Nivolumab-Induced Cytokine Release Syndrome: A Case Report and Literature Review

Francis Ntwali, Quentin Gilliaux, Patrick M. Honoré

Corresponding Author: Francis Ntwali, e-mail: francisntwali@gmail.com
Financial support: None declared
Conflict of interest: None declared

Patient: Male, 65-year-old
Final Diagnosis: Cytokine release syndrome
Symptoms: Hypotension • hypoxemia • shock
Clinical Procedure: Critical Care Medicine • Oncology

Objective: Unusual clinical course

Background: CRS (cytokine release syndrome) is a massive activation of the inflammatory system characterized by a supra-physiological rate of inflammatory cytokines. The interleukin 6 cytokine plays a central role in CRS. The main clinical sign of CRS is fever, but CRS can lead to multiple organ failure in severe cases. CRS is usually described in sepsis, more recently in SARS COV-2 infection, and in chimeric antigen receptor T-cell therapy. However, it can also be associated with immune checkpoint inhibitors (ICIs), which is infrequently described. ICIs have growing indications and can lead to CRS by causing an uncontrolled activation of the immune system. There are currently no treatment guidelines for ICI-induced CRS.

Case Report: We report a rare case of grade 3 CRS induced by nivolumab associated with 5-fluorouracil and oxaliplatin for gastric cancer. The patient was 65-year-old man with an adenocarcinoma of the cardia. CRS developed during the tenth course of treatment and was characterized by fever, hypotension requiring vasopressors, hypoxemia, acute kidney injury, and thrombopenia. The patient was transferred quickly to the Intensive Care Unit. He was treated for suspected sepsis, but it was ruled out after multiple laboratory examinations. There was rapid resolution after infusion of hydrocortisone.

Conclusions: The use of ICIs is expanding. Nivolumab-induced CRS is rarely described but can be severe and lead to multiple organ dysfunction; therefore, intensive care practitioners should be informed about this adverse effect. More studies are needed to better understand this condition and establish treatment guidelines.

Keywords: Cytokine Release Syndrome • Immune Checkpoint Inhibitors • Nivolumab • Receptors, Chimeric Antigen • Sepsis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/941835

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
**Background**

Cytokine release syndrome (CRS), or cytokine storm, can be described as a major inflammatory syndrome resulting from a supra-physiological rate of inflammatory cytokines. There is no largely accepted definition, because the line between a physiological and pathological inflammatory response is not well defined [1]. Making this differentiation is all the more difficult as some cytokines are useful to fight the invasion of pathogens and can also be harmful for the host. These inflammatory mediators are interdependent and interact in a complex manner, resulting in a massive activation of the inflammatory system [1,2].

Immune checkpoint inhibitors (ICIs) are key tools in cancer therapy, and their use is expanding. ICIs inhibit negative regulators of the immune system, causing immune-related adverse events and CRS. Among ICIs, programmed cell death 1 (PD-1) inhibitors and, in particular, nivolumab have been indicated for various cancer treatments. Food and Drug Administration (FDA)-approved conditions are mismatch repair deficient colorectal cancer, head and neck squamous cell carcinomas, hepatocellular carcinoma, melanoma, classic Hodgkin lymphoma, non-small-cell lung carcinoma, renal cell carcinoma, urothelial cancer, and small-cell lung carcinoma [3,4]. European Medicines Agency indications also include mesothelioma [4]. Moreover, other indications are still in trial [5].

**Case Report**

We report a case of cytokine release syndrome (CRS) following a combination treatment by nivolumab, 5-fluorouracil, and oxaliplatin for gastric cancer.

The patient was a 65-year-old man with a history of smoking. He was not on any daily medication. He was diagnosed with adenocarcinoma of the cardia. Extension workup showed locoregional adenopathy and liver metastases. The cancer was staged T3N3M1. The baseline C-reactive protein (CRP) level was 90 mg/L.

