Major Adverse Events With Chimeric Antigen Receptor T-Cell Therapy: Presentation, Diagnosis, and Resuscitation

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With continued advances in targeted cancer treatment, such as chimeric antigen receptor T-cell (CAR-T) therapy, emergency departments (EDs) across the United States should be prepared to diagnose and care for patients who experience unique adverse events related to CAR-T administration. CAR-T therapy is the first genetically modified cellular therapy approved by the Food and Drug Administration for treatment of several hematologic malignancies, including leukemia, lymphoma, and myeloma. The side effect profile differs from conventional chemotherapy and consists of a spectrum of immune-mediated clinical manifestations, particularly cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and the more recently described immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. Cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome can present with nonspecific symptoms and signs and should be differentiated from other life-threatening pathologies such as sepsis and meningitis. There is limited guidance for emergency physicians and staff regarding the recognition and management of CAR-T complications, both in adult and pediatric patient care settings. This clinical review provides insight into the common and less common CAR-T toxicities, including symptomatology, diagnostic approach, and fundamental principles of complication management in adult and pediatric patients undergoing CAR-T therapy. [Ann Emerg Med. 2026;87:229-238.]

Keywords: Chimeric antigen receptor T-cell therapy, Cytokine release syndrome, Immune effector cell-associated neurotoxicity syndrome, Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome, CAR-T toxicity management.

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INTRODUCTION

Chimeric antigen receptor T-cell (CAR-T) therapy has been a revolutionary breakthrough in the treatment of hematologic malignancies. To date, the Food and Drug Administration (FDA) has granted approval for 7 autologous CAR-T products.[1] Among these, tisagenlecleucel is the only agent currently approved for patients aged 0 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukemia. Encouraging rates of durable complete remission in patients who failed to respond to first-line therapies make CAR-T therapy a preferred therapeutic regimen endowed with curative potential.

BIOLOGICAL CONCEPTS OF CAR-T THERAPY

To generate autologous CAR-T cells, the patient's own T cells are collected and genetically engineered with a CAR ex vivo to recognize an antigen on the surface of malignant cells. On infusion of the CAR-T product into the patient, CAR-T cells engage the tumor antigen, become activated, and proliferate rapidly while eliciting cancer cell killing and tumor elimination. This process is associated with overproduction of cytokines and CAR-T expansion in blood, which usually peaks between days 2 and 14 postinfusion.

Given their targeted and unique mechanism of action, CAR-T therapies are accompanied by a unique spectrum of side effects that are directly associated with the induction of a powerful immune effector response through cytokines such as IL-6, interferon, and IL-1.[2] Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are two of the most prevalent adverse events in patients receiving these therapies.[3] Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) is emerging as a rare and underdiagnosed adverse event entity.[2] Multiple studies showed that the incidence of CRS in patients receiving CAR-T therapy is more than 50% and appears to be even higher in the pediatric population.[3-5] Around a quarter of these patients required ICU admission

Table 1. CRS Grading as per ASTCT CRS Consensus Grading.[14]

	Grade			
CRS	**I**	**II**	**III**	**IV**
Fever			≥38 °C	
With			With	
Hypotension	None	No vasopressors	Vasopressor ± vasopressin	Multiple vasopressors (excluding vasopressin)
And/or			And/or	
Hypoxia	None	Low flow or blow by oxygen	High flow, facemask, non-rebreather, or Venturi mask oxygen	Positive pressure oxygenation (CPAP, BiPAP, mechanical ventilation)

ASTCT, American Society of Transplant and Cellular Therapies; *BiPAP,* bilevel positive airway pressure; *CPAP,* continuous positive airway pressure; *CRS,* cytokine release syndrome.

and care due to severe CRS, which was again higher in pediatric patients.[4,5] The median time from infusion to onset of symptoms was 3 days, but can range widely from 1 day to 3 weeks and longer.[6] ICANS rates tend to be lower, with around 20% to 40% of those studied experiencing some neurotoxicity and slightly more than 10% exhibiting severe ICANS.[4,6] Higher rates of CRS have been observed with use of axicabtagene ciloleucel CAR-T therapy, likely related to its unique CAR signaling domain.[3,7] Increased incidence of CRS is also associated with higher disease burden/tumor bulk at the time of CAR-T cell infusion.[8] Real-world data using CAR-T products suggest that early management of CRS prevents high grade or more serious manifestations.[9]

Recently, an HS/macrophage activation syndrome (HLH/MAS)-like phenotype has been described that differs from other CAR-T related inflammatory complications. This has been observed in phase I CD22 CAR-T cell trial in relapsed/refractory B-acute lymphoblastic leukemia after prior CD19 CAR-T administration, where it occurred in patients with prior CRS, CAR-T cell re-expansion, and with a time delay of about 2 weeks, suggesting a unique pathophysiology.[10] This unique entity has now been defined as IEC-HS.

