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UNDERSTANDING THE DISEASE

# Understanding cytokine release syndrome

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## Introduction

The cytokine release syndrome (CRS) is an uncontrolled systemic inflammatory reaction that can become life-threatening. It is most commonly observed following administration of immune-based biotherapeutics. As illustrated by the recent approval of several novel immunotherapeutics, e.g., pembrolizumab and tisagenlecleucel, immuno-oncology has emerged as a rapidly growing subspecialty. Many of these immunotherapeutic drugs are associated with a high risk of CRS. As a result of the growing use of these agents there will be an increase in patients presenting with severe CRS (sCRS). Intensive care specialists therefore should be familiar with the management of this condition.

## Epidemiology

CRS has been observed with varying frequency following immunotherapy. Immunotherapeutic agents that are associated with CRS include monoclonal antibodies such as rituximab or brentuximab [1, 2]. CRS can also occur after conventional chemotherapy or immunomodulatory therapy with lenalidomide. In particular T cell-engaging immunotherapeutic strategies, such as chimeric antigen receptor T cell therapy (CART), bispecific antibodies, or checkpoint blockade are associated with a high risk of CRS [3, 4]. A recent analysis of patients receiving CART for the treatment of acute lymphocytic leukemia revealed that 94% of patients experienced CRS and 27% developed sCRS [5].

Clinical manifestations of CRS can range from unspecific to severe life-threatening symptoms. Patients with CRS frequently present with fever, malaise, headache, nausea, vomiting, rash, myalgia, arthralgias, and rigor. sCRS can be accompanied by life-threatening respiratory, cardiac, or neurologic toxicities. Respiratory symptoms such as dyspnea, tachypnea, and hypoxia occur frequently. Cardiac complications include tachycardia, hypotension, and rapid onset cardiac dysfunction with elevated troponin levels. In addition, vascular leakage is common and manifests as peripheral and pulmonary edema. Neurologic toxicities might span from mild confusion, headaches, and hallucinations to aphasia, somnolence, hemiparesis, cranial nerve palsies, and seizures [6–9]. Of note, neurologic symptoms might also occur after the peak of CRS, indicating an independent yet unknown pathomechanism.

The onset of CRS symptoms seems to be dependent on the administered dose of the active agent or the proliferation kinetics of adoptively transferred cells and ranges from a few minutes up to 14 days but usually occurs within the first week after administration of therapy. The most important risk factors for sCRS are high disease burden, age, and the presence of comorbidities [6, 7, 10].

## Pathophysiology

The pathophysiology of CRS remains incompletely understood. CRS results from a massive release of cytokines due to the interaction between tumor and immune effector cells. The initial source of cytokines can be either target cells themselves or immune cells that have been recruited to the tumor site. This sets off a "chain reaction" leading to excessive activation of immune cells, e.g., macrophages, which in a positive feedback loop induces further release of cytokines like IL-1, IL-6, IL-8, IL-10, and MCP-1 culminating in a cytokine storm with an overshooting inflammatory response [4, 6, 11, 12]. IL-6 is a central mediator of the inflammatory response in CRS and is responsible for many of the clinical hallmarks of

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CRS such as vascular leakage as well as activation of the complement and coagulation cascades and subsequent disseminated intravascular coagulation [11] (Fig. 1).

## Diagnosis

Early recognition is critical for the effective management of CRS, and referral to ICU is justified when there is a suspicion of sCRS to ensure close monitoring and prompt aggressive treatment. Since the majority of symptoms are non-specific, it is often difficult to reliably make the diagnosis of CRS. Temporal association with one of the known triggers is a crucial diagnostic hint. Abnormal laboratory findings include increased creatinine, elevated liver enzymes, and derangements of coagulation. Markedly elevated markers of inflammation such as ferritin are typical of sCRS. Although implicated in CRS pathophysiology the levels of IL-6 do not necessary correlate with severity and treatment response [12].

Differentiation of CRS from conditions with similar clinical presentation is critical as therapy differs largely

