ASTCT
American Society for
Transplantation and Cellular Therapy

November 7, 2019

American Society for Transplantation and Cellular Therapy
330 N. Wabash Avenue
Suite 2000
Chicago, Illinois, 60611

To: Ms. Pickett, Ms. Bullock, and Ms. Hue
National Center for Health Statistics
ICD-10 Coordination and Maintenance Committee
Via email: nchsicd10cm@cdc.gov, wrp8@cdc.gov, dfp4@cdc.gov and Marilu.Hue@cms.hhs.gov

Re: Coding request for Cytokine Release Syndrome (CRS) diagnosis codes

Dear Ms. Pickett, Ms. Bullock, and Ms. Hue:

The American Society for Transplantation and Cellular Therapy (ASTCT) is writing to support the need for ICD-10-CMS diagnosis codes for complications that arise in patients who receive immune effector cellular (IEC) therapy, including Chimeric Antigen Receptor T-cell (CAR-T) therapy. These complications include Cytokine Release Syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS). Because CRS and ICANS are both common complications of CAR-T therapy, it is critical that providers who deliver this therapy have precise codes available with which to capture their incidence and severity.

The ASTCT is a professional membership association of more than 2,200 physicians, scientists, and other healthcare professionals that promote blood and marrow transplantation and cellular therapy through research, scholarly publication and clinical standards. We are dedicated to improving the application and success of hematopoietic cell transplants (HCT) and other cellular therapies in addition to CAR-T. The ASTCT has been at the forefront of CAR-T. Our membership of hematologists and blood and marrow transplant physicians are the providers who primarily administer these innovative cellular therapies.

Background on ASTCT's Consensus Grading Workgroup Process

Evaluating for CRS and ICANS and assessing the grade of CRS and/or ICANS is a key component of managing patients who received CAR-T and are being monitored post-administration. Regular documentation in the record of which grade the patient presented with during examinations at specific time intervals allows clinicians to track the onset of complications and their severity, which is vital to ongoing management of the patient by the cellular therapy clinician team.

Grading for CRS and ICANS has been a key component of patient management, both in the research setting and since the approval of the first product. Until the end of 2018, however, several different criteria were in use across institutions that provided CAR-T products. *All of these criteria included grades to describe the complications of CAR-T as described in detail in ASTCT's paper, "Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells."*[1] However, the manner in which the symptoms were distributed (and how many symptoms were included per grade)

[1] ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, Lee, Daniel W. et al. Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

330 North Wabash Avenue, Suite 2000 • Chicago, Illinois 60611 • P: (312) 321-6820 • F: (312) 673-6733

varied slightly. We draw significantly upon this seminal paper in our comments. (The full report is attached for more detailed review.)

For example, although early clinical trials modified the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grading for 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."[2] The Lee criteria redefined the clinical signs and symptoms associated with CRS – notably the inclusion, for the first time, of fever as a hallmark of CRS. Lee and colleagues further redefined the grading criteria for CRS to include hypoxia requiring oxygen supplementation, hypotension, and other end-organ toxicities.

In contrast to the Lee criteria, the University of Pennsylvania developed the "Penn criteria," which assigns the same grade (grade 3) to patients who require any amount of intravenous fluids for hypotension, patients requiring low-dose vasopressors, patients requiring minimal oxygen supplementation, and those requiring more aggressive support, including CPAP. The group at Memorial Sloan Kettering Cancer Center (MSKCC) identified objective factors that distinguished severe versus non-severe CRS in its early clinical trials; however, these factors relied on the availability of real-time serum cytokine levels in patients.[3] Upon further study—and in recognition that assays for serum cytokines are not readily available at most centers, thereby limiting the utility of its approach—MSKCC redefined the CRS grading used in its clinical trials.[4]

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.[5] The CARTOX CRS grading differs slightly from the Lee criteria, as it includes grade 1 organ toxicity to be considered under grade 1 CRS and defines fever, hypotension, and hypoxia for grading of CRS in adults. In addition, a separate system was proposed for neurotoxicity grading.

While there are clearly many differences among the Lee, Penn, MSKCC, and CARTOX criteria described above, it is notable that all had five grades (with the fifth being death), and all involved the same signs and symptoms that were arrayed differently across the various grades. We recommend the NCHS team review Table 1 in the Consensus Grading Paper, [6] which clearly illustrates the major different criteria and grades associated with each system.

The ASTCT leadership saw the need to consolidate these numerous criteria and grading scales to describe CAR-T complications. Doing so, the ASTCT believed, was necessary to facilitate clinicians' ability to assess patient complications in a consistent manner and to record this in the patient's medical record, enabling more accurate comparisons of cases treated within and across hospitals providing CAR-T therapy.

---

[2] Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188–195.

[3] Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6: 224ra25.

[4] Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378:449–459.

[5] Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy _ assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15:47–62.

