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

<table>
<thead>
<tr>
<th></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>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>✗</td>
<td>Yes, but no treatment needed</td>
<td>Yes, treatment needed</td>
<td>Yes, aggressive treatment needed</td>
</tr>
<tr>
<td>Low oxygen levels</td>
<td>✗</td>
<td>Yes, minimal intervention needed</td>
<td>Yes, moderate intervention needed</td>
<td>Yes, aggressive/life-saving intervention needed</td>
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*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