Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult

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.

TABLE OF CONTENTS

CRS = cytokine release syndrome
CTCAE = Common Terminology Criteria for Adverse Events
CRES = CAR-related encephalopathy syndrome

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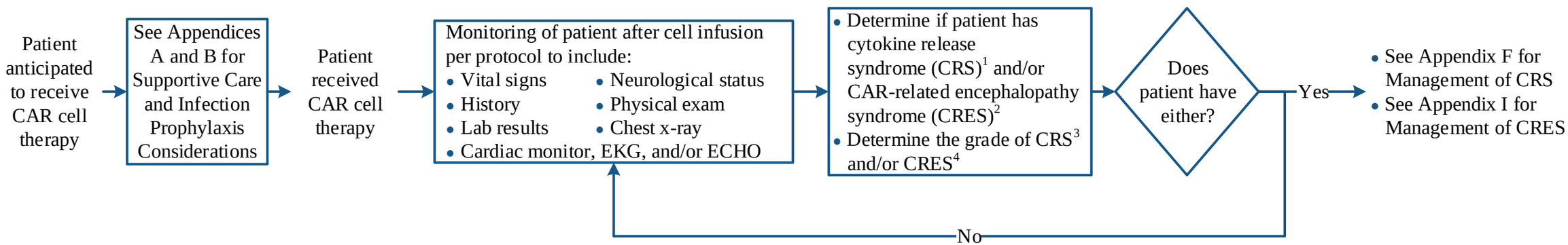
INITIAL EVALUATION

MANAGEMENT



[1]The 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)

[2]The patient may have CRES if any of the following are present:

- Somnolence
- Encephalopathy
- Seizure
- Agitation
- Dysgraphia
- Cerebral edema
- Confusion
- Dysphasia
- Tremor
- Incontinence or motor weakness
- Raised intracranial pressure

[3]See Appendix C for Grading of CRS

[4]See Appendix H for Grading of CRES

Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 10/31/2017

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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):

- **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)**[1]
  - Anti-human T-cell lymphotrophic virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagin RPR – Syphilis
  - Cytomegalovirus (CMV) IgG and IgM
  - West Nile Virus Nucleic Acid Test
  - T Cruzi Antibody
  - 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):

- 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
  - 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
  - Ferritin daily
  - Chemistries daily
  - LDH daily

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

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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.

Infection Type	Medication (Doses need to be adjusted for renal dysfunction)	Who Should Receive?	Duration
Viral (herpes simplex or varicella zoster)	Valacyclovir 500 to 1,000 mg[1] PO daily **or** Acyclovir 400 to 800 mg[1] PO twice daily	All patients	Start within 7 days of cell infusion Continue until CD4 greater than 200 cell/mcL May continue longer if protocol requires
Pneumocystis carinii/jiroveci	**Preferred agent:** 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 *Patients with contraindication or allergy to sulfamethoxazole/trimethoprim may be given pentamidine, atovaquone, or dapsone instead*	All patients	Initiate by day 30, unless otherwise dictated by research protocol Continue until CD4 greater than 200 cell/mcL May continue longer if protocol requires
Bacterial	Levofloxacin 500 mg PO/IV daily **or** Ciprofloxacin 500 mg PO or 400 IV twice daily	Use if neutropenia[2] expected for greater than 1 week	Start by day of cell infusion May stop when neutropenia[2] resolves
Fungal	Fluconazole 200 to 400 mg PO/IV daily	Use if neutropenia[2] expected for greater than 2 weeks	Start by day of cell infusion May stop when neutropenia[2] resolves

[1] Patients with history of varicella zoster (shingles) may require higher doses
[2] Neutropenia defined as absolute neutrophil count (ANC) of 0.5 K/microliter or less

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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)

