center

Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 01/30/2018
SUGGESTED READINGS


Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric

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.

DEVELOPMENT CREDITS

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

- Jessica S. Foglesong, MD (Pediatrics – Patient Care)
- Alison Gulbis, PharmD (Pharmacy Clinical Programs)
- 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)
- Michael Rytting, MD (Pediatrics – Patient Care)
- Elizabeth Shpall, MD (Stem Cell Transplantation)
- John Slopis, MD (Neuro-Oncology)
- Anita M. Williams
- Sonal Yang, PharmD

*T Core Development Team Lead
* Clinical Effectiveness Development Team