[6] ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, Lee, Daniel W. et al. Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

330 North Wabash Avenue, Suite 2000 • Chicago, Illinois 60611 • P: (312) 321-6820 • F: (312) 673-6733

Additionally, the ASTCT believed the use of a single grading scale would help ensure that future research, presentations, and publications on patient complications and outcomes would be better understood by the medical community.

In order to reach a consensus, the ASTCT brought all of the stakeholders together to reach agreement on one set of grades that they would be able and willing to deploy in their institutions. On June 20-21, 2018, ASTCT hosted a meeting to discuss the development of a single grading scale for CRS and ICANS. The 49 attendees represented all aspects of the field and included leaders from major academic medical centers involved in CAR-T research, along with representatives from CIBMTR, ASH, and the National Cancer Institute (NCI), among others. Part of this group's work was to review all of the grading scales in use and evaluate similarities and differences with the goal of arriving at a consolidated scale that would be objective, reproducible, easy to use by all healthcare providers involved in patient care; foster rapid and dynamic assessment; enable grade-based management of toxicities; and ensure accurate categorization of the severity of these toxicities in clinical trials and in the post-approval clinical setting.

The Consensus Group's goal was to reach agreement on the differences between the various criteria in use and create a uniform consensus grading system for CRS and neurotoxicity associated with immune effector cell therapies. Ultimately, the Workgroup proposed new definitions and a grading scale for immune effector cell-associated CRS and neurotoxicity. The group also re-named neurotoxicity to "Immune Effector Cell-Associated Neurotoxicity Syndrome," or ICANS. The first manuscript on the new scale was released in the fall of 2018. In January 2019, the ASTCT published a paper on the formal consensus grading in the official journal of the ASTCT, then named *Biology of Blood and Marrow Transplantation*. The table below shows the new consensus grading scale:

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)

To facilitate the use of the consensus grading scale, the ASTCT developed a free application and a web-based tool to help clinicians grade patients, for use at the bedside. Since its release, the application has been downloaded more than 5,000 times. Clinicians are using the scale for patient care and to document the specific complications of CRS and/or ICANS and the specific grade in each patient's medical record. ASTCT recently hosted a webinar for our members with premier clinicians from Children's Hospital of Philadelphia (Dr. Stephen Grupp) and M.D. Anderson Cancer Center (Dr. Sattva Neelapu), each of whom presented on the grading scale to an audience of more than 100 participants. The ASTCT will continue to provide ongoing education and resources regarding the CRS and ICANS grading scales.

The ASTCT receives regular positive feedback about the grading scale's use across institutions and we know from clinicians that the tool is in widespread use.

330 North Wabash Avenue, Suite 2000 • Chicago, Illinois 60611 • P: (312) 321-6820 • F: (312) 673-6733

Additionally, the NCHS should understand that clinicians explicitly document the specific grades of CRS and ICANS in the patient's medical record, eliminating guesswork on the part of coders about what grade(s) the patient had. ***Grades are never assigned by coders or those reviewing the record; the grades are assigned by the treating physician and are clearly documented in the patient's record.*** Coders across many institutions have confirmed that they see clinician documentation regarding the grade of CRS and/or ICANS in the patient's medical record.

Request for ICD-10-CM Codes for CAR-T Complications

On behalf of our clinicians, the Society submitted our initial letter on the need for complication codes to the National Center for Health Statistics (NCHS) in 2018. The ASTCT recognizes that a request for new codes is a complex undertaking and one that is likely beyond our level of expertise. Therefore, we are grateful that the Alliance of Dedicated Cancer Centers (ADCC) prepared a coding proposal that it developed with the assistance of its expert coders and clinicians. This coding proposal respects the fundamentals of ICD-10 while being consistent with the grading (for CRS and ICANS) finalized by the ASTCT Consensus Grading Workgroup (described above).

We note that the ADCC submitted this comprehensive coding proposal to the NCHS in July 2018, for discussion in September 2018; again in December 2018, for discussion in March 2019; and, most recently, in July 2019, for discussion at the September 11, 2019 public meeting.[7] While we were pleased that a version of the ADCC's proposal for CRS diagnosis codes was presented at the September public meeting, specifically "option 2," we were disappointed that no definitive recommendation was finalized at that time. We were also disappointed that ICANS was not discussed at the meeting, since it is an important complication with differing grades, about which our Consensus Grading Workgroup reached agreement.

The NCHS put forth "option 1," representing a single code for CRS rather than recommending the ADCC's proposal (option 2), which specifies differentiated codes for each grade. We believe this was partly due to the NCHS' lack of confidence that grade assignments are consistent across different institutions providing CAR-T therapy. We fully understand and appreciate this concern, and it is exactly for this reason that we formed the Consensus Grading Workgroup. We too were concerned about the different grading scales being used around the country and wanted clinicians to come together to consolidate these various tools into a single grading tool for use by all institutions providing CAR-T therapy.

