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MANAGEMENT OF CAR-T EARLY TOXICITIES

Gabriele Magliano

Adult Bone Marrow Transplant Unit

ASST Spedali Civili, Brescia

UNIVERSITY OF BRESCIA

Chair of Hematology
Unit of Blood Disease and Bone Marrow Transplantation

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Disclosures of Gabriele Magliano

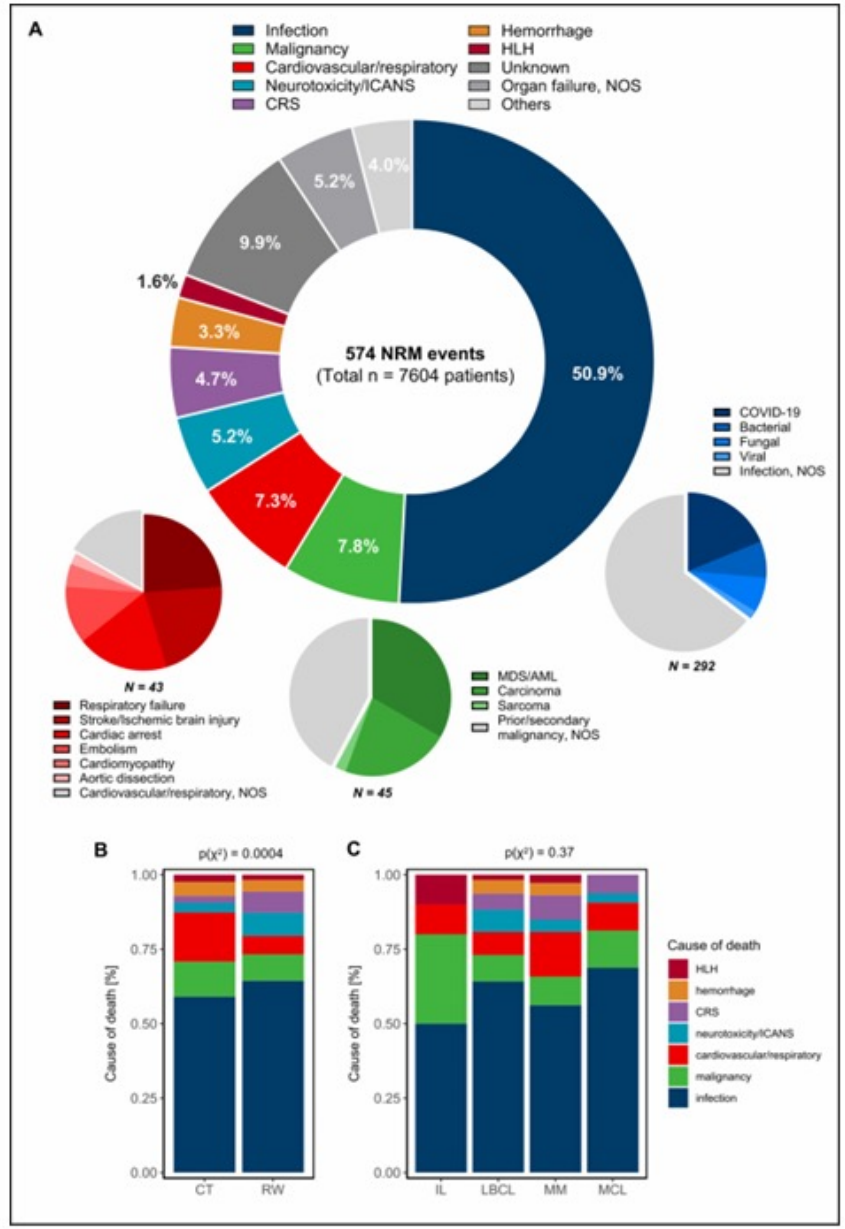
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Background

- CAR-T cells represent an established treatment for patients with relapsed/refractory large B-cell lymphomas (LBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), B cell acute lymphoblastic leukemia (B-ALL), and multiple myeloma (MM). The therapeutic efficacy of CAR-T reaches a plateau of progression-free survival ranging from 25 to 45%, mainly differing according to CAR-T product and type of disease

- Supraphysiologic T cell activation, expansion, and systemic hyperinflammatory response mediated by cytokine production can result in potentially severe and life-threatening early (within the first month) and late toxicities that require careful monitoring and prompt interventions

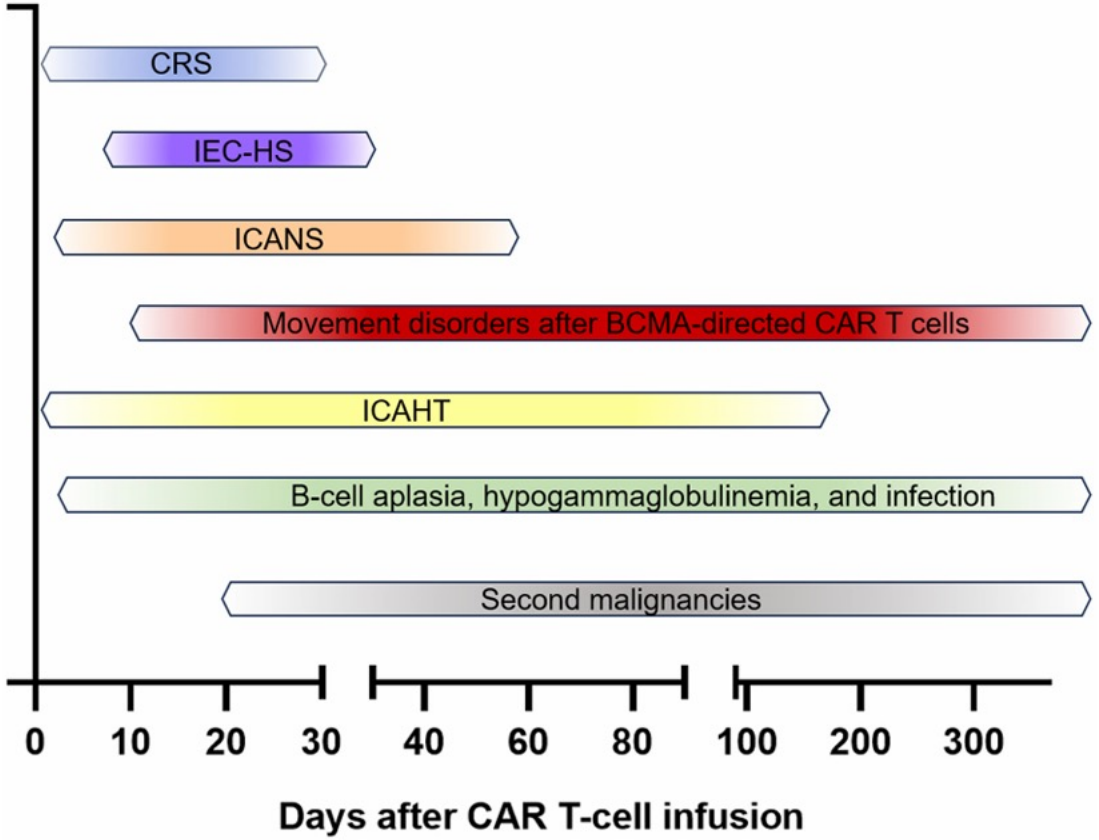
- A recent systematic meta-analysis extended to 7,604 patients enrolled in 18 clinical trials, and 28 real world studies analyzed the NRM observed after CAR-T, which significantly differed varying across MCL (10.6%), MM (8%), LBCL (6.1%), and indolent lymphoma (5.7%). CAR-T products impacted NRM in a disease-specific manner

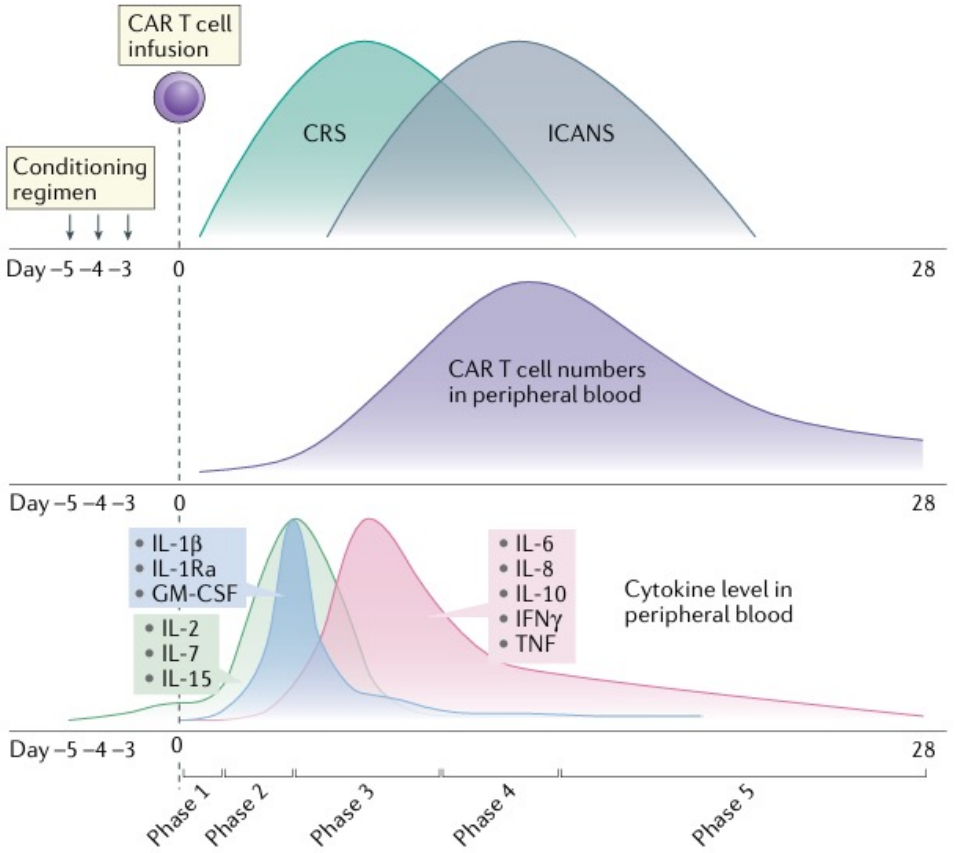


Cordas Dos Santos DM, et al. A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. Nat Med. 2024 Sep;30(9):2667-2678

Background

The prototypical CAR T cell toxicities of CRS and ICANS are closely related to cytokine release during early CAR T cell expansion and rapidly improve after contraction. While toxicities such as IEC-HS or delayed neurological symptoms are likely initiated during expansion, they clinically manifest during the downward trajectory of the expansion curve—although sustained expansion or re-expansion may also contribute to toxicity severity





Morris EC et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol. 2022 Feb;22(2):85-96

- With the expected expanded indications for CAR T cell therapy in hematologic malignancies, as well as potential applications in solid tumors and autoimmune disease, optimizing prevention and treatment of the associated toxicities will become increasingly important to establish frameworks for institutions and health care providers to ultimately improve patient outcomes

TABLE 1 Incidence of immune effector cell-associated toxicities seen on registrational trials for approved CAR T cell therapies.

CAR T	Indication	CRS	Neurotoxicity	Cytopenias	Infection
Tisa-cel NCT02435849 (2)	R/R B-ALL for age < 25	77% 47% G ≥ 3 Median onset 3 days	40% 13% G ≥ 3	24% with cytopenia G ≥ 3 not resolved by day 28	43% 24% G ≥ 3
Tisa-cel JULIET (3)	R/R LBCL ≥ 2 prior LOT	58% 22% G ≥ 3 Median onset 3 days	21% 12% G ≥ 3	32% with cytopenia G ≥ 3 not resolved by day 28	34% 20% G ≥ 3
Axi-cel ZUMA-1 (4)	R/R LBCL ≥ 2 prior LOT	93% 13% G ≥ 3 Median onset 2 days	64% 28% G ≥ 3	78% G ≥ 3 neutropenia 38% G ≥ 3 TCP 43% G ≥ 3 anemia	Not reported
Axi-cel ZUMA-7 (7)	Primary refractory LBCL or relapse within 12 months of 1st line therapy	92% 6% G ≥ 3 Median onset 3 days	60% 21% G ≥ 3	29% with G ≥ 3 cytopenia not resolved by day 30	41% 14% G ≥ 3
Axi-cel ZUMA-5 (8)	R/R follicular lymphoma	78% 6% G ≥ 3 Median onset 4 days	56% 15% G ≥ 3	33% with G ≥ 3 cytopenia not resolved by day 30	18% G ≥ 3
Liso-cel TRANSCEND NHL 001 (5)	R/R LBCL ≥ 2 prior LOT	42% 2% G ≥ 3 Median onset 5 days	30% 10% G ≥ 3	37% with G ≥ 3 cytopenia not resolved by day 28	12% G ≥ 3
Liso-cel TRANSFORM (6)	Primary refractory LBCL, relapse within 12 months of 1st line therapy, relapse and not eligible for HSCT	49% 1% G ≥ 3 Median onset 5 days	11% 4% G ≥ 3	43% with G ≥ 3 cytopenia not resolved by day 35	15% G ≥ 3
Brexu-cel ZUMA-3 (10)	Adult B-ALL	89% 24% G ≥ 3 Median onset 5 days	60% 26% G ≥ 3	36% with G ≥ 3 cytopenia not resolved by day 30	25% G ≥ 3
Brexu-cel ZUMA-2 (9)	R/R mantle cell lymphoma	91% 15% G ≥ 3 Median onset 2 days	63% 31% G ≥ 3	26% with G ≥ 3 cytopenia not resolved by day 90	32% G ≥ 3
Ide-cel KarMMa (11)	RRMM with ≥ 4 prior LOT	84% 5% G ≥ 3 Median onset 1 day	18% 3% G ≥ 3	52% with G ≥ 3 neutropenia and 62% with G ≥ 3 TCP not resolved by day 28	22% G ≥ 3
Cilta-cel CARTITUDE-1 (12)	RRMM with ≥ 4 prior LOT	95% 5% G ≥ 3 Median onset 7 days	17% ICANS 2% G ≥ 3 12% other neurotoxicities, 9% G ≥ 3	30% with G ≥ 3 neutropenia and 41% with G ≥ 3 TCP not resolved by day 30	20% G ≥ 3

CRS, cytokine release syndrome; R/R, relapsed/refractory; B-ALL, B-cell acute lymphoblastic leukemia; G, grade; LBCL, large B-cell lymphoma; LOT, lines of therapy; IEC-HS), immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; TCP, thrombocytopenia; HSCT, hematopoietic stem cell transplantation; RRMM, relapsed/refractory multiple myeloma.

Ferreri CJ and Bhutani M (2024) Mechanisms and management of CAR T toxicity. Front. Oncol. 14:1396490

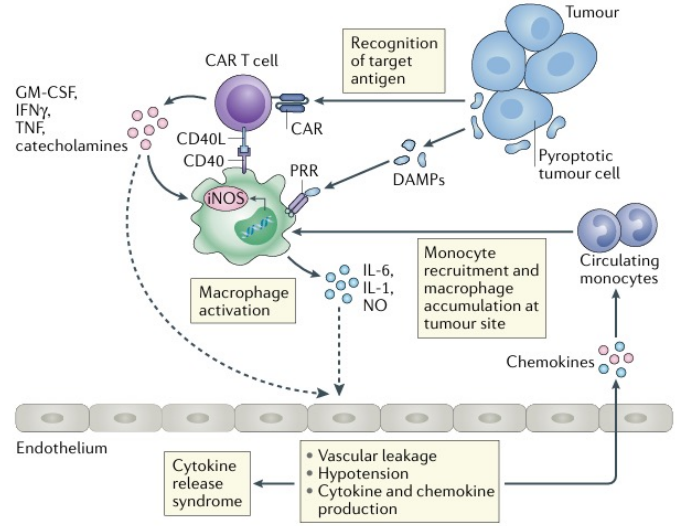
Cytokine release syndrome

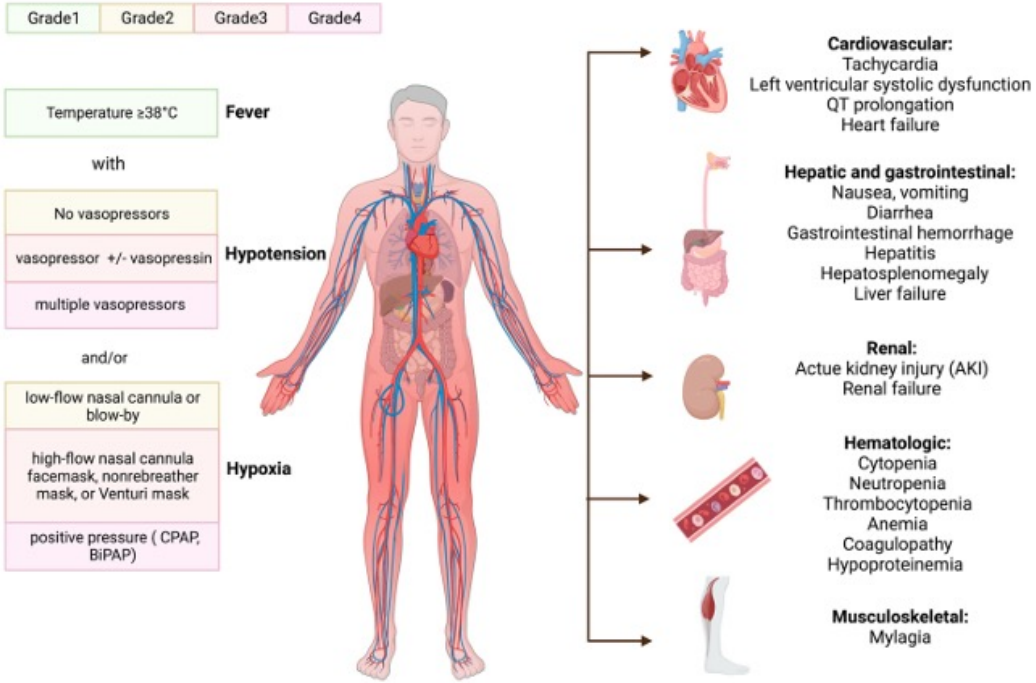
- "Supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction." (ASTCT consensus)

- Clinical syndrome affecting multiple organs that is characterized by a multitude of systemic symptoms, initially consisting of fever and tachycardia. In more severe cases, CRS is associated with hypotension, hypoxia, capillary leak syndrome, multiple organ failures, and disseminated intravascular coagulation

  CRS can onset in the very first days after CAR-T infusion, with a duration of some days in most cases (around 2-3 days after anti-CD19 CAR-T and 1-7 days after anti-BCMA CAR-T)

- Inflammatory markers and cytokines implicated include TNF-a, IFN-ɣ, interleukin-1 (IL-1), IL-2, soluble IL2Ra, IL-4, IL-6, IL-8, IL-10, ferritin, C-reactive protein (CRP), granulocyte/ macrophage colony stimulating factor (GM-CSF)





Zhang, Y, et al. Exploring CAR-T Cell Therapy Side Effects: Mechanisms and Management Strategies. J. Clin. Med. 2023, 12, 6124

- The frequency and severity of CRS after CAR-T cell therapy varies between products and disease indications (any grade: 37–93%, G3/4: 1–23%) (Neelapu et al. 2017; Maude et al. 2018; Schuster et al. 2019; Abramson et al. 2020; Wang et al. 2020)

- Since these pivotal trials, several consensus grading systems for CRS have been provided, the one by Lee and Colleagues (2019), being the most routinely used in clinical practice.

