DukeMedicine
Division of Cellular Therapy

ADULT AND PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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Management of Immune Effector Cell Therapy Complications

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APBMT-COMM-045
MANAGEMENT OF IMMUNE EFFECTOR CELL THERAPY COMPLICATIONS

1 PURPOSE

1.1 To outline the management of the complications that may occur following administration of Immune Effector Cells (IEC), including Cytokine Release syndrome (CRS) and neurologic toxicity.

2 INTRODUCTION

2.1 Immune Effector Cells (IEC) are engineered cells used to modulate an immune response for therapeutic intent, such as dendritic cells, natural killer cells, T cells, and B cells. This includes, but is not limited to, genetically engineered chimeric antigen receptor T cells (CAR-T cells) and therapeutic vaccines.

2.2 All staff involved in the prescribing, dispensing, or administration of IEC therapy are required to complete training modules, such as Risk Evaluation and Mitigation Strategy (REMS) specific to each individual product. The knowledge assessment will be kept on file within the Duke Center for Medication Policy.

2.2.1 Training for all staff will include the detection of and management of immune effector cellular therapy complications.

3 SCOPE AND RESPONSIBILITES

3.1 Interdisciplinary

3.1.1 All staff involved in the care of the IEC patient will provide ongoing monitoring of the patient for the detection of complications associated with immune effector cell therapy.

3.1.2 The physician or physician designee will place an order for the IEC product and associated supportive care in the electronic medical record (EMR).

3.1.3 The nurse will provide supportive care and administer any treatment ordered by physician.

3.1.4 The pharmacist will ensure availability of medications adequate to treat expected complications of IEC administration.

3.1.5 In the event that the primary team deems an escalation of care is needed, patients will be promptly transferred to the care of the intensive care service and will include plans for patient monitoring before, during and after transfer and communication of the ongoing care plan.

4 DEFINITIONS/ACRONYMS

4.1 CAR-T Chimeric Antigen Receptor T

4.2 CRS Cytokine Release Syndrome

4.3	EMR	Electronic Medical Record
4.4	DIC	Disseminated intravascular coagulation
4.5	IEC	Immune Effector Cells
4.6	IV	Intravenous
4.7	REMS	Risk Evaluation and Mitigation Strategy
4.8	SOB	Shortness of Breath

5 MATERIALS

5.1 NA

6 EQUIPMENT

6.1 NA

7 SAFETY

7.1 NA

8 PROCEDURE

8.1 Prior to the infusion of the IEC therapy, the provider team will provide education to the patient and caregiver on the potential side effects associated with the applicable IEC administration.

8.1.1 If the patient is to receive commercial product, the patient must be provided with a "wallet card" and/or product-specific education, as applicable, containing information to remind patients of signs and symptoms of common toxicities associated with the product. Check product requirements for applicability.

8.2 Prior to initiation of therapy, the physician and pharmacist will coordinate availability of adequate supplies of medications used to treat complication(s) of IEC therapy.

8.2.1 The Pharmacist will ensure the availability of 2 doses of tocilizumab, or other indicated interventional therapy, prior to administration of applicable IEC therapy.

8.3 IEC Therapy will be administered as per APBMT-COMM-045 *Immune Effector Cell Administration and Patient Management.*

8.4 During and following administration, the provider team, advanced practice providers, and nursing staff will continue regular assessments of the recipient to detect complications of IEC including signs of cytokine release syndrome and neurologic dysfunction, which may be severe or life threatening. The patient and caregiver will be instructed to continue to assess for signs and symptoms of complications when away from the patient care unit. If any complications of IEC therapy are detected, appropriate supportive care and treatment, as applicable, will be initiated.

8.5 Complications of IEC therapy may include any of the following and ongoing evaluation for detection is required during and following IEC administration (see specific product insert for more information for product specific side effects and duration of occurrence):

8.5.1 Cytokine Release Syndrome

8.5.1.1 Symptoms include:

8.5.1.1.1 Fever

8.5.1.1.2 Hypotension

8.5.1.1.3 Hypoxia

8.5.1.1.4 Tachycardia

8.5.1.1.5 Arrhythmia

8.5.1.2 May be associated with:

8.5.1.2.1 Hepatic dysfunction

8.5.1.2.2 Renal dysfunction

8.5.1.2.3 Cardiac dysfunction

8.5.1.2.4 Coagulopathy

8.5.1.2.5 Neurologic Dysfunction

8.5.1.3 CRS Grading Scales

8.5.1.3.1 The Adult BMT group will standardize all CRS grading as per the ASTCT CRS Consensus Grading (*Biol Blood Marrow Transplant.* 2019, 25, 625-638). See Table 1 below.

8.5.1.3.2 The Pediatric BMT group will standardize all CRS grading as per protocol or the ASTCT CRS Consensus Grading (*Biol Blood Marrow Transplant*. 2019, 25, 625-638). See Table 1 below.

