REVIEW

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Intensive Care Management of Chimeric Antigen Receptor (CAR) T-Cell Therapy-Associated Toxicities

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Abstract

Aim: Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed or refractory hematologic malignancies, offering durable responses in selected patients while introducing unique immune-mediated toxicities that can rapidly become life-threatening and require intensive care management. This narrative review provides an evidence-based, practical overview of CAR T-cell therapy, focusing on the recognition and management of its major complications in clinical and critical care settings. Current evidence on CAR T-cell biology, clinical indications, toxicity grading, diagnostic evaluation, and intensive care management is synthesized, with particular emphasis on cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS). Effective management depends on early recognition, standardized grading, close multidisciplinary collaboration, prompt initiation of immunomodulatory therapy, and timely organ support when indicated. Although the use of CAR T-cell therapy is expanding globally, published clinical experience from Türkiye remains limited, highlighting the need for specialized treatment centers, standardized national protocols, multidisciplinary expertise, and prospective outcome registries. This review provides a practical framework for intensivists caring for patients receiving CAR T-cell therapy, particularly in newly established programs and resource-limited settings, and emphasizes strategies to optimize clinical outcomes through early diagnosis and timely intervention.

Keywords: Chimeric antigen receptor T-cell therapy; cytokine release syndrome; immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; immune effector cell-associated neurotoxicity syndrome; intensive care unit; management; toxicities.

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Introduction

Chimeric antigen receptor (CAR) T-cell therapy has emerged as one of the most significant advances in cancer immunotherapy, transforming the treatment landscape for hematologic malignancies. By genetically engineering a patient's T cells to recognize and eliminate malignant cells, CAR T-cell therapy provides targeted, immune-mediated cytotoxic activity that differs substantially from conventional chemotherapy and radiotherapy. Since the approval of cluster of differentiation 19 (CD19)-directed CAR T-cell products, this treatment modality has achieved remission rates of approximately 60%–90%, depending on the dis-

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ease type, CAR T-cell product, and patient population. Its use has rapidly expanded across various B-cell malignancies, including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma.[1,2] In addition, ongoing studies are evaluating its potential role in solid tumors, although important challenges related to the tumor microenvironment and antigenic heterogeneity remain.[3] Beyond hematologic and solid malignancies, CD19-directed CAR T-cell therapy has also shown promise in refractory autoimmune diseases through the depletion of autoreactive B cells and plasmablasts. Early evidence in systemic lupus erythematosus, idiopathic inflammatory myositis, and systemic sclerosis suggests the potential for sustained, drug-free remission with an acceptable safety profile.[4]

As indications broaden and access to treatment increases worldwide, the number of patients receiving CAR T-cell therapy continues to grow. This treatment has recently been introduced in Türkiye and is expected to become more widely available in the coming years.[5] Despite its clinical success, CAR T-cell therapy is associated with a distinct spectrum of toxicities that differs markedly from those observed with traditional chemotherapy or hematopoietic stem cell transplantation. These adverse effects are primarily driven by excessive immune activation and dysregulated cytokine release, which can lead to severe systemic inflammation and multiorgan dysfunction. Among these toxicities, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are the most common and potentially life-threatening complications.[6,7]

From an intensive care perspective, the management of CAR T-cell therapy–associated toxicities presents substantial clinical challenges. Patients may deteriorate rapidly and require advanced hemodynamic monitoring, vasopressor support, invasive or noninvasive mechanical ventilation, renal replacement therapy, and complex immunomodulatory interventions. Furthermore, the dynamic interplay among malignancy, immune dysregulation, infection risk, and critical illness necessitates close multidisciplinary collaboration among intensivists, hematologists, oncologists, neurologists, infectious disease specialists, and other healthcare professionals involved in patient care.[8,9]

As CAR T-cell therapy becomes increasingly integrated into routine clinical practice, intensivists are more frequently involved in the care of these patients. Nevertheless, clinical experience remains heterogeneous across institutions, particularly in countries and centers where CAR T-cell programs are newly established. This highlights the growing need for practical, intensive care unit (ICU)-oriented guidance that integrates current evidence with real-world clinical experience.

This review provides a clinically focused overview of CAR T-cell therapy and its associated toxicities, emphasizing their recognition and management in inpatient and intensive care settings. It examines the underlying mechanisms, clinical indications, major complications, diagnostic and grading approaches, and current treatment strategies, with particular attention to CRS, ICANS, and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS). The review aims to provide intensivists with a practical framework for managing critically ill patients receiving CAR T-cell therapy, with particular relevance to the Turkish context, where clinical experience is limited and institutional infrastructure is still developing. By synthesizing current evidence and real-world clinical experience, this review seeks to address important knowledge gaps in newly established CAR T-cell programs.

What Is Chimeric Antigen Receptor T-Cell Therapy?

CAR T-cell therapy is a form of adoptive cellular immunotherapy in which a patient's T lymphocytes are genetically modified to express synthetic receptors known as chimeric antigen receptors. These receptors are designed to recognize specific tumor-associated antigens. CARs typically consist of an extracellular antigen-recognition domain derived from the single-chain variable fragment (scFv) of a monoclonal antibody, a hinge region, a transmembrane domain, and intracellular signaling domains that mediate T-cell activation and costimulation. Unlike conventional T-cell receptors, CARs recognize surface antigens independently of the major histocompatibility complex (MHC), thereby circumventing an important mechanism of tumor immune evasion, such as MHC downregulation.[10,11]

The CAR T-cell manufacturing process generally involves leukapheresis for T-cell collection, ex vivo genetic modification, most commonly using lentiviral or retroviral vectors, followed by cellular expansion and reinfusion after lymphodepleting chemotherapy. The incorporation of costimulatory domains such as CD28 or

4-1BB represented a major advance in CAR design by improving in vivo persistence, proliferation, and antitumor efficacy. Subsequent generations of CAR constructs have incorporated additional modifications, including cytokine-producing transgenes and strategies designed to enhance tumor penetration and cell function within the immunosuppressive tumor microenvironment.[12,13]

