Cytokine release syndrome (CRS)

What is CRS?

Overview

CRS is an **immune response** that involves the **overproduction of cytokines and other immune cells.**[1–3]

Symptoms

Symptoms can be **mild and flu-like** (e.g. fever, headache, nausea) **or more severe** (e.g. hypotension, hypoxia) and **may progress, leading to life-threatening multi-organ system failure.**[1–3]

What causes CRS?

CRS can be triggered by a number of factors, including **infection** or the **infusion of specific medications**, such as bispecific antibodies and chimeric antigen receptor T-cell immunotherapies.[2,3]

The mechanisms underlying CRS are not completely understood, but the **activation of large numbers of immune cells in response to infection or therapy** is known to lead to overproduction of cytokines.[2,3]

The risk of CRS is influenced by **patient characteristics, underlying disease** and the **type of therapy** being administered.[2]

How is CRS evaluated?

The evaluation of CRS follows a **grade- and intervention-based strategy**.[3]

A **range of scales** are used to classify the severity of CRS, including grading developed by the **American Society for Transplantation and Cellular Therapy**:[4]

	Grade 1	Grade 2	Grade 3	Grade 4
Fever	✓	✓	✓	✓
Low blood pressure	✗	Yes, but no treatment needed	Yes, treatment needed	Yes, aggressive treatment needed*
		And/or		
Low oxygen levels	✗	Yes, minimal intervention needed	Yes, moderate intervention needed	Yes, aggressive/ life-saving intervention needed†

*Multiple blood pressure raising therapies (vasopressors) required; †E.g. mechanical ventilation

Different scales means the **assessment and reporting of CRS is not yet standardised**, resulting in challenges in the ability to compare the rate and severity of CRS observed across clinical trials.

How is CRS managed?

The onset of CRS may occur from **days to weeks** following infusion of therapy.[1]

Patients who develop **early signs of CRS**, such as fever, should be **frequently assessed** for other signs of CRS.[2]

Strategies to prevent the occurrence and/or optimise the management of CRS include:[1–3]

- Pre-treatment and/or early recognition and treatment with **corticosteroids**
- **Reducing the dose** of immunotherapy administered
- **Slower infusion** of the therapy
- Provision of **therapy to reduce the number of circulating tumour cells** and/or **block specific cytokines**

As knowledge of CRS improves, reactions are becoming **easier for healthcare professionals to recognise early and manage effectively.**

"Recognition and management of CRS will **continue to be an important consideration for patients and physicians** as more immune therapies become available for the treatment of haematologic diseases."
- Dr Stephan Grupp, Children's Hospital of Philadelphia, US; CAR-T specialist

References

1. Riegler LL, et al. Ther Clin Risk Manag. 2019;15:323–35. **2.** Shimabukuro-Vornhagen A, et al. J Immunother Cancer. 2018;6:56. **3.** Lee DW, et al. Blood. 2014;124:188–95. **4.** Lee DW, et al. Biol Blood Marrow Transplant. 2019;25:625–38.