Table 1. ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥ 38 degrees C	Temperature ≥ 38 degrees C	Temperature ≥ 38 degrees C	Temperature ≥ 38 degrees C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or+		
Hypoxia	None	Requiring low-flow nasal cannula$ or blow by	Requiring high-flow nasal cannula$, facemask, nonrebreather mask or Venturi mask	Requiring positive pressure (eg. CPAP, BiPAP, intubations and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

*Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
+ CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
$ Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute.

8.5.1.4 CRS Management

8.5.1.4.1 Treatment is based on severity and requires prompt initial evaluation and ongoing evaluation for response.

8.5.1.5 Evaluate need for hospitalization, if applicable.

8.5.1.5.1 Initiate treatment with supportive care.

8.5.1.5.2 Evaluate role for tocilizumab (severe and life threatening CRS) or other approved agents for treatment as outlined in hospital treatment algorithms and initiate treatment, if warranted.

8.5.1.5.3 Evaluate role for corticosteroids (life threatening emergency) and initiate treatment, if warranted.

8.5.1.5.4 See Table 2 below for possible treatment algorithm options. Treatment may be tailored for individual patient, clinical response, and IEC product recommendations.

Table 2. CRS Management Algorithm

CRS Management Algorithm		
CRS Severity	Symptoms	Proposed Management
Prodrome Syndrome	Low grade fever, fatigue, loss of appetite	- Observe in person - Exclude infection and consider antibiotics - Provide supportive care
CRS requiring mild intervention	One or more of the following: - high fever - hypoxia - mild hypotension	Consider the following: Antipyretics Oxygen IV fluids Low dose vasopressors as needed
CRS requiring moderate to aggressive intervention	One or more of the following: -Hemodynamic instability despite IVF and vasopressor support -Worsening respiratory distress, including increased oxygen requirement and or need for mechanical ventilation -Rapid clinical deterioration	Consider the following: -High dose vasopressors -Oxygen -Mechanical ventilation -Supportive care -Administer Tocilizumab: -Administer dose #1 and evaluate for response -Repeat as needed at a minimum of 8 hours if no improvement -If no response, give 3rd dose or pursue alternate treatment for CRS -Limit to a maximum of 4 doses Consider Corticosteroids: -If no response to 1st dose of Tocilizumab within 12 to 18 hours, start methylprednisolone. -Continue until vasopressors and high-flow oxygen are no longer needed. Taper dosing at that time.

8.5.2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

8.5.2.1 The Adult BMT group utilizes the Immune Effector Cell-Associated Encephalopathy (ICE) score for all encephalopathy assessments as outlined in Table 3 below.

8.5.2.2 Note: Pediatrics does not utilize ICANS scoring.

Table 3. Immune Effector Cell-Associated Encephalopathy (ICE) Scoring

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points • **Naming**: ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Following commands**: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention**: ability to count backwards from 100 by 10: 1 point
Scoring: 10, no impairment; 7-9, grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

8.6 ICANS Symptoms

8.6.1 Symptoms include:

8.6.1.1 Anxiety

8.6.1.2 Agitation

8.6.1.3 Aphasia

8.6.1.4 Confusion

8.6.1.5 Delirium

8.6.1.6 Disorientation

8.6.1.7 Encephalopathy

8.6.1.8 Headache

8.6.1.9 Mutism

8.6.1.10 Peripheral neuropathy

8.6.1.11 Seizures

8.6.1.12 Sleep disorders

8.6.1.13 Tremor

8.7 Neurotoxicity Grading Scales

8.7.1 The Adult BMT group will standardize all neurotoxicity grading as per the ASTCT ICANS Consensus Grading for Adults as seen below (*Biol Blood Marrow Transplant.* 2019, 25, 625-638). See Table 4 below.

8.7.2 The Pediatric BMT group will standardize all neurotoxicity grading utilizing two grading scales, one assessing delirium and one assessing encephalopathy both as markers for neurotoxicity:

8.7.2.1 Cornell Assessment of Pediatric Delirium tool with developmental anchor points. (Nature Reviews Clinical Oncology 2019, 16:45-62. See supplemental tables). See Table 5 below.

8.7.2.2 CAR-T cell-related encephalopathy syndrome grading management as per the PALISI HSCT Sub-group Consensus Statement. (Nature Reviews Clinical Oncology 2019, 16:45-62) See Table 6 below.

8.7.3 Neurotoxicity may occur concurrently with CRS or after CRS resolution.

Table 4. ASTCT ICANS Consensus Grading For Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

***A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.**
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Table 5. Cornell Assessment of Pediatric Delirium tool with developmental anchor points.

