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# Example of Clinical Staff Reference for Immune Effector Cell Toxicity Management – Cytokine Release Syndrome and Neurotoxicity

Disclaimer: This example is just one of many potential examples of clinical reference materials for immune effector cell (IEC) toxicity management that can be compiled for internal use. Many clinical sites will be administering IECs on protocols for which the investigator/sponsor has specified context, doses, and sequence for medications such as steroids and anti-cytokine therapies. However, a general approach to diagnosis, grading, treatment, and communication pathways must be available. This example is similar to information that may be referenced in the Standard Operating Procedure(s) (SOPs) that outline the general approach.

The general expectation is that the IEC program has clinical SOPs to manage expected toxicities of any IEC product (especially for CAR T cells). These documents would address, for example, identifying patients at risk, evaluating appropriate symptoms, initial management response, workflows for appropriate communication between teams and escalation of care, and accessing specialized medications for treatment of severe toxicities. If this example is used, the program is responsible for updating it as new information becomes available.

# EXAMPLE GUIDELINES OF CARE MANAGEMENT OF ADVERSE REACTION TO INFUSION OF IMMUNE EFFECTOR CELLS

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## **Purpose**

To describe the procedure for identification and reporting early ( $\leq 24$  hours after infusion) or late ( $> 24$  hours after infusion) adverse reactions to infusion of immune effector cell therapies. This applies to both autologous and allogeneic immune effector cell recipients. Management of these recipients on dedicated clinical teams and experienced nursing staff should be pursued as possible.

## **Early Reactions within 24 hours**

Early reactions are usually, but not always, related to the cryopreserved components. Common early reactions from infusion of lymphocyte products include mild increase in blood pressure not requiring intervention and mild headache. Side effects from cryopreserved components may include mild flushing, slight slowing of the heart rate, and a “bad taste” in the mouth.

Severe immediate reactions after lymphocyte infusions may include acute pulmonary edema and dyspnea, persistent nausea and vomiting, changes in blood pressure that do not respond to medication with standard doses, fever, anaphylactic shock, changes in heart rate and/or cardiac arrest.

## **Management of Early Reactions**

Most common early reactions do not require any intervention, but may require monitoring. In event of a severe reaction, the treating physician and study Principal Investigator (PI, or designee) must be immediately notified. Patient may need to be transferred to a telemetry bed or to the ICU/PICU for close monitoring. Treatment is usually supportive and symptomatic and includes BP support, oxygen supplementation, bronchodilators, diphenhydramine, and management of anaphylaxis (as indicated). Intravenous steroids may be administered (as well as other immunosuppressive medications) to reduce inflammation stemming from infused lymphocytes, but this should be discussed with treating clinicians prior to administration. Close communication with the treating physician or PI (or designee) is needed as reactions to lymphocyte infusions include tumor lysis which indicates that the patient’s tumor is responding to the administration of cellular therapy. Thus, a balance may need to be struck between immunosuppression to relieve adverse reactions and maintain beneficial anti-tumor effects.

## **Late Reactions after 24 hours**

Late reactions may be seen with cryopreserved or fresh immune effector cell products, and include:

- 1) Tumor lysis, as result of the graft versus tumor effect incited by the infused product
- 2) Cytokine release syndrome (CRS), or an uncontrolled inflammatory response in the host as result of the in vivo proliferation of infused cellular product. Cytokine profile mirrors macrophage activation

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syndrome/hematophagocytic lymphohistiocytosis. It is characterized by markedly elevated soluble IL2, IL6, IL10, IFNg; elevated CRP, ferritin; decreased fibrinogen

3) Neurologic dysfunction, inflammatory response in the host brain as result of the in vivo proliferation of infused cellular product, manifesting as confusion, aphasia, seizure, or coma

4) Sepsis, as a result of microbiological contamination of product

Frequency of monitoring will be determined by clinical scenario but consider vital signs q4 hours, neurologic checks q8 hours, and daily physical while in the hospital setting. If patients manifest changes, frequency and intensity of monitoring will be dictated by clinical status.

