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Guideline

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

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A B S T R A C T

Chimeric antigen receptor (CAR) T cell therapy is rapidly emerging as one of the most promising therapies for hematologic malignancies. Two CAR T products were recently approved in the United States and Europe for the treatment of patients up to age 25 years with relapsed or refractory B cell acute lymphoblastic leukemia and/or adults with large B cell lymphoma. Many more CAR T products, as well as other immunotherapies, including various immune cell- and bispecific antibody-based approaches that function by activation of immune effector cells, are in clinical development for both hematologic and solid tumor malignancies. These therapies are associated with unique toxicities of cytokine release syndrome (CRS) and neurologic toxicity. The assessment and grading of these toxicities vary considerably across clinical trials and across institutions, making it difficult to compare the safety of different products and hindering the ability to develop optimal strategies for management of these toxicities. Moreover, some aspects of these grading systems can be challenging to implement across centers. Therefore, in an effort to harmonize the definitions and grading systems for CRS and neurotoxicity, experts from all aspects of the field met on June 20 and 21, 2018, at a meeting supported by the American Society for Transplantation and Cellular Therapy (ASTCT; formerly American Society for Blood and Marrow Transplantation, ASBMT) in Arlington, VA. Here we report the consensus recommendations of that group and propose new definitions and grading for CRS and neurotoxicity that are objective, easy to apply, and ultimately more accurately categorize the severity of these toxicities. The goal is to provide a uniform consensus grading system for CRS and neurotoxicity associated with immune effector cell therapies, for use across clinical trials and in the postapproval clinical setting.

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INTRODUCTION

Chimeric antigen receptor (CAR) T cell therapies are revolutionizing the management of B cell leukemias and lymphomas and are quickly being extended to numerous other malignancies. Two CD19 CAR T cell products were recently approved in the United States and Europe [1-4], and more indications are expected in the coming years. Tisagenlecleucel has been approved for multiply relapsed or refractory B cell acute lymphoblastic leukemia (ALL) in patients up to age 25 years, as well as for relapsed or refractory large B cell lymphoma in adults, and axicabtagene ciloleucel has been approved for relapsed or refractory large B cell lymphoma in adults. These therapies are now being tested in earlier lines of treatment, signaling the growing scope of CAR therapy in the management of these diseases. CAR therapies targeting CD22 in B cell malignancies [5] and B cell maturation antigen (BCMA) in multiple myeloma [6] have been highly successful in early trials and are also forthcoming, along with combination approaches targeting multiple antigens simultaneously.

Early clinical trials of CD19 CAR T cells quickly uncovered greater toxicities than those seen in other cellular therapies, indicating profound and generalized immune system activation. Some of these toxicities, especially cytokine release syndrome (CRS), were reminiscent of those seen in a study in which all 6 healthy young male volunteers who received a low dose of TGN1412 (a superagonist monoclonal antibody to CD28) required critical care for the rapid onset of multiorgan failure [7]. Symptoms induced by TGN1412 included fever, rigors, hypotension requiring vasopressor support and other aggressive management, tachycardia, hypoxia, respiratory failure, capillary leak, acute kidney injury, coagulopathy, and even neurologic manifestations, including poor concentration and delirium. Retrospective analysis revealed marked elevations in C-reactive protein (CRP), INF-γ, TNF-α, IL-6, IL-10, IL-2, and IL-1β, among other cytokines. Although all volunteers eventually recovered with the use of high-dose methylprednisolone, the IL-2 receptor antagonist daclizumab, and aggressive supportive care, the rapidity and severity of the toxicities precluded further development of TGN1412.

Similar toxicities were observed in the initial patients treated with CD19 CAR T cells. In the first pediatric ALL patient treated [8,9], it became clear that supraphysiologic cytokine elevation was responsible for the vast majority of symptoms, suggesting that these toxicities were the result of CRS. Investigators struggled with the then-accepted definition of and grading scheme for CRS. In the Common Terminology Criteria for Adverse Events version 3 (CTCAE v3 [10]), which was in effect when many of these studies began, CRS onset was defined as within 24 hours of initiation of therapy, which is atypical for CRS associated with CAR T cells as well as other immune effector cell therapies. In CTCAE v4.03 [11] (Table 1), the definition did not include fever as a prerequisite for CRS, and the grading was dependent in part on whether the drug infusion was interrupted, a feature not applicable to CAR T cells, which generally are infused in a single dose in a concise time frame (2 to 30 minutes). Indeed, CTCAE v4.03 was more applicable to toxicity seen with antibody infusions rather than with cell infusions.

Without a clear and accurate consensus available, CRS grading has varied widely among institutions and has evolved over time, making toxicity comparisons between products and trials exceedingly difficult. For these reasons, and because immune effector cell-associated CRS can be fatal if not recognized and treated promptly, a CRS grading system that more accurately captures the potentially severe syndrome observed after immune effector cell therapies is needed. In addition, this CRS grading system should have broad applicability across multiple institutions and/or CAR products and other cellular immunotherapies with minimal effort for implementation.

Along with CRS, another common toxicity observed after CAR T cell therapy is neurotoxicity [12]. Immune effector cell-associated neurotoxicity syndrome (ICANS) may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema. In addition, headache is very common and might not represent neurotoxicity per se. Previously considered in aggregate with CRS, neurotoxicity is now treated as a separate entity owing to its distinct timing and response to intervention. Neurologic symptoms may occur during or more commonly after CRS symptoms (but rarely before CRS), vary among patients, and have an unclear pathophysiology, distinct from CRS. One challenge has been to identify the symptoms most relevant to neurotoxicity. Investigators have used multiple different terms for similar symptomatology, resulting in considerable variation in grading across trials and also across different institutions within the same trial. For example, a patient experiencing encephalopathy after CAR T cell therapy may be reported as having any or a combination of the following vague, overlapping CTCAE adverse event terms: confusion, delirium, encephalopathy, cognitive disturbance, concentration impairment, somnolence, and depressed level of consciousness [13]. Ascertainment has changed over time and even within trials as the issue of neurotoxicity has become more apparent. Moreover, CTCAE grading of neurologic toxicities based on the ability to perform instrumental and self-care activities of daily living are not always applicable to children or for hospitalized adult CAR T patients who may be bedridden for related comorbidities. The multiple adverse event terms used to grade neurologic toxicities are also not practical for application at the bedside for rapid and dynamic assessment of patients, so discerning the appropriate terms is difficult and often highly subjective. Therefore, there is a need for an objective, reproducible, easy-to-use, and practicable tool that can be used by all health care providers and possibly caregivers to recognize and assess immune effector cell-associated neurologic toxicities in the inpatient or outpatient setting.