- Patients receiving CAR-T cells should be monitored continuously or at regular intervals in an appropriate inpatient or ambulatory setting, Patient aspects should be considered such as age, performance status, disease bulk, distance from accommodation to the hospital and access to care-giver.

- CRS grading requires measurement of the temperature, cardiovascular function and oxygen saturation. The first sign of CRS is usually fever which alone is grade 1 CRS which can initially be observed.

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Fever ≥38°C (not attributable to any other cause). In patients who have CRS then receive antipyretics 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			
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Requiring low-flow oxygen (delivered at ≤6L/min)	Requiring high-flow oxygen (delivered at >6L/min)	Requiring positive pressure (e.g. CPAP, BiPAP, intubation, and mechanical ventilation)

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625 638
The EU CAR-T Handbook, 2° edition

- Tocilizumab is approved by the EMA and FDA for the treatment of CRS. Prophylactic, preemptive or risk-adapted use may reduce the risk of severe CRS, (but not severe neurotoxicity) and is not currently recommended for prophylaxis against CAR-T cell related adverse events (Locke et al. 2024; Kadauke et al. 2021).

- In the absence of improvement within 24 hours in grade 1 CRS, early use of tocilizumab is now recommended.
  ZUMA-1 cohort 4 examined the earlier use of tocilizumab and steroids at grade 1 (if no improvement after 1-3 days), with very low rates of grade 3 CRS -2%- (Topp et al. 2021)

- Short courses of steroids do not seem to have detrimental effects on CAR-T cell expansion and survival or clinical outcome (Topp et al. 2021)

- G-CSF given from D+2 is associated with a reduced risk of febrile neutropenia without increasing the risk of severe CRS (Lievin et al. 2022).

- Most centres administer broad-spectrum antibiotic treatment in cases of neutropenic fever.

CRS Grade	Pharmacotherapy Recommendations
Grade 1	• Broad-spectrum antibiotics if concomitant neutropenia • Anti-pyretics (acetaminophen) • Consider Tocilizumab for persistent or refractory cases
Grade 2	• Intravenous fluids for hypotension and/or supplemental oxygen • Tocilizumab 8 mg/kg IV may be given every eight hours for a maximum of four total doses • Consider adjunctive dexamethasone 10 mg IV every 12 hours for persistent or refractory cases
Grade 3 or Grade 4	• Vasopressors for hypotension and/or supplemental oxygen • Tocilizumab 8 mg/kg IV may be given every eight hours for a maximum of four total doses • Adjunctive dexamethasone 10 mg IV every 6 hours (or equivalent), which can be escalated up to a dose of methylprednisolone 1,000 mg IV every 12 hours for refractory cases • Consider alternative anti-cytokine or immunosuppressive therapies for refractory cases after tocilizumab

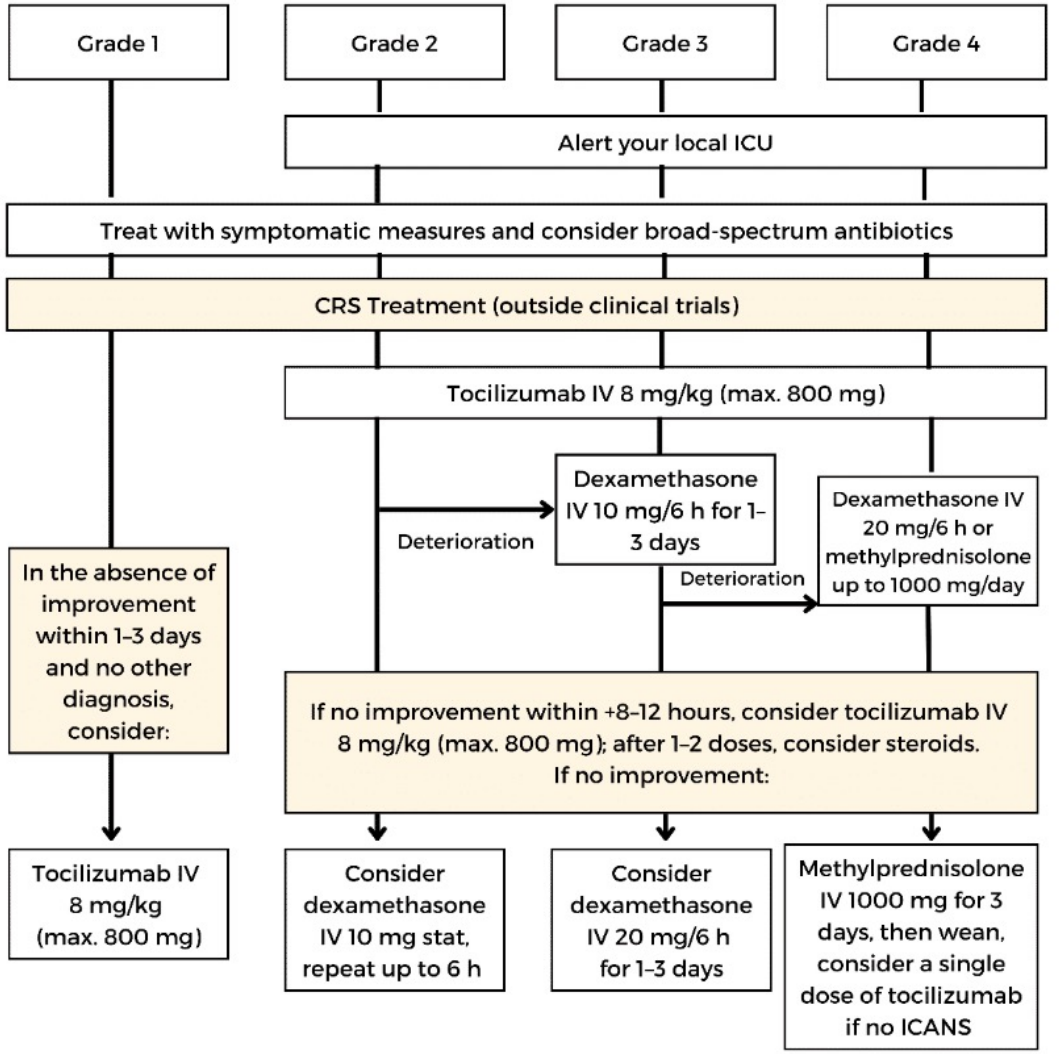


Fig. 40.1. Management of CRS – modified from Yakoub-Agha et al. 2020

- There is less clarity about the definition of **CRS resolution.**

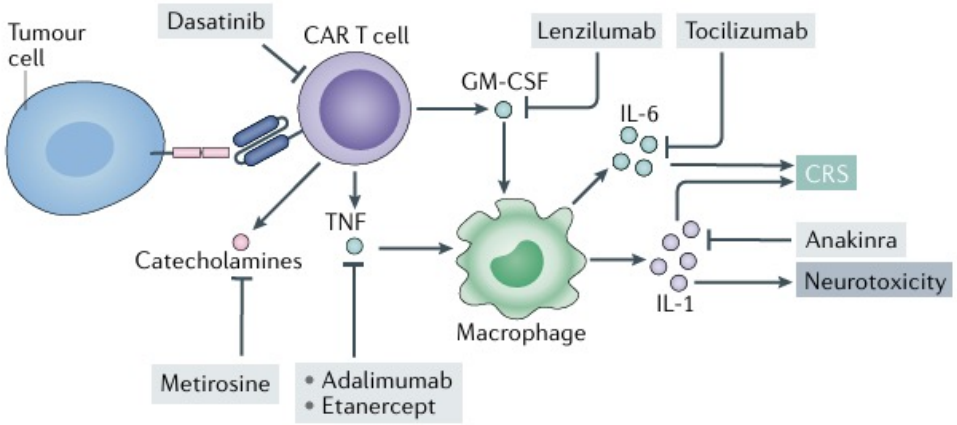
Temperature often normalizes within a few hours after tocilizumab administration, whereas the other components of CRS take longer to resolve. Once anticytokine therapies are used, the patient is considered to still have CRS, even in the absence of fever, until all signs and symptoms leading to the diagnosis of CRS have resolved

- The management of **refractory CRS** can be targeted with broad- spectrum cytokine inhibition through different mechanisms

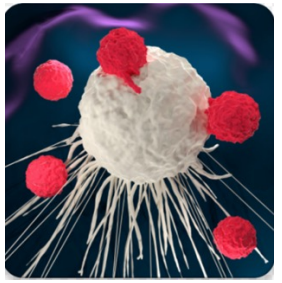
- **Anakinra** has demonstrated greater efficacy in the treatment of refractory ICANS, but it has been shown to facilitate resolution of refractory CRS in case reports and retrospective studies
- **Siltuximab** binds directly to IL-6 preventing its interaction with IL-6 receptors. It has been demonstrated to be efficacious in the treatment of CRS both alone and in combination with tocilizumab.
- **Etanercept** and **Emapalumab** have shown to abate CRS in case reports of both anti-CD19 and anti-BCMA CAR T cell therapies
- **Dasatinib**, **itacitinib** and **ruxolitinib** have been demonstrated to inhibit lymphocyte-specific protein tyrosine kinases, impair downstream signaling and cytokine production, cytolytic activity, and in decreased CAR T cell proliferation in both in vitro and in vivo models

Alternative Therapies for Refractory CRS
Anakinra – IL-1 receptor antagonist, case reports and retrospective studies demonstrating efficacy (63, 64)
Siltuximab – IL-6 inhibitor, demonstrated efficacy (5, 65, 66)
Etanercept – TNF-α receptor inhibitor, demonstrated efficacy in case reports (26, 67)
Emapalumab – IFN-γ inhibitor, demonstrated efficacy in case report (69)
Dasatinib – tyrosine kinase inhibitor, demonstrated efficacy in case report (72)
JAK-STAT inhibitors • Itacitinib has been shown to reduce levels of CRS-related cytokines in pre-clinical studies (73), and has been shown to reduce grade ≥ 2 CRS when used as prophylaxis prior to axi-cel (79) • Ruxolitinib has demonstrated efficacy in several case reports (74–77)

CRS, cytokine release syndrome; IV, intravenous; mg, milligrams; kg, kilogram; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.



Ferreri CJ and Bhutani M (2024) Mechanisms and management of CAR T toxicity. Front. Oncol. 14:1396490

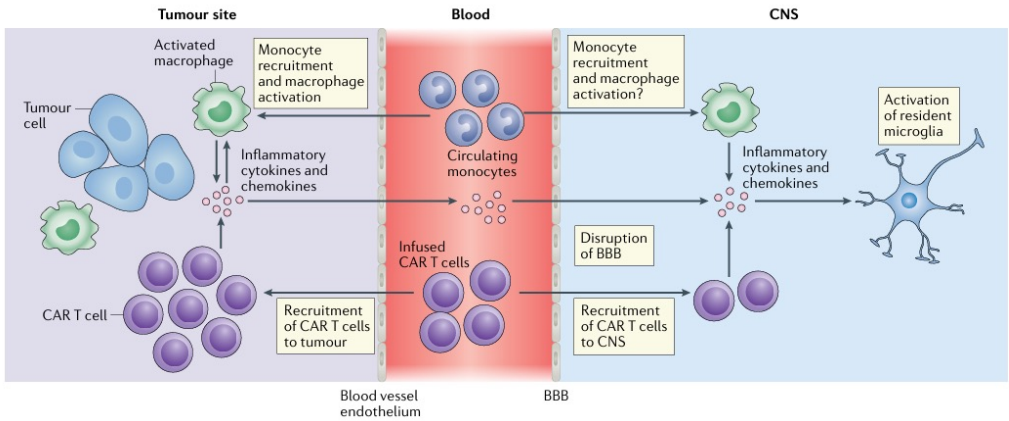


Comparisons of the ASCO, EBMT/EHA, SITC, and NCCN Toxicity Management Guidelines

	ASCO[43]	EBMT/EHA[44]	SITC[45]	NCCN[46]
CRS *				
indication for first dose of tocilizumab	≥ Gr 2 CRS; Consider for Gr 1 CRS with fever > 3 days	≥ Gr 2 CRS; Consider for Gr 1 CRS with fever/symptoms > 3 days Note: repeat tocilizumab for ≥ Gr 2 CRS with absence of improvement in first 12 hrs	-Consider for Gr 2 CRS for elderly patients, those with comorbid conditions, and pediatric patients with prolonged Gr 2 CRS and/or intolerance of fever. -Administer for all Gr 3-4 CRS -Administer a second dose of tocilizumab with steroids if no improvement in CRS	≥ Gr 2 CRS and for Gr 1 CRS lasting > 3 days in patients with significant symptoms, comorbidities, and/or > 65 years old. -Consider for Gr 1 CRS after axi-cel or brexu-cel lasting > 24 hrs. -Consider for Gr 1 CRS starting < 72 hrs after liso-cel infusion +/– 10 mg dexamethasone. -Repeat in 8 hrs if no improvement. No more than 3 doses in 24 hrs, maximum 4 total doses.
indication for first dose of corticosteroids	Gr 2 CRS → hypotension persisting despite 2 IV fluid boluses AND 1-2 doses of tocilizumab OR any Gr 3-4 CRS	Gr 2 CRS refractory to 1 dose of tocilizumab OR any Gr 3-4 CRS	Any CRS refractory to 1 dose of tocilizumab (steroids administered with a second dose of tocilizumab)	Persistent refractory hypotension after 1-2 doses of anti-IL-6 therapy, or for ≥Gr 2 CRS as per product-specific recommendations below.
corticosteroid dosing recommendations *	-refractory Gr 2 CRS → dexamethasone 10 mg IV q 12 hrs -Gr 3 CRS → dexamethasone 10 mg IV q 6 hrs with taper upon improvement -Gr 4 CRS → methylprednisolone 500 mg IV q 12 hrs with taper upon improvement	refractory Gr 2 CRS OR Gr 3 CRS → dexamethasone 10 mg IV q 6 hrs for 1-3 days. -Gr 4 CRS → dexamethasone 20 mg IV q 6 hrs x 3 days, progressive tapering within 3-7 days	-Example dosing regimens are methylprednisolone 2 mg/kg/day or dexamethasone dosed as 0.5 mg/kg (max 10 mg per dose).	Gr 2 CRS → dexamethasone 10 mg IV q 12-24 hrs depending on product: -axi-cel: Consider dexamethasone 10 mg IV q 24 hrs after initial tocilizumab, regardless of tocilizumab response. -liso-cel: Consider dexamethasone 10 mg IV q 12-24 hrs if CRS occurs < 72 hours after CAR T-cell infusion. -ide-cel: dexamethasone 10 mg IV q 12-24 hrs. -Gr 3 CRS → dexamethasone 10 mg q 6-12 hrs.
dose escalation of corticosteroids	If refractory symptoms after intervention at any grade, treat per recommendations for the next highest grade	If refractory symptoms or deterioration in symptoms after intervention at any grade, treat per recommendations for the next highest grade	Not specified	-Gr 4 or refractory Gr 3 CRS → dexamethasone 10 mg IV q 6 hrs.
Recommendations for refractory high-grade CRS	-methylprednisolone 500 mg IV q 12 hrs; consider anakinra, siltuximab, ruxolitinib, cyclophosphamide, and antithymocyte globulin	-methylprednisolone 1000 mg IV daily x 3 days with taper; consider 1 additional dose of tocilizumab	-For CRS refractory to 2 doses of tocilizumab and corticosteroids, consider anakinra, siltuximab, and high-dose methylprednisolone	-Continued refractory Gr 3-4 CRS despite dexamethasone 10 mg IV q 6 hrs → consider 3 doses of IV methylprednisolone 1-2 grams/day, depending on product prescribing information; for continued refractory CRS, consider q 12 hr dosing.^ -Third line: consider anakinra -Fourth line: consider ruxolitinib, cyclophosphamide, intravenous immunoglobulins, antithymocyte globulin, intrathecal chemotherapy, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT). Must be balanced with risk of infection.