CAR T-cell therapy has demonstrated remarkable efficacy in relapsed or refractory hematologic malignancies, particularly B-cell malignancies. Currently approved products for lymphoma and leukemia primarily target CD19, whereas therapies for multiple myeloma target B-cell maturation antigen (BCMA). U.S. Food and Drug Administration (FDA)-approved CD19-directed therapies include tisagenlecleucel (tisa-cel, Kymriah®), the first FDA-approved CAR T-cell therapy, initially approved for acute lymphoblastic leukemia (ALL) in 2017 and subsequently indicated for other B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL); axicabtagene ciloleucel (axicel, Yescarta®), the second FDA-approved CAR T-cell therapy, initially approved for DLBCL and subsequently indicated for other B-cell malignancies, including FL; lisocabtagene maraleucel (liso-cel, Breyanzi®), indicated for DLBCL; and brexucabtagene autoleucel (brexu-cel, Tecartus®), indicated for mantle cell lymphoma (MCL) and ALL. BCMA-targeted therapies approved for multiple myeloma include ciltacabtagene autoleucel (cilta-cel, Carvykti®) and idecabtagene vicleucel (ide-cel, Abecma®). Additional antigen targets under investigation include CD20, CD22, dual-target CAR T-cell strategies, and G protein-coupled receptor class C group 5 member D (GPRC5D) for multiple myeloma.[14,15]

Beyond hematologic malignancies, CAR T-cell therapy is being investigated for solid tumors, including melanoma and lung, colorectal, ovarian, hepatocellular, and bone cancers such as osteosarcoma. However, its efficacy in solid tumors remains limited by tumor heterogeneity, the scarcity of suitable tumor-specific antigens, T-cell exhaustion, and the immunosuppressive tumor microenvironment.[16,17]

Autoreactive B cells also play a central role in the pathogenesis of several autoimmune diseases, contributing to chronic inflammation, progressive organ damage, and increased mortality. Conventional B-cell–targeted therapies can deplete B cells or inhibit their activation; however, sustained drug-free remission remains difficult to achieve, and prolonged immunosuppression is often required. By targeting CD19, CAR T-cell therapy may induce more profound B-cell depletion and durable immune reprogramming. Emerging evidence from case reports and small clinical series supports the feasibility and early efficacy of this approach in severe autoimmune diseases, including lupus erythematosus and systemic sclerosis.[4]

As the applications of CAR T-cell therapy expand, novel approaches, including nanotechnology-based delivery systems, allogeneic "off-the-shelf" CAR T cells, natural killer (NK) cell-based therapies, and induced pluripotent stem cell-derived platforms, are being investigated to improve efficacy, accessibility, and safety.[18,19]

Despite its substantial clinical benefits, CAR T-cell therapy is associated with unique and potentially severe toxicities. The following sections address the major life-threatening complications of CAR T-cell therapy, particularly CRS, ICANS, and IEC-HS, which may necessitate intensive care management.

Cytokine Release Syndrome

Definition and Pathophysiology

Cytokine release syndrome is the most common acute toxicity associated with CAR T-cell therapy and results from a supraphysiologic systemic inflammatory response triggered by CAR T-cell activation and expansion. When CAR T cells engage target antigens on malignant cells, rapid proliferation and activation of immune effector cells occur, leading to the release of large amounts of proinflammatory cytokines and chemokines. Key mediators include interleukin-6 (IL-6), IL-1, IL-2, IL-8, IL-10, interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1beta (MIP-1β), and tumor necrosis factor-alpha (TNF-α), which collectively drive systemic inflammation. The inflammatory cascade also induces endothelial activation, reflected by increased circulating levels of biomarkers such as von Willebrand factor and angiopoietin-2.

In addition to CAR T-cells, monocytes and macrophages play a central role in amplifying the cytokine cascade, particularly through IL-6 production. Serum IL-6 levels correlate strongly with CRS severity. Endothelial activation further contributes to nitric oxide production, increased vascular permeability and capillary leak, coagulopathy, and hemodynamic instability with hypotension. The resulting clinical picture resembles sepsis and is

characterized by fever, vasodilatory shock, and varying degrees of organ dysfunction.[20,21]

Prevalence and Risk Factors

Cytokine release syndrome of any grade has been reported in approximately 40%–95% of patients receiving CAR T-cell therapy, whereas severe CRS (grade ≥3) develops in approximately 10%–25% of cases, depending on the specific product and patient population. Several factors influence the incidence and severity of CRS, including high tumor burden, higher CAR T-cell dose, baseline inflammatory status, specific CAR constructs and costimulatory domains, rapid in vivo CAR T-cell expansion, and, in some studies, older age. Thus, patients with a high disease burden and aggressive hematologic malignancies are at particularly high risk for severe CRS and ICU admission. CAR T-cell products containing CD28 domains generally induce earlier and, in some settings, more severe CRS than those containing 4-1BB domains.[22,23]

Clinical Presentation

Cytokine release syndrome typically occurs within the first several days after CAR T-cell infusion, with a median onset of approximately three days. However, onset may range from a few hours to 10–15 days after infusion, depending on the CAR construct, disease burden, and product characteristics. Peak severity generally occurs within the first 1–2 weeks after infusion.

The clinical spectrum ranges from mild, self-limited symptoms to life-threatening shock requiring vasopressor support and invasive mechanical ventilation (IMV). Fever (≥38°C) is the hallmark initial manifestation and may be accompanied by influenza-like symptoms, including chills, malaise, fatigue, myalgias, arthralgias, and rash. As CRS progresses, systemic inflammation and endothelial dysfunction may result in capillary leak syndrome, pulmonary edema, acute respiratory distress syndrome (ARDS), shock, disseminated intravascular coagulation (DIC), hepatic dysfunction, acute kidney injury, cardiac dysfunction, and multiorgan failure.

Cardiovascular complications include arrhythmias, left ventricular dysfunction, vasodilatory shock, and, rarely, cardiogenic shock. Respiratory failure may rapidly progress from a mild supplemental oxygen requirement to severe ARDS requiring IMV.

Common laboratory abnormalities include elevated C-reactive protein (CRP), hyperferritinemia, cytopenias, coagulopathy, elevated liver enzymes, hyperlactatemia, and other markers of organ dysfunction. Although IL-6 levels often correlate with CRS severity, IL-6 is not routinely measured in clinical practice.

Because CRS frequently mimics infection or septic shock, concurrent evaluation for infection and prompt initiation of empiric antimicrobial therapy are essential.[24,25]

Grading

The severity of CRS is commonly graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria, which are based primarily on three clinical parameters: fever, hypotension, and hypoxia. Severity ranges from mild (grade 1), characterized by fever alone, to severe (grade 3–4), characterized by significant hemodynamic compromise and/or respiratory failure requiring escalating levels of cardiovascular or respiratory support.

