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Reply

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To the Editor:

We thank Ms Brown and Dr Gutierrez for their comments regarding our recent publication of the ASBMT CRS and ICANS Consensus Grading [1], and we agree that there are significant clinical differences between patients requiring a low dose versus a high dose of 1 vasopressor. This was an active area of discussion among the larger group. However, we expressly stated that the Consensus Grading is not a treatment guideline, and no inference in such regard should be made. Rather, grading of CRS is entirely dependent on the interventions the patient requires and is not meant as a tool to suggest one intervention or another. The Consensus Grading was designed expressly to be simple to use so that it can be implemented in a meaningful way across all current and future centers with varying degrees of data management capabilities providing immune cell-engaging therapies, across clinical studies and commercial products. A grading system that requires assessment of pressor doses (low- versus high-dose vasopressors), which often change by the hour, is antithetical to this approach.

In addition, the commenters focus on management of sepsis. Although there are commonalities between sepsis management and CRS, and both involve shock, sepsis is not CRS, and cytokine blockade is not used routinely or successfully in sepsis. Although we agree that patients requiring 2 vasopressors are of course sicker and at increased risk (hence the difference between grades 3 and 4 in the grading), we treat vasopressin separately because of how it is used. It provides a small to moderate but fixed amount of pressor effect and has been shown to reduce the dose of norepinephrine needed [2]. Because many intensivists use vasopressin as an adjunct in this manner, it is difficult to consistently designate it as an independent vasopressor associated with increased CRS severity.

Although we have proposed 4 grades for CRS and set clear boundaries to separate them so that the grading can be simple, objective, and reproducible across centers, it is important that clinicians recognize that CRS is a continuous spectrum (eg, varying doses of vasopressors) and should take this into account while managing patients. Thus, we disagree with the comparisons drawn between sepsis and CRS. The 2 entities are very distinct. CRS is often easily and even spontaneously reversible with no lasting sequelae. Moreover, because of the efficacy of cytokine blockade in CRS, the course of grade 4 CRS is often very different from that of severe sepsis. In addition, hypotension due to CRS frequently responds to anti-IL-6 therapy with or without corticosteroids, unlike in sepsis. Finally, although peripheral vasodilation is a symptom of both sepsis and CRS, the pathophysiology of the 2 likely differs given the response to anti-inflammatory interventions in CRS but not in sepsis. Again, these are 2 different entities with differing management.

We do agree that there will be opportunities to refine these grading criteria over time and with new IEC interventions. In fact, we welcome ongoing discussion as new therapies are launched and additional data are collected as these therapies become more widespread.

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REFERENCES

1. Lee DW, Santomasso BD, Locke FL, et al. ASBMT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2018.
2. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877–887.