The patient was started on a combination therapy of nivolumab, 5-fluorouracil, and oxaliplatin. He went through the first 8 cycles of treatment with good tolerance. A few hours after the treatment cycle 9, the patient presented with fever and shivering. The next day, he was admitted in the Emergency Department with fever, shivering, tachycardia, with a heart rate of 113 beats per min, hypoxemia, with 92% SpO2, CRP level of 126 mg/dL, white blood cell count (WBC) of 4380/µL, platelet count of 117 000/µL, and creatinine level of 1.56 mg/dL. A chest radiograph showed diffuse nonspecific pulmonary infiltrates. He was hospitalized with a diagnosis of pulmonary sepsis and progressed well with antibiotic treatment by piperacillin-tazobactam. Three weeks later, in a follow-up visit, a computed tomography scan showed persistence of the pulmonary infiltrates. A diagnosis of possible diffuse interstitial lung disease was made.

During treatment cycle 10, he presented with fever, nausea, rash of the face and trunk, and hypotension. He was hospitalized in the Oncology Department and received 40 mg of methylprednisolone and 5 mg of polaramine. The next day, he was admitted to the Intensive Care Unit (ICU) for hypotension, with an arterial pressure of 59/28 mm Hg (mean of 36 mm Hg), not responding to 2 L of normal saline infusion, tachycardia with a heart rate of 133 beats per min, and hypoxemia requiring 2 L of nasal oxygen per min. He also had a fever of 39.8°C and diarrhea. Laboratory test results showed a CRP level of 233 mg/dL, white blood cell count of 32 000/µL, platelet count of 87 000/µL, and acute kidney injury KDIGO 3, with creatinine level of 2.79 mg/dL (Figure 1).

Initial ICU treatment consisted of hemodynamic stabilization with fluid therapy and norepinephrine up to 0.14 µg/kg/min. Septic shock was suspected, and the patient was treated with broad-spectrum antibiotics (ceftazidime (2 g/24 h adapted to renal function) and vancomycin (charge dose of 25 mg/kg, followed by a continuous infusion for a plasmatic dosage of 25 to 30 mg/L) after a complete bacteriological sampling, which came back negative. The patient had an implanted port, which was removed, and bacteriological analysis was negative. Chest radiograph showed an increase in the pulmonary infiltrate previously described, and abdominal imagery showed no abnormality. On day 4 after ICU admission, the patient was still on norepinephrine, fever was persistent, CRP level was 126 mg/dL, and platelet count continued decreasing, to 35 000/µL. Antibiotics were discontinued on day 5. On day 6, the patient received hydrocortisone of 100 mg per 24 h after a bolus dose of 100 mg. The fever ceased the same day. Norepinephrine was discontinued at day 7. On day 8, the patient was discharged from the ICU with 1 L of nasal oxygen, CRP level of 47 mg/dL, platelet count of 143 000/µL, and normalized creatinine level of 0.83 mg/dL. A chest radiograph showed a decrease of the pulmonary infiltrates. On day 15, the patient was discharged from the hospital. During a follow-up visit, the patient underwent a sensitivity test with oxaliplatin, which was negative.

**Discussion**

**Causes of CRS**

**First Classical Cause: Sepsis**

CRS can be triggered by various conditions and therapies, including sepsis.
This dysregulation of the immune system is widely described in sepsis. The Third International Consensus Definitions Task Force for Sepsis defined sepsis as a “life-threatening organ dysfunction caused by a dysregulated host response to infection” [6]. The treatment strategy for sepsis consists of organ support and pathogen elimination via administration of antibiotics.

Some studies focused on controlling the immune dysregulation in sepsis via extracorporeal hemoadsorbent devices.

A randomized controlled pilot study by Hawchar et al studied Cytosorb as a standalone treatment in septic shock. The primary endpoint was the clinical effect of the treatment. The
results showed reduction in norepinephrine requirements and procalcitonin and Big-endothelin-1 concentrations in the Cytosorb group. Also, there were no related adverse events [7]. However, a randomized controlled trial in 2017 by Schädler et al. studied Cytosorb in septic shock. The primary outcome was change in interleukin (IL)-6 concentration. Mortality was a secondary outcome. The results showed no reduction of serum IL-6 levels, despite up to 18% elimination by the adsorption filter [8]. This could mean that simply removing the cytokines from the serum does not treat the dysregulation, and the body reacts by making more cytokines. The results also showed no impact on mortality, organ dysfunction, and days on mechanical ventilation. The benefit of treatments targeting cytokines directly via extracorporeal hemoadsorbent devices is still unclear.