Accurate grading is essential because it directly guides therapeutic decision-making, escalation of care, and ICU referral (Table 1).[24-26]

Monitoring and Follow-up

Before CRS Development

Before CAR T-cell infusion, patients should undergo a comprehensive baseline evaluation, including cardiac and respiratory assessments, measurement of baseline inflammatory markers, complete blood count and coagulation profile, liver and renal function tests, infection screening, and neurologic assessment.

Patients with a high tumor burden or other established risk factors for CRS should undergo enhanced monitoring during the early post-infusion period.[27]

After CRS Development

Once CRS develops, monitoring should include continuous assessment of vital signs, serial neurologic examinations, close monitoring of fluid balance and urine output, and frequent laboratory evaluation, including complete blood count (CBC), CRP, ferritin, coagulation parameters, renal and liver function tests, lactate, other clinically indicated markers. Continuous cardiac telemetry should be considered in patients with grade ≥2 CRS.

Because CRS may progress rapidly within hours, frequent clinical reassessment and timely escalation of care are essential. Early involvement of the ICU team is recommended for patients with escalating oxygen or vasopressor requirements or rapidly progressive CRS.[27]

Table 1. Assessment and management of cytokine release syndrome (CRS)

Grade	Clinical definition	Recommended management
Grade 1	Fever ≥38°C without hypotension or hypoxia	• Supportive care, including antipyretics and intravenous fluid administration; initiate empiric antimicrobial therapy when infection is suspected • Granulocyte colony-stimulating factor (G-CSF) may be considered for prolonged neutropenia according to institutional practice • Close clinical monitoring • Consider tocilizumab 8 mg/kg IV (maximum 800 mg) for persistent fever (>48–72 hours), clinically significant symptoms, older adults (>65 years), or selected high-risk patients • In selected patients receiving B-cell maturation antigen (BCMA)-directed CAR T-cell therapy, particularly for multiple myeloma, some institutional protocols incorporate dexamethasone 10 mg IV every 24 hours
Grade 2	Fever ≥38°C with hypotension not requiring vasopressors and/or hypoxia requiring low-flow supplemental oxygen	• Tocilizumab 8 mg/kg IV; repeat every 8 hours as clinically indicated, for a maximum of four doses • Dexamethasone 10 mg IV every 12–24 hours if hypotension persists after tocilizumab or in selected recipients of BCMA-directed CAR T-cell therapy • Continue supportive care • Consider ICU consultation or early transfer if hemodynamic status worsens • If there is no clinical improvement within 24 hours, escalate therapy as clinically indicated and reassess for progression to grade 3 CRS
Grade 3	Fever ≥38°C with hypotension requiring one vasopressor, with or without vasopressin, and/or hypoxia requiring high-flow nasal cannula or facemask oxygen	• ICU admission or management in an ICU setting • Tocilizumab 8 mg/kg IV (maximum four doses) • Dexamethasone 10–20 mg IV every 6–12 hours • Intensive supportive care, including fluid administration, vasopressor support, supplemental oxygen, and empiric antimicrobial therapy • If there is no clinical response or further deterioration occurs, escalate therapy and reassess for progression to grade 4 CRS
Grade 4*	Life-threatening CRS characterized by hypotension requiring multiple vasopressors and/or hypoxia requiring positive-pressure ventilation, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or invasive mechanical ventilation, or severe organ dysfunction	• Immediate ICU management • Tocilizumab 8 mg/kg IV (maximum four doses) • Dexamethasone 10–20 mg IV every 6–12 hours • In refractory cases, consider methylprednisolone 0.5–1 g/day IV for three days, with further escalation individualized according to clinical response • Provide comprehensive organ support, including vasopressor therapy, mechanical ventilation, and renal replacement therapy when indicated • Administer broad-spectrum antimicrobial therapy and provide transfusion support as clinically indicated

*In refractory CRS, additional therapies may be considered, including anakinra (interleukin-1 [IL-1] receptor blockade; 100–200 mg IV or SC every 6–12 hours), siltuximab (an anti-IL-6 monoclonal antibody; 11 mg/kg IV administered over 1 hour as a single dose), and ruxolitinib (Janus kinase 1/2 inhibition; 5–10 mg orally twice daily).

ICU Admission Criteria

Intensive care unit admission should be strongly considered in patients with persistent hypotension, vasopressor requirement, escalating oxygen needs (particularly those requiring high-flow nasal oxygen or noninvasive mechanical ventilation), altered mental status, rapidly progressive organ dysfunction, severe metabolic abnormalities such as metabolic acidosis, hyperlactatemia, or clinically significant electrolyte disturbances, or cardiac complications such as arrhythmias or ventricular dysfunction. Most patients with severe CRS (grade ≥3) require ICU-level care. Early ICU admission may also be appropriate for older patients or those with limited physiologic reserve, high tumor burden, substantial comorbidity, rapidly progressive symptoms, concomitant neurologic manifestations, or an inadequate response to initial treatment. Early ICU transfer is preferable to delayed transfer after advanced organ failure has developed.[28]

ICU Management

In addition to supportive critical care, immunomodulatory therapies, particularly tocilizumab and corticosteroids, are central to the management of moderate-to-severe CRS and are discussed below. Early recognition and timely intervention are critical to preventing progression to irreversible organ dysfunction.

Hemodynamic instability should be managed according to standard critical care principles, including judi-

cious fluid resuscitation, avoidance of fluid overload given the risk of capillary leak, dynamic assessment of fluid responsiveness, and early initiation of vasopressor therapy, most commonly with norepinephrine. Bedside echocardiography and, when clinically indicated, invasive hemodynamic monitoring may assist in evaluating refractory shock or complex hemodynamic profiles.

Respiratory support may range from supplemental oxygen to noninvasive ventilation and, in severe cases, IMV. Supportive respiratory strategies include high-flow nasal oxygen, noninvasive ventilation, and lung-protective IMV in patients with ARDS, together with a conservative fluid management strategy in patients with pulmonary edema.[24-26]

Close monitoring for organ dysfunction, including renal and hepatic impairment and coagulation abnormalities, is also essential. Additional ICU management may include renal replacement therapy, management of coagulopathy, cardiac monitoring and support, nutritional support, and administration of broad-spectrum antimicrobials while infection is being evaluated. Because CRS and sepsis may coexist, initiation of empiric antimicrobial therapy is strongly recommended.[24-26]

Targeted and Immunomodulatory Therapies

Targeted immunomodulatory therapy is a cornerstone of the management of moderate-to-severe CRS (Table 1). Tocilizumab, an IL-6 receptor antagonist, is the principal targeted therapy for CRS and can rapidly reverse CRS-related manifestations, particularly fever, hypotension, capillary leak, and oxygen requirements. The standard adult dose is 8 mg/kg intravenously and may be repeated at intervals of at least 8 hours as clinically indicated, for a maximum of four doses. Importantly, tocilizumab does not appear to significantly compromise CAR T-cell antitumor efficacy. Early administration in patients with progressive CRS has been associated with improved symptom control without adversely affecting treatment outcomes.