CAR-T products are administered in specialized medical centers certified by CAR-T manufacturers for compliance with risk elimination and mitigation strategies imposed on the sponsor by the FDA. Risk elimination and mitigation

Table 2. CRS grade and incidence by CAR-T product and indication.

		CRS Incidence by Grade (≤8 wk after infusion)		
Disease Indication	**Treatment**	**Any Grade n (%)**	**III n (%)**	**IV n (%)**
B-cell acute lymphoblastic leukemia (B-ALL)	Tisagenlecleucel ELIANA Trial,[6] n (%) n=75	58 (77%)*	16 (21%)*	19 (25%)*
	Brexucabtagene autoleucel (adult B-ALL) ZUMA-3 Trial,[17] n (%) n = 78	72 (92%)	Grade >/= 3: 20 (26%)	
Diffuse large B-cell lymphoma	Tisagenlecleucel JULIET Trial,[4] n (%) n=111	64 (58%)*	15 (14%)*	9 (8%)*
	Axicabtagene ciloleucel ZUMA-1 Trial,[7] n (%) n=111	94 (93%)	Grade >/= 3: 13 (13%)	
Follicular lymphoma (FL)	Tisagenlecleucel ELARA Trial,[18] n (%) n=97	47 (48.5%)	Grade >/=3: 0	
Mantle cell lymphoma (MCL)	Brexucabtagene autoleucel ZUMA-2 Trial,[19] n (%) n=68	62 (91%)	8 (12%)	2 (3%)
Multiple myeloma (MM)	Idecabtagene vicleucel KarMMa-3 Trial,[20] n (%) n=225	197 (88%)	6 (3%)	3 (1%)

B-ALL, B-cell acute lymphoblastic leukemia; *CRS,* Cytokine Release Syndrome; *DLBL,* diffuse large B-cell lymphoma; *FL,* follicular lymphoma; *MCL,* mantle cell lymphoma; *MM,* multiple myeloma.
*≤8 weeks after infusion.

Table 3. ICANS Grading for Adults as per ASTCT ICANS Consensus Grading.[14]

	Grade			
ICANS	**I**	**II**	**III**	**IV**
ICE score	7-9	3-6	0-2	0 (Not obtainable, patient unarousable and unable to perform ICE)
Level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Does not react, is unarousable, or requires vigorous or repetitive tactile stimuli to wake
Seizures	N/A	N/A	Any clinical seizure that is not status epilepticus, non-convulsive seizure on EEG that resolves without intervention	Status epilepticus or repetitive clinical seizures, or electrical seizures without return to baseline in between
Motor symptoms	N/A	N/A	N/A	Deep focal motor weakness (eg, hemiparesis, paraparesis)
Increased ICP/cerebral edema	N/A	N/A	Focal edema on neuroimaging	Diffuse edema on neuroimaging, decerebrate posturing, decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

strategies certification mandates the center to have management guidelines for CRS and ICANS, and availability of 2 doses of the IL-6 inhibitor tocilizumab on site at the time of CAR-T administration for each subject. CAR-T patients are often treated in inpatient units but are increasingly cared for in an outpatient setting. This has been shown to have comparable outcomes and offers a more patient-friendly and cost-effective alternative to inpatient administration.[11] In the pediatric setting, although lymphodepleting chemotherapy and the CAR-T cell infusion are commonly administered in the inpatient setting, many patients meet eligibility for outpatient monitoring thereafter. Many centers have outpatient CAR-T programs and involve emergency physicians for CAR-T management training, or pursue the strategy of direct admissions to the specialized units. In the ELIANA study, 24% of patients received tisagenlecleucel infusion in the outpatient setting, and 26% of patients were treated in the outpatient setting in the JULIET study.[6,12] Additionally, Bachier et al[13] reported a favorable experience with outpatient CAR-T infusion with an admission rate of 24% within 72 hours post infusion and a median of 4 days.