**Second Important Cause: COVID-19**

COVID-19 is caused by SARS-CoV-2 infection and can lead to sepsis and CRS. Nevertheless, treatment strategies are different from those in sepsis [9]. High levels of IL-6 in COVID-19 are correlated with disease severity and high mortality [10]. The RECOVERY study showed that dexamethasone reduces mortality in severe COVID-19 cases and is harmful in mild cases [11]. These results suggest that bad outcomes in severe cases of COVID-19 are due to a dysregulated immune response. This is not the case in mild cases, hence the gain from corticoids in severe cases.

**Less Frequent Causes: Immunotherapies, Including Chimeric Antigen Receptor T-cell Therapies**

There are 2 types of toxicities caused by immunotherapies: autoimmune toxicity and cytokine-associated toxicity [2]. Autoimmune toxicity relates to “on target off-tumor toxicity” and occurs when the immune system targets a specific antigen that is also expressed on healthy tissues [12]. These adverse effects are well described and there are specific management recommendations according to the organ or system affected [13]. Cytokin-associated toxicity relates to CRS and is an uncontrolled activation of the immune system unrelated to a specific antigen.

Immune effector cell-associated neurotoxicity, also known as chimeric antigen receptor (CAR)-T-cell-related encephalopathy syndrome, is a neurotoxicity associated with immunotherapy that can be associated with CRS [14]. CRS is mostly reported following CAR T-cell therapy. The incidence ranges from 57% to 93% [15]. CRS has also been reported following bispecific antibody therapy. CRS following ICI therapy has been rarely described, and factors leading to high-grade CRS are not well understood.

A 2020 report from the WHO global pharmacovigilance database Vigibase addressed 80700 ICI-related adverse events, among which were 58 cases of CRS. The report showed that 59% of the CRS cases happened following anti-PD-1 therapies and 36% followed treatment with nivolumab [16]. In this series, CRS developed in a median of 4 weeks after ICI initiation. Severity of the cases was not graded, but 17% of the CRS cases were considered life-threatening. Positive outcome after CRS was associated with younger age (<65 years), monotherapy, and prolonged treatments [14].

Tay et al. published a case series of 25 patients who developed CRS after ICI therapy. Among the 25 cases, 68% involved anti-PD-1 therapies. High-grade CRS (grade 3 and above) occurred in 32% of patients. In this series, CRS developed in a median of 11 days after ICI initiation [17]. No association was made between patient characteristics and outcome.

As mentioned above, indications for ICI are expanding. Moreover, new molecules are being studied [18]. These treatments are often used in combination with other cancer therapies to improve efficacy. However, the combination can increase the risk of immune-related adverse events [19]. As shown by Ceschi et al., monotherapy is a good prognostic factor in ICI-induced CRS [16]. Since more patients are being treated with immunotherapies and ICI, intensive care practitioners should be informed about their adverse effects, especially

---

**Table 1. Cytokine release syndrome grading according to the Common Terminology Criteria for Adverse Events.**

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>Fever with or without constitutional symptoms</td>
<td>Hypotension responding to fluids; hypoxia responding to &lt;40% O2</td>
<td>Hypotension managed with 1 vasopressor; hypoxia requiring ≥40% O2</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

orders and cancer. Therefore, the increase in cytokine levels can trigger a CRS reaction. Baseline cytokine values can be elevated in several diseases, including sepsis, acute respiratory distress syndrome, and anti-inflammatory effects and has a central role in CRS. IFN-γ testing is unavailable in most hospitals. However, serum reticulocytes and hypertriglyceridemia can be indicators of CRS. CRP is elevated in CRS cases, and high CRP levels, leukopenia, thrombocytopenia, liver and renal test results, and coagulopathy are other common findings. Chemotherapy can cause CRS, and in 2022, the American Society for Transplantation and Cellular Therapy (ASTCT) published guidelines on grading CRS caused by CAR T-cells therapy [35], including 4 grades. Fever is a mandatory parameter in all grades. Patients presenting with grade 3 CRS or above will generally be taken care of in an ICU because they will have hypotension requiring vasopressors or hypoxemia requiring high-flow oxygen or oxygen masks (Table 3).