Corticosteroids, most commonly dexamethasone, are recommended for severe CRS, CRS refractory to tocilizumab, concomitant ICANS, or rapidly progressive clinical deterioration. A commonly used regimen is dexamethasone 10 mg intravenously every 6–12 hours. Although corticosteroids are effective in controlling inflammation, their use should be balanced against their potential effects on CAR T-cell persistence.

Failure to improve after one or two doses of tocilizumab should prompt reassessment for alternative diagnoses, including infection, macrophage activation syndromes such as IEC-HS, and progressive CRS requiring escalation of immunomodulatory therapy. In refractory CRS, additional therapies may be considered, including anakinra (IL-1 receptor blockade), siltuximab (an anti-IL-6 monoclonal antibody), ruxolitinib (Janus kinase 1/2 inhibition), and therapies targeting granulocyte-macrophage colony-stimulating factor (GM-CSF). However, evidence supporting these approaches remains limited.[24-26]

Immune Effector Cell-Associated Neurotoxicity Syndrome

Definition and Pathophysiology

Immune effector cell-associated neurotoxicity syndrome is among the most frequent and potentially severe toxicities associated with CAR T-cell therapy. It encompasses a broad spectrum of neurologic manifestations resulting from immune-mediated dysfunction of the central nervous system (CNS). Neurotoxicity may occur concurrently with CRS, after CRS has resolved, or, less commonly, as an isolated complication.

The pathophysiology of ICANS remains incompletely understood and is considered multifactorial. Current evidence suggests that systemic inflammation, endothelial activation, and blood–brain barrier (BBB) disruption are central mechanisms. Elevated circulating cytokines, particularly IL-1, IL-6, IFN-γ, GM-CSF, and other inflammatory mediators, increase BBB permeability and promote cytokine trafficking into the CNS. Endothelial dysfunction and microvascular injury further contribute to cerebral edema and neuroinflammation. In addition, activation of resident CNS immune cells, including microglia, may amplify local inflammatory responses, ultimately leading to neuronal dysfunction and diffuse encephalopathy. CAR T cells and other immune cells have been detected within the CNS; however, their direct contribution to the pathogenesis of ICANS remains incompletely defined. As with CRS, the degree of endothelial activation appears to correlate with the severity of neurotoxicity.[29]

Prevalence and Risk Factors

ICANS develops in approximately 15%–65% of patients receiving CAR T-cell therapy, whereas grade ≥3 neurotoxicity occurs in approximately 10%–31% of cases, depending on the CAR T-cell product, disease indication, and grading criteria. Higher incidences have been reported in pediatric ALL cohorts and with certain CAR T-cell con-

structs, with neurologic complications occurring in up to 70%–80% of patients and severe neurotoxicity in 30%–40%. These variations likely reflect differences in patient populations, CAR products, and diagnostic criteria.

The timing of ICANS is also variable. Neurotoxicity typically develops 5–7 days after CAR T-cell infusion but may occur within hours of infusion or be delayed for up to 2–3 weeks, depending on the CAR T-cell product and clinical course.

Several factors have been associated with an increased risk of ICANS, including high tumor burden, severe or concurrent CRS, acute lymphoblastic leukemia, pediatric age, older age in some adult cohorts, substantial comorbidity, preexisting neurologic disease or CNS injury, elevated baseline inflammatory markers such as CRP, early post-infusion hyperferritinemia, thrombocytopenia, intensive lymphodepleting chemotherapy with fludarabine and cyclophosphamide in some studies, and rapid CAR T-cell expansion.

BCMA-directed CAR T-cell therapies have additionally been associated with delayed or persistent neurologic toxicities, including movement disorders and cranial or peripheral neuropathies.[30,31]

Clinical Presentation

ICANS typically begins with subtle neurocognitive abnormalities and may progress rapidly over hours to days. Early manifestations commonly include headache, impaired attention, mild confusion, word-finding difficulties, dysgraphia, tremor, and behavioral changes. Expressive aphasia is a particularly characteristic and sensitive early manifestation and may precede more severe neurologic deterioration. As neurotoxicity progresses, patients may develop delirium, global aphasia, agitation, psychosis, altered level of consciousness, focal neurologic deficits, motor weakness, ataxia, seizures, status epilepticus, and coma. Diffuse cerebral edema is a rare but devastating complication of severe ICANS and is associated with high mortality.[32,33]

Unlike CRS, fever is not required for the diagnosis of ICANS. Neuroimaging findings may remain normal despite severe clinical manifestations. Electroencephalography (EEG) frequently demonstrates diffuse slowing and may identify otherwise unrecognized nonconvulsive seizures or nonconvulsive status epilepticus. Cerebrospinal fluid (CSF) analysis may reveal elevated protein concentrations and lymphocytic pleocytosis.

Monitoring and Grading

Early detection of ICANS relies on systematic neurologic assessment. All patients receiving CAR T-cell therapy should undergo baseline neurologic evaluation before infusion and regular reassessment thereafter. The Immune Effector Cell-Associated Encephalopathy (ICE) score is widely used for bedside assessment and evaluates orientation, naming, ability to follow commands, writing, and attention. The ICE score comprises the following components: orientation (correctly identifying the year, month, city, and hospital; 1 point each, maximum 4 points), naming (correctly naming three objects, such as a clock, sink, and computer; 1 point each, maximum 3 points), following commands (correctly following a simple command; 1 point), writing (writing a complete sentence; 1 point), and attention (counting backward from 100 by 10; 1 point). The maximum score is 10, with lower scores indicating greater neurologic impairment. Serial assessment is essential for detecting subtle changes and facilitating timely intervention.