INITIAL ATTEMPTS TO BETTER DEFINE AND GRADE CRS

Although early clinical trials modified the CTCAE v4.03 grading of CRS, further refinement was achieved when a multi-institutional group of pediatric oncologists leading CAR T cell trials across the United States published what is now commonly referred to as the Lee criteria [14]. This work redefined the clinical signs and symptoms associated with CRS (Table 1). Of note, neurologic toxicities such as confusion, delirium, aphasia, and so on were included but are now generally accepted to be a separate syndrome (although cytokines have been implicated in the pathophysiology of this syndrome), owing to the differential time of presentation compared to the other signs of CRS and lack of knowledge surrounding its etiology and pathophysiology. The new constellation of symptoms incorporated the experience across CAR T studies in hematologic malignancies and included, for the first time, fever as a hallmark of CRS.

Lee and colleagues then redefined the grading criteria for CRS revolving around hypoxia requiring oxygen supplementation, hypotension, and other end-organ toxicities (Table 1) [14]. In contradistinction to conventional CTCAE grading schemes, hypotension responsive to low-dose vasopressors was considered a grade 2 CRS. Early experience demonstrated that reliance on i.v. fluids (IVF) alone to manage persistent hypotension was inferior to early vasopressor use owing to significant capillary leak and subsequent pulmonary edema and effusions after IVF management, leading to a cascade of events that can quickly result in life-threatening toxicity. Furthermore, patients who are easily managed with minimal vasopressors are decidedly distinct in terms of CRS severity from

Table 1
Published CRS Grading Systems

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 4.03 [11]	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate)	Life-threatening consequences; pressor or ventilatory support indicated
CTCAE version 5.0 [13]	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention needed
Lee criteria [14]	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to i.v. fluids or low dose of one vasopressor OR • Grade 2 organ toxicity*	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity* or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity* (excluding transaminitis)
Penn criteria [17]	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for i.v. therapies (not including fluid resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
MSKCC criteria [16]	Mild symptoms requiring observation or supportive care only (eg, antipyretics, antiemetics, pain medication)	Hypotension requiring any vasopressors <24 h Hypoxia or dyspnea requiring supplemental oxygen <40%	Hypotension requiring any vasopressors ≥24 h Hypoxia or dyspnea requiring supplemental oxygen ≥40%	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation
CARTOX criteria [12]	Temperature ≥38°C Grade 1 organ toxicity†	Hypotension responds to i.v. fluids or low-dose vasopressor Hypoxia requiring FiO_2 <40% Grade 2 organ toxicity†	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥40% Grade 3 organ toxicity† or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity† except grade 4 transaminitis

NSAIDs indicates nonsteroidal anti-inflammatory drugs; LFTs, liver function tests; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.
* As per CTCAE version 4.03.
† Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum alanine aminotransferase, aspartate aminotransferase, bilirubin level), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatologic (rash), or coagulopathy (disseminated intravascular coagulation).

those who require high-dose or multiple vasopressors, a key difference accounted for by the grading criteria.

Likewise, the grading schema distinguished between those patients who require minimal oxygen supplementation and those who require aggressive supplementation or continuous positive airway pressure (CPAP) support. A fraction of inspired oxygen (FiO_2) of 40% was arbitrarily chosen as the dividing line between grade 2 and grade 3 CRS. This aspect of the definition is problematic, however, because delivery of oxygen to patients [14] will vary significantly from hospital to hospital, from patient to patient, and from shift to shift. Similar to patients requiring low-dose versus aggressive vasopressor support, patients requiring minimal oxygen supplementation are distinct in terms of severity from those who require more aggressive intervention, ranging from CPAP to intubation.

OTHER GRADING SCHEMES FOR CRS

The Lee criteria have been widely adopted by many CAR T cell groups, in particular because it was the first to link a specific grade to a suggested treatment algorithm. The group at Memorial Sloan Kettering Cancer Center (MSKCC) identified objective factors that distinguished severe versus nonsevere CRS in their early clinical trials; however, this relies on the availability of serum cytokine levels in patients in real time [15]. Recognizing that assays for serum cytokines are not readily available at most centers, thereby limiting the utility of this approach, MSKCC redefined the CRS grading used in their clinical trials (Table 1) [16]. Hypotension requiring $<$24 hours of vasopressor use was deemed grade 2, whereas $\geq$24 hours of vasopressor use defines grade 3, and hypotension not corrected with high-dose vasopressor within 3 hours defines grade 4. Hypoxia also contributes to CRS grading, with a required FiO_2 of 40% serving as the demarcating line between grade 2 and grade 3. Intubation triggers grade 4, but there is no mention of other methods of delivering positive pressure, such as CPAP.

The University of Pennsylvania published a grading scale that has been used in their CD19 CAR T cell trials (Penn criteria; Table 1) [17]. In contrast to the Lee criteria, the Penn criteria assign the same grade 3 CRS to patients requiring any amount of IVF for hypotension and patients requiring low-dose vasopressors, and to patients requiring minimal oxygen supplementation and those requiring more aggressive support, including CPAP. Owing to these differences and the inclusion of neutropenic fever as a trigger for grade 2 CRS, the Penn criteria tend to assign a higher grade of CRS compared with the Lee criteria, hindering comparisons of clinical trial safety data across centers.

Most recently, a multi-institutional group of investigators on several industry-sponsored CAR T cell trials published a manuscript on CAR toxicity (CARTOX) grading and management of CRS and CAR-associated neurotoxicity [12]. The CARTOX CRS grading differs slightly from the Lee criteria by including grade 1 organ toxicity to be considered under grade 1 CRS and defining fever, hypotension, and hypoxia for grading of CRS in adults (Table 1). In addition, a separate system was proposed for grading of neurotoxicity. Differences among the Penn, MSKCC, CARTOX, and Lee approaches to managing CRS are outside the scope of the present discussion.