CAR-T therapy is FDA-approved in relapsed and refractory pediatric B-acute lymphoblastic leukemia and is being studied in other pediatric malignancies, bringing forth the need to adapt current knowledge to a population where variations in clinical presentation are common. As with the adult population, a high index of suspicion should be raised for a pediatric or young adult patient with a history of hematologic malignancy treated with CAR-T. Given the broadening indications for CAR-T therapy, it is increasingly important for first-contact physicians to recognize, resuscitate, and treat patients who suffer adverse events of CAR-T therapy.

CLINICAL PRESENTATION AND DIAGNOSIS

Cytokine Release Syndrome

The clinical presentation of CRS is complex and difficult to distinguish from sepsis. The most common symptoms include fever, hypotension, and hypoxia.[14] Early studies varied in the grading and evaluation of CRS; therefore, the American Society of Transplant and Cellular Therapies (ASTCT) developed a consensus grading system (Table 1)[14] based on the presence and nature of fever, hypotension, and hypoxia. Tachycardia is another common nonspecific feature of CRS, and fever may additionally be accompanied by symptoms such as nausea, headache, and rash, though at a less frequent rate.[15,16] Neurotoxicity can be concomitant with CRS and requires separate grading for ICANS (Tables 2 and 3).[4,6,7,14,17-20]

ICANS

The clinical presentation of ICANS can mimic several pathological processes, including toxic/metabolic encephalopathy, stroke, sepsis, and seizures. The earliest symptoms suggestive of ICANS include headache, slowing of cognitive function, delayed response to questions, difficulties naming objects, dysgraphia, expressive aphasia, tremors, impaired attention, and lethargy.[14,21] The progression to severe symptoms can range from a couple of hours to a couple of days and is sometimes preceded by waxing and waning lethargy.[21] Patients can develop nonconvulsive seizures; therefore, electroencephalography (EEG) monitoring in patients with an altered level of consciousness is recommended. Status epilepticus

Table 4. ICANS grade and incidence based on treatment option.

		Neurologic Event Incidence by Grade		
Disease Indication	**Treatment**	**Any Grade**	**III**	**IV**
B-cell acute lymphoblastic leukemia (B-ALL)	Tisagenlecleucel ELIANA Trial[6], n (%)	30 (40%)*	10 (13%)*	0*
	Brexucabtagene autoleucel (adult B-ALL) ZUMA-3 Trial[17], n (%) Total n = 78	68 (87%)	27 (35%)	
Diffuse large B-cell lymphoma (DLBCL)	Tisagenlecleucel JULIET Trial[4], n (%)	23 (21%)*	8 (7%)*	5 (5%)*
	Axicabtagene ciloleucel ZUMA-1 Trial[7], n (%) Total n=111	65 (64%)	Grade >/= 3: 28 (28%)	
Follicular lymphoma (FL)	Tisagenlecleucel ELARA Trial[18], n (%) Total n=97	36 (37.1%)	Grade >/= 3: 3 (3.1%)	
Mantle cell lymphoma (MCL)	Brexucabtagene autoleucel ZUMA-2 Trial[19], n (%) Total n=68	43 (63%)	15 (22%)	6 (9%)
Multiple myeloma (MM)	Idecabtagene vicleucel KarMMa-3 Trial[20], n (%) Total n=225	34 (15%)	5 (2%)	2 (1%)

B-ALL, B-cell acute lymphoblastic leukemia; *DLBL*, diffuse large B-cell lymphoma; *FL*, follicular lymphoma; *MCL*, mantle cell lymphoma; *MM*, multiple myeloma.
*(≤8 weeks after infusion).

can occur, demanding a high level of suspicion given the potential for nonconvulsive seizures. The defining symptoms and scores used for grading ICANS in the new ASTCT consensus[14] include the Immune Effector Cell-Associated Encephalopathy (ICE) score. The presence of a coma, seizures, motor findings, and increased intracranial pressure (ICP) or cerebral edema are signs of progressive ICANS and represents a neurologic emergency. The ICE score is a simple bedside tool for adults to evaluate cognitive function and includes orientation, naming, following simple commands, short-term memory, writing a standard sentence, and attention.[22]