Brudno JN, et al. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev. 2019 Mar;34:45-55

ICANS



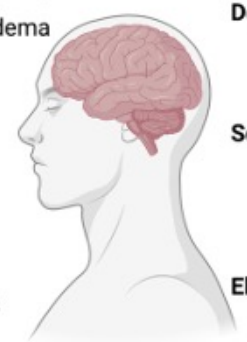
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) occurs in 20-60% of CAR-T patients, of whom 12-30% develop severe manifestations (Grade 3 or higher). The underlying mechanism is supposed to be driven by the release of inflammatory cytokines, the increasing vascular permeability and the endothelial activation leading to blood brain barrier breakdown

- The onset is generally around 5 days following CAR-T cell transfusion, sometimes concurrently with or shortly after CRS. However, about 10% of patients present more than 3 weeks after CAR-T cell transfusion, known as delayed ICANS. Risk factors include high disease burden, patient age, CAR-T expansion and the specific CAR-T-cell product.

- It consists of an acute, typically monophasic constellation of mental status alteration, language disturbances and mild tremor, that may progress to more severe manifestations, such as agitation, seizures, coma, and cerebral edema/haemorrhage

- A prominent and early feature of ICANS is hesitancy of speech and deterioration in handwriting, which can progress to aphasia with both expressive and receptive components, whereby the patient is alert but mute.

Encephalopathy
Cerebral edema
Headache
Dysphasia
Delirium
Tremor
Ataxia
Myoclonus
Seizures



	Grade1	Grade2	Grade3	Grade4
ICE score	7-9	3-6	0-2	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	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention		Life-threatening prolonged seizure (>5 mins); or Repetitive clinical or electrical seizures without return to baseline in between	
Elevated ICP/cerebral edema	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	
Motor findings	Deep focal motor weakness such as hemiparesis or paraparesis			

Zhang, Y, et al. Exploring CAR-T Cell Therapy Side Effects: Mechanisms and Management Strategies. J. Clin. Med. 2023, 12, 6124

- All patients should be proactively monitored for subtle changes in cognition, using the 10-point Immune Effector Cell Encephalopathy (ICE) score, which evaluates orientation, attention, writing and language. This score is then integrated into an overall assessment of neurological function to give an ICANS grade.

- Any patient with an ICE score less than 2 or with seizures is classified as severe (Grade 3 or 4) and should be transferred to Intensive Care. Factors associated with a higher risk of ≥ grade 3 ICANS include low platelet count, increasing ferritin, and the development of early and severe CRS.

- ICANS is a clinical diagnosis : MRI brain scans and CSF studies are rarely helpful in ruling out alternative diagnoses. The EEG recording can be normal, but can also demonstrate a pattern of variable abnormalities, including non-convulsive status epilepticus.

Table 41.1. Immune Effector Cell Encephalopathy (ICE) Score

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: **1 point**
Attention: ability to count backwards from 100 by 10: **1 point**

Table 2. Neurologic testing in the management of CAR T-cell therapy toxicities

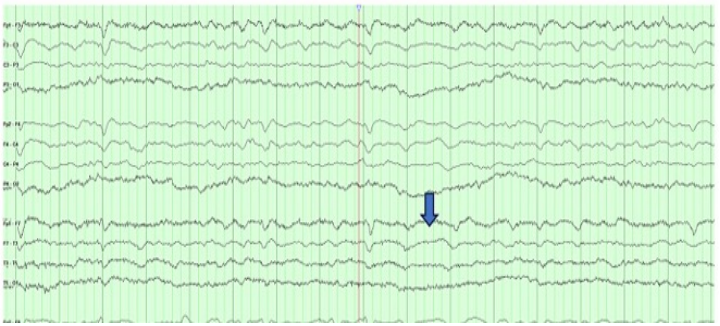
	Before CAR T-cell therapy	From 1 to 30 d after CAR T-cell therapy	1 mo after CAR–T-cell therapy
Neurological assessment	YES, baseline mental status, neuro history (Nervous system toxicity from prior therapy, seizure, stroke, migraine, CNS disease, radiation, trauma, andneuropathy).	YES, monitor ICANS, additional attention to handwriting, movement, and personality changes for BCMA-CAR T-cell therapy. High-prolonged CRS increases the risk of ICANS.	YES, full assessment at 1-3-6 months may be indicated in the case of delayed or prolonged neurotoxicity or in the case of BCMA products to screen for early signs of movement and MNTs.
EEG	Generally, not helpful unless a history of epilepsy.	YES, during ICANS to r/o nonconvulsive seizures and to monitor critically ill patients.	YES, consider if any recurrent altered mental status.
Neuroimaging	YES, if history of CNS disease in cases of preexisting neurologic injury.	YES, if ICANS occurs.	YES, for any delayed neurologic symptoms.
CAR T measurements (blood and CSF)	N/A	Unclear utility in the short-term management.	May be helpful if available. High levels of CAR T cells in blood have been associated with recurrent symptoms/ delayed neurotoxicity. The role of CSF CAR measurement is unclear.
LP for CSF evaluation	YES, strongly consider if history of CNS disease.	May be diagnostic and therapeutic during ICANS.	May be diagnostic and therapeutic to rule out alternative etiologies in case of new neurologic symptoms.

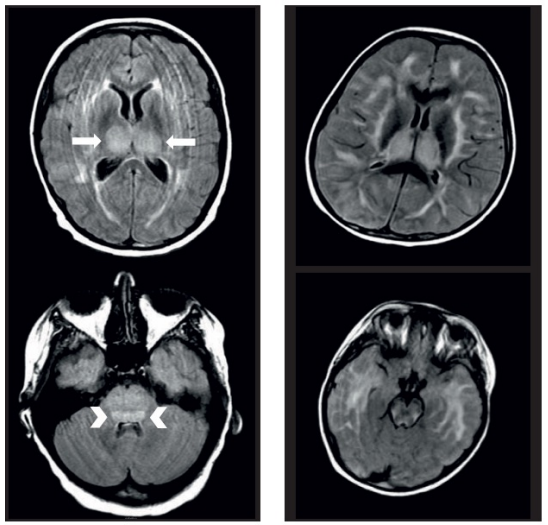
Overall ICANS Grade	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli 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 oedema	N/A	N/A	Focal/local oedema on neuroimaging§	Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

- For patients with rapidly declining neurologic status and/or signs of increased intracranial pressure, treatment of cerebral edema must be promptly started. Neuroprotective and intracranial pressure-lowering measures, including normotension (acetazolamide, mannitol), normothermia, normocarbia, raising the head of the bed, hypertonic saline, and pentobarbital coma, are warranted. There is no clear role for neurosurgical intervention, whereas in cases of severe ICANS without overt cerebral edema, CSF removal is often accompanied by symptomatic improvement.

- Seizures are treated with intravenous lorazepam, levetiracetam, or fenobarbital in refractory cases, along with intensive supporting therapy. Maintenance therapy and continuous EEG monitoring are recommended

- Intrathecal therapies, such as corticosteroids and chemotherapy, and supplementation of high-dose thiamine have been advocated by some groups





ICANS GRADE	Management
GRADE 1	• Supportive care only • Twice daily neurocognitive assessment using ICE score
GRADE 2	• Supportive care as per Grade 1 • Administer dexamethasone 10-20 mg IV every 6 hours • Consider an increased frequency of neuromonitoring using ICE score (e.g. 3-4x(d))
GRADE 3	• Transfer patient to intensive-care unit (ICU) and assessment by a neurologist • Administer dexamethasone 10-20 mg IV every 6 hours or methylprednisolone 1000 mg/day for 3 day until improvement to Grade 1 and then rapid taper (e.g. 250 mg – 125 mg – 60 mg for 1 day each) • Treat seizures with lorazepam 0.5mg IV or other benzodiazepines as needed, followed by loading with levetiracetam. • Consider neuroimaging (CT or MRI) if patient does not improve after three days
GRADE 4	• Management as per Grade 3 • Administer methylprednisolone 1000mg/day for 3 days, then taper at 250mg every 12 hrs for 2 days, then 125mg every 12hrs for 2 days, then 60mg every 12 hrs for 2 days • For convulsive status epilepticus, seek urgent advice from neurologist • For management of raised intracranial pressure, elevate head of bed, set ventilatory settings to hyperventilation and consider hyperosmolar therapy with mannitol

Santomasso BD, et al. How I treat unique and difficult-to-manage cases of CAR T-cell therapy-associated neurotoxicity. Blood. 2023 May 18;141(20):2443-2451

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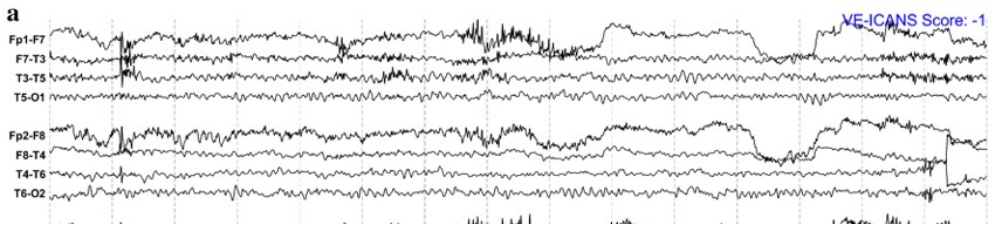
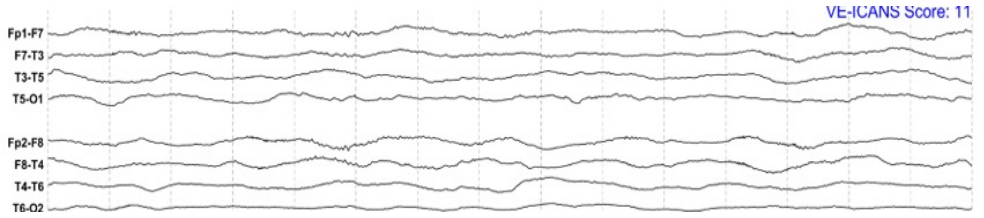
EEG-based grading of immune effector cell-associated neurotoxicity syndrome

Daniel K. Jones[1,2,3,4,9], Christine A. Eckhardt[1,2,3,5,9], Haoqi Sun[1,2,3], Ryan A. Tesh[1,2,3], Preeti Malik[1,2,3], Syed Quadri[1,2,3], Marcos Santana Firme[1,2,3], Meike van Sleuwen[1,2,3], Aayushee Jain[1,2,3], Ziwei Fan[1,2,3], Jin Jing[1,2,3], Wendong Ge[1,2,3], Fábio A. Nascimento[8], Irfan S. Sheikh[1,2], Caron Jacobson[5,6], Matthew Frigault[1,2,6], Eyal Y. Kimchi[1,2], Sydney S. Cash[1,2], Jong Woo Lee[2,5], Jorg Dietrich[1,2,6] & M. Brandon Westover[1,2,3,7]

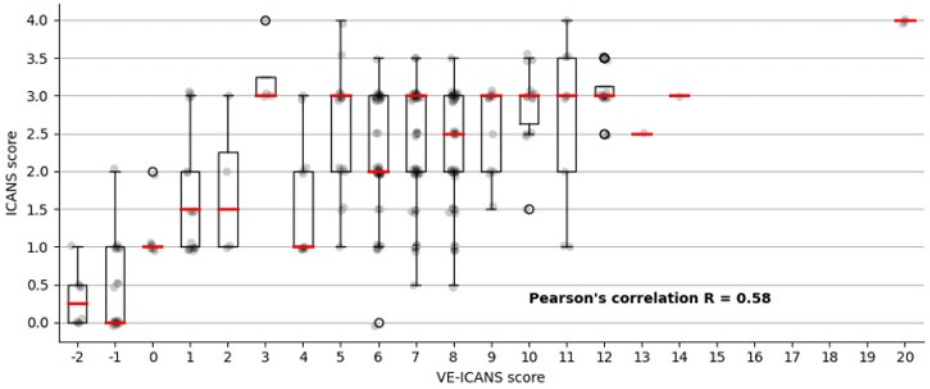
- Retrospective observational study of 120 CAR-T cell therapy patients who had received EEG monitoring. Visually assessed EEG features and machine learning techniques were used to develop the Visual EEG-Immune Effector Cell Associated Neurotoxicity Syndrome (VE-ICANS) grading scale, that harbored a strong correlation to ICANS severity. The lower EEG frequencies (< 8 Hz) were the most predictive features in the model.

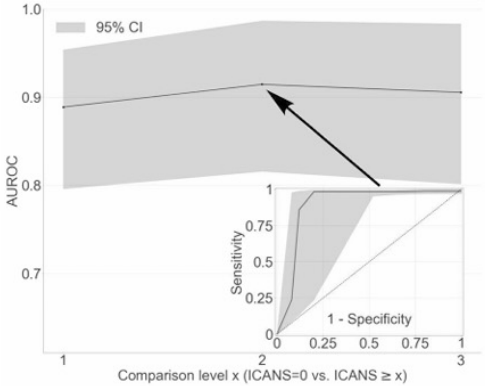
- In other studies, EEG features such as discontinuity, absence of posterior dominant rhythm, and presence of generalized sharp waves were statistically significantly associated with higher ICANS grade (Mao D, Sci Rep 2024)





EEG Feature	Score
Delta frequency 1 Hz or less	+10
Delta frequency 1–2 Hz	+6
Delta frequency 2–3 Hz	+5
Delta frequency 3–4 Hz	+3
Moderately low voltage (< 20 µV)	+2
GRDA (Gen. rhythmic delta activity)	+2
GPDs (Gen. Period Discharges)	+2
Theta frequency 4–5 Hz	+2
Theta frequency 5–8 Hz	+1
Alpha frequency > 9 Hz	−1
PDR present	−1
NCSE (Nonconvulsive Status Epilepticus) Low voltage: Extreme/ECS (Electrocerebral Silence) Burst suppression@Unreactive EEG	Maximal score





Jones DK et al., Scientific Reports 2022

- **Steroid-refractory ICANS (srICANS)** can be defined as occurring when there is no improvement of ICANS after 3 days of high-dose steroids (Velasco et al. 2023) . It is associated with a worse prognosis.
  Possible treatment options include:

- **Anakinra:** SC or IV formulations have become a mainstay therapy for srICANS based on preclinical data and clinical safety experience Institution dependent approaches associated with an overall response rate of 77%. High-dose IV Anakinra (up to 12 mg/kg/d, usually 800 mg/d), led to a faster resolution of ICANS within 7 days, and lower treatment-related mortality at 28 days, when compared with a low-dose regime (i.e. 100-200 mg/d) (Gazeau et al. 2023). There is an ongoing randomised trial examining whether prophylactic Anakinra could prevent severe ICANS (Strati et al. 2023).

- **Intratecal therapy** with hydrocortisone, methotrexate, and cytarabine have been administered in a cohort with srICANS (Zurko et al. 2022

- **Dasatinib, siltuximab** and **ruxolitinib** have shown efficacy in preclinical data and case series

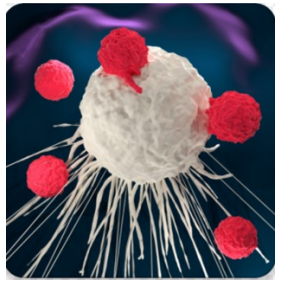
ICANS Grade	Pharmacotherapy Recommendations
Grade 1	• Supportive care, consider dexamethasone 10 mg and reassess
Grade 2	• Dexamethasone 10 mg IV every 12 hours, can escalate dosing to 10 mg every 6 hours for persistent grade 2 ICANS • Continue corticosteroids until improvement to grade 1 ICANS, then rapidly taper as clinically appropriate
Grade 3 or Grade 4	• Dexamethasone 10 mg IV every 6 hours • Can escalate up to methylprednisolone 1,000 mg IV given two to three times daily for refractory grade 3 or grade 4 ICANS • Seizures and/or status epilepticus should be managed with anti-epileptics with neurology assistance as per institutional guidelines • Alternative therapies should be considered for the treatment of ICANS refractory to corticosteroids

Alternative Therapies for Refractory ICANS
Anakinra – IL-1 receptor antagonist, multiple retrospective studies demonstrating efficacy (64, 102, 103)
Siltuximab – IL-6 inhibitor, pre-clinical rationale without significant clinical demonstration of efficacy. Note that tocilizumab (IL-6R inhibitor) should only be used for concomitant CRS as inhibition of the receptor causes transient increases in free IL-6 which may exacerbate ICANS (65, 97, 104)
Dasatinib – tyrosine kinase inhibitor, demonstrated efficacy in case report (72)
Intrathecal hydrocortisone and/or chemotherapy – direct targeting of CAR T cells in CSF, demonstrated efficacy in case reports and retrospective studies (105, 106)
Antithymocyte globulin (ATG) – direct targeting of CAR T cells, demonstrated efficacy when used as part of multimodal therapy in case report (104)
Cyclophosphamide – Chemotherapeutic targeting of CAR T cells, demonstrated efficacy in case report (107)

Table 1. Therapeutic approaches for CAR T-cell therapy–related neurotoxicity

Therapy	Timing	Comments
IV corticosteroids	Therapeutic[14-16]	Among patients who received corticosteroids at the onset of grade 3 (ZUMA-1 C 1+2) and earlier for grade 1 NEs (C4), rates of grade ≥3 NEs were 28% and 17%, respectively.
IV corticosteroids	Prophylactic[28,29]	The incidence of grade ≥3 NEs in ZUMA-1 C6 (13%) was comparable to that of C4 (17%), and both rates were comparably lower than C1+2 (28%). In ZUMA-1 C6, patients received once-daily oral dexamethasone at 10 mg plus C4 management on d 0 (before axi-cel), 1, and 2. The updated follow-up included a few additional NEs and the total incidence of grade ≥3 NEs was 15%.
Anakinra	Therapeutic[30-32]	Four of 6 patients who received anakinra for the management of high-grade ICANS experienced clinical benefit.[32] In 9 out of additional 14 patients with ICANS, the reduction of peak ICANS could be reached within 1 day after the last anakinra dose.[30] Twenty three patients treated with anakinra for steroid-refractory ICANS. CRS/ICANS improvement was observed among 73% of patients; higher response rates in patients receiving higher doses (8 mg/kg per d).[33]
Anakinra	Prophylactic[34]	#NCT04148430: 31 patients received anakinra starting on d 2 or after 2 documented fevers of ≥38.5°C before day 2, whichever time point was earlier. The overall severe ICANS rate was 6%. Other ongoing clinical trials include #NCT04432506, #NCT04359784, #NCT04150913, and #NCT04205838.
Tocilizumab	Therapeutic	Approved for use in CRS but is not effective for isolated neurotoxicity and may be associated with worsening neurotoxicity.[27]
Tocilizumab	Prophylactic[35]	Not recommended. ZUMA-1 C3, which incorporated prophylactic tocilizumab on d 2 after axi-cel had grade ≥3 NEs 41% compared with 28% in C1+2.[35]
Siltuximab	Therapeutic	Ongoing clinical trial #NCT04975555. No data available.
Siltuximab	Prophylactic	Ongoing clinical trial #NCT05665725. No data available.
Intrathecal therapy	Therapeutic[36,37]	2 cases were treated with a rapid and sustained resolution of ICANS.[10] Use with other immunosuppressive agents may be associated with sepsis.

