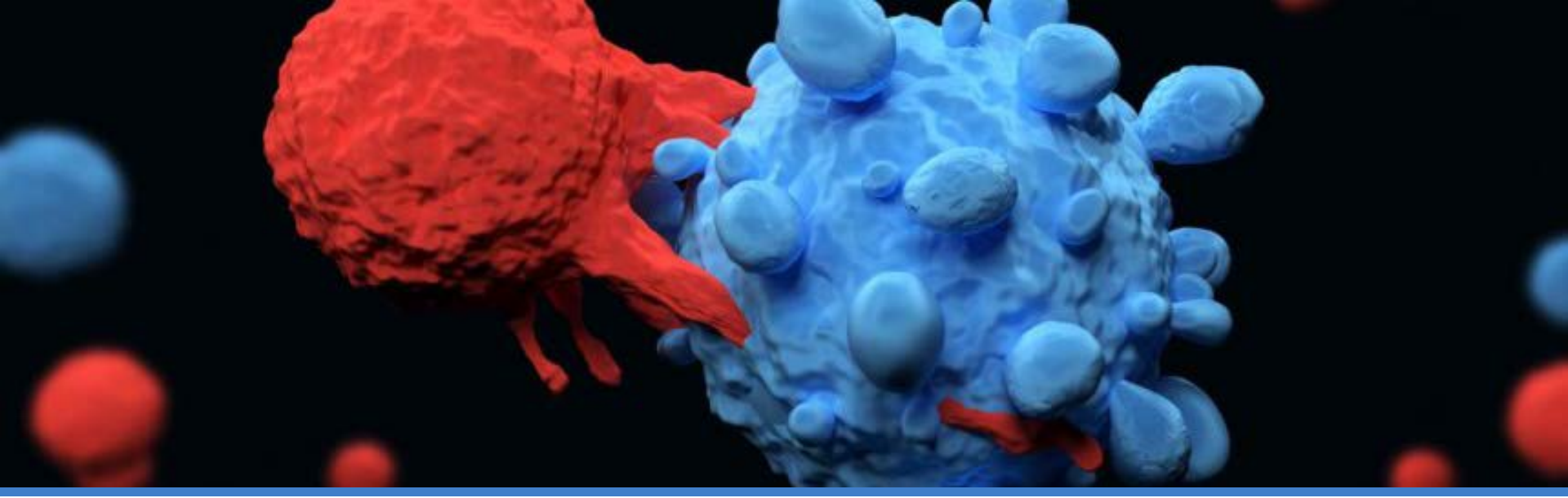

THE UNIVERSITY OF TEXAS
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Chimeric Antigen Receptor (CAR) T-cell Toxicities

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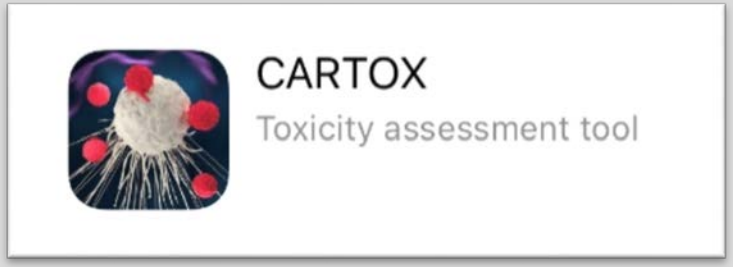
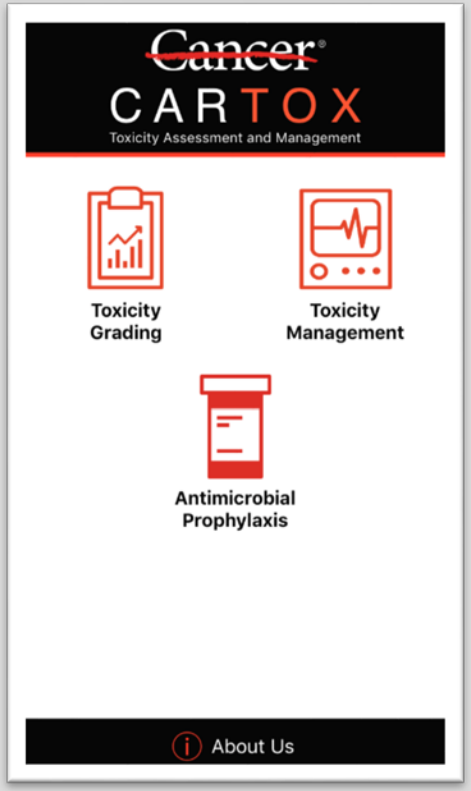
CARTOX: Toxicity Assessment and Management App



- Download the CARTOX app now
- Available in the app store
- Quick, intuitive tool to assist in CAR T-cell related toxicity grading and management



Disclosure Statement

Anne Rain Brown and the planning committee/staff have no relevant financial relationships to disclose.

Objectives

1. Summarize the current consensus criteria to grade a chimeric antigen receptor (CAR) T-cell related toxicity
2. Identify the appropriate treatment for a patient according to the toxicity grade