Category	Sign/Symptom	CRS Grade 1[1]	CRS Grade 2[2]	CRS Grade 3[2]	CRS Grade 4[2]
Vital signs	**Temperature greater than or equal to 38°C**	Yes	Any	Any	Any
	SBP less than 90 mmHg	No	Responds to IV fluids or low-dose vasopressor	Requires high-dose or multiple vasopressors[3]	Life-threatening
	Needing oxygen to maintain O_2 saturation greater than 90%	No	FiO_2 less than 40%	FiO_2 greater than or equal to 40% and/or requiring BiPAP	Requires ventilator support
Organ Toxicity	**See Appendix E**	Grade 1	Grade 2	Grade 3 or grade 4 transaminitis	Grade 4 except grade 4 transaminitis

[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

FiO_2 = fraction of inspired oxygen
BiPAP = bilevel positive airway pressure

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

Vasopressor	Definition of High-dose Vasopressor
Norepinephrine monotherapy	Greater than or equal to 20 mcg/minute
Dopamine monotherapy	Greater than or equal to 10 mcg/kg/minute
Phenylephrine monotherapy	Greater than or equal to 200 mcg/minute
Epinephrine monotherapy	Greater than or equal to 10 mcg/minute
Vasopressin	Vasopressin + norepinephrine equivalent of greater than or equal to 10 mcg/minute[4]
Combination vasopressors (not including vasopressin)	Norepinephrine equivalent of greater than or equal to 20 mcg/minute[5]

[4]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 E: CTCAE Grading of Common Organ Toxicities

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

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

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

Continued on next page

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APPENDIX E: CTCAE Grading of Common Organ Toxicities - *continued*

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

Category	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hepatic	**AST or ALT increased**	Greater than ULN to 3 x ULN	Greater than 3 x ULN to 5 x ULN	Greater than 5 x ULN to 20 x ULN	Greater than 20 x ULN
	Total bilirubin increased	Greater than ULN to 1.5 x ULN	Greater than 1.5 x ULN to 3 x ULN	Greater than 3 x ULN to 10 x ULN	Greater than 10 x ULN
Renal	**Urine output decreased**	-	-	Oliguria (less than 80 mL / 8 hours)	Anuria (less than 240 mL / 24 hours)
	Acute kidney injury	Creatinine 1.5-2 x above baseline	Creatinine 2-3 x above baseline	Creatinine greater than 3 x baseline or greater than 4 mg/dL	Life-threatening; dialysis indicated
Coagulopathy	**Disseminated Intravascular Coagulation (DIC)**	-	Laboratory findings with no bleeding	Laboratory findings with bleeding	Life-threatening; urgent intervention indicated
Skin	**Rash acneiform**	Papules and/or pustules covering less than 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	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	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	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
	Rash maculo-papular	Macules/papules covering less than 10% BSA with or without symptoms (*e.g.*, pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (*e.g.*, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering greater than 30% BSA with or without associated symptoms; limiting self-care ADL	-

ULN = upper limit of normal BSA = body surface area

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APPENDIX F: Management of CRS and Organ Toxicity

CRS Grade	Sign/Symptom	Management
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
	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
	Grade 2 organ toxicity	• 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

Continued on next page

[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

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APPENDIX F: Management of CRS and Organ Toxicity - *continued*

CRS Grade	Sign/Symptom	Management
Grade 3	**Hypotension**	• IV fluid boluses as needed as in Grade 2 CRS • IL-6 antagonist[1] 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
	Hypoxia	• Use supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Use IL-6 antagonist[1], corticosteroids as above and supportive care
	Grade 3 organ toxicity or Grade 4 transaminitis	• Manage organ toxicity as per standard guidelines • Use IL-6 antagonist[1], corticosteroids as above and supportive care • Manage fever and constitutional symptoms as in Grade 1 CRS
Grade 4	**Hypotension**	• IV fluids, IL-6 antagonist[1], vasopressors, and hemodynamic monitoring as in Grade 3 • High-dose methylprednisolone[1] • Manage fever and constitutional symptoms as in Grade 1
	Hypoxia	• Mechanical ventilation • Use IL-6 antagonist[1], high-dose methylprednisolone[1] and supportive care
	Grade 4 organ toxicity excluding transaminitis	• Symptomatic management of organ toxicity as per standard guidelines • Use IL-6 antagonist[1], high-dose methylprednisolone[1] and supportive care