EFFORTS TO HARMONIZE IMMUNE EFFECTOR CELL-ASSOCIATED CRS AND NEUROTOXICITY DEFINITIONS AND GRADING

Recognizing the disparity in published grading schemes and the need for harmonization of definitions and grading systems for immune effector cell-associated CRS and neurotoxicities seen after immune effector cell therapies including CAR T therapy, 49 experts from all aspects of the field met in Arlington, VA on June 20-21, 2018, at a meeting supported by the American Society for Transplantation and Cellular Therapy (ASTCT; formerly American Society for Blood and Marrow Transplantation, ASBMT). Attendees included leaders from major academic centers involved in CAR T cell therapy research as well as representatives from industry, the Center for International Blood and Marrow Transplant Research (CIBMTR), the American Society of Hematology (ASH), and the National Cancer Institute (NCI). Key presentations regarding immune effector cell-associated CRS and neurotoxicity were followed by focused discussion of salient points. The writing group was then tasked with generating language encompassing a new consensus that is both easily applied at the bedside and easily verifiable during chart reviews. A full, iterative drafting and vetting process was undertaken. In addition, these guidelines were presented at the CIBMTR CT Registry Forum on October 25, 2018, for discussion and comment. The participation at this second meeting included a broad group of multiple stakeholders including investigators, industry, payors, and National Institutes of Health and other governmental agencies. Here we report the consensus and rationale of the group as related to grading and reporting of toxicities.

IS CYTOKINE RELEASE SYNDROME THE APPROPRIATE TERM FOR IMMUNE EFFECTOR CELL-ASSOCIATED TOXICITY?

We first discussed whether "cytokine release syndrome" is the most appropriate term to assign to the constellation of symptoms occurring after CAR T cell and other immune effector cell therapies. The pathophysiology of the syndrome is unclear, because no animal models of CRS existed until recently [18,19]. In patients, most CD19 CAR T cell clinical trials to date have found marked inflammatory cytokine elevations in association with the onset of symptomatology and degree of severity. In addition, rapid clinical stabilization is frequently seen with use of the IL-6 receptor antagonist tocilizumab, strongly implicating cytokines, especially IL-6 [8,20-22], in the pathophysiology of the syndrome. In the absence of data suggesting an alternative mechanism, we conclude that CRS is the most appropriate term for these immune effector cell-associated symptoms and signs. We recognize that as CAR T and other immune effector cell therapies are successfully adapted to treat both hematologic malignancies and solid tumors, additional or alternative mechanisms of toxicity may be found.

DEFINITION OF CRS

The CTCAE v4.03 defines CRS as "a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells [11]." Although inclusive of many of the features of immune effector cell-associated CRS, this definition does not include fever, the hallmark of immune effector cell-associated CRS. CTCAE v5.0 refined the definition as "a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines [13]." Although this list of associated symptoms is more in line with what is seen clinically during immune effector cell-associated CRS, this definition limits the cause to cytokines alone and is not contextually defined. For example, in bacterial sepsis, high levels of many cytokines are produced, and symptoms such as fever and hypotension overlap with CRS, but there is no infection and the overall clinical picture is distinctly different from immune effector cell-associated CRS.

It is also important to note that CRS is observed not just with CAR T and other immune effector cell therapies. In addition to the TGN1412 experience, it has been described in many patients treated with blinatumomab, a bi-specific T cell engaging molecule consisting of 2 covalently linked single chain antibody fragments targeting CD3 on T cells and CD19 on normal and malignant B cells [23,24]. Preclinical studies suggest that CRS could be observed with CAR NK cell therapy as well [25]. Because the same constellation of symptoms has been observed after treatment with multiple agents each working in different ways to activate T and/or other immune effector cells, CRS as we have described it appears to be an immune effector cell-associated phenomenon. Therefore, we define CRS as "a 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." CRS should be applied to any immune effector

cell-engaging therapy, not just with CAR T cells. Cytokine profiles with other therapies might not be the same, and this may have therapeutic implications. As new, effective immunotherapies centered around cell types other than T cells are developed, the definition may need to be altered.

SYMPTOMS DEFINING CRS MUST BE ATTRIBUTED TO IMMUNE EFFECTOR CELL ENGAGEMENT

The common symptoms of CRS are not unique to CRS. Indeed, practitioners must be cautious and exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress, such as an overwhelming infection. Bacteremia and other infections have been reported concurrent with and even mistaken for CRS. A reasonable temporal relationship to the cell therapy must be present. Although immune effector cell-associated CRS may have a delayed onset, it rarely presents beyond 14 days after initiation of therapy. Patients exhibiting symptoms consistent with CRS presenting outside this window should be carefully evaluated for other causes.

TOXICITIES EXCLUDED FROM THE DEFINITION OF CRS

As stated before, neurotoxicity is a frequent complication of CAR T cell and other T cell-engaging therapies. Unlike the classic symptoms of CRS, immune effector cell-associated neurotoxicities do not usually respond to tocilizumab, which is not surprising given the observation that i.v. tocilizumab administration does not generate significant levels of the drug in the cerebrospinal fluid [26]. Given this finding, along with the paucity of mechanistic data, the lack of known CD19 expression in the CNS, and the propensity for neurotoxicities to develop well after the classic symptoms of CRS have resolved, we conclude that immune effector cell-associated neurotoxicities should be excluded from the definition of CRS.

Despite this, CRS can impact neurotoxicity and complicate its assessment. High fever and drug therapy can cause delirium. A sedated and/or intubated patient might not be assessable for neurotoxicity. As more insight is gained, this may need to be reevaluated. In the meantime, we recommend the use of a separate grading scale for immune effector cell-associated neurotoxicities as described below.

Hemophagocytic lymphohistiocytosis or macrophage activation syndrome (HLH/MAS) overlaps substantially with CRS, as illustrated by ferritin elevations seen in many CAR T cell recipients during CRS [2,12,20,22,27]. CRS and classic acquired HLH/MAS have many shared features, and the 2 entities likely are not distinct, reflecting the activation of the reticuloendothelial system initiated by T cell-mediated inflammation. Most patients with moderate to severe CRS have laboratory results that meet the classic criteria for HLH/MAS but may or may not have hepatosplenomegaly, lymphadenopathy, or overt evidence of hemophagocytosis. In addition, refractory HLH/MAS has been described only in rare cases of immune effector cell-associated CRS [2,28], whereas in the vast majority of patients, the symptoms (and characteristic elevated cytokines) suggestive of HLH/MAS resolve with CRS resolution [22]. Given this overlap, and the absence of a need to directly treat HLH/MAS in most cases, we conclude that HLH/MAS should be excluded from the definition of CRS. Patients may meet some of the criteria for HLH/MAS after CAR T cell infusion, but this is part of the CRS. Because of the inability to separate CRS from HLH/MAS, and because grading of HLH/MAS is not available as a separate CTCAE term, the group did not see a need to grade this entity separately.