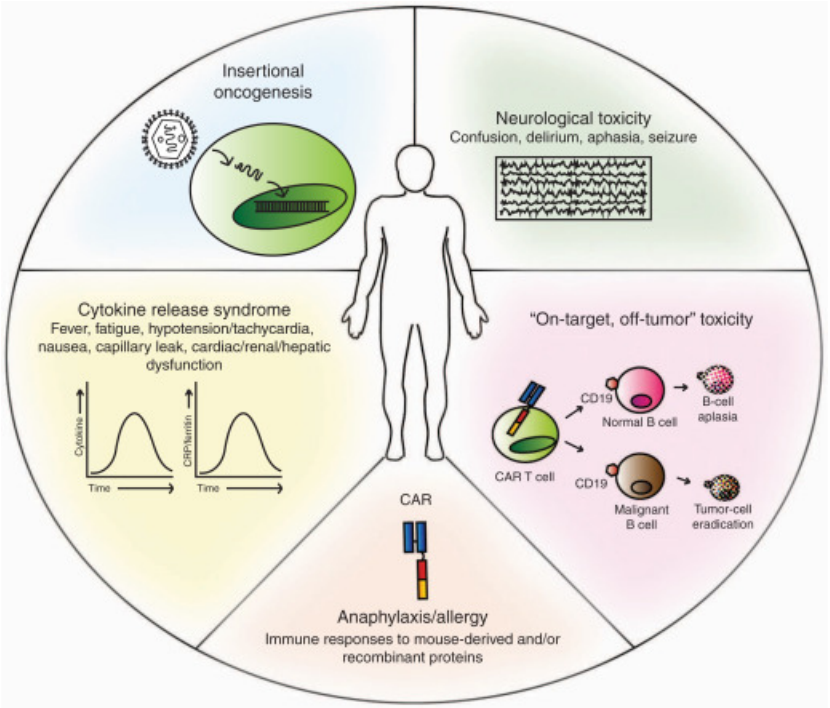
The Toxic Side of CAR T-Cell Therapy

- More than 1000 patients have received CAR T-cells in the US alone, with over 250 active clinical trials world-wide
  - Current FDA approved products target CD-19
    - Axicabtagene ciloleucel (axi-cel), Yescarta
    - Tisagenlecleucel, Kymriah
- CAR T-cells have produced impressive responses, but also toxicities
- Toxicities carry substantial morbidity and occasionally mortality
- Several groups have developed systems to grade toxicities and guide intervention
  - American Society for Transplantation and Cellular Therapy (ASTCT)

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019; 25(4):625-38

CAR T-cell Therapy Toxicities

- Infusion reactions
- Cytokine Release Syndrome (CRS)
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- Macrophage Activation Syndrome (MAS) or Hemophagocytic lymphohistiocytosis (HLH)
- Cytopenias, B-cell aplasia and hypogammaglobulinemia



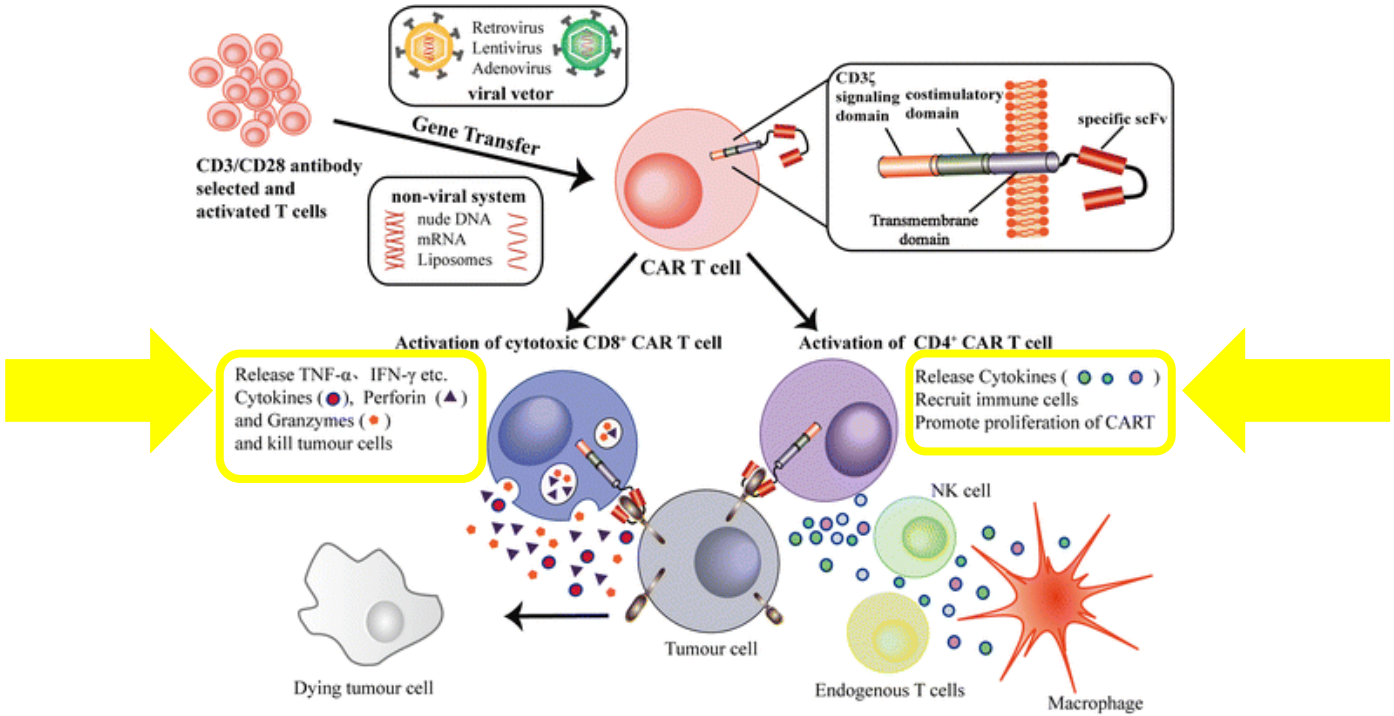
Bonifant CL, et al. *Mol Ther Oncolytics.* 2016; 3:16011. Figure 1; p. 2