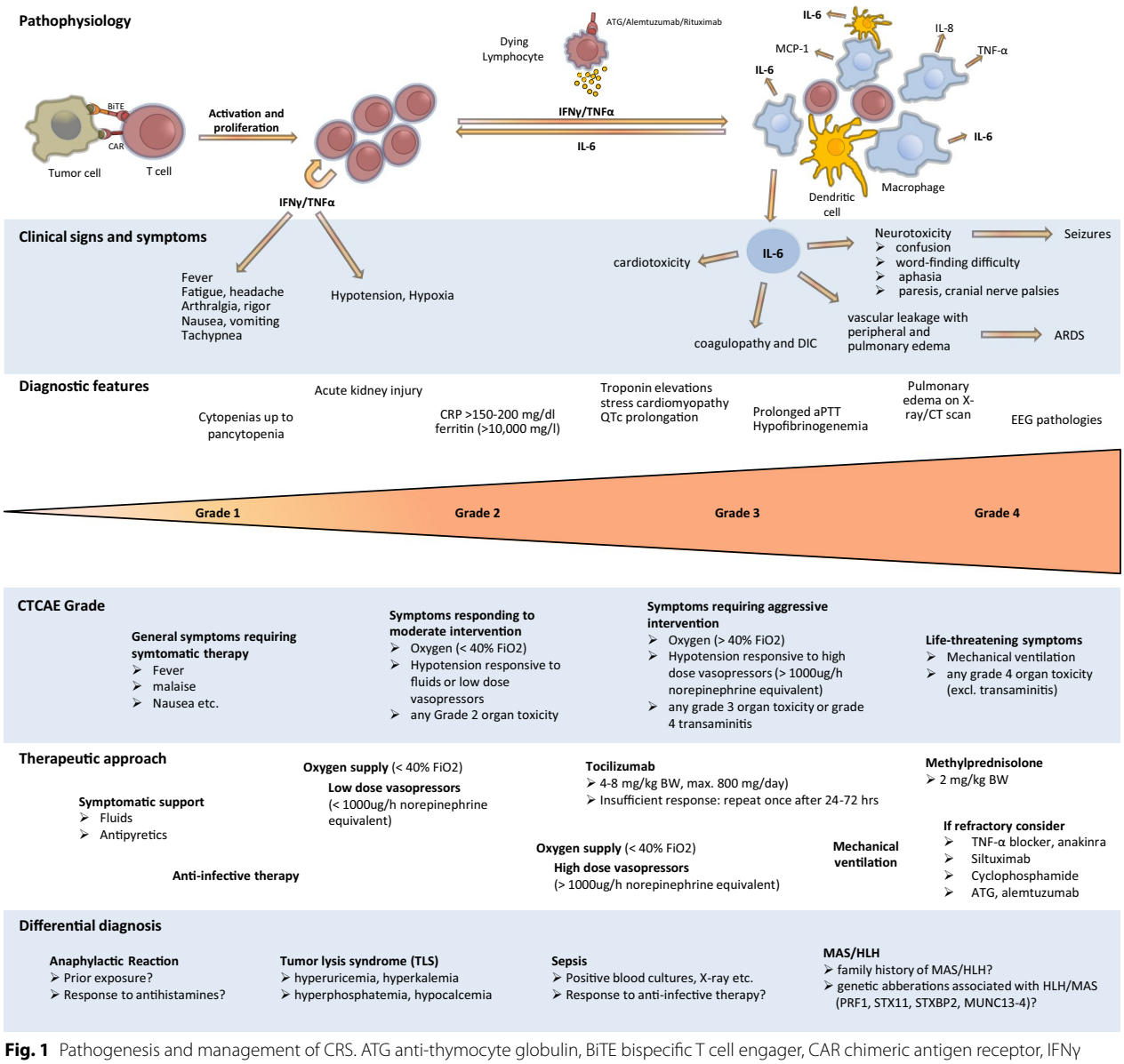


**Fig. 1** Pathogenesis and management of CRS. ATG anti-thymocyte globulin, BiTE bispecific T cell engager, CAR chimeric antigen receptor, IFNγ interferon gamma, TNFα tumor necrosis factor alpha, IL-6 interleukin 6, MCP-1 monocyte chemoattractant protein 1, DIC disseminated intravascular coagulation, ARDS acute respiratory distress syndrome, FiO2 fraction of inspired oxygen, BW body weight, MAS macrophage activation syndrome, HLH hemophagocytic lymphohistiocytosis

and might abrogate the desired immune effect of the applied immunotherapy. sCRS shares many features of macrophage activation syndrome and hemophagocytic lymphohistiocytosis [4]. Furthermore, tumor lysis syndrome might present similarly to CRS and can occur concurrently. Hypersensitivity reactions typically present with rash, fever, dyspnea, hypotension, and gastrointestinal symptoms. However, these symptoms generally develop after at least one uneventful exposition and usually respond well to treatment discontinuation, antihistamines, or corticosteroids. Importantly, most cancer patients are immunosuppressed and sepsis is clinically not distinguishable from CRS. Therefore prompt initiation of empiric antibiotic therapy is warranted if infection cannot be ruled out.

## Prevention

There are a number of strategies that have been successfully used to decrease the risk of sCRS. Dose adaption based on tumor burden has been shown to be effective in preventing sCRS [7, 10, 13]. Furthermore, predictors for sCRS may guide risk-adapted monitoring and therapy. Unfortunately, there is inconsistent data regarding clinical predictors for CRS such as prolonged and high fever, hypotension and hypoxia, neurologic symptoms, or high levels of CRP and ferritin (> 10,000 µg/l) [10, 13]. Cytokine assays to better predict CRS risk are under development. In addition, progress in the design of immunotherapeutic agents will likely result in a decreased incidence of sCRS.

## Treatment

The management of CRS is complex since one has to balance the need for immunosuppressive therapy to dampen the inflammatory reaction with the risk of compromising the therapeutic activity of immunotherapy, as some degree of cytokine release is thought to be a prerequisite for response to immunotherapy. Current recommendations propose a risk-adapted approach to monitoring and management of CRS. Low grade CRS should be treated symptomatically and patients should be monitored closely. sCRS, on the other hand, requires prompt treatment. Given appropriate management, sCRS has a favorable prognosis, even if organ failure is present [9]. Tocilizumab has shown clinical effectiveness in treatment of the inflammatory component of CRS, without blunting the antitumor response and clinical improvement usually occurs within hours. Therefore, it has recently been approved by the FDA and should currently be considered the mainstay of therapy for sCRS [6, 7, 9]. Owing to their broad immunosuppressive effects, corticosteroids should only be used for severe neurologic toxicities or in cases refractory to tocilizumab [6, 7].

## Conclusion

Immunotherapeutic drugs show impressive therapeutic success but are also accompanied by severe and life-threatening adverse effects. Thus, intensive care medicine will become a key component in the management of the complications of modern cancer therapies such as CRS.

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