**Grading CRS**

The American Society for Transplantation and Cellular Therapy (ASTCT) published guidelines on grading CRS caused by CAR T-cells therapy [35], including 4 grades. Fever is a mandatory parameter in all grades. Patients presenting with grade 3 CRS or above will generally be taken care of in an ICU because they will have hypotension requiring vasopressors or hypoxemia requiring high-flow oxygen or oxygen masks (Table 3).

**Treatment of CRS**

At this time, there are no treatment guidelines for ICI-induced CRS. In 2020, the Society for Immunotherapy of Cancer released guidelines on CAR T-cell-induced CRS [18]. Recommendations consist of tocilizumab (8 mg/kg) and methylprednisolone (2 mg/kg). Dexamethasone (0.5 mg/kg) is used in case of neurological symptoms because of its good blood-brain barrier penetration. If a patient presents with grade 2 CRS or above, the recommended treatment is 1 dose of tocilizumab. In the absence of improvement, it is recommended that the patient receive corticoid treatment and 1 supplementary dose of tocilizumab.

IL-6 is a central mediator in CRS. Therapy targeting IL-6 has proven to be effective in CAR T-cell-induced CRS [37]. Tocilizumab is a humanized monoclonal antibody that competitively inhibits binding of IL-6 to its receptor. Tocilizumab was approved by the FDA in 2017 for the treatment of CAR T-cell-induced CRS and in 2022 for the treatment of severe forms of COVID-19 [38]. Common adverse effects of tocilizumab include infections, neutropenia, hypercholesterolemia, and liver test disturbances [39].

Corticosteroids are not recommended as a first line therapy, because they have pleiotropic effects on the immune system. Corticoids have been shown to inhibit IL-1, IL-6, IL-8, tumor necrosis factor (TNF) alpha, TNF receptors 1 and 2, and nitric oxide formation [40]. There is concern that they would have negative effects on the CAR-infused T cells. Meanwhile, the evidence for these negative effects is poor, and some authors are in favor of initial bitherapy with tocilizumab and glucocorticoids in cases of life-threatening CRS induced by ICIs [2].

**Table 1**

| CRS, given that patients presenting with a CRS grade above 3 need to be treated in the ICU (Table 1). |

**Signs and Symptoms of CRS**

A wide range of signs and symptoms can be observed in CRS. Fever (core temperature above 38°C) is a key clinical sign and is present in the vast majority of CRS cases [1,2]. Fever is present in the beginning of CRS and can be high, up to 40.5°C. Mild forms of CRS can be accompanied by fatigue, headaches, rash, diarrhea, and arthralgia. Severe forms can be accompanied by any organ dysfunction: hypotension, acute renal failure, acute respiratory distress syndrome, cardiac dysfunction, and shock, requiring quick and appropriate ICU treatment.

As discussed above, severe CRS typically presents with fever and organ dysfunction. The first diagnosis to rule out is septic shock, since in this case, antibiotics should be started immediately [20]. CRS diagnosis is mainly based on signs and symptoms, so it should be evoked as soon as other obvious diagnostic hypothesis are ruled out according to the clinical context. In the context of cancer therapy, CRS diagnosis should be evoked in cases of fever occurring after treatment with CAR-T cells, but also with ICIs, particularly nivolumab. Time to onset is variable. In our case, fever occurred 140 days after nivolumab initiation and minutes after the last dose. In the series published by Tay et al, CRS developed in a median of 11 days after ICI initiation [17]. In the series published by Ceschi et al using the WHO global pharmacovigilance database, the authors found a median of 4 weeks [16]. We retrieved 12 cases of nivolumab-induced CRS and created our own case series, in which the median was 8 days (Table 2).