Reported Deaths after CAR T-cell Therapies

Study	Malignancy	Patient age (years)	CAR-T-cell product* (designation or name)	CAR-T-cell dose (per kg)	Day of death after CAR-T-cell infusion	Cause of death‡
Morgan *et al.* (2010)[55]	Metastatic colon cancer	39	HER2-28-137-ζ	1×10^{10} total cells	5	ARDS
Brentjens *et al.* (2010)[34]	CLL	69	CD19-28-ζ (19-28z)	$1.2–3.0\times10^{7}$	2	CRS
Frey *et al.* (2014)[44]	B-ALL	>18	CD19-137-ζ (tisagenlecleucel, previously known as CTL019)	6.5×10^{6}	5	CRS (+ Influenza B)
				6.7×10^{6}	15	CRS (+ Pseudomonas sepsis, pneumonia)
				8.4×10^{6}	15	CRS (+ Stenotrophomonas sepsis, pneumonia)
Kochenderfer *et al.* (2015)[11]	PMBCL	30	CD19-28-ζ	2.5×10^{6}	16	Unknown (possibly cardiac arrhythmia)
Chong *et al.* (2016)[93]	FL	>18	CD19-137-ζ (tisagenlecleucel)	NA	NA	Encephalitis
Neelapu *et al.* (2016)[24] (ZUMA-1)	DLBCL	>18	CD19-28-ζ (axicabtagene ciloleucel; axi-cel, also known as KTE-C19)	2×10^{6}	NA	HLH
Locke *et al.* (2016)[96] (ZUMA-1)	NHL	>18	CD19-28-ζ (axi-cel)	2×10^{6}	NA	Cardiac arrest
Turtle *et al.* (2016)[17]	B-ALL	48	CD19-137-ζ	11.6×10^{6} $CD4^{+}$ + 8.4×10^{6} $CD8^{+}$	3	CRS
		52	CD19-137-ζ	1×10^{6} $CD4^{+}$ + 1×10^{6} $CD8^{+}$	122	Neurotoxicity
Turtle *et al.* (2016)[15]	NHL	>18	CD19-137-ζ	10×10^{6} $CD4^{+}$ + 10×10^{6} $CD8^{+}$	30	CRS (+ GI bleed)
				10×10^{6} $CD4^{+}$ + 10×10^{6} $CD8^{+}$	13	Neurotoxicity (+ CNS bleed)
ROCKET (2017)[64,69]	B-ALL	NA	CD19-28-ζ (JCAR015)	NA	NA	Cerebral oedema (5 cases)
ZUMA-1 (2017)[70]	NHL	>18	CD19-28-ζ (axi-cel)	NA	NA	Cerebral oedema
Turtle *et al.* (2017)[19]	CLL	62	CD19-137-ζ	1×10^{6} $CD4^{+}$ + 1×10^{6} $CD8^{+}$	11	Cerebral oedema

Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62

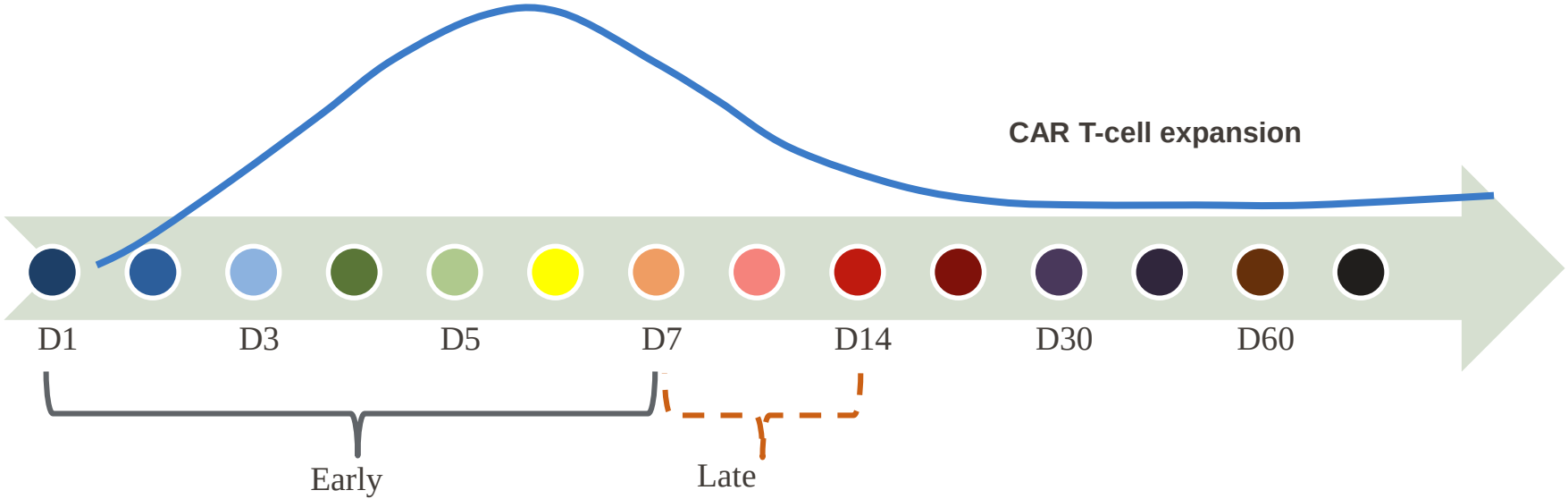
CAR T-cell Activation and Toxicity



Fan M, et al. *J Hematol Oncol*. 2017; 10(1):151. Figure 1; p. 2

Prevalence and Onset of CRS

- CRS will occur in 90% of patients
- CRS Grade ≥ 3 will occur in ~ 15% of patients