Santomasso BD, et al. How I treat unique and difficult-to-manage cases of CAR T-cell therapy-associated neurotoxicity. Blood. 2023 May 18;141(20):2443-2451



Comparisons of the ASCO, EBMT/EHA, SITC, and NCCN Toxicity Management Guidelines

	ASCO[43]	EBMT/EHA[44]	SITC[45]	NCCN[46]
ICANS *				
indication for first dose of corticosteroids	-Gr 2 ICANS in high-risk patients or for high-risk products -All Gr 3-4 ICANS	-Gr 2-4 ICANS	-Gr 2 ICANS due to axi-cel or brexu-cel; consider for Gr 2 ICANS due to other products -All Gr 3-4 ICANS	-≥Gr 2 ICANS. -Consider for Gr 1 ICANS occurring < 72 hrs after infusion of liso-cel or ide-cel.
corticosteroid dosing recommendations	-Gr 2 ICANS → dexamethasone 10 mg IV x 2 doses and reassess -Gr 3 ICANS → dexamethasone 10 mg IV q 6-12 hrs or methylprednisolone 1 mg/kg IV q 12 hrs -Gr 4 ICANS → methylprednisolone 1,000 mg IV 1-2 times daily x 3 days	-Gr 2-3 ICANS → dexamethasone 10 mg IV q 6 hrs x 1-3 days - Gr 4 ICANS → methylprednisolone 1000 mg IV daily x 3 days, then 250 mg twice daily for x 2 days, 125 mg twice daily for x 2 days, 60 mg twice daily x 2 days.	-Recommendations not specified. -Give at least 2 doses and taper quickly once ICANS has improved. -In agreement with axi-cel package insert, may give dexamethasone 10 mg IV q 6 hrs for Gr 2-3 ICANS; give methylprednisolone 1000 mg daily x 3 days for Gr 4 ICANS.	- Gr 1 ICANS occurring < 72 hrs after infusion of liso-cel or ide-cel → dexamethasone 10 mg q 12-24 hrs x 2 doses and reassess. -Gr 2 ICANS: 1 dose of dexamethasone 10 mg and reassess. Can repeat q 6-12 hrs if no improvement. -Gr 3 ICANS: dexamethasone 10 mg q 6 hrs or methylprednisolone 1 mg/kg IV q 12 hrs. Consider methylprednisolone 1 gram/day x 3-5 days for 3-5 days for axi-cel and brexu-cel.
Recommendations for refractory high-grade ICANS	-methylprednisolone 1,000 mg IV 2-3 times daily; consider anakinra, siltuximab, ruxolitinib, cyclophosphamide, antithymocyte globulin, or intrathecal hydrocortisone (50 mg) plus methotrexate (12 mg)	-Consider anakinra, siltuximab, intrathecal chemotherapy, or systemic chemotherapy	Not specified	-Gr 4 ICANS: High dose corticosteroids such as IV methylprednisolone 1-2 grams q 12-24 hrs.^ -corticosteroid refractory → anakinra 100 mg q 6 hrs.

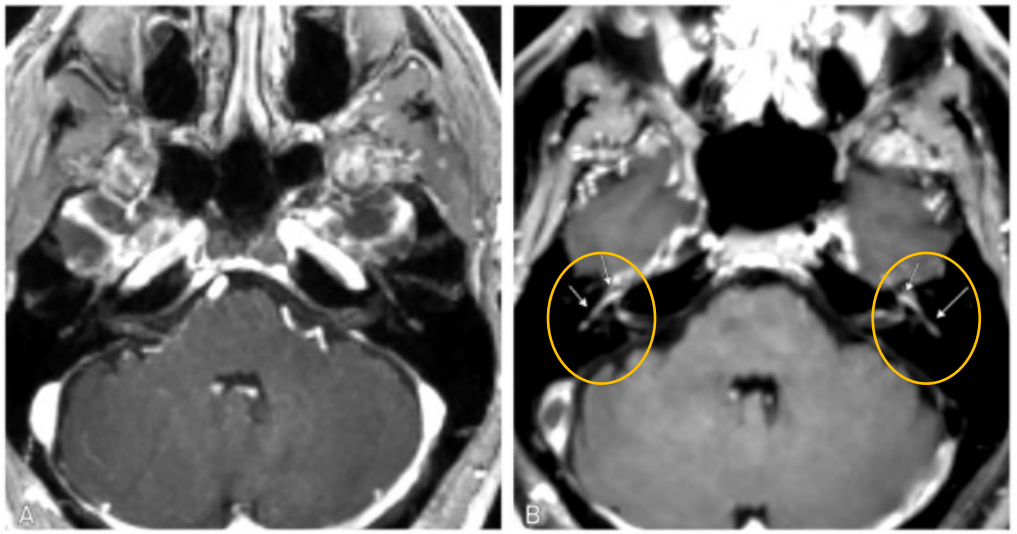
Brudno JN, et al. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev. 2019 Mar;34:45-55

- **Cranial and peripheral neuropathy:** both cranial neuropathy (bilateral facial neuropathy in a third of patients) and Guillain-Barré syndrome are seen following anti-BCMA CAR-T cell infusion, but are uncommon (3-9%) early complications. Treatment with a short course of oral corticosteroids is recommended, while the treatment of GBS is with intravenous corticosteroids and immune globulin. Patients may show gradual, often incomplete recovery (Graham et al. 2024)

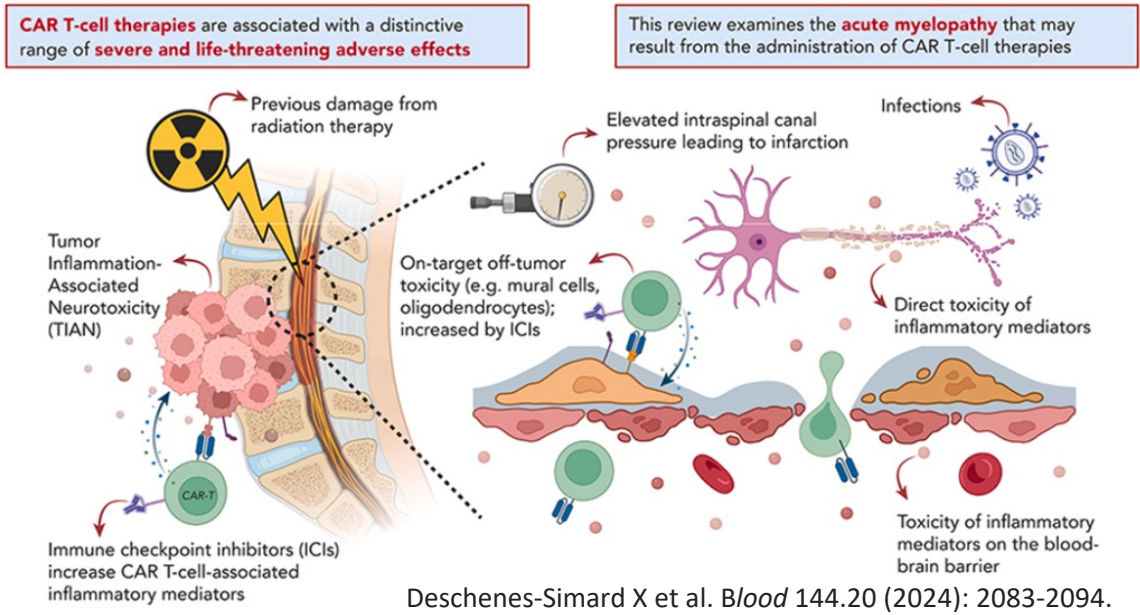
- **Myelopathy** is exceptionally rare following CAR-T transfusion, typically presenting as an acute flaccid paraplegia, occurring either concurrently with or shortly after the onset of ICANS. Empirical treatment with pulse-dose corticosteroids, thiamine, IV immunoglobulin or plasmapheresis may be considered, with Anakinra as a further option (Graham et al. 2024; Deschênes-Simard, Santomasso and Dahi 2024)

- **Ischemic stroke** has been described in 1-3% of patients receiving CD19 CAR-T, and tends to occur in patients with either current or prior severe ICANS (Graham et al. 2024)

- **Progressive Multifocal Leucoencephalopathy:** as CAR-T cell patients may be heavily immunocompromised, they are more susceptible to opportunistic CNS infections which can be confused with ICANS, such as PML induced by JC virus (Montoya M et al. 2024). Fludarabine-induced acute toxic leukoencephalopathy is extremely rare and invariably fatal (Winter et al. 2021).



Richards A er al. Mayo Clinic Proceedings, Volume 98, Issue 10, 1579 - 1580

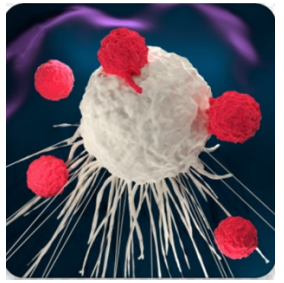


Deschenes-Simard X et al. B*lood* 144.20 (2024): 2083-2094.

Santomasso BD, et al. How I treat unique and difficult-to-manage cases of CAR T-cell therapy-associated neurotoxicity. Blood. 2023 May 18;141(20):2443-2451

- There has also been investigation in to whether prophylactic or preemptive approaches to toxicity management can decrease the incidence and severity of both CRS and ICANS. Such attempts include early intervention with tocilizumab or corticosteroids for lower grade toxicity, as well as prophylaxis strategies with corticosteroids, tocilizumab, anakinra, or the JAK1 inhibitor itacitinib.

- Preclinical studies did not suggest hindrance of antitumor activity with IL-1, IL-6 and IFN-ɣ inhibition in this setting. A retrospective analysis regarding the timing of tocilizumab administration for patients treated with anti-BCMA CAR T cell therapy demonstrated that patients receiving tocilizumab earlier (<12 hours from CRS onset) experienced a shorter median duration of CRS without negative effect on response or median progression-free survival outcomes (Banerjee R, Transplant Cell Ther 2021)



Agent/Study	Outcomes	Comparator	Comments
Dexamethasone 10 mg on days 0, 1, and 2 ZUMA-1, cohort 6 (88)	CRS 80% G ≥ 3 CRS 0% ICANS 58% G ≥ 3 ICANS 13%	ZUMA-1, cohorts 1–2 (no prophylactic dex): CRS 93%, G ≥ 3 13% ICANS 64%, G ≥ 3 28%	Lower baseline tumor burden in prophylactic dex cohort compared to cohorts 1–2
Tocilizumab on day 2 after axi-cel infusion Safety expansion cohort of ZUMA-1 (87)	G ≥ 3 CRS 3% G ≥ 3 ICANS 35%	ZUMA-1, cohorts 1–2 (no prophylactic toci): G ≥ 3 CRS 13% G ≥ 3 ICANS 28%	Peak IL-6 levels were higher in prophylactic toci cohort
Anakinra on days 0–7 NCT04432506 (91)	CRS 95% G ≥ 2 CRS 40% G ≥ 3 CRS 5% ICANS 35% G ≥ 3 ICANS 20%	Tumor-burden matched retrospective cohort: G ≥ 2 CRS 50% G ≥ 3 ICANS 30%	No observed impact on expansion kinetics or CAR T efficacy
Anakinra on day 2 through at least day 10 post-CAR T NCT04148430 (92)	CRS 74% G ≥ 3 CRS 6.4% ICANS 19% G ≥ 3 ICANS 9.7%	No comparison cohort	Favorable reduction in all grades of ICANS compared to historical controls

Agent/Study	Outcomes	Comparator	Comments
Itacitinib (JAK1 inhibitor) starting day -3 through day +26 after CAR T NCT04071366 (79)	CRS 65% Grade 2 CRS 17% G ≥ 3 CRS 0% ICANS 13% G ≥ 2 ICANS 9%	Placebo-controlled cohort: CRS 87% Grade 2 CRS 57% G ≥ 3 CRS 0% ICANS 35% G ≥ 2 ICANS 22%	Tocilizumab use lower in itacitinib arm (17% v. 57%). Persistent G ≥ 3 neutropenia and TCP at day 28 higher in itacitinib arm
Defibrotide on days -5 to -3 pre-CAR T and days 0–7 post-CAR T; NCT03954106 (93)	ICANS 50% G ≥ 3 ICANS 25%	No comparison cohort	Study terminated early as unlikely to meet 1° endpoint
Lenzilumab (GM-CSF inhibitor) 6 hours prior to axi-cel ZUMA-19 (94)	G ≥ 3 CRS 0% G ≥ 3 ICANS 17%	No comparison cohort	Met 1° endpoint for safety, but terminated after only 6 patients

Ferreri CJ and Bhutani M (2024) Mechanisms and management of CAR T toxicity. Front Oncol 2024. 14:1396490

IEC-HS

- Haemophagocytic lymphohistiocytosis-like toxicities following CAR-T infusion can occur across patient populations and CAR-T constructs and seem not clearly superimposed with CRSas initially described. Delayed manifestations are being reported more frequently.

- ASTCT proposed diagnostic criteria and proposed the term immune effector cell HLH-like syndrome (IEC-HS). Treatment of IEC-HS is focused on early identification and intervention with corticosteroids and anakinra.

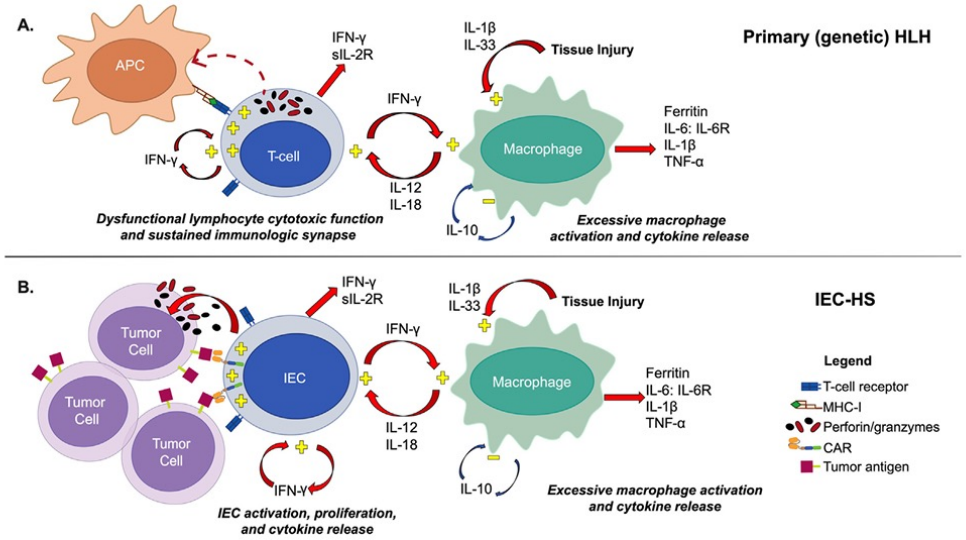


Table 1
IEC-HS: Definition and Identification

Definition of IEC-HS	The development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to IEC therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis
Criteria for Identifying IEC-HS*	**Clinical/Laboratory Manifestations**
Most common manifestations†	Required: elevated ferritin (>2 × ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment)
	Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS-directed therapy‡
	Hepatic transaminase elevation§ (>5 × ULN (if baseline was normal) or >5 × baseline if baseline was abnormal)
	Hypofibrinogenemia (<150 mg/dL or <LLN)‖
	Hemophagocytosis in bone marrow or other tissue‖
	Cytopenias (new onset, worsening, or refractory¶)
Other manifestations that may be present	Lactate dehydrogenase elevations (>ULN)
	Other coagulation abnormalities (eg, elevated PT/PTT)
	Direct hyperbilirubinemia
	New-onset splenomegaly
	Fever (new# or persistent)‖
	Neurotoxicity
	Pulmonary manifestations (eg, hypoxia, pulmonary infiltrates, pulmonary edema)
	Renal insufficiency (new onset)
	Hypertriglyceridemia (fasting level, >265 mg/dL‖)

ULN indicates upper limit of normal; LLN, lower limit of normal.
* Diagnosis was made only when not attributable to alternative etiologies, including CRS, infection and/or disease progression.
† Constellation of findings typically simultaneously (eg, all within 72 hours).
‡ Although most cases of IEC-HS have been seen with antecedent CRS, this may not always be the case, and emerging experience will shed light on how IEC-HS may present.
§ Consistent with grade 3 hepatic transaminase elevations according to Common Terminology for Adverse Events version 5.0.
‖ According to HLH-2004.
¶ Generally at least 1 lineage will be a grade 4 cytopenia (platelets, neutrophils, hemoglobin).
# As distinguished from CRS onset or recrudescence.