The ASTCT has developed a standardized grading system for ICANS incorporating the ICE score, level of consciousness, seizure activity, motor findings, and evidence of increased intracranial pressure or cerebral edema. Severity ranges from grade 1, representing mild neurologic impairment, to grade 4, representing life-threatening neurologic dysfunction (Table 2).

Serial neurologic assessments should be performed in hospitalized patients and daily in outpatient settings during the period of highest risk. The frequency of assessment should be individualized according to the patient's clinical status, severity of ICANS, and level of care, including outpatient, inpatient ward, intermediate care, or ICU settings. Accurate grading is critical because it guides both the need for ICU admission and the intensity of therapeutic interventions. Patients with high-grade ICANS frequently require ICU care because of the risks of seizures, impaired airway protection, and, rarely, malignant cerebral edema, which is associated with substantial mortality.[31-33]

ICU Management

Patients with high-grade ICANS (grades 3–4), rapidly progressive neurologic symptoms, seizures, depressed consciousness, suspected cerebral edema, or impending airway compromise should be transferred promptly to the ICU. ICU management requires a structured, multidisciplinary approach with close neurologic monitoring and rapid escalation of care when deterioration occurs. Serial

Table 2. Classification and management of immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade	ICE score	Clinical definition	Recommended management*
Grade 1	7–9	Mild cognitive impairment without depressed level of consciousness, seizures, motor deficits, or evidence of cerebral edema	• Close neurologic monitoring with serial immune effector cell-associated encephalopathy (ICE) assessments • Brain computed tomography (CT) or magnetic resonance imaging (MRI) and electroencephalography (EEG) as clinically indicated • Supportive care • Consider dexamethasone 10 mg IV for persistent or progressive symptoms
Grade 2	3–6	Moderate cognitive impairment; patient awakens to voice, without seizures, motor deficits, or evidence of cerebral edema	• Frequent neurologic assessments • Brain CT or MRI and EEG as clinically indicated • Dexamethasone 10 mg IV; reassess after 6–12 hours and continue every 6–12 hours if symptoms persist • Consider ICU admission because of the risk of rapid neurologic deterioration
Grade 3	1–2	Severe encephalopathy; patient awakens only to tactile stimulation and/or has brief seizures responsive to treatment, nonconvulsive seizures detected on EEG, or focal cerebral edema	• ICU management • Continuous neurologic monitoring • Brain imaging and EEG monitoring • Prompt initiation of appropriate antiseizure therapy when indicated • Dexamethasone 10–20 mg IV every 6 hours or methylprednisolone 1-2 mg/kg IV daily
Grade 4	0	Life-threatening condition characterized by unresponsiveness or coma, prolonged or recurrent seizures, severe motor deficits, diffuse cerebral edema, or increased intracranial pressure	• Immediate ICU management, with airway protection and mechanical ventilation when indicated • Continuous EEG monitoring and neuroimaging • Aggressive management of seizures and cerebral edema • Pulse-dose corticosteroid therapy (methylprednisolone 500–1,000 mg IV daily for 3 days, followed by tapering according to clinical response) • In steroid-refractory cases, consider anakinra 100–200 mg IV or SC every 6–12 hours

*When ICANS occurs concurrently with CRS of any grade, consider adding tocilizumab (8 mg/kg IV, up to a maximum of four doses)

neurologic assessment should be performed at a frequency appropriate to the patient's clinical condition and level of care, preferably using standardized tools such as the ICE score. Continuous EEG monitoring should be considered in patients with persistent altered mental status or suspected seizures because nonconvulsive seizure activity may occur. Brain computed tomography (CT) or magnetic resonance imaging (MRI) should be performed when clinically indicated to evaluate for cerebral edema, structural abnormalities, and alternative causes of neurologic deterioration. If imaging demonstrates substantial cerebral edema or findings suggestive of increased intracranial pressure, early neurosurgical consultation should be considered.

Some centers use antiseizure prophylaxis with antiepileptic agents such as levetiracetam, particularly in patients with moderate-to-severe ICANS; however, practices vary across institutions. Clinical seizures should be treated promptly according to established critical care protocols. High-dose corticosteroids should be initiated promptly in patients with moderate-to-severe ICANS.

In cases of suspected or confirmed cerebral edema, neurocritical care principles should be applied, including head-of-bed elevation, osmotherapy (e.g., hypertonic saline or mannitol), and careful optimization of oxygenation and ventilation. Airway protection and mechanical ventilation may be required in patients with a decreased level of consciousness or refractory seizures.

Close attention should also be paid to concurrent systemic toxicities, particularly CRS, because these conditions frequently overlap and may contribute to clinical deterioration.[31-33]

Targeted and Immunomodulatory Therapies

Unlike CRS, the management of ICANS primarily relies on corticosteroids as first-line therapy. Dexamethasone is commonly used for moderate ICANS, whereas high-dose methylprednisolone may be required for severe or rapidly progressive neurotoxicity. Tocilizumab, an IL-6 receptor antagonist, is generally ineffective for isolated ICANS because of its limited penetration across the BBB, and is therefore not recommended as monotherapy in this setting. When ICANS occurs concurrently with CRS,

tocilizumab should be administered to treat the CRS component, while corticosteroids remain the primary therapy for the neurologic manifestations.

Emerging evidence suggests a potential role for IL-1 blockade with anakinra and other immunomodulatory therapies in refractory ICANS. Among available adjunctive agents, anakinra, an IL-1 receptor antagonist, has accumulated the greatest clinical experience in refractory cases. Other agents, including siltuximab, an anti-IL-6 monoclonal antibody, have also been used in selected refractory cases. However, the available evidence remains limited, and these therapies are generally reserved for selected patients managed in specialized centers (Table 2).

The decision to initiate immunosuppressive therapy should balance the need for rapid control of neurotoxicity against the potential impact on CAR T-cell treatment efficacy. Nevertheless, available clinical data suggest that the appropriate use of corticosteroids for toxicity management does not substantially compromise treatment efficacy.[31-33]

Chronic and Delayed Neurotoxicity

Although ICANS is usually reversible, delayed neurologic complications have increasingly been recognized, particularly following BCMA-directed CAR T-cell therapy. Reported manifestations include parkinsonism, cognitive impairment, personality changes, cranial and peripheral neuropathies, persistent tremor, and gait abnormalities.