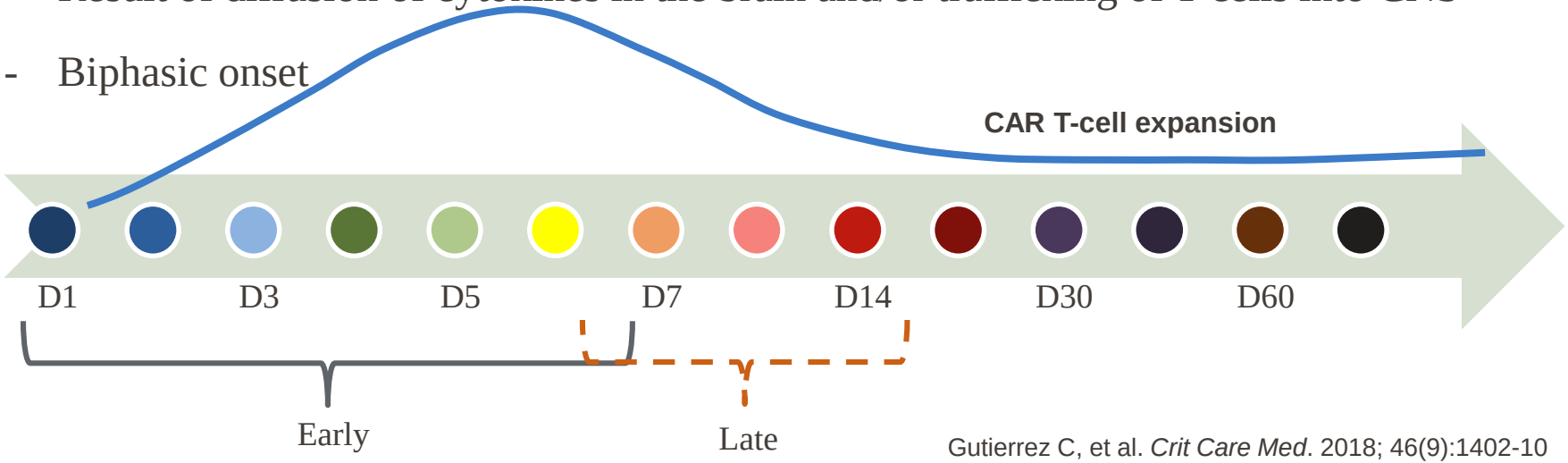


Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10

Prevalence and Onset of ICANS

- ICANS will occur in 40-64% of all patients
- ICANS Grade ≥ 3 will occur in ~30% of patients

- Result of diffusion of cytokines in the brain and/or trafficking of T cells into CNS
- Biphasic onset



Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10

Types of Neurologic Toxicity

ACUTE

- Concurrent with CRS and high fevers
- Result of elevated cytokines
- Symptoms include tremor, expressive aphasia, decreased attention, confusion, disorientation, delirium, ataxia

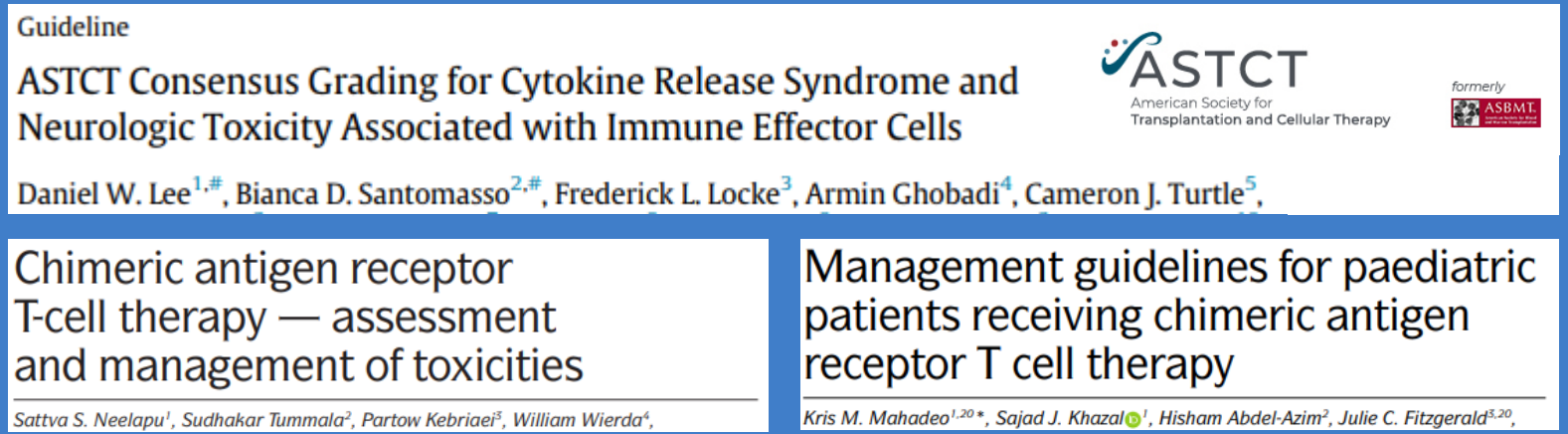
DELAYED

- Occurs within days to weeks following CRS, often on resolution of CRS
- Range of symptoms, particularly global aphasia, motor weakness, and/or seizures
- Generally reversible, typical duration ~ 3 days

CEREBRAL EDEMA

- Rare
- Idiosyncratic
- Rapid, acute onset
- Requires immediate ICU transfer and intervention
- May be fatal

Assessment and Management of Toxicities



Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

ASTCT American Society for Transplantation and Cellular Therapy

formerly ASBMT

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5],

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

Sattva S. Neelapu[1], Sudhakar Tummala[2], Partow Kebriaei[3], William Wierda[4],

Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy

Kris M. Mahadeo[1,20]*, Sajad J. Khazal[1], Hisham Abdel-Azim[2], Julie C. Fitzgerald[3,20],

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019; 25(4):625-38
Mahadeo KM, et al. *Nat Rev Clin Oncol*. 2019; 16(1):45-63
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°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, intubation and mechanical ventilation)

- Organ toxicities associated with CRS are graded according to CTCAE v5.0 but they do not influence CRS grading
- May include:
  - Cardiovascular toxicities – tachycardia, arrhythmias, heart blocks
  - Pulmonary capillary leak – noncardiogenic pulmonary edema, progressing to ARDS
  - Acute kidney injury, hepatic failure, and DIC

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019; 25(4):625-38. Table 2; p. 630

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 nonconvulsive 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 most severe event not attributable to any other cause

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019; 25(4):625-38. Table 6; p. 634