ICANS grade 1 is defined by a mildly decreased ICE score with an unaffected level of consciousness. ICANS grade 2 presents with a moderately decreased ICE score and may include a slightly depressed level of consciousness with preserved response to vocal stimuli. A significantly diminished ICE score, decreased arousal, self-terminating seizures, and focal edema on neuroimaging define ICANS grade 3. A patient in ICANS grade 4 is near comatose and unable to perform ICE. Status epilepticus or focal motor weakness, such as hemi- or paraparesis, can be present, as well as diffuse cerebral edema on neuroimaging and signs of increased ICP.[14] Because ICE scoring has limitations for use in children, the authors of the ASTCT consensus guidelines developed a grading system for children younger than 12 using the Cornell Assessment of Pediatric Delirium (CAPD).[14] When the ICE score is not appropriate to use due to the young age of the patient, it can be substituted with the CAPD score, where ICANS grade 1 and 2 are defined by a CAPD score of 1 to 8 points and ICANS grade 3 and 4 by a score of more than 8 points. The remaining grading criteria of the ASTCT consensus (level of consciousness, seizures, motor symptoms, and increased ICP or cerebral edema) can be used in children of any age.[14]

DIAGNOSTIC EVALUATION OF CRS AND ICANS

Early diagnosis of CRS in the emergency setting requires physician awareness of recent CAR-T cell therapy and a high level of suspicion. CAR-T cell recipients are required to wear a bracelet or carry a CAR-T product card alerting health care providers about their CAR-T infusion. Medical history and medication history are critical to consider CAR-T complications. A summarization of adult and pediatric CAR-T trials, including CRS and neurologic event incidence with different products, can be found in Tables 2 and 4.[4,6,7,17-20] The onset of CRS typically occurs between 1 and 7 days and is rarely noted to occur later than 10 days after infusion.[23]

Table 5. Diagnostic Criteria for CAR-T-cell-related HLH/MAS per Hines et al 2023.[34]

Diagnosis of IEC-HS per Hines et al 2023	
Criteria for identification of IEC-HS	**Clinical or laboratory manifestations**
Most common manifestations	**Required:** Elevated ferritin (>2x upper limit of normal or baseline at time of infusion) and/or rapidly rising per clinical assessment
	Onset with resolving or resolved CRS, or worsening inflammatory response after initial improvement of CRS with CRS directed therapy
	Hepatic transaminase elevation of >5x upper limit of normal or >5x documented baseline if abnormal lab values at baseline
	Hypofibrinogenemia as per HLH-2004
	Hemophagocytosis in bone marrow or other tissue as per HLH-2004
Other manifestations that may be present	Elevations of lactate dehydrogenase above the upper limit of normal
	Other coagulation abnormalities (eg, elevated PT, PTT)
	Direct hyperbilirubinemia
	New onset splenomegaly
	New fever, distinguished from CRS onset or recurrence, or persistent febrile temperatures
	Neurotoxicity
	Pulmonary manifestations (eg, hypoxia, pulmonary infiltrates, or edema)
	New onset renal insufficiency
	Hypertriglyceridemia (fasting level, >265 mg/dL as per HLH-2004)

CAR-T, chimeric antigen receptor T-cell therapy; *HLH/MAS*, Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome; *IEC-HS*, Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-like syndrome; *CRS*, Cytokine Release Syndrome; *PT*, prothrombin time; *PPT*, partial thromboplastin time.

The differential diagnosis in patients where there is concern for CRS/ICANS mainly includes systemic infection, sepsis, meningitis, encephalitis, delirium, or drug adverse effects.[14] The initial diagnostics include a complete blood count with differential, complete metabolic panel including liver function tests, lactate level, blood gas, and blood cultures to rule out infection. Reduced organ perfusion may be manifested by reduced creatinine clearance, increased liver transaminases, increased lactate, and blood gas showing metabolic acidosis. Pancytopenia (anemia, thrombocytopenia, and leukopenia) is common, and patients may be neutropenic (absolute neutrophil count <1,000) when they present to ED due to recent lymphodepleting chemotherapy preceding CAR-T therapy or from ongoing myelosuppression. Coagulation studies may show an increased partial thromboplastin time and international normalized ratio, as well as hypofibrinogenemia and increased D-dimer.[24] C-reactive protein is a useful surrogate for cytokine levels (IL-6, interferon γ, tumor necrosis factor) and is a useful marker when CRS is considered, especially for sequential monitoring to assess the trajectory of cytokine dynamics. However, CRP is a nonspecific marker of inflammation and cannot differentiate sepsis and infection from CRS. Although procalcitonin does not reliably distinguish between underlying causes of inflammation, data support procalcitonin level use in risk stratification of patients at increased risk for infection following CAR-T.[25] Interleukin levels are not practical in the ED setting, given the assay is not routinely available and the processing time is long.[26] Standard diagnostic workup of fever, particularly neutropenic fever, should include blood cultures, chest imaging with radiographs or advanced imaging, and urinalysis, plus additional testing that is driven by the symptoms exhibited by the patient. Bacterial sepsis after CAR-T therapy may present at the same time as CRS and ICANS.[8] Patients presenting with symptoms of CRS may fulfill sepsis criteria in severe CRS, even to the point of septic shock.[27]