Table 1. Symptoms of CRS

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

Table 2. Grading of CRS

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	Symptoms require and respond to moderate intervention. Oxygen requirement <40%, or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity	Symptoms require and respond to aggressive intervention. Oxygen requirement ≥40%, 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)	Death

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The development of a severe late reaction necessitates immediate notification of the treating clinician, study PI or designee. The patient should be referred to the nearest emergency center for urgent medical evaluation and admission if he/she is an out-patient when the reaction occurs. When stable the patient should be transferred to an inpatient center at an experienced center for further management. It is extremely important to have the patient evaluated and therapy initiated as quickly as possible since rapid deterioration in medical condition can occur. Consider early transfer to ICU with early notification of ICU team. Given potential need for specialized medications, involvement of pharmacy staff is recommended at this point. Because serious late reactions can occur, patients should be advised to stay close to their treating institution for 4 weeks after immune effector infusions, as clinically applicable and feasible.

The immediate assessment may include (in addition to protocol-specified evaluation if part of a clinical trial):

- Intensive monitoring (Vitals including pulse, temperature, blood pressure and respirations, pulse oximetry +/- ABG)
- Lab studies: Complete blood counts, comprehensive metabolic panel, PT/PTT, fibrinogen, Lactic acid level, C-reactive protein, ESR, ferritin, urinalysis, cytokines as feasible (IFN- $\gamma$ , IL-6, TNF- $\alpha$ , IL-2, IL-2R)
- CXR
- Microbiological studies (especially blood cultures)
- Serial clinical history and physical examination, to include neurological checks in patients with neurologic symptoms.
- Serial ferritin, ESR, and C-reactive protein in patients with CRS and MAS until infusion reaction (e.g., cytokine storm) possibly, probably, or definitively attributed to the infused lymphocytes has resolved