These syndromes may develop weeks to months after CAR T-cell infusion and are often poorly responsive to dopaminergic therapies, including levodopa. Management remains largely supportive and is not well established; however, corticosteroids and strategies aimed at eliminating persistent CAR T cells have been explored in severe or refractory cases.[30,31]

Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome

Definition and Pathophysiology

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome is a rare but potentially life-threatening hyperinflammatory complication that may develop after immune effector cell therapies, particularly CD19- and BCMA-directed CAR T-cell therapy. Although IEC-HS resembles secondary hemophagocytic lymphohistiocytosis (HLH), growing evidence suggests that it represents a distinct clinicopathologic entity with unique biological mechanisms and temporal characteristics. It is characterized by uncontrolled immune activation, cytokine excess, macrophage and histiocyte proliferation, cytopenias, coagulopathy, hepatic dysfunction, and multiorgan failure.[34,35]

IEC-HS frequently overlaps with CRS and may also occur in patients with ICANS, making diagnosis particularly challenging in critically ill patients.

The pathophysiology of IEC-HS is incompletely understood but appears to involve profound dysregulation of both innate and adaptive immune responses following immune effector cell activation. After CAR T-cell infusion, rapid activation and expansion of CAR T cells results in the release of inflammatory cytokines, including IL-6, IL-1, IFN-γ, TNF-α, IL-18, and GM-CSF. Persistent immune activation may subsequently trigger excessive macrophage and histiocyte activation, resulting in a hyperinflammatory cascade resembling that observed in macrophage activation syndrome (MAS) and HLH.[34,35]

Key pathophysiologic features include excessive cytokine production (cytokine storm), hyperactivation of macrophages and monocytes, endothelial dysfunction with increased capillary leak, dysregulation of cytotoxic T-cell and natural killer (NK)-cell function, hemophagocytosis in the bone marrow, liver, spleen, and lymphoid tissues, and abnormalities of coagulation and fibrinolysis.

Although CRS and IEC-HS share several inflammatory pathways, IEC-HS generally develops later, may persist despite CRS-directed therapy, and is characterized by more pronounced hyperferritinemia, hypofibrinogenemia, cytopenias, and progressive organ dysfunction.

Epidemiology and Prevalence

IEC-HS is an uncommon but increasingly recognized complication of CAR T-cell therapy. Its reported incidence varies substantially because of differences in diagnostic criteria and grading systems. Published studies have reported an incidence of approximately 1%–6% among adult CAR T-cell recipients, although higher rates have been reported in pediatric patients with acute lymphoblastic leukemia.[34,35]

Mortality may be substantial in severe cases, particularly when recognition and initiation of immunomodulatory therapy are delayed. Earlier studies may have underesti-

mated the incidence of IEC-HS because some cases were classified as severe CRS before standardized diagnostic criteria for IEC-HS became available.

Risk Factors

Several factors have been associated with an increased risk of IEC-HS, including severe or prolonged CRS, high tumor burden, aggressive hematologic malignancy, baseline systemic inflammation, preexisting hepatic dysfunction, rapid CAR T-cell expansion, early elevations in cytokines, and prior allogeneic hematopoietic stem cell transplantation. Among these factors, severe CRS appears to be one of the strongest predictors of subsequent IEC-HS.

Several laboratory abnormalities may serve as early indicators of evolving IEC-HS or support its diagnosis, including rapidly rising ferritin levels, elevated CRP, cytopenias, hypertriglyceridemia (fasting triglycerides >265 mg/dL), elevated lactate dehydrogenase, transaminitis (>5 times the upper limit of normal), direct hyperbilirubinemia, and hypofibrinogenemia (<150 mg/dL or below the lower limit of normal).[34,35] These abnormalities should be interpreted in the context of the overall clinical presentation rather than in isolation.

Clinical Manifestations

IEC-HS typically develops several days to weeks after CAR T-cell infusion, most commonly as CRS is resolving or after its resolution.

Common manifestations include persistent or recurrent fever, cytopenias, new-onset hepatosplenomegaly, hypotension, capillary leak, respiratory failure, acute kidney injury, neurologic abnormalities, coagulopathy, and multiorgan failure.[34,35]

Bone marrow examination may demonstrate hemophagocytosis; however, this finding is neither sufficiently sensitive nor specific and is not required for the diagnosis of IEC-HS.

Diagnosis

The diagnosis of IEC-HS remains challenging because its clinical and laboratory features overlap with those of CRS, sepsis, DIC, disease progression, classical HLH, drug-induced liver injury, and thrombotic microangiopathy. In critically ill patients, a comprehensive evaluation for infection is essential, particularly before escalation of immunosuppressive therapy, because occult infection may coexist with IEC-HS and may worsen with further immunosuppression.

Diagnostic approaches to IEC-H vary across guidelines. The American Society of Clinical Oncology (ASCO) guidelines have described criteria that include marked hyperferritinemia (ferritin >10,000 ng/mL) together with evidence of organ toxicity, such as bone marrow or organ hemophagocytosis, significant hepatic or renal dysfunction, or pulmonary edema. An ASTCT expert panel has proposed defining IEC-HS as a pathologic and biochemical hyperinflammatory syndrome that is attributable to immune effector cell (IEC) therapy that is clinically distinct from CRS and ICANS. Characteristic features include new or progressive cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, transaminitis, and other manifestations consistent with MAS/HLH.[36,37]

Grading

The ASTCT has proposed a grading system that categorizes IEC-HS severity according to the degree of organ dysfunction and the intensity of interventions required (Table 3).

This framework helps guide clinical monitoring, escalation of immunomodulatory therapy, and decisions regarding ICU management. Early recognition of progression from mild disease to fulminant hyperinflammation is essential to facilitate timely escalation of immunosuppressive therapy and supportive care.

ICU Management

Management of IEC-HS requires rapid control of the hyperinflammatory response while preserving antitumor immune activity whenever possible.

ICU management includes hemodynamic support, supplemental oxygen or mechanical ventilation as needed, renal replacement therapy when indicated, blood product support, correction of coagulopathy, and empiric broad-spectrum antimicrobial therapy when infection is suspected or cannot be reliably excluded.

Outcomes in IEC-HS depend on early recognition, the severity of organ dysfunction, response to immunomodulatory therapy, the presence of concurrent infection, and the status of the underlying malignancy. Delayed diagnosis, severe coagulopathy, refractory shock, and multiorgan failure are associated with increased mortality.[34-36] Serial monitoring of ferritin, fibrinogen, complete blood counts, liver function tests, coagulation parameters, and markers of organ dysfunction is essential for assessing disease progression and response to therapy.