[1]See Appendix G for Interleukin-6 Antagonist and Corticosteroid Dosing Tables

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APPENDIX G: Interleukin-6 (IL-6) Antagonist and Corticosteroid Dosing Tables

IL-6 Antagonist Dosing

Drug	Recommended Dose for CRS and/or CRES	Maximum Dose	Mechanism of Action	Comments
Tocilizumab[1]	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
Siltuximab[2]	11 mg/kg IV once	No more than 1 dose in a 3-week period	Binds to both soluble and membrane bound IL-6 Neutralizes IL-6	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

Drug	Recommended Dose for CRS and/or CRES	Comments
Dexamethasone	10 to 20 mg IV either as a one-time dose or every 6 hours	Frequency of dosing depends on severity of symptoms and response
Methylprednisolone	1 mg/kg IV every 12 hours	May be used in place of dexamethasone for CRES
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

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APPENDIX H: Grading of CRES

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

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

[1]Papilledema grading is performed according to Modified Frisén scale

CSF = cerebrospinal fluid
EEG = electroencephalogram
CARTOX = CAR T-cell therapy-associated TOXicity

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APPENDIX I: Management of CRES

Grade	Management
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 CARTOX 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; 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 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[1] 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[1], 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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APPENDIX J: Management of Non-Convulsive Status Epilepticus

- Assess CAB / airway protection / high flow O_2, check blood glucose
- Lorazepam 0.5 mg IV × 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 × 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

Stage 1 and 2 papilledema with CSF OP less than 20 mmHg without cerebral edema	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)
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 $PaCO_2$ 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) ◦ Imminent herniation - dose to be administered by physician: 30 mL of 23.4% hypertonic saline IV (may repeat in 15 minutes) • 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

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APPENDIX L: Management of Convulsive Status Epilepticus

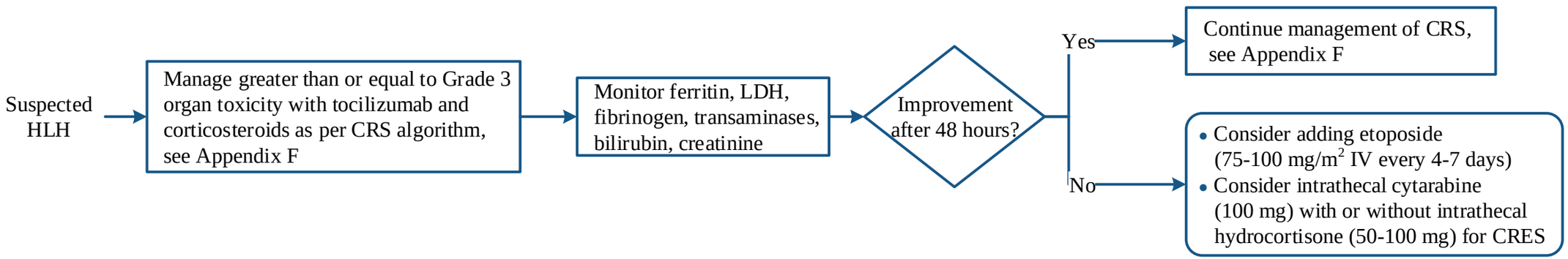
- Assess CAB / airway protection / high flow O_2, check blood glucose
- Transfer to ICU
- Lorazepam 2 mg IV × 1 with additional 2 mg IV after at least 1 minute to a total of 4 mg to control seizures
- Levetiracetam 500 mg IV bolus (in addition to maintenance dose)
- If seizures persist, and add a second 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

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[1]
  - Greater than or equal to Grade 3 oliguria or increase in creatinine[1]
  - Greater than or equal to Grade 3 pulmonary edema[1]
  - Presence of hemophagocytosis by morphology and/or CD68 immunohistochemistry in bone marrow or organs
- Obtain baseline fasting triglyceride level and soluble IL-2

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

MANAGEMENT OF CAR-RELATED HLH / MAS



SUGGESTED READINGS

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Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult

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.

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