Please answer the following based on your interactions with the patient over the course of your shift:

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

1. Holds gaze. Prefers primary parent. Looks at speaker.
2. Reaches and manipulates objects, tries to change position, if mobile may try to get up
3. Prefers primary parent, upset when separated from preferred caregivers. Comforted by familiar objects (for example, a 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

Table 6. CAR-T Cell-Related Encephalopathy Syndrome Grading Management

Grade 1 CRES	Grade 2 CRES	Grade 3 CRES	Grade 4 CRES
Signs and symptoms			
For patients aged >12 years (with age-appropriate cognitive performance): • Grade 1 somnolence, confusion, encephalopathy, dysphasia, seizure (brief partial seizure without loss of consciousness), and/or tremor[a] • Neurological assessment score 7–9 according to CARTOX-10 grading system[37] For patients aged ≤12 years: • Grade 1 CNS toxicities as above and CAPD[116] score <9	For patients aged >12 years (with age-appropriate cognitive performance): • Grade 2 somnolence, confusion, encephalopathy, dysphasia, seizure (brief generalized seizure), and/or tremor[a] • Neurological assessment score 3–6 For patients aged ≤12 years: • Grade 2 CNS toxicities as above and CAPD score <9	For patients aged >12 years (with age-appropriate cognitive performance): • Grade 3 somnolence, confusion, encephalopathy, dysphasia, seizure (multiple seizures despite medical interventions), tremor and incontinence or motor weakness[a], and/or elevated intracranial pressure (stage 1 or 2 papilloedema[b] with CSF opening pressure <20 mmHg) • Neurological assessment score 0–2 For patients aged ≤12 years: • CAPD score ≥9	• Patient is critical, obtunded, and/or unable to perform CAPD • High-grade (stage 3–5) papilloedema[b], CSF opening pressure ≥20 mmHg, or cerebral oedema • Life-threatening prolonged repetitive seizure • Requirement for invasive mechanical ventilation
Management			
• Vigilant supportive care with aspiration precautions and i.v. hydration • Withhold oral intake of food, medicines, and fluids and assess swallowing • Substitute all oral medications and/or nutrition with i.v. forms if swallowing is impaired • Avoid medications that cause CNS depression • Low doses of lorazepam (0.05 mg/kg (maximum 1 mg per dose) i.v. every 8 hours) or haloperidol (0.05 mg/kg (maximum 1 mg per dose) i.v. every 6 hours) can be used, with careful monitoring, for agitated patients • Neurology consultation • Fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast and diagnostic lumbar puncture with measurement of opening pressure; include MRI of the spine if focal peripheral neurological deficits have been observed. CT scan of brain can be performed if brain MRI is not feasible • Perform EEG: if no seizures on EEG, continue prophylactic treatment with levetiracetam (BOX 1); if EEG shows non-convulsive status epilepticus, treat patient according to algorithm A (BOX 4) • Consider anti-IL-6 therapy if CRES is associated with concurrent CRS	• Supportive care and neurological work-up as per grade 1 CRES • Administer anti-IL-6 therapy if associated with concurrent CRS • Dexamethasone 0.5 mg/kg (maximum 10 mg per dose) i.v. every 6 hours or methylprednisolone 1–2 mg/kg per day divided every 6–12 hours for CRES that is not associated with concurrent CRS or is refractory to prior anti-IL-6 therapy • Consider transfer to PICU if associated with grade ≥2 CRS (TABLE 2)	• Supportive care and neurological work-up as per grade 1 CRES • PICU transfer is recommended • Administer anti-IL-6 therapy if associated with concurrent CRS and if not administered previously • Dexamethasone 0.5 mg/kg (maximum 10 mg per dose) i.v. every 6 hours; increase to 20 mg i.v. every 6 hours if patient is refractory to initial doses or methylprednisolone 1–2 mg/kg per day divided every 6–12 hours around the clock if symptoms worsen despite anti-IL-6 therapy or for CRES without concurrent CRS • Continue corticosteroid treatment until improvement to grade 1, and then taper or stop • For patients with stage 1 or 2 papilloedema[b] with a CSF opening pressure <20 mmHg, treat according to algorithm A (BOX 5) • Consider repeat neuro-imaging (CT or MRI) every 2–3 days if ≥3 grade CRES persists	• Supportive care and neurological work-up as per grade 1 CRES • PICU monitoring; consider mechanical ventilation for airway protection • Neurosurgical evaluation • Consider repeating CT scans • Obtain chemistry panels frequently (every 6–8 hours), adjust medication and provide osmotherapy to prevent rebound cerebral oedema, renal failure, hypovolemia and/or hypotension, and electrolyte abnormalities • Anti-IL-6 therapy and repeat neuro-imaging as for grade 3 CRES • Consider high-dose corticosteroids (for example, methylprednisolone 1 g per day i.v. for 3 days followed by rapid taper) • Continue corticosteroids until improvement to grade 1 CRES, and then taper • For patients with convulsive status epilepticus, treat according to algorithm B (BOX 4) • For patients with stage 3, 4, or 5 papilloedema, CSF opening pressure ≥20 mmHg, or cerebral oedema, treat per algorithm B (BOX 5)