LABORATORY PARAMETERS ARE NOT INCLUDED IN THE DEFINITION OR GRADING OF CRS

Significant alterations in many laboratory parameters clearly occur with CRS. Cytokine aberrations have been well described, but such data are not routinely available in most academic centers in a time frame that is useful for assigning grade and planning management of a patient experiencing CRS. CRP is a widely available and relatively inexpensive laboratory test and initially appeared to be a useful biomarker of CRS. However, CRP is not specific for CRS, several scales of measurement exist, and our experience suggests that changes in CRP lag behind clinical changes by at least 12 hours. For these reasons, although CRP is often used to follow inflammation, we excluded the use of laboratory parameters from the definition and grading of CRS and favor a system based on clinical observation; however, we do encourage the continued measurement of cytokines, CRP, ferritin, and other parameters so that additional data may be generated for future study.

IMPLICATIONS OF A GRADING SYSTEM BASED ON PRACTITIONER INTERVENTION

Hospitals have varying capacities and policies for providing escalating care to their patients experiencing serious complications. Our proposed schema separates grade of CRS based largely on the degree or type of intervention administered to a patient, for example, i.v. fluid versus vasopressor use for managing hypotension or admission to the intensive care unit. There are several circumstances (eg, % oxygen supplementation; see below) in which strict definitions are confounded by wide variability in clinical practice. In the end, many definitions in use reflect the treatment decisions made by the clinical team at the bedside. There was some concern that some practitioners might alter their usual practice and rely longer on i.v. fluids for hypotension and/or delay transfer to the intensive care unit in an effort to prevent upgrading a patient. Such a practice is not the intent of the grading system and is strongly discouraged, given that prolonged fluid resuscitation without pressor use is associated with worse outcome and because early and aggressive supportive care, early use of vasopressors, and timely anti-cytokine therapy are paramount to mitigating life-threatening CRS.

CONSENSUS ON CRS GRADING

Grade 1 CRS

We define grade 1 CRS as fever ($\geq$38.0°C) with or without constitutional symptoms (Table 2). The associated constitutional symptoms may be reported in accordance with CTCAE v5.0 but do not affect CRS grade. All CRS grading schemes proposed to date mostly agree on what constitutes grade 1 CRS; however, not all systems include fever as a requirement. The constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely.

Grade 2 CRS

We define grade 2 CRS as fever ($\geq$38.0°C) with hypotension not requiring vasopressors and/or hypoxia requiring the use of oxygen delivered by low-flow nasal cannula ($\leq$6 L/minute) or blow-by. Lee et al [14] attempted to separate grading for patients who require minimal vasopressor support from those that require intensive vasopressor use (also a feature of the Penn grading) and those requiring minimal oxygen supplementation

Table 2
ASTCT CRS Consensus Grading

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

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

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

from those requiring more aggressive assistance. This was done in part out of concern that intervening with anticytokine therapy such as tocilizumab, as well as early, prolonged, or high-dose corticosteroids, would abrogate the antitumor response. Although prospective clinical trials evaluating the timing of intervention are lacking, retrospective analyses suggest that this is not the case, at least when such therapies are implemented after CRS is well under way [2,21]. How the use of preemptive or prophylactic tocilizumab or corticosteroids affect the antitumor response or alter the natural history of other immune effector cell-associated toxicities, such as neurotoxicity, remains an open question that merits further exploration in well-controlled studies.

The trend in many groups has been to move toward the use of anticytokine therapy earlier in the development of severe CRS rather than later. For example, many investigators will administer tocilizumab with any vasopressor requirement, even low-dose, or with a significant oxygen requirement, representing a shift in the treatment algorithm initially proposed by Lee et al [12,14], as well as much of the early Penn experience. In general, we agree with this approach because it initiates CRS management earlier, allowing for earlier resolution while still preserving efficacy. We also differentiate this practice shift from the prophylactic or preemptive use of tocilizumab, which remains experimental. Nonetheless, the goal of the work was to define a grading system, and the group clearly recognized the reality of and need for variations in practice in initiating and escalating CRS treatment.

Despite this shift toward earlier intervention, we recognize there is a distinct difference between patients requiring low-dose vasopressor or minimal oxygen supplementation and those who require more aggressive interventions. We sought to capture this difference in our CRS grading scheme, because significantly less resources are needed to support the former compared with the latter. Our scheme is also aligned with the general concept in the CTCAE that toxicities requiring specific intervention (eg, anticytokine therapy) meet the criteria for grade 3 at least. However, it is important to recognize that fever might not always be present concurrently with hypotension or hypoxia because it may be masked by such interventions as antipyretics, anticytokine therapy, and/or corticosteroids, whereas hypotension and hypoxia may take longer to resolve.

Grade 3 CRS

We define grade 3 CRS as fever (≥38.0°C) with hypotension requiring 1 vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, nonrebreather mask, or venturi mask not attributable to any other cause. Several key features of these criteria merit discussion.

The Lee and Penn criteria relied on established definitions of low-dose versus high-dose vasopressor use in defining lower-grade versus higher-grade CRS [14,17]. Although these definitions are well accepted in the critical care literature, they are cumbersome in practice when assigning or auditing CRS grade. The MSKCC criteria used duration of any vasopressor dose for less than or greater than 24 hours as differentiating between grades 2 and 3 CRS [16]; however, that arbitrary time point might not accurately distinguish patients requiring minimal versus significant critical care support. As a result, and owing to real differences in severity between patients requiring 1 vasopressor versus 2 or more vasopressors, we use this distinction (1 versus ≥2 vasopressors) in our proposed grading system.

Many critical care practitioners administer vasopressin simultaneously with any dose of norepinephrine to capitalize on its vasoconstrictive effects in an effort to mitigate capillary leak and minimize norepinephrine dose requirements. The use of vasopressin in this setting is not in response to escalating toxicity, so our grading scheme is agnostic to its use. There was also discussion regarding the inotrope milrinone, which is often used to aid in contractility and does not escalate the grade of CRS.

Although previous versions of CRS grading relied on capturing the FiO_2 value required to maintain normoxia, this data point can fluctuate from hour to hour, making interpretation and auditing data difficult. To remedy this problem, we elected to separate grade of CRS due to hypoxia by the device used to deliver oxygen; for example, a simple, low-flow nasal cannula (≤6 L/minute) is considered grade 2, whereas high-flow devices are grade 3. This distinction serves as a surrogate for the severity of oxygenation deficit.

What constitutes hypoxia—or, more accurately, what oxygen saturation is sufficiently low or what clinical signs are sufficient to warrant supplemental oxygen—varies widely across centers, among nursing practice, and according to patient age. Normalizing all centers to a single set of criteria is an exceedingly difficult task. For similar reasons, we cannot dictate criteria for which supplemental oxygen is no longer needed in all situations. Therefore, we allow practitioner discretion and recommend that grading be determined by the minimal oxygen delivery device required to correct the perceived deficit(s).