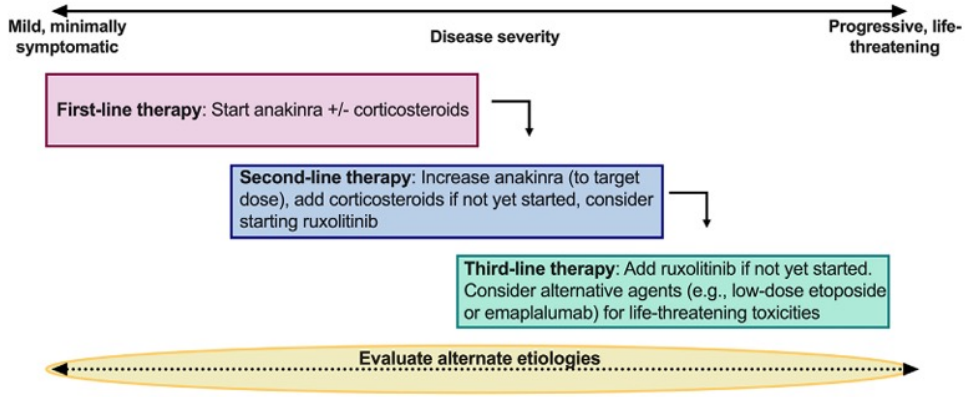
Hines MR et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplant Cell Ther. 2023 Jul;29(7):438.e1-438.e16

- Therapy generally should be initiated with corticosteroids with or without anakinra before the development of life threatening complications and, if possible, a time interval to evaluate for efficacy (eg, 48 hours) should elapse before additional agents are added to avoid cumulative toxicity

- **Anakinra** was recommended as a first-line agent owing largely to its side effect profile, its use in sHLH, and the experience in CRS and ICANS treatment. Future prospective efforts will be needed to evaluate the optimal timing of initiation, dosing, and duration of therapy.

- **Corticosteroids** also are considered an acceptable first-line agent for use with or without anakinra. The general approach recommends lower doses initially, with up-titration for increasing disease severity.

- **Ruxolitinib** is considered a reasonable therapeutic option following anakinra and/or corticosteroids for patients who require additional agents (eg, with worsening inflammatory parameters and/or with evidence of progressive end-organ involvement.



Potential Pharmacologic Approaches for Treatment of IEC-HS

Agent	Mechanism and Rationale for Inclusion in IEC-HS Treatment Algorithm	Side Effect Profile and Potential Considerations	Starting Dose in IEC-HS; General Considerations
Anakinra	Recombinant IL-1 receptor antagonist. Elevated IL-1β present in MAS/sHLH; blockade with anakinra has documented efficacy in both rheumatologic and non-rheumatologic etiologies, including in severe disease [86,88-91]. IL-1β upregulation has been documented specifically in the IEC-HS context [8,48]. Evidence of efficacy in treatment/prevention of other CAR T-associated toxicities (refractory CRS, ICANS) [10,103,104]. Relatively high degree of familiarity with use in the HLH context. A short half-life, allowing rapid titration to effect and, conversely, rapid clearance if necessary.	Well-studied, well-tolerated side effect profile (in rheumatology context) [143]; less data regarding side effect profile in the CAR T context but appears similar [104]. Unknown effect on CAR T efficacy but expected to be minimal.	Adults: 100-200 μg s.c./i.v. every 6-12 hr Pediatrics: can start at 5-7 mg/kg/d or use higher dose of 8-10 mg/kg/d divided in 2 or 3 doses or 4 mg/kg i.v. every 6 hr Continuous i.v. infusion regimens have been used for other indications. Discuss with rheumatology consultants.
Corticosteroids	Established use in conjunction with multiple other agents in pHLH [112,113] and sHLH [2,76,77]. Evidence of efficacy in treatment, prevention, and reduction of severity of other CAR T-associated toxicities (CRS, ICANS) [101,102,144].	Known but prominent side effect profile. Mixed data on impact of corticosteroids on long-term CAR T-efficacy and outcomes [105,107,145].	Adults: dexamethasone 10-40 mg daily (10 mg every 6 hr most common) Pediatrics: dexamethasone 10 mg/m^2/day or methylprednisolone 1-2 mg/kg i.v. or orally every 6-12 hr
Ruxolitinib	Inhibition of JAK1/JAK2, thereby blocking downstream transduction via the JAK/STAT pathway, attenuating the action of multiple key proinflammatory cytokines including IFN-γ, IL-2, and IL-6 [92]. Evidence of efficacy in sHLH in both frontline [93] and refractory [94,95] settings. Theoretical therapeutic rationale for use exists in IEC-HS, eg, inhibition of multiple cytokines shown to be involved in IEC-HS pathogenesis [8]. Relatively commonly used agent in HSCT/cell therapy setting; high degree of familiarity. A short half-life allowing rapid titration to effect and, conversely, rapid clearance if necessary.	Risk of exacerbating post CAR-T cytopenias and increased risk of infection, especially viral reactivation [146]. CYP3A4 inhibition: risk of drug interaction especially with azole prophylaxis [146]. Unknown effect on CAR-T efficacy (expected to be minimal)	Adults ($\geq$14 yr): 10 mg twice daily (and can consider increasing to 20 mg twice daily) Pediatrics ($<$14 yr): $>$25 kg: 5 mg twice daily; $<$25 kg: 2.5 mg twice daily (can consider increasing). Dosage adjustment required with strong CYP450 inhibitors (eg, azoles).

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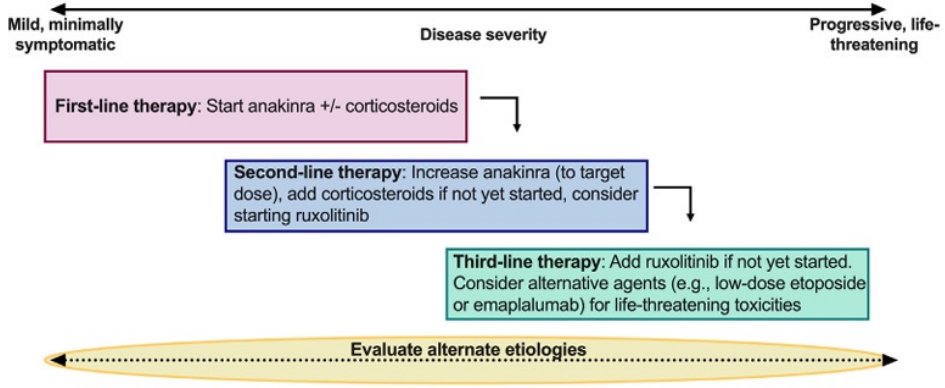
- **Etoposide** is the preferred T cell-depleting agent over alternative strategies that may be more immunosuppressive (eg, alemtuzumab) or for which clinical data are sparse (eg, dasatinib. It is warranted that it may be best used at a one-time moderate dose of 50 to 100 mg/m2, with subsequent monitoring for response with consideration for redosing on a once-weekly basis.

- **Emapalumab** can be considered as a possible agent for life-threaten in IEC-HS. However, the literature supporting use of emapalumab is limited to a small pediatric pHLH cohort, and the cost and procurement under urgent circumstances may be prohibitive
- **Targetable safety switches** (eg, cetuximab for truncated EGFR-based constructs), "turning off" the CAR T cells with directed specificity should be considered

- **Long acting drugs** (eg, alemtuzumab, basiliximab, antithymocyte globulin) must be used with caution based on an elevated risk of infection.

Etoposide	Inhibition of topoisomerase II Robust evidence of efficacy in pHLH [112,113], and most studies show evidence of efficacy in sHLH [31,78-81,83,84]. Strong theoretical mechanistic rationale for use in IEC-HS (eg, targeted induction of T cell apoptosis and blunting of subsequent inflammatory response) [66,67]. May best be used as last-line therapy in or to prevent high-grade/life-threatening IEC-HS. Impact on CAR T cells is unknown, but given the direct impact on lymphocytes, it also may eradicate/diminish CAR T cells).	Significant side effect profile compared to other agents discussed. Importantly, however, use of etoposide for IEC-HS would be at a substantially lower dose than with induction dosing for pHLH. Evidence of extended use in adults as well as children [82]. Risk of secondary malignancy – likely very low with the suggested dosing [112–115]. Putative effect in IEC-HS is via direct ablation of activated T-lymphocytes [68]; removal of CAR T cells therefore possible.	50-100 mg/m^2/dose (× 1 to initiate)
Emapalumab	Human IgG1 anti-IFN-γ monoclonal antibody; binds both free and receptor-bound IFN-γ. May be considered as a possible alternative agent in severe/life-threatening IEC-HS, especially in the setting of documented IFN-γ elevation. Elevated IFN-γ has been documented in both pHLH [124–126] and CAR T-associated toxicities [119,121,122]. Evidence of clinical efficacy in pediatric pHLH in both frontline and salvage settings [75]. (Notably, several patients required additional etoposide.) Directly measured cytokine levels	Increased infection risk, including viral and fungal [75]. Otherwise relatively low side effect profile, but limited data available, and no adult data reported. Minimal (but positive) data supporting use in pediatric sHLH [99,100]. No data supporting use in adult patients. Potentially cost-prohibitive.	Per standard package insert, starting dose 1 mg/kg (x 1 to initiate)



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Hematological toxicity

- **Cytopenias** represent the most frequent high-grade adverse event of CAR T cell therapy. While early cytopenia is expected after lymphodepleting chemotherapy, low counts can last weeks, months, or even years after CAR-T, and can predispose to significant infectious complications and hospitalization

- **Neutropenia** follows distinct 'phenotypes' of recovery, including a transient lymphodepletion-associated neutropenia ('quick' phenotype), and a biphasic temporal course ('intermittent' phenotype). A smaller proportion of patients exhibit severe bone marrow aplasia, refractory to growth factor support ('aplastic' phenotype)

- **Thrombocytopenia** is observed in >50% of CAR T cell recipients, although its nadir occurs in the second month

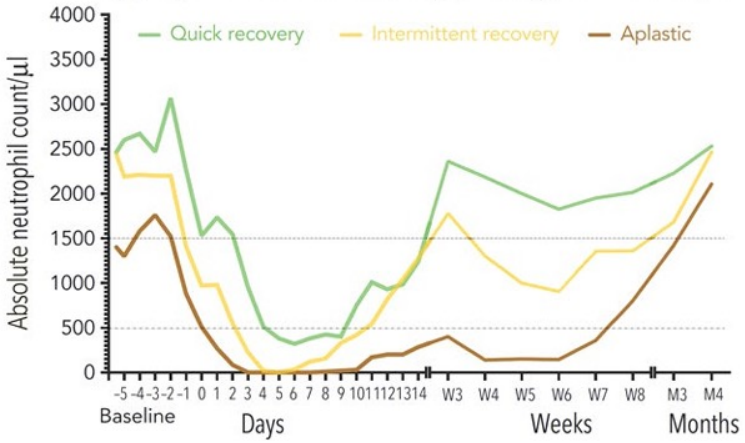


Table 1. Incidence of post CAR-T cytopenias in clinical trials

Trial/product	Disease	Target/endodomain/ vector	Lymphodepletion	Grade ≥3 neutropenia, %	Grade ≥3 thrombocytopenia, %	Grade ≥3 anemia, %	Reference
ZUMA-3 Brexu-cel	BCP-ALL	CD19/CD28z/RV	Flu 25 mg/m² × 3 Cy 900 mg/m² × 1	27%	30%	49%	Shah et al. Lancet 2021[3]
ZUMA-1 Axi-cel	LBCL	CD19/CD28z/RV	Flu 30 mg/m² × 3 d Cy 500 mg/m² × 3 d	78%	38%	43%	Locke et al. Lancet Oncol 2019[73]
JULIET Tisa-cel	LBCL	CD19/4–1BB/LV	Flu 25 mg/m² × 3 d Cy 250 mg/m² × 3 d	33%	28%	39%	Schuster et al. NEJM 2019[74]
TRANSCEND Liso-cel	LBCL	CD19/4–1BB/LV	Flu 30 mg/m² × 3 d Cy 300 mg/m² × 3 d	60%	27%	37%	Abramson et al. Lancet 2020[75]
ZUMA-7 Axi-cel	LBCL	CD19/CD28z/RV	Flu 30 mg/m² × 3 d Cy 500 mg/m² × 3 d	69%	15%	30%	Locke et al. NEJM 2022[1]
TRANSFORM Liso-cel	LBCL	CD19/4–1BB/LV	Flu 30 mg/m² × 3 d Cy 300 mg/m² × 3 d	82%	50%	52%	Abramson et al. Blood 2023[2]
ZUMA-2 Brexu-cel	MCL	CD19/CD28z/RV	Flu 30 mg/m² × 3 d Cy 500 mg/m² × 3 d	85%	51%	50%	Wang et al. NEJM 2020[4]
ELARA Tisa-cel	FL	CD19/4–1BB/LV	Flu 25 mg/m² × 3 d Cy 250 mg/m² × 3 d	32%	9%	13%	Fowler et al. Nat Med 2022[76]
ZUMA-5 Axi-cel	FL	CD19/CD28z/RV	Flu 30 mg/m² × 3 d Cy 500 mg/m² × 3 d	33%	9%	25%	Jacobson et al. Lancet Oncol 2022[77]
KarMMa-1 Ide-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m² × 3 d Cy 300 mg/m² × 3 d	89%	52%	60%	Munshi et al. NEJM 2021[78]
KarMMa-3 Ide-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m² × 3 d Cy 300 mg/m² × 3 d	76%	42%	51%	Rodriguez-Otero et al. NEJM 2023[79]
CARTITUDE-1 Cilta-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m² × 3 d Cy 300 mg/m² × 3 d	95%	60%	68%	Berdeja et al. Lancet 2021[80]
CARTITUDE-4 Cilta-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m² × 3 d Cy 300 mg/m² × 3 d	90%	41%	36%	San-Miguel et al. NEJM 2023[81]

Rejeski K et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021 Dec 16;138(24):2499-2513

- The EHA/EBMT panel defined ICAHT as a distinct toxicity category and developed a grading system incorporating the cumulative duration of neutropenia and the timing from infusion

- the CAR-HEMATOTOX model, which included markers associated with hemato poietic reserve and baseline inflammation , was validated in independent cohorts, and discriminated patients with severe neutropenia (≥ 14 days to <14days). A high score resulted in a longer duration of neutropenia and a higher incidence of severe thrombocytopenia and anemia

- Severe early ICAHT (grade 3 or higher) was associated with an increased infection rate (particularly severe and bacterial infections), co-occurrence of severe anemia and/or thrombocytopenia, higher infection-driven NRM and poor treatment outcomes.

- A tailored grading system termed T-ICAHT was recently developed and validated in order to define patterns and severity of thrombocytopenia following CAR T (Rejeski, Blood 2025)

Grading System		Grade 1	Grade 2	Grade 3	Grade 4
Early ICAHT (day 0-30)*	Severe Neutropenia (ANC <0.5 G/L)	1-6 days	7-13 days	≥14 days	Never above ANC 500/µL
	Profound Neutropenia (ANC <0.1 G/L)	-	-	≥7 days	≥14 days
Late ICAHT (after day 30)**	ANC	<1500/µL	<1000/µL	<500/µL	<100/µL

*refers to consecutive neutropenia (longest streak of neutropenia). *Non-transient neutropenia, see additional definitions from Liang et al. (Liang et al. 2024) clarifying the necessary second measurement of ANC <1500/µL within a certain time period.