The onset of ICANS symptoms after infusion is variable, with a median of around 4 days, and usually no later than 14 days after therapy.[28] Neurologic symptoms are nonspecific and, therefore, the differential remains broad. Other causes of encephalopathy need to be considered and worked up, including vascular/bleeding complications, toxic, metabolic, infectious, and epileptic etiologies, as well as the progression of central nervous system oncologic or metastatic disease.[29] Advanced imaging, such as magnetic resonance imaging (MRI) or computed tomography imaging, can be used to rule out other causes of encephalopathy. Brain imaging with MRI

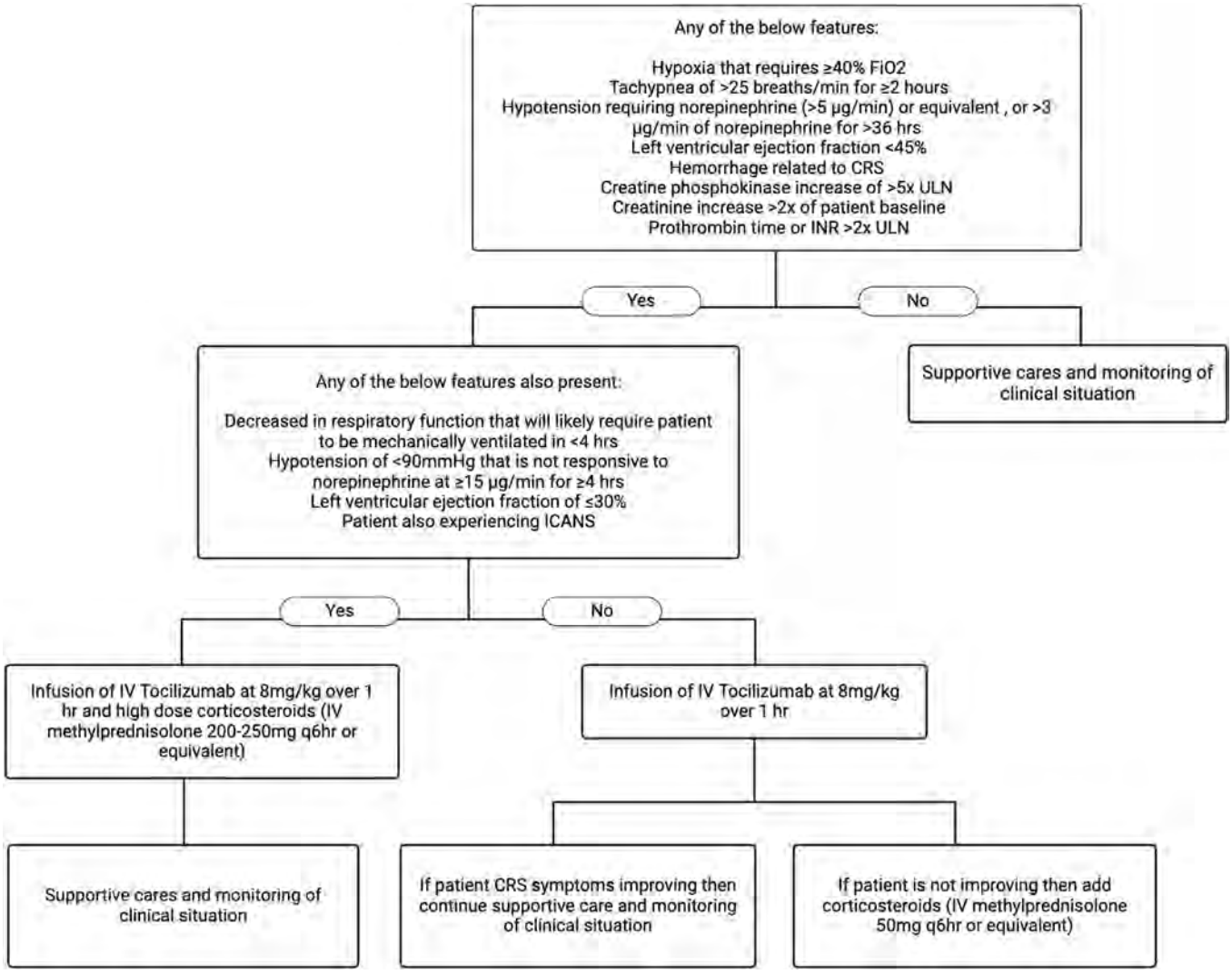

Figure 1. Management of CRS (adapted from Brudno and Kochenderfer[36] and Jain et al[9])

in severe ICANS can show T-2 hyperintensities in white matter or in the bilateral thalami and deep gray matter, but these findings are not specific for ICANS.[30] More than 60% of patients with ICANS do not show any abnormalities on brain MRI. Imaging findings that have been reported in ICANS patients include leptomeningeal enhancement, multifocal microhemorrhages, cortical diffusion restriction, and, in late stages, cerebral edema.[30] EEG diagnostics are critical if there is a seizure concern in a patient experiencing ICANS. Either generalized tonic-clonic or nonconvulsive status epilepticus has been reported.