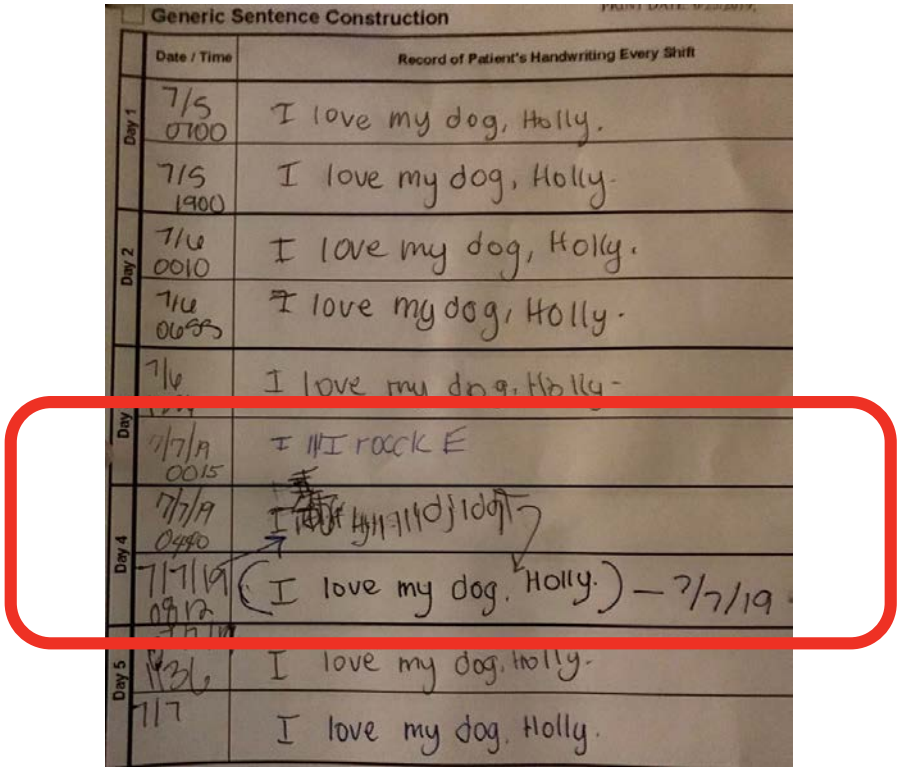
Adult Assessment of Encephalopathy:
Immune Effector Cell-Associated Encephalopathy (ICE) Score

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.

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019; 25(4):625-38. Table 5; p. 634

ICE Score: Writing a Standard Sentence



ASTCT ICANS Consensus Grading for Children

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for children age ≥12 years*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for children age <12 years	1-8	1-8	≥9	Unable to perform CAPD
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive 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 weakness (any age)‡	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging§	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

*ICANS grade is determined by most severe event not attributable to any other cause

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019; 25(4):625-38. Table 8; p. 636

Pediatric Assessment of Encephalopathy:
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]

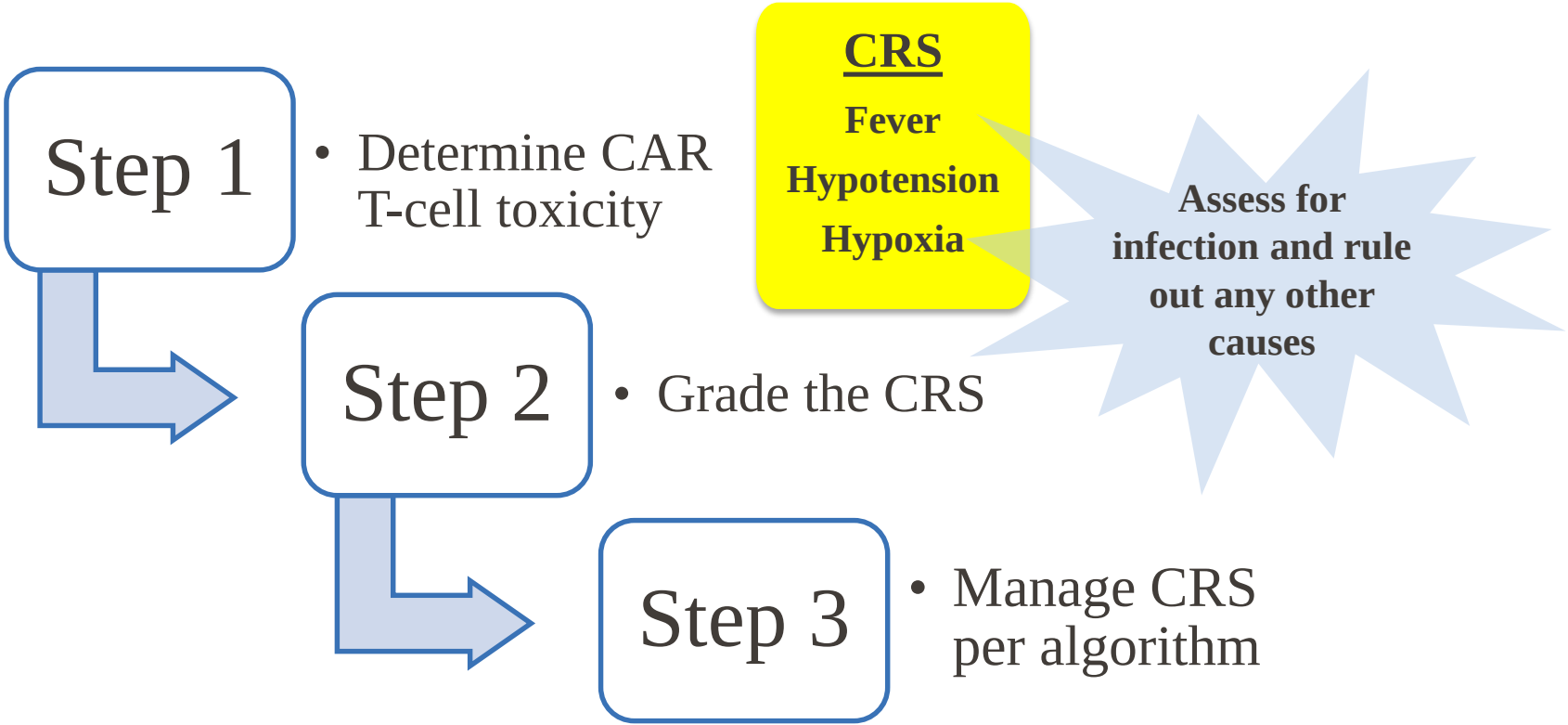
1. Does the child make eye contract with the caregiver?	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	5. Is the child restless?	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0
2. Are the child's actions purposeful?						6. Is the child inconsolable?					
3. Is the child aware of his/her surroundings?	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