Grade 4 CRS

We define grade 4 CRS as fever (≥38.0°C) with hypotension requiring multiple vasopressors (excluding vasopressin) and/

or hypoxia requiring positive pressure (eg, CPAP, bilevel positive airway pressure, intubation, mechanical ventilation) not attributable to any other cause. Irrespective of total cumulative dose, the use of multiple vasopressors constitutes grade 4 CRS. An exception for vasopressin is again made, based on the foregoing reasoning. Outside of vasopressin, adding a second agent is a strong indication that the patient remains hemodynamically unstable after the first intervention. Such a scenario would be consistent with grade 4 CRS.

As CRS progresses, capillary leak often leads to pulmonary edema and impairment of ventilation in addition to oxygenation. These patients tend to respond to positive pressure ventilation, which may be accomplished in several ways, up to and including intubation and mechanical ventilation. Any use of positive-pressure ventilation constitutes a grade 4 CRS.

Intubation may be indicated in patients who have a degree of neurotoxicity where there is concern for their ability to maintain a patent airway. This may occur either in the setting of CRS or after CRS has resolved. The severity of the neurotoxicity driving the decision for intubation will be captured by the grading of that neurotoxicity and should not be captured again as a grade 4 CRS when the other criteria for such are not met. In other words, intubation of a patient without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not, by definition, grade 4 CRS. By extension, a patient experiencing seizures in which a compromised airway affects oxygenation and intubation reverses such deficits is not considered to have grade 4 CRS, because the seizure rather than CRS is the cause of the hypoxia. Furthermore, a patient who remains intubated for a neurologic cause is not considered to have CRS when the other signs of CRS have resolved.

Grade 5 CRS

By convention, grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

CRS SEVERITY IS DETERMINED BY HYPOTENSION AND HYPOXIA

The clinical manifestations of CRS are varied and frequently involve multiple organ systems. Arrhythmia, cardiomyopathy, prolonged QTc, heart block, renal failure, pleural effusions, transaminitis, and coagulopathy are but a few of the significant complications of CRS. Although it is important to document all adverse events experienced by CAR T cell recipients, we determined that such significant events are uncommon in the absence of significant hypotension, hypoxia, or both. Moreover, these organ dysfunctions are usually managed symptomatically in accordance with standard guidelines and do not influence the decision to use CRS-specific interventions, such as anticytokine therapy and corticosteroids. Thus, hypotension and hypoxia are the principle determinants of our consensus grading scale. For these reasons, and to simplify reporting, references to other specific organ toxicities have been removed from CRS grading. However, organ toxicities associated with CRS may be graded according to CTCAE (currently v5.0) and reported as required.

DEFINITION OF FEVER, HYPOTENSION, AND HYPOXIA AS RELATED TO CRS GRADING

Fever is defined in the CTCAE v5.0 as "a disorder characterized by elevation of the body's temperature above the upper limit of normal," and a temperature $\geq$38.0 °C is considered grade 1 fever [13]. We propose to use this same definition to define fever associated with CRS.

The CARTOX criteria defined hypotension as a systolic blood pressure (SBP) <90 mmHg in adults, whereas other CRS grading scales did not specifically define hypotension [11-14,17]. However, an SBP of 80 to 90 mmHg is considered normal in many children. We also noted that some base the definition of hypotension on SBP, whereas others consider only the mean arterial pressure (MAP). Both are acceptable and can be used to determine CRS grade. Therefore, hypotension should be determined on a case-by-case basis, accounting for age and the patient's individual baseline. Indeed, hypotension is defined in CTCAE v5.0 as "a disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment" [13]. For practical purposes of CRS grading, an individual requiring IVF boluses or vasopressors to maintain normal blood pressure may be considered to have hypotension.

Hypoxia is another term that is not defined consistently. The CTCAE v5.0 defines hypoxia as "a disorder characterized by a decrease in the level of oxygen in the body [13]," but does not specifically define what level of decrease is considered abnormal or even how to measure it. In fact, most physicians cannot agree. Many consider hypoxia as an oxygen saturation (SaO_2) <94% or even 88%, whereas others base it on other measurements, such as the partial pressure of arterial oxygen. For CRS grading, an individual requiring supplemental oxygen to correct a deficit in oxygenation is considered to have hypoxia. Oxygen provided only as a comfort measure should not be used to inform CRS grade.

DEFINITION OF CRS RESOLUTION

Although most centers are comfortable defining the onset and grade of CRS at its presentation, there is less clarity about when CRS is considered resolved. This is due in large part to anticytokine therapies that dramatically and effectively treat fever. Temperature often normalizes within a few hours after tocilizumab administration, whereas the other components of CRS take longer to resolve. Our definition and grading of CRS require fever. Anticytokine therapies are indicated only for patients with CRS, that is, patients who have fever and meet the definition of CRS. Once such 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. Likewise, CRS can be downgraded in an afebrile patient treated with anticytokine therapy as their hemodynamic status and/or hypoxia improves. Typically, a patient with severe CRS in whom fever, oxygen, and pressor requirements have resolved may be assumed to have resolved CRS unless there are alternative causes for the fever, hypoxia, and/or hypotension. Any neurotoxicity occurring concurrent with or subsequent to the period of CRS does not inform the grade of CRS but is instead captured separately in the neurotoxicity scale.

SYMPTOMS OF ICANS

Symptoms of ICANS (Table 3) have come into better focus through early clinical trials and to date have generally been graded using CTCAE. Although symptoms can be more diverse than those of CRS, many patients with neurotoxicity have a stereotypic evolution of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Headache is a nonspecific symptom, frequently occurring during fever or after chemotherapy in patients without other neurologic dysfunction. Thus, headache alone is not a useful marker of ICANS.

Table 3
Neurologic and Psychiatric Adverse Reactions Reported with Approved CAR T Products

Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism **Delirium:** includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness **Headache:** includes headache and migraine **Anxiety** **Sleep disorder:** includes sleep disorder, insomnia, nightmares	**Encephalopathy:** includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor **Delirium:** includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness **Headache** **Dizziness:** includes dizziness, presyncope, syncope **Aphasia:** includes aphasia, dysphasia **Motor dysfunction:** includes muscle spasms, muscular weakness **Tremor** **Ataxia** **Seizure** **Dyscalculia** **Myoclonus**

Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS. A Phase I clinical trial identified expressive aphasia as the most characteristic feature, developing in 19 of 22 patients who went on to develop severe neurotoxicity [29]. Expressive aphasia, starting as impaired naming of objects, paraphasic errors, hesitant speech, and verbal perseveration, may progress to global aphasia, characterized by expressive and receptive difficulty. Patients with global aphasia may appear wide awake but are mute and unable to follow commands (akinetic). Many patients have myoclonus or tremor and increased tone. There may be depressed level of consciousness with mild lethargy progressing to obtundation, stupor, or even coma. Mild symptoms may wax and wane with fever initially only to recur a few days later after CRS has resolved.