[29] The most common pattern found on EEG was diffuse slowing.[30,31] Lumbar puncture should be considered on a case-by-case basis, mostly to look for alternative causes and driven by situational clinical suspicion, given the increased risk of infection and bleeding in patients at risk for significant hematologic cell suppression.[32]

Both CRS and ICANS are diagnoses of exclusion, where other causes of disease need to be ruled out quickly to allow for the timely treatment of these conditions. Ferritin levels may help admitting physicians evaluate the severity of CRS and ICANS. Levels above 2,000 mg/dL and, particularly, a rapid doubling time of 24 hours or less are highly worrisome for the development of IEC-HS.

HS/MAS AND IEC-HS

HS/MAS are hyperinflammatory syndromes where hyperactivated macrophages and cytotoxic T cells employ massive cytokine production, leading to immune-mediated multiorgan toxicity and risk of organ failure.[3] IEC-HS as a complication following CAR-T therapy is rare but likely underreported. Severe cases occur in about 1% to 5% of patients after CAR-T therapy.[33] However, the associated

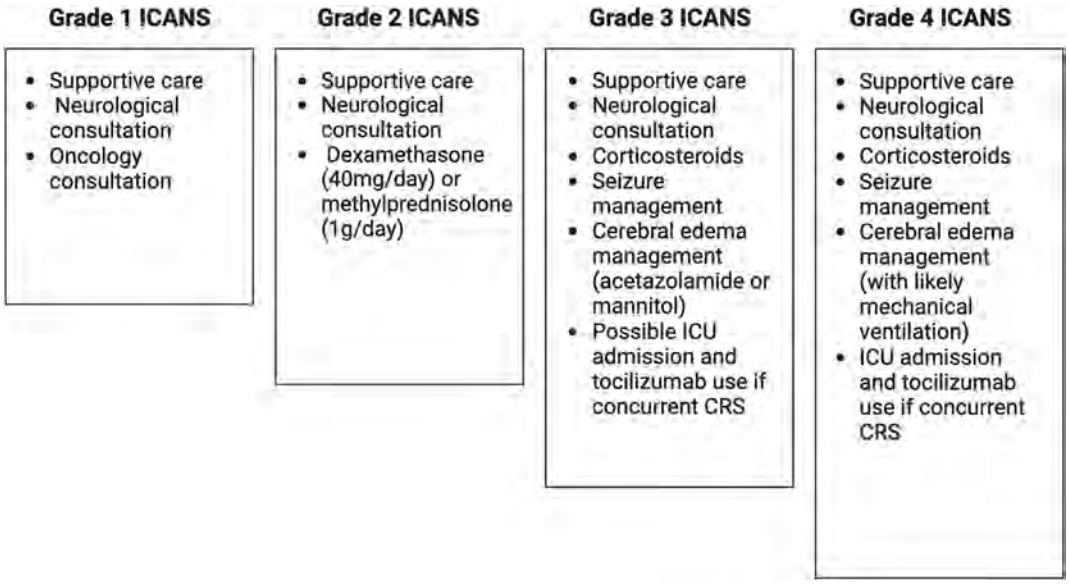

Figure 2. Management of ICANS (adapted from YESCARTA insert[39] and Jain et al[9])