[1]+4 Combative; +3 Very Agitated; +2 Agitated; +1 Restless; 0 Alert and Calm; -1 Drowsy; -2 Light sedation; -3 Moderate sedation; -4 Deep sedation; -5 Unarousable

[2] For patients age 1-2 years, use the following guidelines for questions: 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 (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

Traube C, et al. *Crit Care Med*. 2014; 42(3):656-63

3 Step Approach to Assessment and Management



Differential Diagnosis of CAR T Related Toxicities

Clinical Presentation	Diagnosis
Respiratory failure	Pneumonia Diffuse alveolar hemorrhage Cardiogenic pulmonary edema On-target, off-tumor toxicity
Shock	Neutropenic sepsis Cardiogenic shock Hemorrhagic shock On-target, off-tumor toxicity
Encephalopathy	ICH or ischemic stroke Medication induced Septic encephalopathy Meningitis
Liver failure	Medication induced Hypoperfusion Infectious hepatitis HLH On-target, off-tumor toxicity
Acute renal failure	Medication induced Tumor lysis syndrome Obstructive uropathy

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10

CRS Management: Grade 1

CRS Parameter	Grade 1	Anti-IEC Therapy	Supportive Care

Fever	Temperature ≥ 38°C	• Consider **tocilizumab* for 1 dose** for persistent fever lasting greater than 3 days	• Acetaminophen and hypothermia blanket as needed for fever
			  • If not controlled, give ibuprofen (caution in thrombocytopenia)
			• Assess for infection
			  • Consider antibiotics and filgrastim (if neutropenic)
			• IV fluid as needed

Hypotension	None		
Hypoxia	None		

*Tocilizumab 8 mg/kg, may repeat every 8 hours for up to 3 doses in 24 hour period

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

CRS Management: Grade 2

CRS Parameter	Grade 2	Anti-IEC Therapy	Supportive Care
Hypotension	Not requiring vasopressors	• **Tocilizumab* for 1 dose and consider dexamethasone 4-10 mg IV for 1 dose** • Reassess in 6 hours or earlier if clinically indicated	• IV fluid bolus 500 – 1000 mL • If hypotension persists after IV fluids, tocilizumab, and dexamethasone, start vasopressors and transfer patient to ICU
Hypoxia	Requiring low-flow nasal cannula or blow-by		• Use supplemental oxygen

*Tocilizumab 8 mg/kg

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

CRS Management: Grade 3

CRS Parameter	Grade 3	Anti-IEC Therapy	Supportive Care
Hypotension	Requiring a vasopressor with or without vasopressin	• **Tocilizumab*** if not previously administered • If on 1 vasopressor: **dexamethasone 10 mg IV q6h** • If on 2 vasopressors: **dexamethasone 20 mg IV q6h** • If NEE ≥ 15 mcg/min, follow Grade 4	• Transfer patient to ICU • IV fluid bolus 500 – 1000 mL • Use vasopressors as needed
Hypoxia	Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask	• **Tocilizumab and dexamethasone 10 mg IV q6h** • If there is no improvement within 24 hours or rapid progression, increase dexamethasone to 20 mg IV q6h	• Use supplemental oxygen

*Tocilizumab 8 mg/kg, may repeat every 8 hours for up to 3 doses in 24 hour period
Once CRS improves to ≤ Grade 1, taper and/or stop steroids based on clinical situation

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

CRS Management: Grade 4

CRS Parameter	Grade 4	Anti-IEC Therapy	Supportive Care
Hypotension	Requiring multiple vasopressors (excluding vasopressin)	• **Tocilizumab*** if not previously administered • **Methylprednisolone 1000 mg/day** in divided doses IV x 3 days followed by a rapid taper • If hypotension is refractory for > 24 hours or patient is rapidly deteriorating, consider additional therapies or activation of safety switches	• Transfer patient to ICU • IV fluid bolus 500 – 1000 mL • Use vasopressors as needed
Hypoxia	Requiring positive pressure (eg. CPAP, BiPAP, intubation ad mechanical ventilation	• **Tocilizumab and high-dose methylprednisolone as above** • If hypoxia is refractory for > 24 hours or patient is rapidly deteriorating, consider additional therapies or activation of safety switches	• Positive pressure ventilation