The tempo of progression to severe neurotoxicity may be hours or days. Subclinical electrographic or clinical seizures may then develop, accompanied in some cases by motor weakness. When seizures occur, it is often after the development of severe (global) aphasia. In rare cases, diffuse cerebral edema develops, in some cases after seizures have occurred, but more often cerebral edema may have fulminant onset and few antecedent clinical warning signs, suggesting that it may have a distinct pathophysiology from more reversible neurotoxicity. There appears to be variability in the presentation of neurotoxicity with different CAR products. Nevertheless, there has been progress toward understanding and defining relevant signs and symptoms of neurotoxicity in the progression toward severe toxicity that might trigger intervention in the acute setting.

DEFINITION OF ICANS

Neurologic symptoms may be observed in association with pathological processes including hepatic failure, severe hypertension, eclampsia, infection, electrolyte abnormalities, and immunosuppressive and cytotoxic drug therapies. ICANS may have features that overlap with other encephalopathies but has the more specific characteristic of an awake patient who is mute and does not respond verbally or physically to an examiner. ICANS may have a unique pathophysiology compared with other encephalopathies. In a recent report, Gust et al [30] suggested a role for endothelial activation and blood-brain barrier disruption in the pathophysiology of neurotoxicity. Another report found elevated levels of the excitatory NMDA receptor agonists glutamate and quinolinic acid in cerebrospinal fluid from patients with neurotoxicity [26]. Several reports suggest a role for proinflammatory cytokines and myeloid cells besides activated T cells [2,18,29,31-33]. The term CAR-related encephalopathy syndrome (CRES) has been proposed to describe neurotoxicity associated with CAR T cell therapy [12]. We acknowledge that encephalopathy is a dominant feature of the neurologic changes that occur; however, we prefer the term ICANS to be inclusive of other symptoms, as well as to acknowledge other cellular immunotherapies and therapeutics, such as bispecific antibodies, that may have similar neurologic side effects. We define ICANS as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema." Similar to CRS, ICANS should be applied to any immune effector cell engaging therapy, not just CAR T cells.

SYMPTOMS AND SIGNS EXCLUDED FROM THE DEFINITION OF ICANS

Although other neurologic symptoms and/or signs, such as headache, tremor, myoclonus, asterixis, and hallucinations, may occur and possibly be attributable to immune effector cell-engaging therapies, we have excluded them from the definition of neurotoxicity because they are less specific, are usually managed symptomatically, and do not trigger specific interventions, such as corticosteroids, to abrogate activation of T cells and other immune cells. Weakness and balance problems may occur owing to deconditioning and loss of muscle mass from immobility and are frequently seen in the transplantation and intensive chemotherapy setting and are excluded from the definition of ICANS. Intracranial hemorrhage with or without associated edema may occur due to coagulopathies in these patients and is also excluded. We recommend that practitioners capture and report such associated events in accordance with CTCAE v5.0 [13].

CONSENSUS ON ICANS GRADING FOR ADULTS

Although early clinical trials used CTCAE v4.03 for grading neurotoxicity, further refinement was achieved when a multi-institutional group of oncologists leading CAR T cell trials across the United States published the CARTOX criteria for adults on grading of neurotoxicity. The CARTOX system grades neurotoxicity by assessing multiple neurologic domains that span the constellation of signs and symptoms associated with neurotoxicity (Table 4). An important development was a 10-point screening tool called the CARTOX-10, which incorporated key elements of the Mini-Mental State Examination (MMSE) to evaluate the alterations in speech, orientation,

Table 4
Published Neurotoxicity Grading Systems

Grading System	Adverse Event Term/Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE v5.0 [13],*	Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
	Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New-onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences
	Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly	
	Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	
	Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	
	Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
	Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated
	Cerebral edema			New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated
CARTOX criteria [12]	Neurologic Assessment Score (CARTOX-10)	7-9 (mild impairment)	3-6 (moderate impairment)	0-2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
	Elevated ICP	N/A	N/A	Stage 1-2 papilledema† or CSF opening pressure <20 mmHg	Stage 3-5 papilledema†, or CSF opening pressure ≥20 mmHg, or cerebral edema
	Seizures or motor weakness	N/A	N/A	Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness

ADL indicates activities of daily living; CSF, cerebrospinal fluid; EEG: electroencephalography.

* CTCAE: Under CRS listing: "Also consider neurologic toxicities such as psychiatric disorders: hallucinations or confusion; nervous system disorders: seizure, dysphasia, tremor, headache."

† Papilledema grading is performed according to the Modified Frisén scale [35].

handwriting, and concentration that are highly suggestive of the encephalopathy observed in patients with ICANS (Table 5). This screening tool was designed to overcome the subjectivity in grading many overlapping encephalopathy terms, such as encephalopathy, delirium, aphasia, confusion, and others. It moved away from defining the grade of encephalopathy according to impairment of ability to perform activities of daily living, which can be difficult to assess in hospitalized patients.

The CARTOX grading system for neurotoxicity also included evaluation of other domains including level of consciousness, motor symptoms, seizures, and signs of elevated intracranial pressure (ICP) (Table 4). For evaluation of raised ICP and determination of neurotoxicity grade, the guidelines suggested using elevated cerebrospinal fluid opening pressure and papilledema grade by the Frisén Scale (Table 4). Unfortunately, these measurements are cumbersome, potentially inaccurate, and difficult to extend to routine practice. For example, lumbar puncture can be difficult to perform in critically ill patients, and when it is done, opening pressure may vary with age, body habitus, positioning, systemic blood pressure, mechanical ventilation, and pharmacologic sedation [34]. In the case of papilledema grading, hospitals have differing capacities for rapid grading of papilledema, leading to variable grading (Frisén grade 2 versus 3) depending on the individual performing the examination, use of fundus photography, and other factors.