Table 3. Suggested grading and management of immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)

Grade	Clinical definition	Recommended management
Grade 1	Mild or asymptomatic laboratory abnormalities with minimal or no organ dysfunction	• Close clinical and laboratory monitoring • Supportive care • Consider corticosteroid therapy in patients with progressive laboratory abnormalities: dexamethasone 10 mg IV every 6 hours or methylprednisolone 0.5–1 mg/kg/day IV)
Grade 2	Moderate clinical manifestations requiring medical intervention, with moderate cytopenias or coagulopathy and mild organ dysfunction	• Initiate corticosteroid therapy with dexamethasone 20 mg IV every 6 hours or methylprednisolone 1–2 mg/kg/day IV • Consider pulse-dose methylprednisolone 500–1,000 mg IV daily for 3 days in patients with rapidly progressive disease • Consider early initiation of anakinra 100–200 mg IV or SC every 6–12 hours • Consider ICU consultation for patients with clinical deterioration or evolving organ dysfunction
Grade 3	Severe organ dysfunction with significant hypoxemia and/or hypotension requiring ICU-level care	• ICU admission and management • Administer high-dose corticosteroids with dexamethasone 20 mg IV every 6 hours or methylprednisolone 1–2 mg/kg/day IV, alternatively, consider pulse-dose methylprednisolone 500–1,000 mg IV daily for 3 days • Administer anakinra 100–200 mg IV or SC every 6–12 hours • Provide comprehensive organ support as clinically indicated • In corticosteroid-refractory disease, consider second-line therapy with ruxolitinib (10 mg orally twice daily), emapalumab (1 mg/kg IV as an initial dose), or etoposide (50–100 mg/m² IV as an initial dose)
Grade 4	Life-threatening multiorgan failure requiring mechanical ventilation, vasopressor therapy, or other advanced organ support, with severe coagulopathy and/or encephalopathy	• Immediate ICU management with comprehensive organ support • Administer pulse-dose methylprednisolone 500–1,000 mg IV daily for 3 days • Administer anakinra 100–200 mg IV or SC every 6–12 hours • In refractory progressive disease, consider escalation to second-line immunomodulatory therapy with ruxolitinib (10 mg orally twice daily), emapalumab (1 mg/kg IV as an initial dose), or etoposide (50–100 mg/m² IV as an initial dose) • Ensure multidisciplinary management involving hematology, intensive care, and infectious diseases specialists

Targeted and Immunomodulatory Therapies

Corticosteroids are considered first-line therapy for IEC-HS, with dexamethasone or methylprednisolone commonly used according to disease severity. Pulse-dose corticosteroids may be required in fulminant cases. Tocilizumab may be considered when IEC-HS occurs concurrently with CRS; however, IL-6 receptor blockade alone is generally insufficient for isolated IEC-HS. Anakinra is increasingly used in moderate-to-severe IEC-HS because of its established role in MAS, favorable safety profile, and growing clinical experience.

Emapalumab, a monoclonal antibody targeting IFN-γ and approved for primary HLH, has been used in selected refractory cases, although clinical experience in IEC-HS remains limited.

Ruxolitinib has emerged as a potential therapeutic option for refractory hyperinflammatory syndromes because of its ability to inhibit multiple cytokine signaling pathways. Etoposide may also be considered in refractory or rapidly progressive disease, particularly when the clinical presentation resembles fulminant HLH despite initial immunomodulatory therapy (Table 3).

However, immunomodulatory therapies should be used cautiously because they may impair CAR T-cell persistence, cause significant myelosuppression, and increase the risk of infection.[34-36]

Other Complications

Cytopenias

Many patients develop leukopenia/neutropenia, anemia, and/or thrombocytopenia as adverse effects of lymphodepletion or CAR T-cell therapy itself. Some patients may remain cytopenic for weeks to months and, rarely, indefinitely. Persistent or unexplained cytopenias beyond approximately two months should prompt bone marrow evaluation to exclude disease relapse, myelo-

dysplasia, infection, or other bone marrow pathology.

Management of cytopenias should be individualized according to severity. Patients with Grade 1 cytopenias (hemoglobin >10 g/dL, absolute neutrophil count >1,500/mm³, or platelet count >75,000/mm³) generally require only close monitoring and supportive care. For Grade 2 cytopenias (hemoglobin 8–10 g/dL, absolute neutrophil count 1,000–1,500/mm³, or platelet count 50,000–75,000/mm³), careful clinical assessment and ongoing supportive management are recommended. Patients with Grade 3–4 cytopenias (hemoglobin <8 g/dL, absolute neutrophil count <1,000/mm³, or platelet count <50,000/mm³) typically require blood product support, including red blood cell and platelet transfusions, in accordance with institutional transfusion thresholds and clinical indications. Granulocyte colony-stimulating factor (G-CSF) may be considered for severe or prolonged neutropenia but is generally deferred until cytokine release syndrome has completely resolved because of concerns about the potential exacerbation of inflammatory toxicity, although practice patterns vary across institutions. In patients with persistent cytopenias following prior hematopoietic stem cell transplantation, infusion of previously cryopreserved autologous stem cells may be considered when available.[38,39]

B-Cell Aplasia/Hypogammaglobulinemia

B-cell aplasia following CD19-directed CAR T-cell therapy may result in prolonged hypogammaglobulinemia, sometimes persisting for up to two years, thereby increasing the risk of recurrent infections. Immunoglobulin (Ig) levels should be monitored regularly. In patients with IgG levels below 400–600 mg/dL who experience serious or recurrent infections, monthly intravenous immunoglobulin (IVIG) replacement therapy (up to 400–500 mg/kg) may be considered. IVIG therapy may be continued until IgG levels recover and infections resolve. Considerable variability exists in clinical practice regarding the use of IVIG replacement therapy.[40]

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is an uncommon but potentially life-threatening complication associated with CAR T-cell therapy, most frequently occurring in the context of severe CRS or IEC-HS. Management focuses on treating the underlying inflammatory syndrome and providing supportive critical care. Supportive measures include transfusion of blood products when indicated, correction of hypofibrinogenemia and other coagulation abnormalities, serial monitoring of coagulation parameters, and management of organ dysfunction. Immunomodulatory therapies, such as tocilizumab, corticosteroids, or anakinra should be considered based on the underlying CRS or IEC-HS rather than on the presence of DIC itself.[38-40]