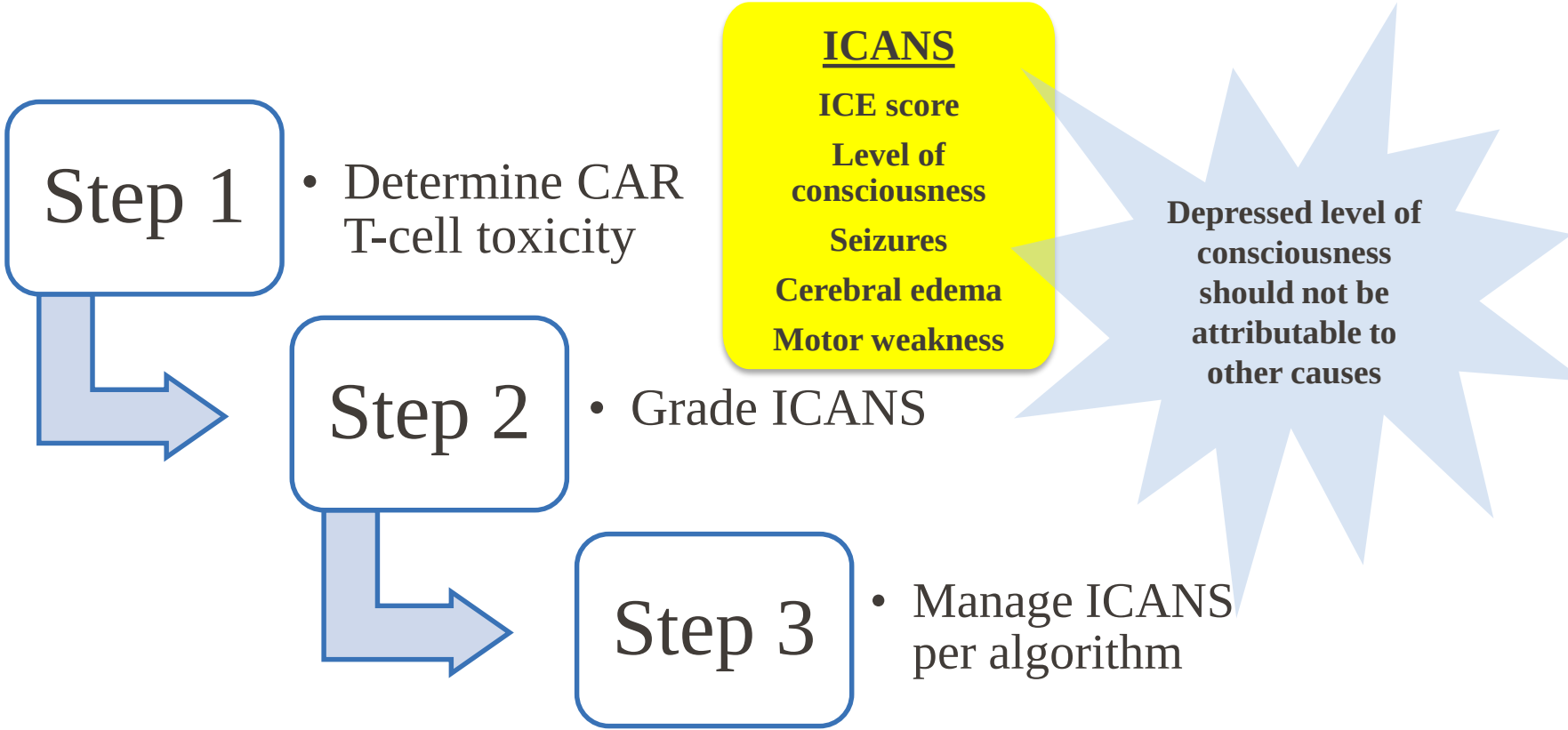
*Tocilizumab 8 mg/kg, may repeat every 8 hours for up to 3 doses in 24 hour period
Once CRS improves to ≤ Grade 1, taper and/or stop steroids based on clinical situation

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

CRS Treatment Summary

- Guidelines for CRS management may vary by institution and/or protocol
- Management of CRS is based on clinical parameters, not laboratory values
- Goal is to avoid grade progression
- Tocilizumab in combination with supportive care is the first line treatment for Grade $\geq$ 2 CRS
- If CRS does not improve after tocilizumab administration, consider alternative therapies (steroids, siltuximab, anakinra, suicide switch, etc)

3 Step Approach to Assessment and Management



ICANS Management: Grade 1

ICANS Parameter	Grade 1	Anti-IEC Therapy	Supportive Care
Encephalopathy or depressed level of consciousness	ICE Score 7-9 and/or Awakens spontaneously	• **Dexamethasone 10 mg IV x 1** • Reassess in 6 hours or earlier if clinically indicated • **If associated with concurrent CRS, add tocilizumab**	• MRI of brain (or CT without contrast if MRI not possible) • Neurology consult • EEG

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
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ICANS Management: Grade 2

ICANS Parameter	Grade 2	Anti-IEC Therapy	Supportive Care
Encephalopathy or depressed level of consciousness	ICE score 3-6 and/or Awakens to voice	• **Dexamethasone 10 mg IV q12h** • **If associated with concurrent CRS, add tocilizumab** • Once ICANS improves to ≤ Grade 1, taper/stop steroids as indicated	• Supportive care per Grade 1

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

ICANS Management: Grade 3

ICANS Parameter	Grade 3	Anti-IEC Therapy	Supportive Care
Encephalopathy or depressed level of consciousness	ICE Score 0-2 and/or Awakens only to tactile stimulus	• **Dexamethasone 10 mg IV q6h** • If associated with concurrent CRS, add Tocilizumab • **If Grade 3 ICANS persists > 24h, increase dexamethasone to 20 mg IV q6h** • Once ICANS improves to ≤ Grade 1, taper/stop steroids as indicated	• Consider ICU transfer • If abnormal findings on brain imaging, control HTN, uremia, coagulopathy
Seizures	Any focal, generalized, or non-convulsive seizure that resolves rapidly	• **Dexamethasone 20 mg IV q6h** • If associated with concurrent CRS, add Tocilizumab • Once ICANS improves to ≤ Grade 1, taper/stop steroids as indicated	• Transfer to ICU • EEG if clinically indicated • **Treat seizures**
Focal cerebral edema	Focal/local edema on neuroimaging	• **Methylprednisolone 1000 mg/day** in divided doses for 3 days followed by taper	• Transfer to ICU • Repeat CT/MRI q24h • Supportive care per Grade 1

Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

ICANS Management: Grade 4

ICANS Parameter	Grade 4	Anti-IEC Therapy	Supportive Care
Encephalopathy or depressed level of consciousness	ICE score 0 and/or Patient is unarousable	• **Methylprednisolone 1000 mg/day** in divided doses for 3 days followed by taper • Once ICANS improves to ≤ Grade 1, taper/stop steroids as indicated • If associated with concurrent CRS, add Tocilizumab • If refractory for > 24 hours, consider additional therapies	• Transfer to ICU • Protect airway • If abnormal findings on brain imaging, control HTN, uremia, coagulopathy
Seizures	Life-threatening, prolonged seizure or repetitive seizures		• **Treat seizures**
Motor Weakness	Deep focal motor weakness such as hemi/paraparesis		• Supportive care as in Grade 1
Diffuse cerebral edema or raised ICP	Diffuse cerebral edema on neuroimaging or signs of ↑ ICP		• **Treat signs of increased ICP** or diffuse cerebral edema