For our consensus grading scheme, we propose the use of a slightly modified version of the CARTOX-10 screening tool,

Table 5
Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [12]	ICE
• **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point	• **Orientation:** orientation to year, month, city, hospital: 4 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

here termed the Immune Effector Cell-Associated Encephalopathy (ICE) score, to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included in the approved CAR T products (Table 3). The updated encephalopathy screening tool (Table 5) includes an element for assessing the receptive aphasia seen in these patients. The total number of points, ease of administration, and categorization of scores remain the same as in the original CARTOX-10 [12]. It is important to note that the 10-point ICE screening tool is helpful for assessing patients for encephalopathy; however, the grading of ICANS requires assessment of the 10-point ICE score as well as evaluation of other neurologic domains, such as level of consciousness, motor symptoms, seizures, and signs of elevated ICP/cerebral edema, which may occur with or without encephalopathy.

In contrast to CTCAE v4.03, in which a generalized seizure was considered grade 2, our consensus guidelines are more aligned with CTCAE v5.0, which considers a new seizure of any type as grade 3 and any life-threatening seizure as grade 4. Compared with the original CARTOX CRES grading and CTCAE v5.0, the new consensus grading has been simplified so that a single clinical or subclinical electrographic seizure of any type is grade 3 and prolonged or repetitive clinical or subclinical electrographic seizures without a return to baseline in between are grade 4 (Table 6). Patients may have electroencephalography changes, such as generalized or frontal slowing or frontal intermittent rhythmic delta activity, which should not be considered seizures.

We have also modified the criteria for assessment of elevated ICP to improve the ease of grading compared with the CARTOX CRES grading system by reducing cerebrospinal fluid opening pressure and the requirement to grade papilledema on the modified Frisén scale [35] (Table 6). This does not negate the importance of making a clinical assessment to determine the presence of elevated ICP, but acknowledges that other signs and symptoms, including simply the presence or absence of papilledema taken in conjunction with depressed level of consciousness, can be used to make this assessment. We have highlighted the importance of evaluating level of consciousness by making it a more detailed factor in the grading.

Table 6
ASTCT ICANS Consensus Grading for Adults

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

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

In the grading system, the final ICANS grade is determined by the most severe event among the different domains.

Grade 1 ICANS

We define grade 1 ICANS as a score of 7 to 9 on the ICE assessment (Table 6). A patient with grade 1 ICANS may have a delay in response or disorientation to time or place, mild inattention with difficulty in counting numbers backward, or impaired handwriting. There may be drowsiness but the patient awakens spontaneously, and when prompted, the patient should be able to complete most of the ICE assessment. Grade 1 ICANS may be seen during CRS waxing and waning with febrile episodes.

Grade 2 ICANS

We define grade 2 ICANS as a score of 3 to 6 on the ICE assessment (Table 6). Patients with grade 2 ICANS often have some expressive aphasia, limiting the ability to communicate spontaneously. Patients also may have difficulty writing a standard sentence due to poor handwriting and apraxia. They have difficulty naming objects due to expressive aphasia and/or following commands due to receptive aphasia and poor concentration. In our experience, expressive aphasia is the most specific first sign of severe neurotoxicity, and early signs in grade 2 include paraphasic errors (the production of unintended syllables and words during attempts to speak) and verbal perseveration (repeating the same words over and over). Patients with grade 2 ICANS are able to communicate their needs with effort. Patients may have a depressed level of consciousness but are arousable to voice and the responses may be slowed.

Grade 3 ICANS

We define grade 3 ICANS as a score of 0 to 2 on the ICE assessment (Table 6). Patients with grade 3 ICANS have severe global aphasia and do not speak or follow commands even when wide awake and thus may be unable to answer any of the ICE questions. Alternatively, they may have excessive drowsiness and need tactile stimulus to attend to the examiner. Any clinical seizure, whether simple partial, complex partial, or generalized, and any electrographic seizures would also meet the criteria for grade 3 ICANS (Table 6). This acknowledges that seizure may be the peak of an excitatory neurotoxicity process that first manifests clinically as progressive aphasia and then peaks with onset of a clinical or electrographic seizure. If neuroimaging shows new focal or local edema, this would also be categorized as grade 3 ICANS (Table 6). However, intracranial hemorrhage due to coagulopathy or other causes with or without associated edema is not considered a neurotoxic feature and is excluded from ICANS grading.

Grade 4 ICANS

We define Grade 4 ICANS as patients who have a score of 0 on the ICE assessment due to being unarousable and unable to perform the ICE assessment. Stupor and coma may be seen; the stuporous patient responds only by grimacing or drawing away from vigorous or repetitive tactile stimuli, and the comatose patient is unarousable and/or unresponsive (Table 6). This depressed level of consciousness should be attributable to no other cause (eg, no sedating medication), which is often a complicating factor in sick patients with CRS. Some patients may require intubation for airway protection. In addition, any patient experiencing prolonged or repetitive clinical or subclinical electrographic seizures without a return to baseline in between or with deep focal motor weakness, such as hemiparesis or paraparesis, would be considered to have grade 4 ICANS (Table 6). Patients with symptoms and signs of elevated ICP, such as projectile vomiting with headache; depressed consciousness; cranial nerve VI palsies; papilledema; Cushing's triad of bradycardia, hypertension, and respiratory depression; decerebrate or decorticate posturing; and diffuse cerebral edema on head imaging, would also be considered to have grade 4 ICANS (Table 6).

The new grading is similar to the CARTOX CRES grading guideline in regard to the CARTOX-10 screening assessment, in that it classifies any patient too obtunded to perform the assessment as having grade 4 ICANS. In contrast to CARTOX CRES, the updated grading classifies an isolated generalized seizure with return to baseline as grade 3 and reserves grade 4

Table 7
Encephalopathy Assessment for Children Age <12 Years Using the CAPD

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

(Adapted from Traube et al [36]; reproduced with permission.)
For patients age 1-2 years, the following serve as guidelines to the corresponding questions:
1. Holds gaze, prefers primary parent, looks at speaker.
2. Reaches and manipulates objects, tries to change position, if mobile may try to get up.
3. Prefers primary parent, upset when separated from preferred caregivers. Comforted by familiar objects (ie, blanket or stuffed animal).
4. Uses single words or signs.
5. No sustained calm state.
6. Not soothed by usual comforting actions, eg, singing, holding, talking, and reading.
7. Little if any play, efforts to sit up, pull up, and if mobile crawl or walk around.
8. Not following simple directions. If verbal, not engaging in simple dialog with words or jargon.

Table 8
ASTCT ICANS Consensus Grading for Children

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for children age ≥12 years*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for children age <12 years	1-8	1-8	≥9	Unable to perform CAPD
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor weakness (any age)‡	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging§	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. Baseline CAPD score should be considered before attributing to ICANS.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

classification for prolonged >5 minutes or repetitive clinical or subclinical (electroencephalography only) seizures without return to baseline in between. This is consistent with life-threatening seizures as defined by CTCAE v5.0.