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 High: ≥2			

Low risk (HT 0-1) | High risk (HT 2-7)

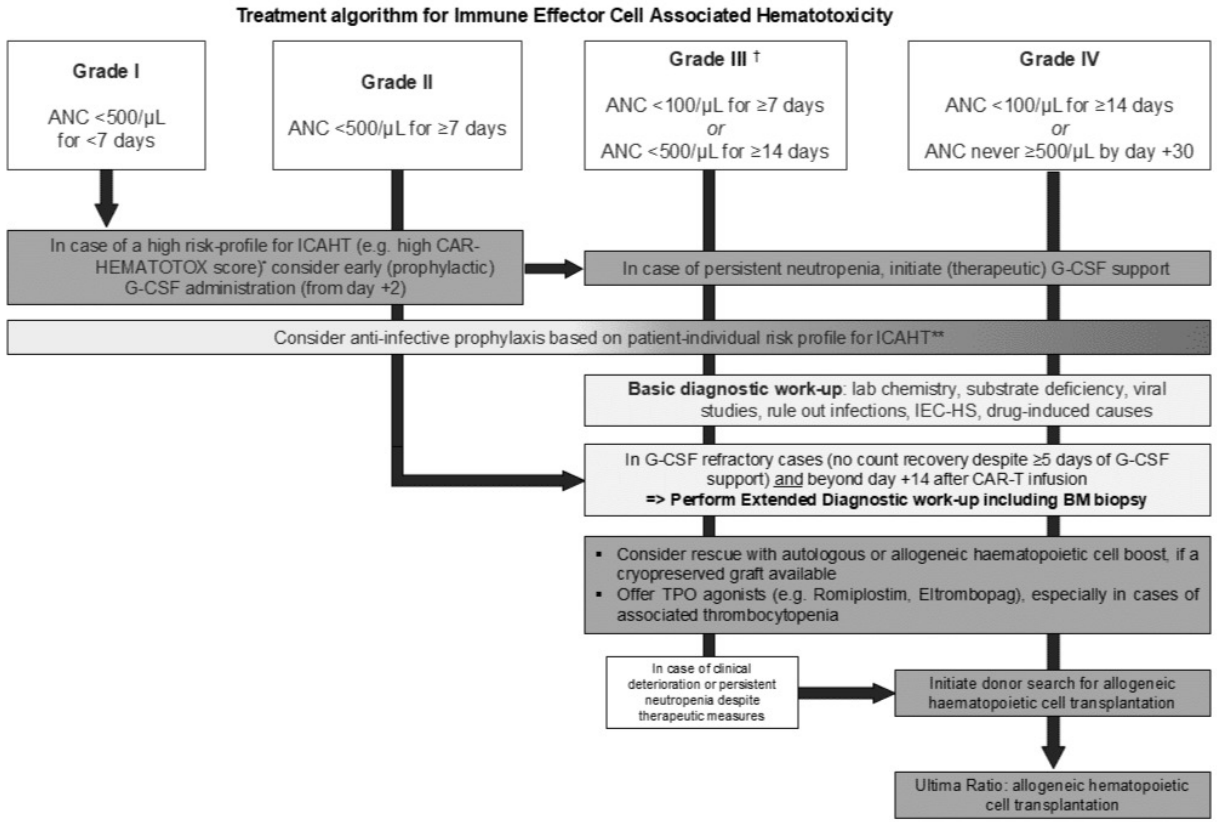
Risk profile

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

Figure 3. Using the CAR-HEMATOTOX score for risk-adapted toxicity management. Reproduced with permission from Rejeski et al., *Blood* 2023.[9]

- The EHA/EBMT consensus also included severity-based guidelines. A critical decision point relates to the identification of patients with grade ≥3 early ICAHT refractory to growth factor support (that is, absent count recovery despite ≥5 days of granulocyte colony-stimulating factor (G-CSF), as they often carry a high risk for protracted bone marrow aplasia and infections.



Rejeski K et al. Recognizing, defining, and managing CAR-T hematologic toxicities. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):198-208.

Table 4. Diagnostic workup

Diagnostic category	Included diagnostic tests	When to initiate	Additional comments
Basis workup (tier 1)	• Check medication list for myelotoxic co-medications • Rule out active infections: blood cultures, procalcitonin • Vitamin deficiency: B12, folic acid • Consider secondary HLH/MAS: serum ferritin	In case of severe neutropenia (ANC <500/µL) beyond day +7 after CAR-T infusion	Low threshold to perform (minimal workup)
Advanced workup in case of severe ICAHT (tier 2)	• Bone marrow aspiration and biopsy • Advanced viral studies (parvovirus B19, CMV)	Grade 3 or higher ICAHT beyond day +14	Especially in patients with underlying marrow infiltration
Clinical suspicion for therapy-related myeloid neoplasm	Immunohistochemistry, flow cytometry, cytogenetics; next-generation sequencing (myeloid panel)	In case of persistent bone marrow aplasia beyond 1 month; unclear and/or new-onset cytopenia; cytopenia refractory to therapeutic measures	t-MN after CAR-T therapy is an emerging field of study*

ANC, absolute neutrophil count; CMV, cytomegaly virus; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; ICAHT, immune effector cell-associated hematotoxicity; t-MN, therapy-related myeloid neoplasm.

*Incidence rate as high as 6% of t-MN after CAR T-cell infusion (see Gurney et al., EHA 2023; abstract number S263[87]).

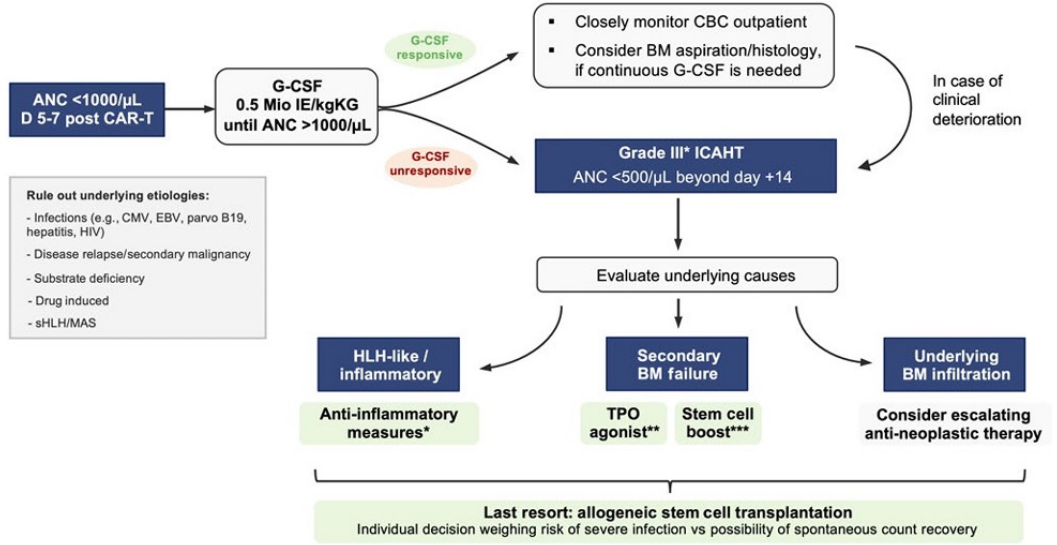


Figure 2. Treatment algorithm for immune effector cell associated hematotoxicity. *Consider dexamethasone-pulse (20 mg over 4 days) or anticytokine-therapy (e.g., anakinra or tocilizumab). **Consider eltrombopag (e.g., 50 mg×7 days). ***If available, contact apheresis unit.

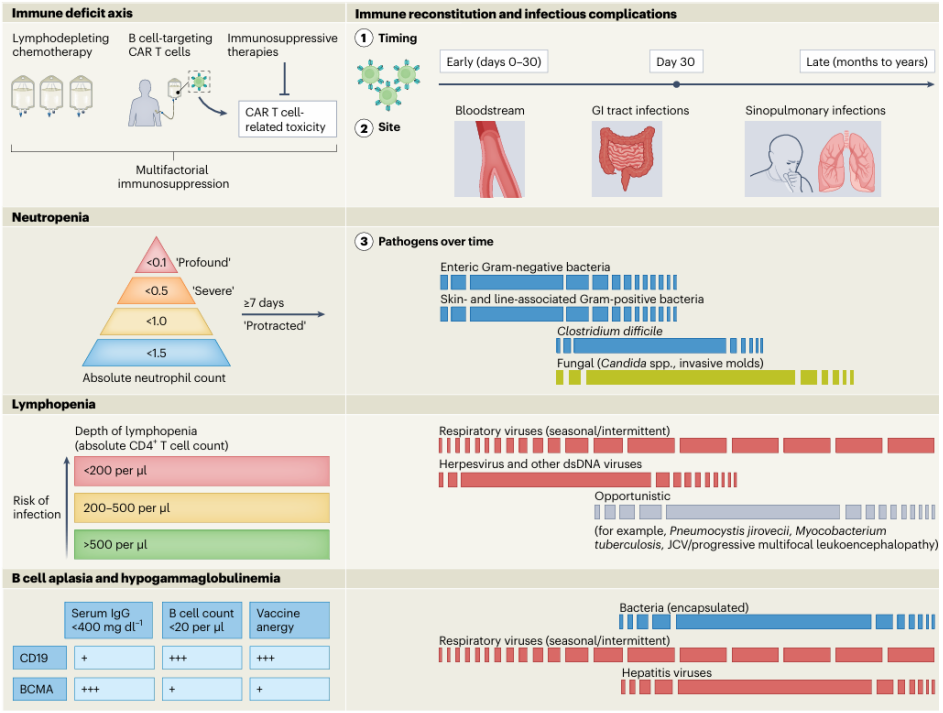
Infections

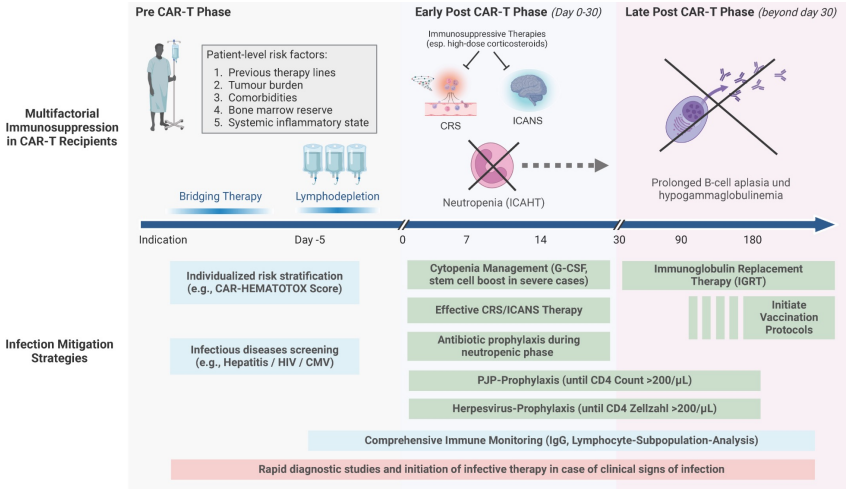
- Infections represent a major complication of CD19- and BCMA-directed CAR-T therapy and can impact morbidity, mortality and patient quality-of-life (Cordas Dos Santos et al. 2024).

- The majority of severe infections occur early within the first 28 days, with bacterial infections being the most common, followed by viral and fungal infections (Hill et al. 2018). Reactivation of herpesviruses (CMV, HHV-6) is driven by a combination of lymphopenia and corticosteroid use (Kampouri et al. 2024).

- The net state of immunosuppression with CAR-T therapy is multifactorial and arises as a result of prolonged neutropenia, long-term CD4 T cell lymphopenia, B cell aplasia, higher CRS/ICANS grades and the extended use of immunosuppressive agents (Kampouri et al. 2023).

- Antiviral and anti-pneumocystis prophylaxis are recommended, until immune reconstitution (for at least 6 months and until the CD4 T cell count exceeds 200 cells/µl)
- Patients considered "high risk" for mold infections should be offered mold-active prophylaxis until neutrophil recovery and cessation of immunosuppressants, while in the absence of high-risk factors, yeast-active prophylaxis can be considered (Garner et al. 2021).
- Routine antibacterial prophylaxis with fluoroquinolones remains controversial. Treatment of infections should follow institutional guidelines (Shahid et al. 2024).





Rejeski et al. Noncanonical and mortality-defining toxicities of CAR T cell therapy. Nat Med. 2025 Jul;31(7):2132-2146.

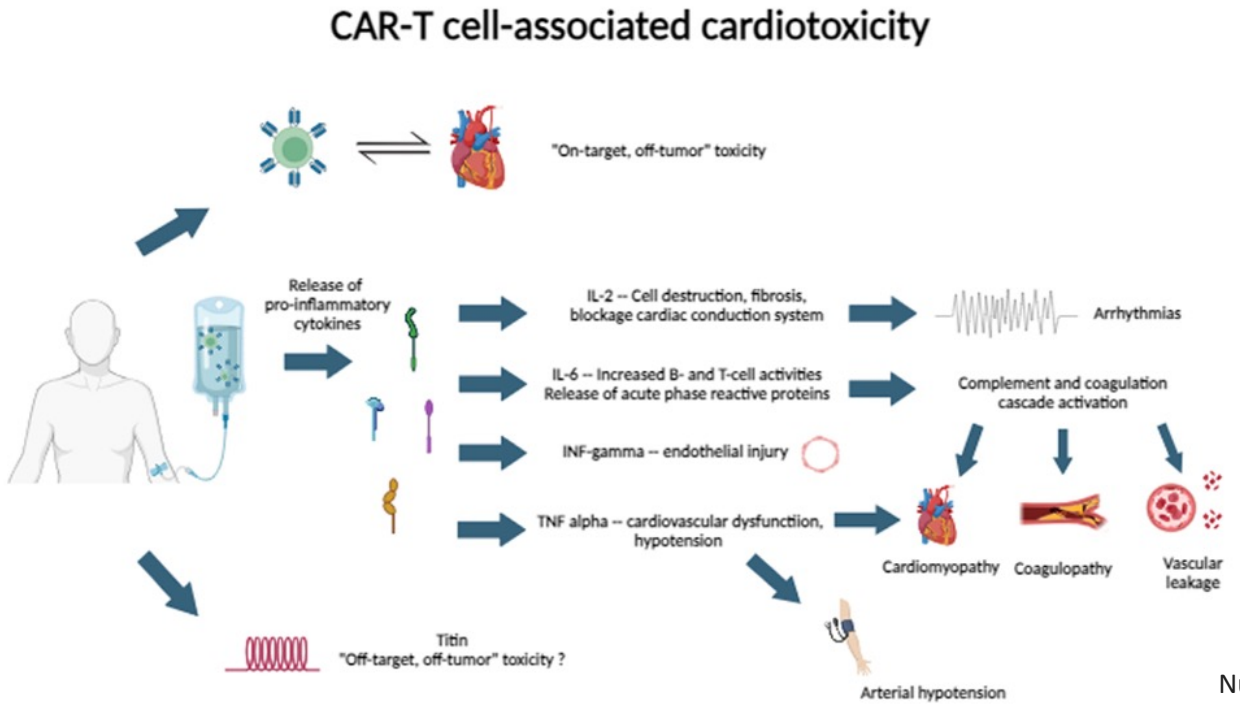
Cardiotoxicity

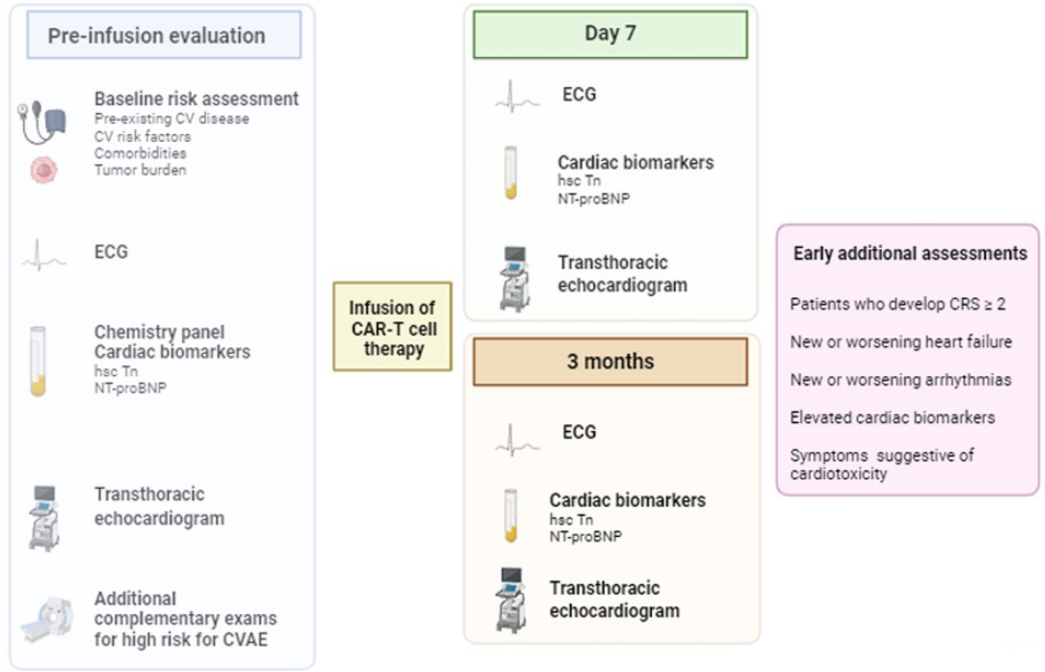
- In a retrospective real-world pharmacovigilance study, cardiotoxicity and CRS overlapped by over 60 %. The most frequent cardiovascular adverse effects (CVAE) described are: arterial hypotension, bradicardia, sinus tachycardia, elevation of serum troponin levels, left ventricular dysfunction, heart failure, arrhythmias and cardiovascular death. Cardio vascular complications are predominantly reported in patients with CRS grade ≥ 2.

- The approach to patients presenting with CVAE involves a multidisciplinary team. Depending on the severity, the necessary measures include intravenous fluids, vasopressor sup port, inotropic therapy, mechanical support, and arrhythmia control.

Table 3 – Conditions associated with increased risk for adverse cardiovascular outcomes.

Presence of cardiovascular risk factors, such as hyperlipidemia, hypertension, diabetes, and smoking
Previous exposure to cardiotoxic chemotherapy
Previous exposure to radiation
Baseline cardiac disease such as heart failure, moderate to severe valvular heart disease, coronary artery disease and arrhythmias
Tumor burden
High intensity lymphodepleting treatment
High CAR-T dose





Nunes F et al. From the mechanism of action to clinical management: A review of cardiovascular toxicity in adult treated with CAR-T therapy. Hematol Transfus Cell Ther. 2025 Jan-Mar;47(1):103693.