Early recognition of and intervention for chimeric antigen receptor (CAR) T cell-related encephalopathy syndrome (CRES) are essential to avoid life-threatening complications. CRES should be suspected if any of the above listed signs and symptoms are present within the first 4 weeks of CAR T cell therapy. CRES grading including patient history, physical examination, and CAR T Cell Therapy-Associated Toxicity 10-point assessment scale (CARTOX-10) neurological assessment score[37] or the Cornell Assessment of Pediatric Delirium (CAPD) tool[116] should be performed at least twice a day and when a change in the patient's clinical status is observed. The trend in CAPD scores within an individual patient is important; increasing scores can be used as a marker for CRES severity. CNS, central nervous system; CRS, cytokine-release syndrome; CSF, cerebrospinal fluid; EEG, electroencephalography; FiO_2, fraction of inspired oxygen; i.v., intravenous; PICU, paediatric intensive-care unit. [a]Graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines[99]; CTCAE-defined neurological toxicities should be assessed for aetiology, in a similar manner to fevers, and if the toxicities are thought to be attributable to CRES, then symptoms should be treated according to the management recommendations provided. [b]Papilloedema scoring according to the modified Frisen Scale[147].

8.7.3.1 Management of Neurologic complications may include:

8.7.3.1.1 Monitoring for signs and symptoms

8.7.3.1.2 Exclude other causes

8.7.3.1.3 Provide supportive care

8.7.3.1.4 Consider prophylaxis with anti-seizure medications for patients with known seizure history or as per IEC product recommendations.

8.7.4 Complications may also include, but is not limited to, any of the following and may be product specific:

8.7.4.1 Hypersensitivity reaction, including anaphylaxis

8.7.4.2 Chills

8.7.4.3 Constipation

8.7.4.4 Diarrhea

8.7.4.5 Disseminated intravascular coagulation (DIC)

8.7.4.6 Fatigue

8.7.4.7 Fever, including neutropenic fever

8.7.4.8 Hypogammaglobinemia

8.7.4.9 Hypertension

8.7.4.10 Infection, including viral reactivation, which may be serious or fatal

8.7.4.11 Shortness of breath (SOB)/dyspnea

8.7.4.12 Macrophage Activation Syndrome

8.7.4.13 Muscle and joint pain

8.7.4.14 Nausea

8.7.4.15 Pain

8.7.4.16 Prolonged cytopenia

8.7.4.17 Risk of secondary malignancy

8.7.4.18 Tumor Lysis Syndrome

8.7.4.19 Vomiting

8.8 Should a deterioration in the inpatient clinical status occur, there will be rapid escalation of care, increased intensity of monitoring, and relative workup to address complications and will include a written plan for communication of the transfer and ongoing management.

8.9 Should a deterioration in the outpatient clinical status occur for adults, there will be rapid escalation of care by calling 911 and the patient will be transferred to the emergency room or directly to the appropriate inpatient unit.

8.10 Should a deterioration in the outpatient clinical status occur for pediatrics, there will be rapid escalation of care, and if indicated, the team will call "A Rapid Response." and the patient will be transferred to the appropriate inpatient unit.

8.11 Communication to clinical staff, intensive care unit, emergency department, and pharmacy will be comprehensive and timely, as applicable. (See Hospital Policies for Patient Transport.)

9 RELATED DOCUMENTS/FORMS

9.1 DUH Pharmacy Policy on Risk Evaluation and Mitigation Strategies

10 REFFERENCES

10.1 Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome [published correction appears in *Blood*. 2015; 126(8):1048]. *Blood.* 2014; 124(2):188-195.

10.2 Lee DW, Santomasso BW, Locke FL, et al. ASTCT Consensus Grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells *Blood*. 2015; 126(8):1048]. *Biol Blood Marrow Transplantation*. 2019; 25:625-638.

10.3 Porter DL, Hwang WT, Frey NV et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med*. 2015; 7(303):303ra139.

10.4 Managing adverse events in patients treated with Kymriah (tisagenlecleucel). Novartis Booklet. 2018.

10.5 Kymriah (tisagenlecleucel) [package insert]. Novartis Pharmaceuticals Corporation, NJ. 2018.

10.6 Yescarta (axicabtagene ciloleucel) [package insert]. Kite Pharma, CA. 2018.

10.7 Mahadeo KM, Khazaol SJ, Abdel-Azim H. et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nature Reviews Clinical Oncology 2019, 16:45-62.

11 REVISION HISTORY

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04	J. Frith	8.5.1.5.2 added or other approved agents for treatment of CRS as outlined in hospital treatment algorithms

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