## **Late Reactions – Management**

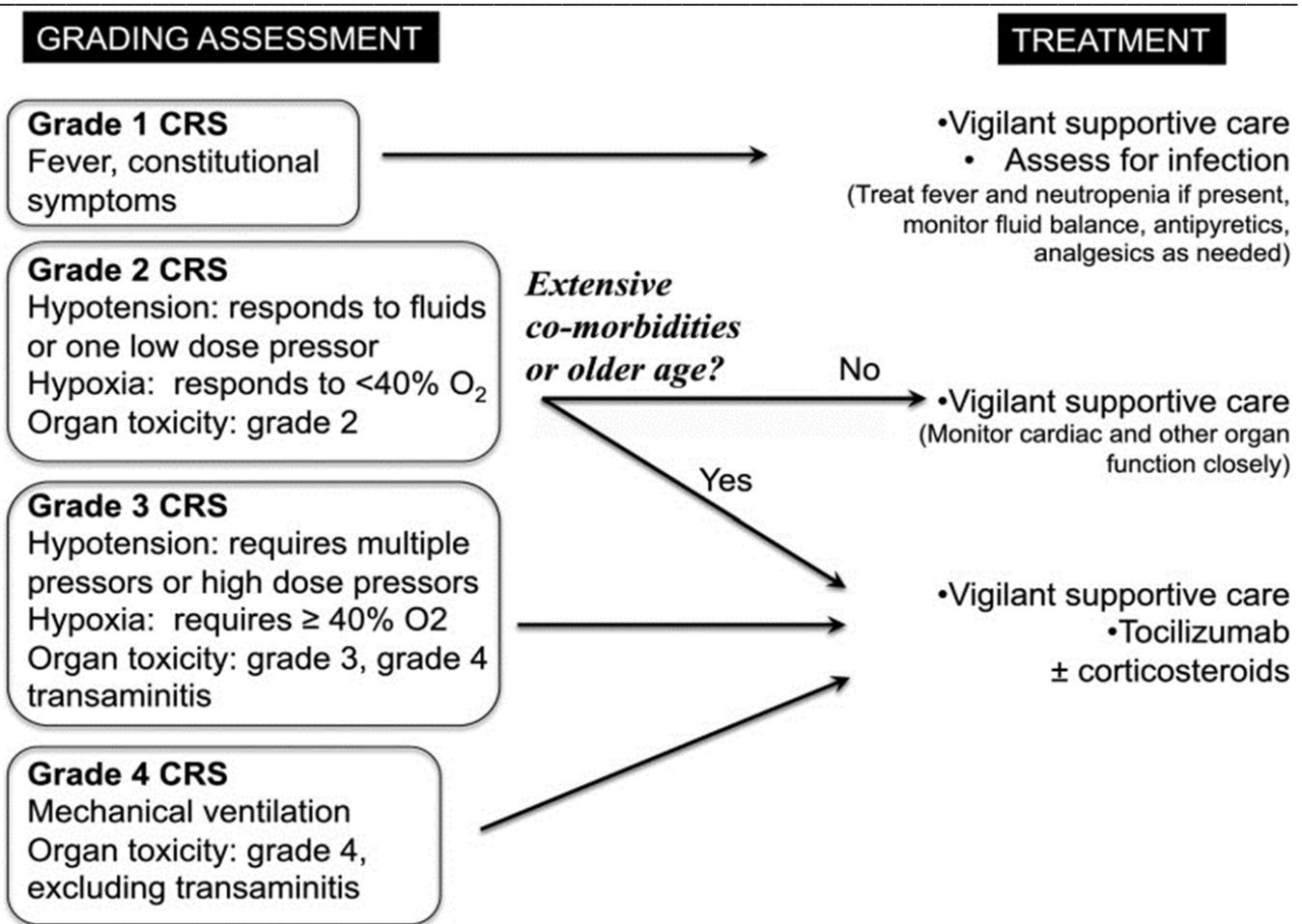
- Initiation of broad-spectrum antibiotics
- Blood pressure/Cardiovascular support- early institution of inotropic medications.
- Fluid management/Renal support- Institute early involvement of the renal service for fluid management especially if evidence of capillary leak syndrome, metabolic disturbances (like hyperuricemia, hyperkalemia), or tumor lysis syndrome.
- Respiratory support - O<sub>2</sub> therapy should be initiated for all hypoxemic patients. Patients also may require intubation and mechanical ventilation.

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- Management of tumor lysis syndrome if laboratory evidence.
- **Pharmacologic treatment may include:**
  - IL-6 receptor antibody Tocilizumab 4-8 mg/kg IV over 60 minutes for CRS, may repeat as clinically indicated
  - Methylprednisolone 2 mg/kg IV bolus followed by 0.5mg/kg IV every 6-12 hours for CRS grade  $\geq 2$ , or neurologic dysfunction. The first dose can be given without consultation with the PI or designee; however, the subsequent doses must be given after the consultation with the study PI or designee.
  - Consider 1 to 2 doses of anti TNF $\alpha$  agents (infliximab or etanercept). The benefits are not known, but since TNF $\alpha$  may rise acutely, it is worth considering early in the disease process.
  - Etanercept 25 mg SC twice a week for 2 doses, given 3 to 4 days apart (0.4 mg/kg twice a week, maximum of 25 mg per dose for patients <17 years of age)
  - Infliximab dose 10 mg/kg IV weekly x 2 doses (adults)  
Infliximab dose 5 mg/kg IV weekly x 2 doses (pediatric patients)

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Eventual reporting of the adverse event to any study-sponsor, FDA, IRB, institutional official will be the responsibility of the study PI or treating clinician and team. Cataloging of safety and efficacy outcomes will be performed by the Clinical Program data management specialists or designee to allow for subsequent review, quality audits and CIBMTR reporting.

### References:

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Latest revisions, review and approval(s) located on the Revision, Review and Approval page which must accompany this document.

<u>AUTHOR / SUBJECT EXPERT</u>	Date
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