Other toxicities

- **Coagulopathy and hypofibrinogenemia** : Over 50% of patients within the first month after CAR-T, usually asymptomatic. PT and thrombin time prolongation, aPTT, and D-dimer elevation typically peak within the first 6-9 days, while fibrinogen nadir may be at 12-14 days. Fibrinogen concentrate or cryoprecipitate are recommended when grade 3-4 CRS occurs and fibrinogen levels are below 1.5 g/L

- **Bleeding and thrombosis:** Bleeding events occur in around 11% of patients within the first 30 days after CAR-T, more frequently in the elderly and with concomitant thrombocytopenia. Thrombotic events are variably seen in 2-11% of cases, having associations with ICANS. They are more likely to occur up to day +90. Anticoagulation medications can be safely administered to patients at moderate to high risk of thrombosis

- **Thrombotic microangiopathy** and **graft-versus-host disease** : rare complications, particularly in patients previously treated with allo-HSCT. Recent surveys of EBMT centres identified only a few cases (Wu et al. 2023, Ortí et al. 2025).

Constitutional -> fever, fatigue, malaise, headache

Cardiovascular → Sinus tachycardia, hypotension, decreased ejection fraction, arrhythmias, QT prolongation, elevated troponins

Respiratory → dyspnea, hypoxia, respiratory failure, pleural effusion

Urinary → increased creatinine levels, renal failure, hyponatremia, hypokalemia, hypophosphatemia, TLS

Gastrointestinal → increased transaminases, hyperbilirubinemia, nausea, vomiting, diarrhea

Hematopoietic -> anemia, thrombocytopenia, neutropenia, hypogammaglobulinemia, increased PTT, PT, reduced fibrinogen, DIC, HLH/MAS

Immunological → increased risk of viral, bacterial, and fungal infections

Musculoskeletal → elevated CPK, myalgias

Neurological → encephalopathy, delirium, cognitive disorders, aphasia, tremors, ataxia, myoclonus, sensory and motor deficits, epileptic seizures, cerebral edema

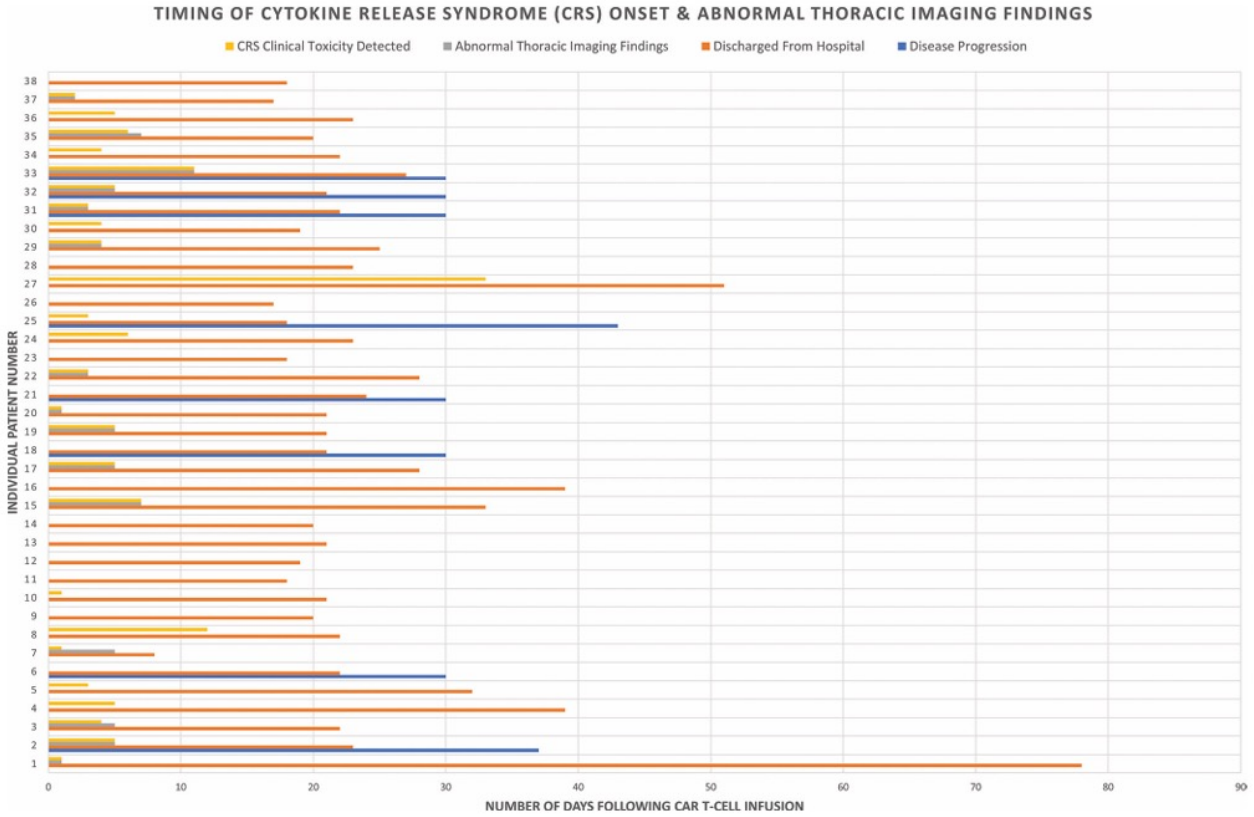
Rejeski et al. Noncanonical and mortality-defining toxicities of CAR T cell therapy. Nat Med. 2025 Jul;31(7):2132-2146.

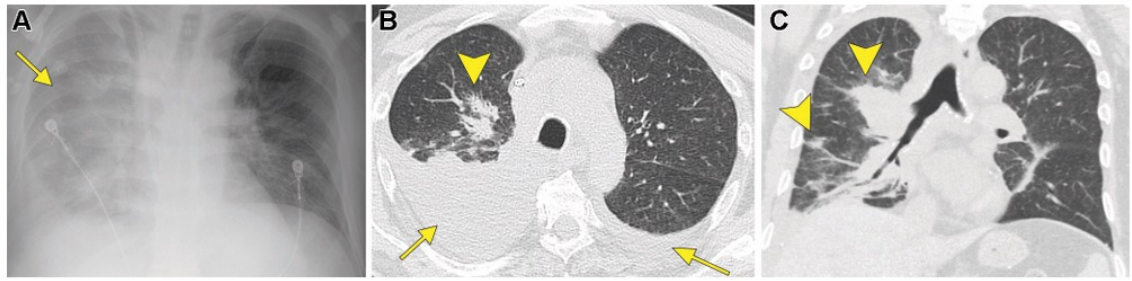
Other considerations…imaging

- Retrospective monocentric study analysing patients with refractory LBCL who received CAR T-cell infusion between 2018 and 2020. Associations between imaging findings and clinical CRS or ICANS grade, and imaging-based response were analyzed using a Wilcoxon signed-rank and x2 tests..

- 38 patients (mean age 59 years) were included. Of these, 24 (63%) and 11 (29%) experienced clinical grade 1 or higher CRS and ICANS, respectively.
- Patients with grade 2 or higher CRS were more likely to have thoracic images with abnormal findings (10 patients [71%] vs 5 [21%] P = .002) and more likely to have imaging evidence of pleural effusions (5 [36%] vs 2 [8.3%]; P = 0.04) and atelectasis (8 [57%] vs 6 [25%]; P = 0.048).

- Positive imaging findings were identified in 3 of 7 patients (43%) with grade 2 or higher ICANS who underwent neuroimaging.





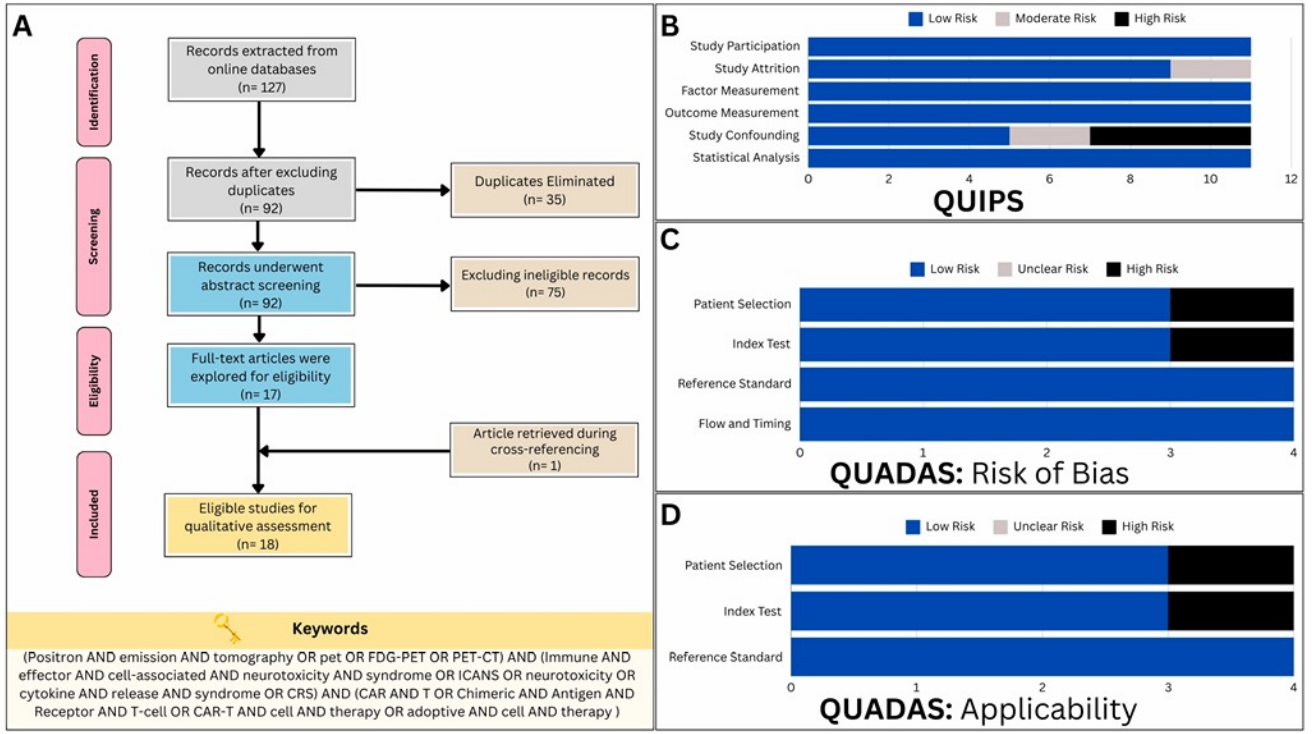
Smith DA et al. Imaging-based Toxicity and Response Pattern Assessment Following CAR T-Cell Therapy. Radiology. 2022 Feb;302(2):438-445

Other considerations…imaging

- A systematic review was conducted to assess the current state of positron emission tomography (PET) in evaluating the adverse effects induced by CAR T-cell therapy until March 2024.
- In total, 18 articles were examined, involving a total of 753 patients. A wide range of utilities were analyzed, including predictive, correlative, and diagnostic utilities.
- While positive outcomes were observed in all the mentioned areas, quantitative analysis of the included studies was hindered by their heterogeneity and use of varying PET-derived parameters.
- The majority of the studies supported the significance of [18F] FDG PET/CT in predicting CAR T-cell therapy toxicity, while only a few disapproved

Studies Reporting Unpredictability		Studies Reporting Predictability	
First Author, Year	Examined PET Parameters	First Author, Year	Examined PET Parameters
Iacoboni, 2021 [36]	Baseline (SUVmax [1], TMTV [2])	Wang, 2019 [31]	Baseline (SUVmax, TMTV *, TLG *)
Cohen, 2021 [35]	Baseline (SUVmax, TMTV, TLG [3])	Derlin, 2021 [41]	Baseline (SUVmax *, TMTV, TLG)
Voltin, 2022 [38]	Baseline (SUVmax, TMTV)	Hong, 2021 [26]	Baseline (SUVmean [4]*, TMTV *, TLG *)
Ligero, 2023 [37]	AI [5] radiomics	Marchal, 2024 [27]	Baseline (SUVmean; liver * and spleen *)
		Morbelli, 2023 [28]	Baseline (TMTV *, TLG *)
		Ababneh, 2023 [39]	Baseline (SUVmax *, TMTV *, TLG *)
		Gui, 2024 [25]	Baseline (SUVmax *, TMTV, TLG *)

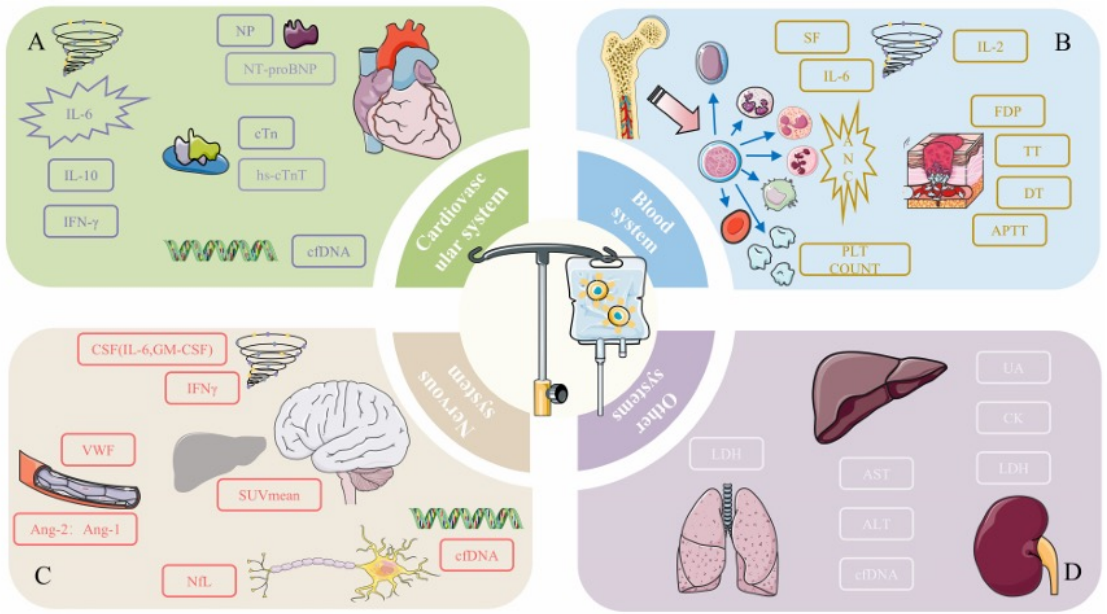
[1] SUVmax: Maximum standardized uptake value; [2] TMTV: total metabolic tumor volume; [3] TLG: total lesion glycolysis; [4] SUVmean: mean standardized uptake value; [5] AI: artificial intelligence; *: statistically significant parameter.



Al-Ibraheem A et al. FDG-PET in Chimeric Antigen Receptor T-Cell (CAR T-Cell) Therapy Toxicity: A Systematic Review. Cancers (Basel). 2024 Apr 29;16(9):1728.

Other considerations…biomarkers

- Researching new biomarkers and searching for specific monitoring indicators can help detect early signs of toxicity and the severity of toxicities, enhancing clinical management and offering personalized medical services to patients.



System	Common Symptom	Possible pathogenesis	Morbidity	Potential Biomarkers and Indicators			
				Prediction	Diagnostics	Severity	Prognosis
Cardiovascular System	arrhythmias, cardiovascular dysfunction, heart failure, cardiovascular death, acute coronary syndrome, cardiomyopathy, cardiac arrest, and other cardiovascular events	CRS induced by targeted therapy	13%-20.5%	cfDNA(ND1、mtCOX2 and Nkx2.5)	Cytokines (IL-6, IL-10, IFN-γ,et al.)	hs-cTnT	——
		off-tumor effects			Biochemical markers (CRP, ferritin, BNP, cTn, et al.)	NT-proBNP	
		off-target effects causing damage				Ang-1:Ang-2	
Blood System	fever, hepatosplenomegaly, cytopenia, liver dysfunction, elevated serum ferritin and transaminases, coagulopathy with hypofibrinogenemia, neurological abnormalities	CRS	2-36%(ICAHT)	CAR-HEMATOTOX	blood counts	blood counts	Cytokines (MDC、FGF-2、TGF-α、VEGF, MIP-1a and MIP-1b, et al.)
		lymphodepletion prior to CAR-T infusion	19%-69% (infection)		Cytokines (IL-6, IL-10,et al.)	Cytokines (IL-6, IL-10, et al.)	
					Biochemical markers (CRP, ferritin)	Biochemical markers (CRP, ferritin)	
		high tumor burden	-3.4% (IEC-HS)	Cytokines (IL-6, IFN-γ, granzyme B, IL-1RA and IL-10,et al.)	PT, APTT	Severity of CRS	occurrence time of cytopenia
		damage to the immune and hematopoietic systems	-56% (Coagulation disorder)		PCT		
Nervous System	tremors, writing disorders, mild speech difficulties (especially naming objects), and certain consciousness disorders, ataxia, delirium, seizures, and cerebral edema	activation of vascular endothelial cells	4.5%-65%	cfDNA	Blood: ferritin	GFAP、NfL(Blood, Cerebrospinal Fluid)	EASIX、mEASIX
					Blood: CPR		
					Blood: Cytokines(Special attention should be given to IL-6; IL-12, which may serve as markers for detecting independent ICANS)	Special amino acids (Amino acid hydroxyproline, Glutamine,et al.)	
		breakdown of the blood-brain barrier					
		damage to central nervous system cells			Cerebrospinal Fluid: Cytokines(IL6, IL8, MCP1, IP10, CD25, GM-CSF, et al)	[18F]FDG PET liver, spleen SUV level	
		infiltration of CAR-T					
Respiratory System	hypoxia, pneumomediastinum, pulmonary embolism, isolated	——	——	——	LDH	——	——
	pleural effusion, allergic rhinitis and respiratory failure						
Digestive System	diarrhea, pancreatitis, constipation, perianal fistula, esophagitis, and vomiting	——	——	——	AST, ALT	——	——
					cfDNA derived from liver cells		
Urinary System	Acute renal failure and water-electrolyte imbalance	——	——	——	UA, CK	——	——

Li J et al. Systemic toxicity of CAR-T therapy and potential monitoring indicators for toxicity prevention. Front. Immunol 2024. 15:1422591.