**Laboratory Findings**

Routine laboratory findings are unspecific, are the markers of a systemic inflammatory response syndrome [2], and include high CRP levels, leukopenia/leucocytosis, thrombopenia, altered liver and renal test results, and coagulopathy. Chemotherapy or the underlying cancer can induce leukopenia, neutropenia, and thrombopenia. CRS can also overlap with a tumor lysis syndrome (laboratory findings include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) and with macrophage activation syndrome (laboratory findings include hyperferritinemia and hypertriglyceridemia) [2,33].

Cytokines are helpful diagnostic and severity markers, but their testing is unavailable in most hospitals. However, serum reveals a high level of circulating cytokines, including IL-6, IL-10, IFNγ, and IL1β. IL-6 is a cytokine with pleiotropic inflammatory and anti-inflammatory effects and has a central role in CRS [2]. Baseline cytokine values can be elevated in several disorders and cancer. Therefore, the increase in cytokine levels...
### Table 2. Case reports on nivolumab-induced cytokine release syndrome.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Cancer type</th>
<th>Pre-existing disease</th>
<th>Number of Nivolumab cycles</th>
<th>Concomitant Treatment</th>
<th>Days Between the First Dose and Fever Onset</th>
<th>CRS Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>72</td>
<td>Male</td>
<td>Colon, liver metastasis</td>
<td>/</td>
<td>4</td>
<td>5-FU, oxaliplatin, CV301 vaccine</td>
<td>44</td>
<td>4</td>
<td>Hydrocortisone 300 mg/j</td>
</tr>
<tr>
<td>Case 2</td>
<td>70</td>
<td>Male</td>
<td>Renal carcinoma, T4N1M1</td>
<td>/</td>
<td>2</td>
<td>Ipilimumab</td>
<td>5</td>
<td>4</td>
<td>Methylprednisolone, MMF, plasmapheresis</td>
</tr>
<tr>
<td>Case 3</td>
<td>28</td>
<td>Female</td>
<td>Hodgkin lymphoma, stage 4</td>
<td>/</td>
<td>1</td>
<td>Stem cell transplantation</td>
<td>31</td>
<td>2</td>
<td>Methylprednisolone 1 mg/kg/12 h, ascorbic acid 20 mg/kg/6 h</td>
</tr>
<tr>
<td>Case 4</td>
<td>29</td>
<td>Female</td>
<td>Alveolar soft part sarcoma, multiple metastasis</td>
<td>/</td>
<td>2</td>
<td>/</td>
<td>4</td>
<td>2</td>
<td>Hydrocortisone (stress dose), tocilizumab</td>
</tr>
<tr>
<td>Case 5</td>
<td>70</td>
<td>Female</td>
<td>Lung adenocarcinoma, T3N0M0</td>
<td>COVID co-infection</td>
<td>2</td>
<td>Ipilimumab, pemetrexed, carboplatin</td>
<td>4</td>
<td>5</td>
<td>Corticosteroids high dose</td>
</tr>
<tr>
<td>Case 6</td>
<td>44</td>
<td>Female</td>
<td>Lung adenocarcinoma, T3N3M0</td>
<td>/</td>
<td>5</td>
<td>/</td>
<td>17</td>
<td>5</td>
<td>Dexamethasone, Tocilizumab</td>
</tr>
<tr>
<td>Case 7</td>
<td>52</td>
<td>Female</td>
<td>Pleomorphic carcinoma of the lung, T4N2M0</td>
<td>/</td>
<td>4</td>
<td>/</td>
<td>13</td>
<td>4</td>
<td>Methylprednisolone 1000 mg/j, prednisolone 50 mg/j, MMF</td>
</tr>
<tr>
<td>Case 8</td>
<td>64</td>
<td>Female</td>
<td>Pleomorphic carcinoma of the lung, T2N0M1</td>
<td>/</td>
<td>/</td>
<td>Ipilimumab</td>
<td>/</td>
<td>4</td>
<td>Methylprednisolone (pulse), tocilizumab, infliximab</td>
</tr>
<tr>
<td>Case 9</td>
<td>58</td>
<td>Female</td>
<td>Melanoma, stage 4</td>
<td>/</td>
<td>1</td>
<td>Ipilimumab</td>
<td>6</td>
<td>4</td>
<td>Methylprednisolone 1 mg/kg, tocilizumab, and Etanercept</td>
</tr>
<tr>
<td>Case 10</td>
<td>55</td>
<td>Male</td>
<td>Non-small cell lung cancer, stage 4</td>
<td>COVID vaccine the day before</td>
<td>/</td>
<td>Ipilimumab</td>
<td>10</td>
<td>1</td>
<td>Steroid pulse</td>
</tr>
<tr>
<td>Case 11</td>
<td>43</td>
<td>Male</td>
<td>Gastric adenocarcinoma liver metastasis</td>
<td>/</td>
<td>1</td>
<td>/</td>
<td>8</td>
<td>1</td>
<td>Prednisolone 1 mg/kg, methylprednisolone 1000 mg</td>
</tr>
<tr>
<td>Case 12</td>
<td>25</td>
<td>Male</td>
<td>Hodgkin lymphoma</td>
<td>/</td>
<td>1</td>
<td>/</td>
<td>6</td>
<td>2</td>
<td>/</td>
</tr>
</tbody>
</table>