Grade 4 patients typically need to be intubated for airway control and seizure management. A patient may be intubated for grade 4 ICANS, but this should not be recaptured as grade 4 CRS when other signs of severe CRS have resolved.

Grade 5 ICANS

By convention, grade 5 ICANS is defined as death due to ICANS where another cause is not the principle factor leading to this outcome.

CONSENSUS ON ICANS GRADING FOR CHILDREN

Although the 10-point ICE assessment is useful for screening adults for encephalopathy, its use in children may be limited to those age ≥12 years with sufficient cognitive ability to perform the ICE assessment. For children age <12 years, the Cornell Assessment of Pediatric Delirium (CAPD) [36,37] (Table 7) is recommended to aid in the overall grading of ICANS, as recently proposed by Mahadeo et al [38]. A CAPD score of ≥9 is suggestive of delirium and should be considered grade 3 ICANS. The CAPD score also may be used in patients age >12 years with baseline developmental delay as it has been validated up to age 21 years. Other domains evaluated to grade ICANS in children are similar to those used in adults and include level of consciousness, motor symptoms, seizures, and signs of raised ICP (Table 8).

DATA COLLECTION AND REPORTING FOR APPROVED CELL THERAPY PRODUCTS

The high unmet medical needs and large effect sizes seen in clinical testing of CD19 CAR T cell therapies allowed approval of the 2 current products based on data collected from <300 total patients on 3 single-arm Phase II trials. As a result, there is broad agreement that further data collection on toxicity and patient outcomes is paramount. The US Food and Drug Administration (FDA) requires that pharmaceutical companies that produce commercial CAR T cell products establish a mechanism to follow recipients of these therapies for 15 years, although this requirement is focused mainly on monitoring for potential long-term genotoxicity. Other health authorities may impose other or more detailed requirements.

This raises important questions on how best to collect appropriate data, especially because these mandates are placed on the companies but carried out by the centers in a largely volunteer effort. Compliance with what could be a significant and unfunded mandate will be enhanced by making sure that data collection is appropriately focused, especially because these data will not be collected in a research setting with research budgets and direct regulatory mandates on the centers. Health authorities will need to harmonize their data requests. In this new field of medicine, companies may have to face the possibility of a gap between what the FDA or European Medicines Agency (EMA) wants them to collect and what centers are actually able to provide. There needs to be a simplified and unified approach to reporting with a single portal for data entry. A registry approach is likely to be the best method of providing as complete data as possible.

The CIBMTR operates a large outcomes database, which for decades has been a valuable resource for the field of transplantation. Most centers with active immune effector cell programs have many years of experience using this database. Recognizing the emergence of the field of cellular immunotherapy, in 2016 the CIBMTR launched a database dedicated to cellular therapy outcomes. This registry tracks long-term follow-up of patients who have received cellular therapies, including CAR T cells and other cellular therapies beyond hematopoietic cell transplantation. As part of this process, the CIBMTR Cellular Therapy Task Force developed new reporting forms specific to cellular therapy [39], which were subsequently piloted and refined.

Since the launch in 2016, centers voluntarily have reported data derived from more than 200 recipients of CAR T cells, which are most commonly used for treatment of non-Hodgkin lymphoma and acute lymphoblastic leukemia. Using a single, standardized database to capture information about recipients of immune effector cell therapies can streamline the process and can

provide a resource for research. The CIBMTR's Cellular Therapy Registry infrastructure is well suited to meet this requirement.

Regulators in other regions are considering more requirements to assess the safety and efficacy of immune effector cell therapies. The EMA organized a workshop in February 2018 to identify a minimal set of data elements for commercial CAR T cells [40]. In addition to common safety endpoints, the EMA report outlined the capture of grade 3 and 4 organ toxicities [41]. Lee et al initially included grade 2 to 4 nonhematologic organ toxicities in their CRS grading criteria [14]; however, organ toxicities are excluded in the new CRS consensus grading scheme proposed here. Requiring reporting of organ toxicities in the postmarket setting would add a considerable burden for data collection, and it runs the risk of being infeasible. This example highlights the need for harmonization in the data requested.

The CIBMTR Cellular Therapy Registry's follow-up form captures toxicities after immune effector cell infusion, at 3 months, 6 months, 1 year, and yearly thereafter. The outcomes routinely captured in the CIBMTR follow-up forms relevant to CAR T cell toxicities include CRS, neurotoxicities, neutrophil and platelet recovery, hypogammaglobulinemia, severe infections, nonhematologic grade 4 toxicities, and death from any cause. For CRS, the registry computes a grade by capturing key information related to CRS, including treatment (eg, use of vasopressors). This approach can accommodate changes in the grading criteria, as proposed in this consensus statement, or comparisons across grading systems. For ICANS, the forms capture the presence of different manifestations, and whether they resolved. Issues raised on the applicability of CTCAE to assess severity in hospitalized patients apply here as well. Beyond the abovementioned toxicities, centers can report subsequent neoplasms and pregnancies at any time through event-driven forms. These forms aid the collection of time-sensitive information or biospecimens, if needed.

We believe that it would be safest and most efficient to use CIBMTR database reporting to meet the mandates placed on the drug companies at a level that is feasible for centers offering immune effector cell therapies outside the research setting. Barring unusual or notable toxicity that any treating physician can choose to report to the FDA on a MedWatch form (as with any other approved therapy), we endorse a system in which the CIBMTR registry is a single resource that centers can use for studies of current and future approved cell therapies. The CIBMTR built the Cellular Therapy Registry to serve the community and to help advance the field by making the data available to investigators. Standardized collection of toxicity data in the real-world setting will help identify ways to make these therapies safer.

CONCLUSION

In conclusion, we have proposed consensus definitions and grading for CRS and ICANS, the 2 most common toxicities associated with immune effector cell therapies. We acknowledge that as new data become available from existing and novel immune effector cell therapies, this grading system may need to be revised in the future. Nonetheless, we believe that our proposed grading system is objective, easy to use, and more accurately categorizes the severity of these toxicities. We strongly recommend the use of this consensus grading system for reporting of CRS and neurotoxicity associated with immune effector cell-engaging therapies across all clinical trials, as well as in the postapproval standard of care setting. This would allow comparison of the safety of different immune effector cell-engaging therapies and also likely facilitate the development of optimal strategies for prevention and/or management of these toxicities.

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