high mortality rates require prompt diagnosis and early management with early initiation of HLH-targeted medication, such as steroids, ruxolitinib, and/or anakinra.[9] Traditional diagnostic criteria for HLH/MAS, such as HLH-2004, initially developed for research purposes, are not specific to IEC-HS. Hines et al[34] presented an updated definition of IEC-HS (Table 5) with defining features of IEC-HS comprising the development of a pathological and biochemical hyperinflammatory syndrome manifesting with macrophage activation/HLH; however, they notably distinguish IEC-HS as a hyperinflammatory syndrome attributed to immune effector cell therapy independent from CRS and ICANS. The diagnosis of IEC-HS is made when not attributable to alternative sources of hyperinflammation, such as CRS; however, it is important to note that cases of IEC-HS have primarily been observed roughly 2 weeks following CRS development and subsequent resolution.[34]

TREATMENT

Early identification is paramount for the successful treatment of both CRS and ICANS and can prevent progression to a higher grade. After recognition of CRS or ICANS, the first step is resuscitation and prevention of organ compromise, multiorgan failure, and cerebral edema. Management of CRS is based on the above grading criteria, with higher grades requiring increasing medical management and interventions.[3] Given the complexity of patients and their management, the on-call hematologist/oncologist with experience in CAR-T therapy should be involved early in treatment decision making and planning in the setting of need for transfer to a facility with expertise in CAR-T therapy.[35] Prior to transfer from the ED to subsequent levels of care management, the primary goal is resuscitation combined with CRS- and ICANS-targeted pharmacologic interventions in cooperation with the on-call hematology/oncology provider.

Grade 1/2 CRS requires supportive care with intravenous fluid therapy and antipyretics/analgesics.[3] At this grade, empiric treatment for febrile neutropenia with broad-spectrum antibiotics is often initiated in the ED.[36] If presenting with hypoxia, intravenous fluid use should be closely monitored due to the potential of exacerbating pulmonary edema. A higher level of oxygen delivery, such as high flow nasal cannula, face mask (grade 3), and positive pressure ventilation (grade 4), may be required.[3,37] Blood pressure not responsive to fluid boluses will require vasopressors. Norepinephrine is often the agent of choice due to its $\alpha$and βagonist properties. The addition of more than one vasopressor may be needed for grade 4 CRS, and admission to the ICU is required.

The IL-6 receptor monoclonal antibody tocilizumab (FDA-approved for CRS) is the mainstay of CRS treatment and should be promptly considered for any grade 2, 3, or 4 CRS. Prolonged grade 1 CRS with fever not responding to antipyretics in 48 hours or associated with other complications such as atrial tachy-arrhythmia should be also treated with tocilizumab. The dose is 8 mg/kg (maximum dose 800 mg, or 12 mg/kg for patients $<$30 kg) once infused for longer than 1 hour.[35,37] Patients often respond promptly, and tocilizumab infusion may be repeated after 8 hours $\times$ 3 doses as needed.

Methylprednisolone at a dose of 1 mg/kg is reserved for CRS not responding to tocilizumab. Prolonged utilization of steroid therapy in CAR-T patients is controversial, with concerns regarding its effect on therapeutic outcomes.[38] Although recent data are suggestive of no detriment to therapeutic efficacy in the setting of steroid use for CRS prophylaxis,[38] further studies are necessary in the continued evaluation of the influence of steroids on cell therapy products. It is recommended to maintain a mindful approach to steroid intervention in close collaboration with a qualified specialist in treatment planning.

For combined presentation of high grade CRS and ICANS, tocilizumab can be combined with methylprednisolone (1 mg/kg intravenously every 6 hours) or dexamethasone 10 mg every 6 hours. Steroids can be added if the patient's vital signs do not improve on IL-6 antagonists alone. For grade 4 CRS with refractory hypotension/hypoxia, or concomitant ICANS, high-dose steroids such as methylprednisolone 1,000 mg every 24 hours can be considered (Figure 1).[9,36]

ICANS is a constellation of symptoms that can present concomitantly with CRS and introduces another layer of challenges for the emergency physician. Tocilizumab is not indicated for isolated ICANS treatment or prevention.[12,35] Supportive care for ICANS includes an elevation of the head of the bed, ICE score assessment, and frequent monitoring of the level of consciousness and orientation. If ICANS is suspected, prophylactic antiepileptic medications should be considered and discussed with consulting specialists. Given the myriad of neurologic findings within ICANS and crossover with other similar presentations, neurologic consultation is recommended for ongoing management. When steroid therapy is involved in the treatment of ICANS, the drug of choice is intravenous dexamethasone 10 mg due to improved central nervous system penetration, where the dosing frequency is typically every 6 to 12 hours, depending on grade.