ICU perspective

- International, multicentre, observational cohort study in 21 intensive care units involving adult patients treated with CAR-T between February 2018-2020
- 942 patients received CAR T-cell therapy, of whom 258 (27%) required admission to intensive care and 241 (26%) were included in the analysis.
- Admission to intensive care was needed within median 4.5 days after CAR T-cell infusion. 90-day mortality was 22.4%.
- Bacterial infection developed in 30 (12%) patients. Life-saving treatments were used in 75 (31%) patients within 24 h of admission to intensive care, primarily vasoactive drugs in 65 (27%) patients
- Factors independently associated with 90-day mortality by multivariable analysis were frailty, bacterial infection and lifesaving therapy within 24 h of admission

Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): an international, multicentre, observational cohort study

Élie Azoulay, Pedro Castro, Adel Maamar, Victoria Metaxa, Alice Gallo de Moraes, Louis Voigt, Florent Wallet, Kada Klouche, Muriel Picard, Anne-Sophie Moreau, Andry Van De Louw, Amélie Seguin, Djamel Mokart, Sanjay Chawla, Julien Leroy, Boris Böll, Nahema Issa, Bruno Levy, Pleun Hemelaar, Sara Fernandez, Laveena Munshi, Philippe Bauer, Peter Schellongowski, Michael Joannidis, Gabriel Moreno-Gonzalez, Gennadii Galstian, Michael Darmon, Sandrine Valade, on behalf of the Nine-I investigators

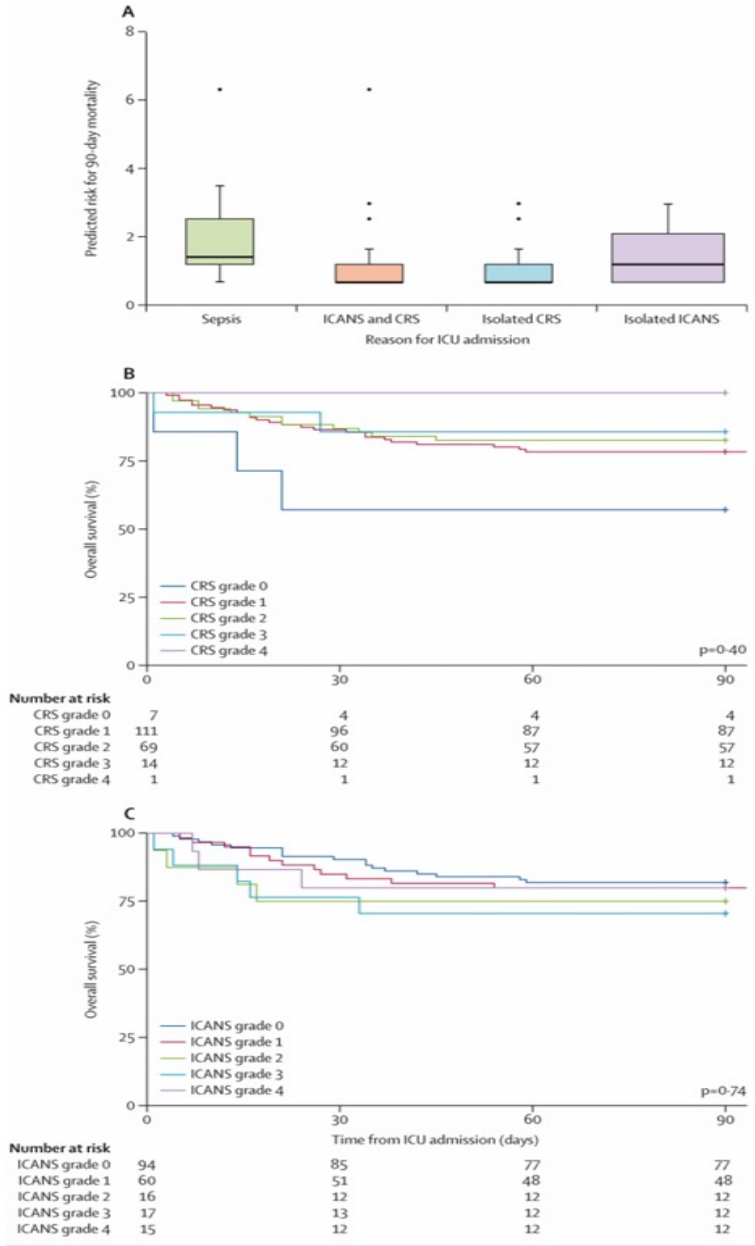
	Participants (n=241)
Age, years	58 (43–66)
Sex	
Female	97 (40%)
Male	144 (60%)
Any comorbid condition	75 (31%)
Cardiovascular comorbidity	60 (25%)
Clinical frailty scale	
1: very fit	23 (10%)
2: well	96 (40%)
3: managing well	71 (29%)
4: vulnerable	24 (10%)
5: mildly frail	5 (2%)
6: moderately frail	5 (2%)
7: severely frail	1 (<1%)
8: very severely frail	1 (<1%)
ECOG performance status	
0: fully active	70 (29%)
1: ambulatory and able to carry out light work	104 (43%)
2: ambulatory and capable of all selfcare but not work activities	46 (19%)
3: capable of only limited selfcare, confined to bed or chair >50% of waking hours	13 (5%)
4: Completely disabled, totally confined to bed or chair	1 (<1%)
Underlying malignancy	
B-cell lymphoma or follicular lymphoma	206 (85%)
Acute lymphocytic leukaemia	31 (13%)
Multiple myeloma	4 (2%)
Time since diagnosis of the malignancy, years	1·5 (0·8–2·8)
Previous stem-cell transplantation	
None	206 (85%)
Autologous	42 (17%)
Allogeneic	13 (5%)

(Table 1 continues in next column)

	Participants (n=241)
(Continued from previous column)	
Number of chemotherapy lines before CAR T-cell therapy	3 (2–4)
Fludarabine plus cyclophosphamide-based lymphodepletion	231 (96%)
Time from CAR T-cell infusion to ICU admission, days	4·5 (2·0–7·0)
Clinical diagnosis upon evaluation in the wards	
Clinical sepsis	39 (16%)
Isolated cytokine release syndrome	101 (42%)
Isolated ICANS	7 (3%)
Cytokine release syndrome and ICANS	93 (39%)
Large pleural effusion related to disease progression	1 (<1%)
Cytokine release syndrome grade 3 or 4 at initial evaluation in the wards	23/194 (12%)
Cytokine release syndrome grade 3 or 4 within 1 day after ICU admission	50/200 (25%)
ICANS grade 3 or 4 within 1 day after ICU admission	38/108 (35%)
CARTOX score at ICU admission	7 (3–9)
Neutropenia at ICU admission	169 (70%)

Data are median (IQR), n (%), or n/N (%). CAR=chimeric antigen receptor. CARTOX=CAR T-cell therapy-associated toxicity. ECOG=Eastern Cooperative Oncology Group. ICANS=immune effector cell-associated neurotoxicity syndrome. ICU=intensive care unit.

Table 1: **Patient characteristics at ICU admission**



Azoulay E et al. Lancet Haematology 2021

Original Research Kidney Medicine

Hemoadsorption as a Supportive Strategy for Severe Toxicity Associated With Chimeric Antigen Receptor T-Cell Therapy: A Case Series

Pasquale Esposito, Massimiliano Gambella, Elisa Russo, Anna Maria Raiola, Elena Beltrametti, Novella Conti, Elisa Porcile, Stefania Bianzina, Monica Centanaro, Francesca Viazzi, and Emanuele Angelucci

- Single center retrospective analysis of a case series describing the use and effects of extracorporeal blood purification with hemoadsorption in managing severe toxicities in 4 patients treated with CAR-T between 2021 and 2023 (3 LBCL and 1 MCL), who progressed to severe cytokine release syndrome with hemodynamic instability and multiple-organ toxicity.

- Despite corticosteroid and anakinra rescue therapy after tocilizumab failure, extracorporeal blood purification with continuous venovenous hemodiafiltration with an AN69ST hemofilter and a CytoSorb cartridge was initiated at a mean of 5.2 ± 1.7 days following CAR-T infusion due to rapid clinical deterioration.

- In the 3 surviving patients, interleukin-6 levels significantly decreased (from −18% to −95%), cytokine release syndrome resolved, and vasoactive support was reduced. Treatment-related complications were not observed

Table 3. Operative Parameters and Laboratory and Clinical Characteristics of CAR-T Patients Treated With Hemoadsorption-Based Blood Purification

Patient	Days From CAR-T Infusion	Blood Purification Modality	Dialysis Membranes	Anticoagulation	No. HA cycles	CVVHDF Duration (d)	IL-6 at HA Start (ng/L)	IL-6 at HA Stop (ng/L)	Delta IL-6 (%)	NE at HA Start (μg/kg/min)	NE at HA Stop (μg/kg/min)	CRS Resolution
1	7	CVVHDF	modified AN69S + *CytoSorb*	RCA	2	6	>5,000[a]	255	−95%	0.03	Stop	Yes
2	3	CVVHDF	AN69ST + *CytoSorb*	RCA	3	11	4,842	559	−88%	0.4	Stop	Yes
3	6	CVVHDF	modified AN69S + *CytoSorb*	RCA	4	5	4,575	1,477	−67%	0.14	Stop	Yes
4	5	CVVHDF	AN69ST + *CytoSorb*	No	1	1	2,452	1,997	−18%	0.5	0.7	No[b]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; CVVHDF, continuous venovenous hemodiafiltration; HA, hemoadsorption; IL-6, interleukin-6; NE, norepinephrine; RCA, regional citrate anticoagulation.
[a]Above laboratory limit.
[b]Patient with concomitant severe cardiomyopathy.

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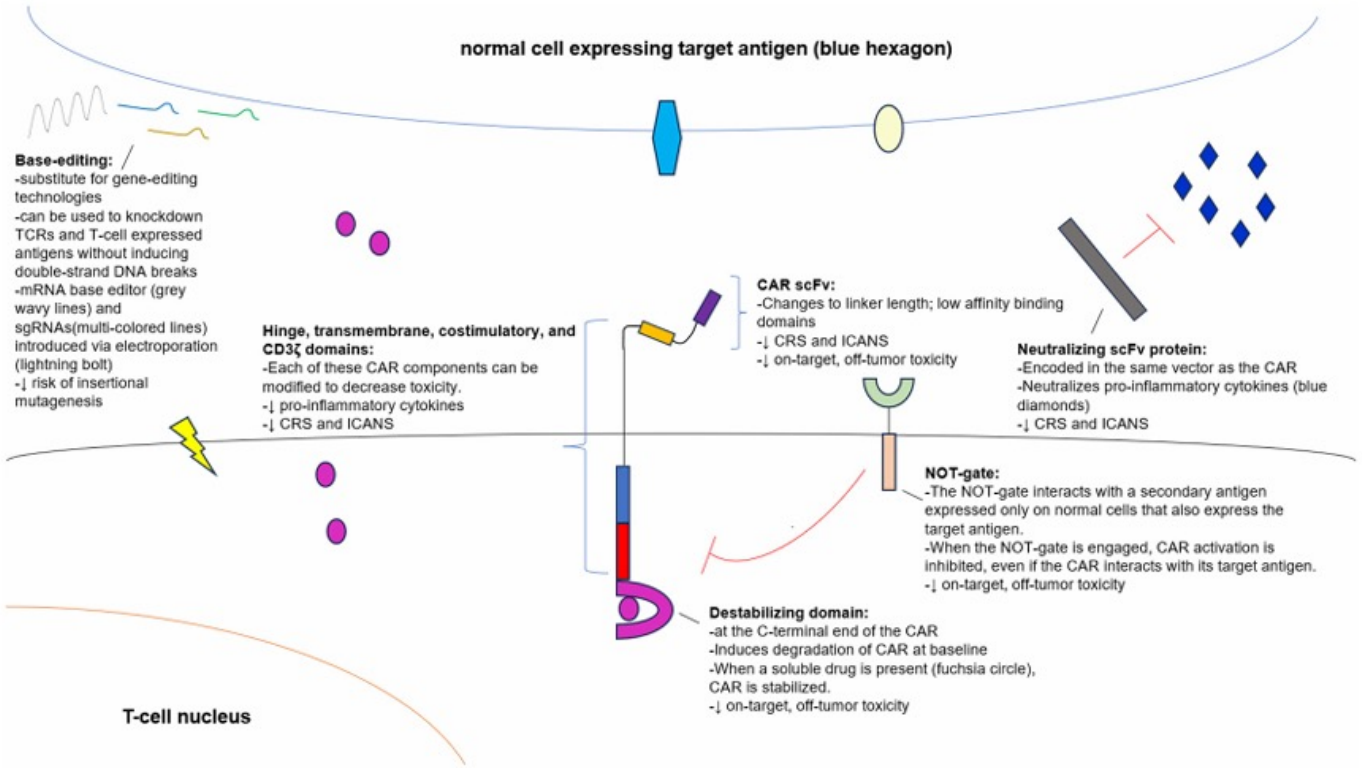
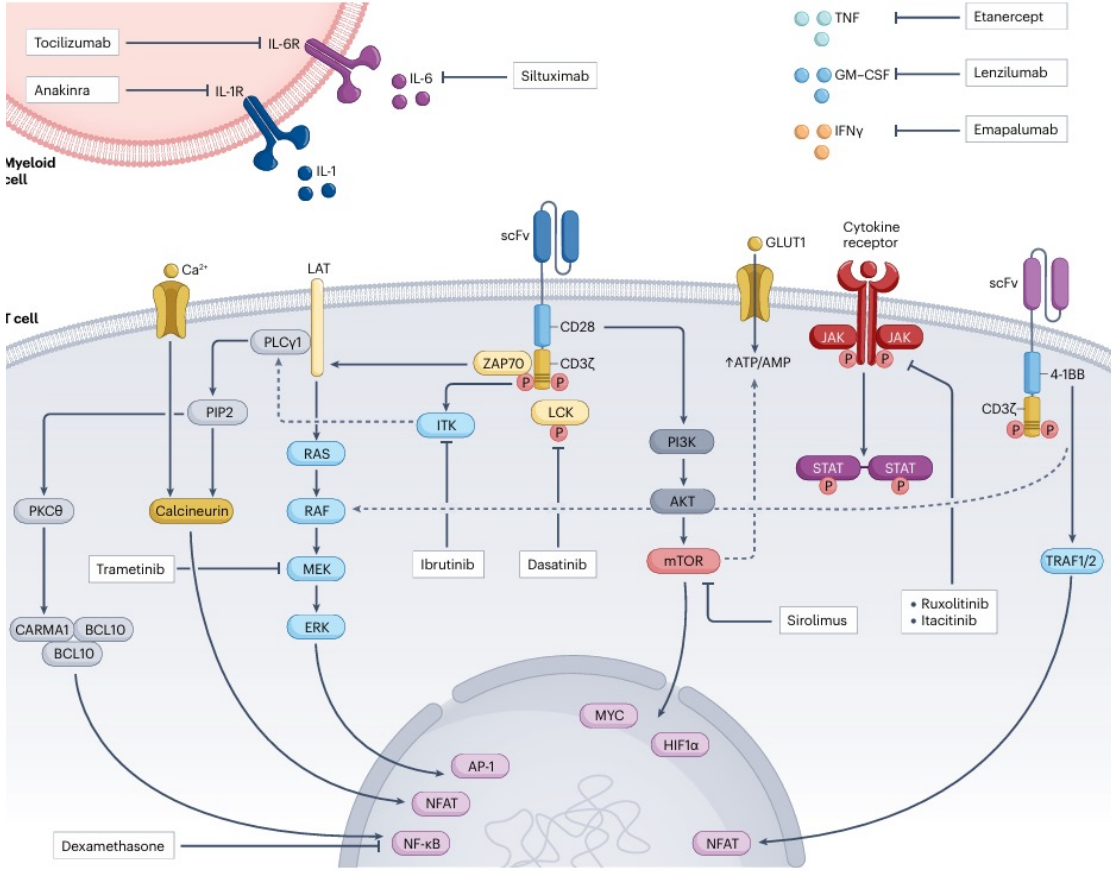
Future strategies





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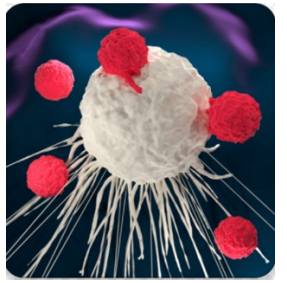
Conclusions



- **Early CAR-T–related toxicities** can involve multiple organ systems and significantly affect patient outcomes, with variability across clinical settings and cellular products
- **Recent and increasingly evidence-based guidelines** have enabled more rapid, effective, and standardized management of toxicities, particularly CRS and ICANS. Growing data support prophylactic strategies and new therapeutic options for managing refractory cases
- **Cytopenias and infections** represent the most frequent high-grade events after CAR-T, even in the early phase; their characterization and management have become increasingly refined in recent years
- **Knowledge of less common toxicities**—whose under-recognition should be avoided—has substantially expanded, alongside a widening therapeutic armamentarium
- **The utility of imaging and biomarkers** in supporting the clinical diagnosis of early toxicities is emerging in recent Literature
- **A multidisciplinary approach** is essential, with an increasingly central role played by the intensive care unit.