We share this level of detail with NCHS in hopes that it will understand why we *strongly* believe the most viable option for CRS codes for 2020 is to have grade-specific diagnosis codes as presented in "option 2," rather than a single code as presented in "option 1." To that end, we were concerned to hear during the public meeting that the American Academy of Pediatrics (AAP) (through Ms. Cheryl Bullock's statement) supports the release of a single code for CRS. We were puzzled by the AAP's position, given that our pediatric oncologists and pediatric hematologists disagree with the use of only a single code for CRS, and have reached out to the AAP on this issue.

As the NCHS continues to deliberate about the most appropriate coding solution to finalize, we ask staff to fully review the ASTCT Consensus Grading Paper,[8] which outlines our work to date in detail.

[7] ICD-10 Coordination and Maintenance Committee Meeting. Available at: https://www.cdc.gov/nchs/data/icd/Topic-packet-Sept-2019-Part2.pdf [Accessed 14 Oct. 2019].

[8] ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, Lee,

330 North Wabash Avenue, Suite 2000 • Chicago, Illinois 60611 • P: (312) 321-6820 • F: (312) 673-6733

Specifically, the NCHS may be interested to note that one of the leading authors of the ASTCT Consensus Grading Paper, was Dr. Lee, creator of the "Lee criteria," which has multiple grades and had been widely adopted by many pediatric CAR-T providers. Dr. Lee and others were able to reach consensus supporting the Consensus Grading Scale for both CRS and ICANS. If one of the originators of an early grading system focused on the pediatric population can enthusiastically adopt the new system aimed at grading pediatric and adult patients consistently, we believe the NCHS should, too.

Finally, we recognize that the codes may have to be revised or expanded over time. Our understanding is that this occurs as part of the usual process for updating codes and keeping them consistent with the clinical community's pioneering of new treatments to treat diseases.

Status Post Cellular Therapy Codes

The ASTCT also understands that the ADCC has submitted a proposal for status post cellular therapy codes within Chapter 21 of the ICD-10-CM code set. We ask the Committee to release a new status code that allows code capture of patients who are seen in the outpatient setting after CAR-T therapy, so they can be tracked as well. This would be a status post-cellular therapy code not unlike the existing status post-transplant code that already exists.

We understand that, to date, the NCHS has been interested in reviewing all of the codes related to CAR-T therapy as a "package." Given the delays that have already occurred, however, we urge the NCHS to finalize the status post CAR-T code as soon as possible. We also request that NCHS separate its review and discussion of this issue from the complication codes, since the public meeting transcript indicates that there was no debate or discussion about the need for this. We support the NCHS' proposed option and language presented at the September meeting.

Conclusion

CAR-T is a new and innovative treatment; the knowledge gathered during these early years is critical to understanding the complications that arise and the treatments provided to resolve them, patient outcomes, and the safety of different immune effector cell therapies that will likely facilitate the development of optimal strategies for prevention and/or management of these toxicities.[9] The complication grades are an important part of this knowledge base; this information will be invaluable to clinicians treating patients, the broader field, researchers pioneering new therapies, analysts, payers, and other stakeholders.

Given that the clinical community has achieved consensus on the grading scale for the complications of CRS and ICANS, we believe the NCHS can confidently move forward with "option 2." Releasing only a single code to describe CRS would conflict with the way that clinicians think about, document, and treat patients today—and would essentially render the code meaningless. The ASTCT simply requests that the NCHS to recognize what is already in practice and to ensure that it can be accurately and consistently conveyed through ICD-10-CM codes reported on claims. We urge the NCHS to finalize "option 2," in time for the new codes to be available for 2020.

Daniel W. et al. Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

[9] ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, Lee, Daniel W. et al. Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

330 North Wabash Avenue, Suite 2000 • Chicago, Illinois 60611 • P: (312) 321-6820 • F: (312) 673-6733

We also request that the ICD-10 Coordination & Maintenance Committee include complications of and status post cellular therapy codes in the FY 2020 ICD-10-CM update. Finally, we recommend the NCHCS continue to work with us and other stakeholders to ensure that codes for ICANS are discussed at the March 2020 meeting.

The Society would be happy to respond to any questions the NCHS has and can connect the Committee with our clinicians. We appreciate the opportunity to comment and welcome further conversation with all stakeholders if that is needed to help the industry, stakeholders, and the Committee better understand our position.

For questions related to this letter, please contact:

Alycia Maloney
Director of Government Relations,
American Society for Transplantation and Cellular Therapy
(202) 367-1254
amaloney@astct.org

Sincerely,

Navneet S. Majhail, MD, MS
Director, Blood & Marrow Transplant Program
Cleveland Clinic
President, ASTCT

330 North Wabash Avenue, Suite 2000 • Chicago, Illinois 60611 • P: (312) 321-6820 • F: (312) 673-6733