Grade 3 and 4 ICANS, which include seizures and increased ICP, require much closer monitoring and more aggressive intervention. Worsening encephalopathy and decreased level of consciousness (grade 2) ICANS is treated with intravenous dexamethasone 10 mg every 6 hours or methylprednisolone 1 g intravenous every 24 hours, which can be utilized for unresponsive patients (grade 4 ICANS).[35] Seizure management should include antiepileptic medications (levetiracetam, benzodiazepines in the acute setting) and continuous EEG monitoring. Neurocritical ICU expert consultation should be obtained if high grade ICANS is recognized. Decreasing the ICP is paramount in higher grade ICANS and requires interventions including elevation of the head of bed, maintenance of mean arterial pressure more than 80 mmHg, sedation, paralysis, mannitol, hypertonic saline solution, and/or acetazolamide.[29,35] Mechanical hyperventilation should only be used for very short acute periods to decrease ICP. Resolution of ICANS in 1 to 3 days is expected in all affected patients, and the ICU care should be focused on preservation of vital organs, prevention of organ injury, and avoidance of iatrogenic complications. Treatment of severe and or refractory CRS/ICANS/IEC-HS is challenging and happens mainly outside of the ED, involving a multidisciplinary team. The agents used are not FDA-approved for specific pathology but are targeted at the syndrome's pathophysiology, such as IL-1 receptor antagonism (anakinra), IL-6 antagonism (siltuximab), IFN-γ blocking antibody (emapalumab), T-cell targeted therapies (alemtuzumab), and tyrosine kinase inhibitors (dasatinib) (Figure 2).[9,39]

PEDIATRIC SPECIFIC CONSIDERATIONS

Although CRS, ICANS, and IEC-HS can occur in adult and pediatric patients, it is necessary to consider important distinctions between these populations in acute care settings. The adult oncology world has been shifting toward preventive strategies for immune-related complications, including prophylactic steroid administration.[9] Preventive tocilizumab is not effective and can be detrimental due to the increased risk of ICANS. Pediatric clinical management recommendations for CRS currently consist of the administration of tocilizumab for children with grade 3 or prolonged grade 2 CRS.[40] Children have an immature immune system with fewer plasma cells, and CD19 CAR-T therapy can lead to further depletion of their immunoglobulin levels with an increased risk of infectious complications.[41] Initiating an aggressive sepsis workup (including blood and urine cultures as well as viral panel) with early broad-spectrum antibiotic therapy is especially important. ICANS grading can be challenging in the pediatric population, and a pediatric specific grading system has been implemented.

DISCUSSION

CAR-T therapy has proven to be a monumental therapeutic breakthrough in the treatment of patients with hematologic malignancies and will potentially expand to nononcologic indications (such as autoimmune disorders) in the near future. Continued research is needed and ongoing toward applications in solid tumor oncology and therapy of nonmalignant conditions. To see the full potential of this innovative therapy, the knowledge of managing unique side effects of this therapy, such as CRS, ICANS, and IEC-HS, is essential. Because CAR-T

therapy has been moving to outpatient settings, ED providers are among the first to manage these complications.

CRS/ICANS has a broad and sometimes remote (days to weeks) clinical presentation after cell product infusion. Presenting symptoms are often indistinguishable from sepsis (fever, hypotension, and hypoxia). Neurologic symptoms such as headache, mental status changes, and delirium can be indicative of ICANS, which can be seen in an overlap presentation with CRS. IEC-HS is a separate hyperinflammatory condition presenting with cytokine-induced systemic toxicities. When caring for these patients in the ED, close collaboration with a qualified hematology/oncology provider and knowledge of these syndromes are necessary. Grading is important because it guides interventions, including the selection of medications. Failure to administer tocilizumab or steroids in a timely manner can be detrimental to the health of the patient and therapeutic outcomes after CAR-T therapy. Our review emphasizes the need for the ability to recognize and treat CRS, ICANS, and IEC-HS promptly and offers tools for a fast-paced ED environment.

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