Infection Risk

Infections remain a significant cause of morbidity and mortality following CAR T-cell therapy, affecting approximately 23%–60% of patients during the post-infusion period. Susceptibility to infection is multifactorial, reflecting the combined effects of the underlying hematologic malignancy, cumulative exposure to prior therapies, lymphodepleting chemotherapy, treatment-related immune dysfunction, and prolonged cytopenias. Additional risk factors include severe CRS requiring immunosuppressive therapy and a greater burden of prior treatment. The spectrum of pathogens evolves over time. Bacterial infections predominate during the first month after CAR T-cell infusion, whereas viral infections—particularly respiratory viral infections and those caused by varicella-zoster virus and herpes simplex virus—become more common between 30 days and one year. Invasive fungal infections, including *Aspergillus* spp., as well as *Pneumocystis jirovecii* pneumonia (PJP), are relatively uncommon but occur more frequently after BCMA-directed than after CD19-directed CAR T-cell therapy. In the late phase, persistent B-cell aplasia, plasma cell depletion, hypogammaglobulinemia, and delayed immune reconstitution become the principal determinants of infectious risk. Consequently, comprehensive infectious risk assessment before CAR T-cell therapy, close monitoring of immune recovery, regular evaluation of Ig levels, and individualized infection-prevention strategies are essential. Antiviral and PJP prophylaxis are routinely recommended, whereas antibacterial and mold-active antifungal prophylaxis should be reserved for selected high-risk patients. IVIG replacement therapy should be considered in patients with significant hypogammaglobulinemia accompanied by recurrent or severe infections.[41]

Secondary Malignancies

Secondary malignancies are an uncommon but recognized late complication of CAR T-cell therapy. Long-term follow-up studies have reported an overall incidence of approximately 4%–16%, although most cases are not considered directly attributable to the CAR T-cell product. Particular concern has been raised regarding the rare

occurrence of T-cell malignancies, including CAR-positive lymphomas, prompting the U.S. Food and Drug Administration to issue safety alerts and mandate boxed warnings for both CD19- and BCMA-directed CAR T-cell therapies. Nevertheless, current evidence indicates that these events are exceedingly rare, and the overall benefit–risk profile of CAR T-cell therapy remains favorable. Moreover, the incidence of secondary malignancies does not appear to exceed that expected in heavily pretreated patients, in whom cumulative exposure to chemotherapy and radiotherapy, together with the underlying disease biology, contributes substantially to the development of subsequent malignancies. Continued long-term surveillance remains essential to better define the true incidence, underlying mechanisms, and clinical significance of these rare events.[38-40]

CAR T-Cell Therapy in Türkiye and Intensive Care–Relevant Outcomes

Experience with CAR T-cell therapy in Türkiye remains limited. According to a report by the Turkish Society of Hematology Scientific Subcommittee on Cell and Gene Therapies (TSH-CGT SSC), approximately 507 patients are estimated to require CAR T-cell therapy annually in Türkiye; however, only 23 patients received this therapy between 2019 and March 2024.[42] Nine patients received treatment as part of an academic study conducted in Türkiye, whereas 14 received treatment abroad, primarily in Germany. Consequently, published national data consist mainly of early academic studies and small retrospective cohorts, providing limited information on clinical outcomes.

The first Turkish academic CAR T-cell study, ISIKOK-19, evaluated a locally developed CD19-directed CAR T-cell product in patients with relapsed/refractory B-cell acute lymphoblastic leukemia and non-Hodgkin lymphoma (NHL). Seven heavily pretreated patients received CAR T-cell infusions, with an overall response rate of 72%. Treatment-related toxicities included CRS, neurotoxicity, and pancytopenia. According to the published report, most adverse events were grade 1–2 and were managed with supportive care, tocilizumab, and corticosteroids as needed. Importantly, the study demonstrated the feasibility of academic CAR T-cell manufacturing and administration in Türkiye.[5]

Additional data from a retrospective cohort of 13 CAR T-cell recipients in Türkiye identified CRS and neurotoxicity as the predominant early complications. Grade 1 CRS occurred in 38.5% of patients, and neurological manifestations, including cognitive impairment, dysgraphia, and somnolence, were also observed. Notably, two patients required ICU admission because of combined CRS and neurotoxicity.[43]

Although the published Turkish experience remains limited, the reported toxicity profile is consistent with international data, with CRS, ICANS, prolonged cytopenias, and infection-related complications among the major adverse events. However, detailed national data on ICU admission rates, organ support requirements, mechanical ventilation, vasopressor use, renal replacement therapy, and ICU mortality are currently lacking. This represents a significant limitation of our review, as the scarcity of local data constrains our ability to tailor recommendations to the Turkish context and may limit the applicability of international guidelines, particularly in resource-limited settings.

The report of the TSH-CGT SSC initiative.[42] highlights considerable challenges in implementing CAR T-cell therapy in Türkiye. These challenges include high costs, inadequate infrastructure, a shortage of trained personnel, regulatory uncertainties, and insufficient reimbursement frameworks. The report also provides strategic recommendations, including the establishment of government funding and reimbursement mechanisms through the Social Security Institution (SGK); standardization of clinical protocols; creation of a centralized system for data collection and outcome monitoring; expansion of certification and training programs to develop a skilled workforce; adoption of Good Manufacturing Practice (GMP)-compliant quality management systems; and strengthening of international collaborations to harmonize standards and foster innovation. By formulating a comprehensive national strategic roadmap, this initiative seeks to facilitate the broader adoption of CAR T-cell therapy and improve access to this advanced treatment modality for patients across Türkiye.

Conclusion

In conclusion, CAR T-cell therapy has reshaped the treatment landscape for several malignant and non-malignant B-cell diseases, particularly relapsed and refractory hematologic malignancies. Although it offers substantial clinical benefits, CAR T-cell therapy is associated with a unique spectrum of potentially life-threatening toxici-

ties. Among these, CRS, ICANS, and IEC-HS are the most clinically significant complications and may require ICU admission and organ support.

As CAR T-cell therapy continues to expand globally and gains momentum in Türkiye, intensivists will play an increasingly pivotal role in the care of these patients. Early recognition, accurate grading, timely initiation of immunomodulatory therapies, and comprehensive organ support are essential to prevent progression to severe organ dysfunction and improve clinical outcomes. Successful management also depends on close multidisciplinary collaboration among intensivists, hematologists, oncologists, neurologists, infectious disease specialists, and other members of the CAR T-cell therapy team.

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