Common adverse effects of methylprednisolone and dexamethasone include immune suppression, decreased resistance to infection, hyperglycemia, and secondary adrenal insufficiency [41]. Tocilizumab is an expensive drug, and its availability can be limited in some settings, while corticoids are widely available and can be used rapidly in case of emergency.

They are no treatment guidelines for ICI-induced CRS. In our case, CRS was successfully treated with hydrocortisone. We used 100 mg of hydrocortisone daily after a bolus of 100 mg, to accelerate the resolution of shock, as recommended by the Surviving Sepsis Campaign guidelines for the treatment of septic shock with ongoing requirement of vasopressors [20]. At this point, CRS was not evoked, and the patient was treated as a patient with septic shock. The Surviving Sepsis Campaign guidelines recommend the dose of 200 mg of hydrocortisone daily, but the patient improved so dramatically that we continued with the lower dosage. Given the patient’s clinical improvement, tocilizumab was not needed to treat the CRS. In the series published by Tay et al, 36% of patients received methylprednisolone, 4% received dexamethasone for neurologic toxicity, and 24% received tocilizumab. Among patients who were treated with tocilizumab, 83% had severe CRS (grade above 3) [17]. In our case series, all the patients were treated with corticoids in a variety of regimens, except for 1 case in which treatment was not specified. Four patients received tocilizumab, 75% of whom had severe CRS (Table 2).

More studies are needed to establish which patients can be treated with corticoids and which patients will require tocilizumab, especially since we cannot predict which patients will develop severe CRS. Also, on admission in the ICU, our patient was treated for suspected sepsis and not for CRS. Cytokine testing was not performed, as it is not done routinely. This testing would have been useful to help with diagnosis, treatment monitoring, and better understanding of this condition.

### Conclusions

The use of ICIs is expanding. Among ICIs, nivolumab has growing indications. ICI-induced CRS, particularly nivolumab-induced CRS, can be severe and lead to multiple organ dysfunction; therefore, intensive care practitioners should be informed about this adverse effect. More studies are needed to better understand this condition and to determine risk factors of severe CRS. The patient in our case was successfully treated with hydrocortisone; however, treatment guidelines are needed to improve clinical management.

### Institution and Department Where Work Was Performed

Intensive Care Unit, Centre Hospitalier Universitaire (CHU) UCL Namur, Yvoir, Belgium.

### Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

### References:


---

**Table 3. Cytokine release syndrome grading according to the American Society for Transplantation and Cellular Therapy.**

<table>
<thead>
<tr>
<th>CRS parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

ASTCT – American Society for Transplantation and Cellular Therapy; CRS – cytokine release syndrome; CPAP – continuous positive airway pressure; BiPAP – bilevel positive airway pressure.


12. Fishman JA, Hogan JI, Maus MV. Inflammatory and infectious syndromes as


36. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cy

37. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric


22. Ohiara J, Kawamoto M, Sugino Y, Kohara N. A case report of fulminant cy


14. Porter DL, Maloney DG. Cytokine release syndrome (CRS). In: UpToDate,


8. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 eli


5. A case of severe cytokine release syndrome accompanied with COVID-19 infec


This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)