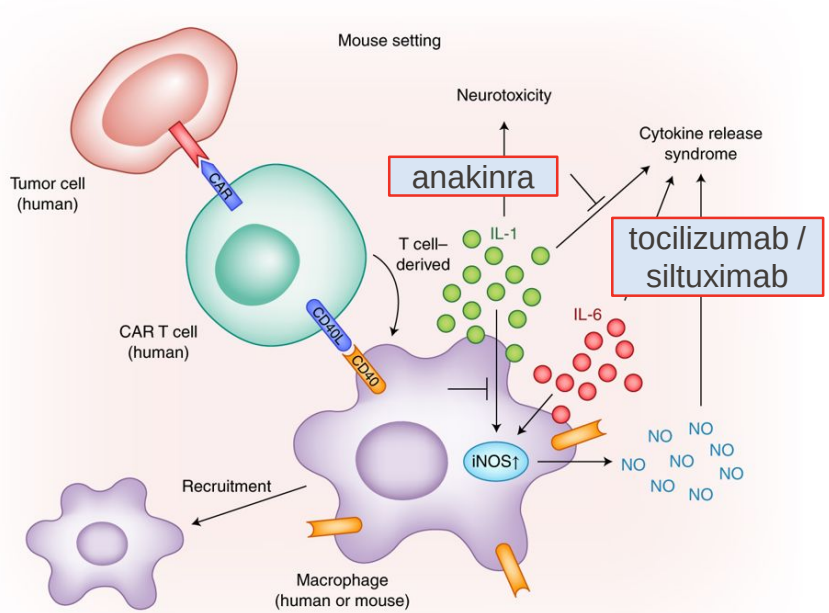
Gutierrez C, et al. *Crit Care Med*. 2018; 46(9):1402-10
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15(1):47-62
IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

Treat the Patient's Toxicities

76yoM with diffuse large B-cell lymphoma admitted for axi-cel infusion

- Day 0: CAR T-cell infusion with axi-cel
- Day 2: fever 39.2°C **CRS Grade 1**
  - **Treat with acetaminophen**
- Day 4: fever 38.7°C, hypotension requiring 3 liters NS **CRS Grade 2**
  - **Treat with fluid, acetaminophen, tocilizumab***
- Day 7: Transferred to ICU overnight for worsening mental status
  - ICE score 8, awakens to voice **ICANS Grade 2**
  - **Treat with dexamethasone 10 mg IV q12h**
- Day 8: RN assess for ICANS at shift change **ICANS Grade 3**
  - ICE score 2, awakens to stimulus
  - **Schedule dexamethasone 10 mg IV q6h**

Anti-Cytokine Therapy



Kotch C, et al. *Expert Rev Clin Immunol*. 2019; 15(8):813-22
Giavridis T, et al. *Nat Med*. 2018; 24(6):731-38; Liu YC, et al. *Expert Rev Hematol*. 2014; 7(5):545-57. Figure 1; p. 546
Norelli M, et al. *Nat Med*. 2018; 24(6):739-48; Rooney C, et al. *Nat Med*. 2018; 24(6):705-06. Figure 1; p. 706

IL-6 Antagonists and Alternative Agents for CRS and ICANS

Drug	Mechanism of Action	Recommend Dose for CRS and/or ICANS	Comments
Tocilizumab	IL-6 receptor antagonist	8 mg/kg IV	Max of 4 doses total over entire course of CRS and ICANS, may be repeated every 8 hours for up to three doses in a 24-hour period
Siltuximab	IL-6 antibody	11 mg/kg IV once	Recommended primarily for patients who are intolerant to tocilizumab No more than 1 dose in a 3 week period
Anakinra	IL-1 receptor antagonist	100 mg subcutaneously daily for 7 days	Consider renal dose adjustment for CrCl < 30 mL/min
Cyclophosphamide	Alkylating agent	1500 mg/m2 IV for one dose	Give with mesna 1500 mg/m2 IV over 24 hours for one dose
Anti-thymocyte globulin (rabbit)	Immunosuppressant	1-2 mg/kg IV daily x 3	Hypersensitivity reactions can occur; pre-medicate
Safety switches	If the IEC product contains a safety switch (e.g., iCapsase-9 or EGFRt-positive), the corresponding drug to eliminate those cells can be considered in doses according to manufacturer e.g. rimiducid to eliminate iCaspase-9 or cetuximab to eliminate EGFRt-positive cells		

IEC Therapy Toxicity Assessment and Management – Adult. Draft V3. Houston (TX): UT MD Anderson Cancer Center; September 2019

Corticosteroids

Mechanism in CAR T-cell related toxicities:

- Suppress inflammatory response
- Suppress T-cell function and/or induce T-cell apoptosis

Indications for use in CAR T-cell patients:

- Consider only when toxicities are refractory to anti-IL-6 therapy
- Avoid use for other indications such as premedication for blood transfusions leading up to and after CAR T-cell therapy

Brudno JN, et al. *Blood*. 2016; 127(26):3321-30
Lee DW, et al. *Blood*. 2014; 124(2):188-95

CAR T Cell Therapy Summary

- Clinical efficacy of CAR T-cell therapy comes at cost of unique and serious toxicities
- All critical care clinicians need to be familiar with the management and recognition of CAR T-cell related toxicities
- CAR T-cell related toxicities need to be recognized and managed rapidly as most are relatively reversible
- Collaboration between oncology, neurology, infectious diseases, and critical care teams is essential in the management of CAR T-cell related toxicities

Post-Assessment Questions

Question 1: Which of the following symptoms do not affect the CRS grade?

1. Hypotension
2. Tachycardia
3. Fever
4. Hypoxia

Question 2: BL received axi-cel 7 days ago. He had low grade CRS with fevers which responded to anti-cytokine on day 3 with no further CRS. Today on day 7 on morning rounds, the nurse notes the ICE score has changed from a 7 to a 0 and the patient is unarousable. Which of the following is the most appropriate plan for management for BL who has now developed Grade 4 ICANS?

1. dexamethasone 10 mg IV every 6 hours
2. Dexamethasone 10 mg IV every 6 hours + tocilizumab 8 mg/kg IV x 1
3. Anakinra 100 mg subcutaneously daily for 7 days
4. methylprednisolone 500 mg IV every 12 hours

Questions?

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