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REVIEW ARTICLE

Systemic complications of (Chimeric Antigen Receptor T-Cell therapy) CAR-T cell therapy: What internal medicine specialists should recognize and manage.

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ABSTRACT... Objective: To integrate current evidence on systemic complications of CAR-T therapy that are most pertinent to internal medicine physicians, specifically regarding recognition, differentiation, early stabilisation, and co-management in the wards and intensive care units. **Study Design:** Evidence Acquisition (Secondary Search, 2020–2026). **Setting:** PubMed/MEDLINE and Google Scholar were used as sources of secondary literature review of studies published. **Period:** January 2020 to March 2026. **Methods:** The search terms consisted of the combination of the terms CAR-T, chimeric antigen receptor, toxicity, cytokine release syndrome, ICANS, infection, cardiotoxicity, coagulopathy, and tumour lysis syndrome. Priority was given to clinical guidelines, consensus statements, systematic reviews, and large observational studies. Case reports and strictly preclinical studies were excluded. **Results:** The most frequent acute complications are typically early hyperinflammatory toxicities, including CRS and ICANS. Subsequent risks include infections associated with cytopenias and B-cell aplasia, hematologic/coagulation disorders, metabolic emergencies such as TLS, acute kidney injury, and cardiopulmonary instability. Other conditions that are not common but are severe in nature, including hemophagocytic lymphohistiocytosis-like hyperinflammation, demand extra attention. **Conclusion:** Internal medicine specialists are considered to be crucial in the early detection and stabilisation of systemic complications in CAR-T. Time-dependent patterns of toxicity, systematic assessment plans, and escalation levels are familiarity requirements that should optimise outcomes in the high-risk population.

Key words: CAR-T, Cytokine Release Syndrome, Coagulopathy, Cardiotoxicity, Hypogammaglobulinemia, HLH/MAS, Inpatient Care, ICANS, Sepsis, Tumor Lysis Syndrome.

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INTRODUCTION

One of the most important innovations in modern hematologic oncology is chimeric antigen receptor T-cell therapy. CAR-T therapy enables targeted cytotoxic attack on malignant cells through genetically engineered autologous T lymphocytes expressing tumor-associated antigens. As the first regulatory approvals have been secured, the number of approved CAR-T products and indications has been systematically growing, and the range of referral networks is no longer confined to specialized transplant centers.

As more patients gain access, there is progressively more involvement of internal medicine physicians in the management of patients after they are exposed to CAR-T or weeks/months later, with the delayed toxicities appearing (Deschenes-Simard X, Santomasso BD, Dahi PB). Even though administration is normally done in oncology-based programmes, numerous complications are exhibited in general medical hospitals, emergency departments, and intensive care units. As a result, non-oncology teams should be ready to distinguish inflammatory syndromes induced by therapy or sepsis, cardiogenic shock, metabolic emergencies, and neurologic disorders.

The review concerns itself with systemic complications of the specialty of internal medicine in an inpatient and critical care facility. It is not to describe the molecular engineering of CAR constructs but rather is a clinically-focused synthesis of recognition patterns, diagnostic approaches, and initial management principles in small and large groups of major complications (Rejeski K, Greco

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R, Onida F et al.). Even though CAR-T therapy is mainly performed in hematologic malignancies, it is often found to have extensive effects on other organ systems, and coordination between different disciplines is necessary.

METHODS

This study was conducted as a scoping review in accordance with PRISMA-ScR guidelines. Considering the fast-changing nature of the immune effector cell therapies, a general mapping strategy was chosen to represent different categories of complications and clinical management models.

Sources of Data and Search Strategy

A good literature search was conducted in PubMed/MEDLINE and Google Scholar. The searches were in publications published since January 1, 2020, up to March 2026. The subsequent search engine query was used: (CAR T) OR (CAR-T) OR (chimeric antigen receptor) AND (toxicity) OR (complications) OR (cytokine release syndrome) OR (ICANS) OR (infection) OR (cardiotoxicity) OR (coagulopathy) OR (tumour lysis) (Qureshi Z, Altaf F, Jamil A et al.). These terms were used in combinations with Boolean operators to make the most out of sensitivity.

Eligibility Criteria

The included studies were reviewed as peer-reviewed articles in the English language that covered adult patients undergoing CAR-T therapy. Emphasis was laid on clinical practice guidelines, statements of consensus by professional societies, systematic review, meta-analysis, and multicenter observational studies (Jain MD, Smith M, Shah NN). The exclusion criteria included case reports of cases as the only form of evidence, only pediatric studies not directly related to adult care extrapolation, and non-clinical animal or laboratory studies that were not clinically based.

Screening and Selection

The screened search results were done in two phases. To filter out studies that were evidently irrelevant, titles and abstracts were reviewed. Potentially eligible articles were then evaluated based on the full texts to be included. The PRISMA-type flow methodology was employed to record the number of records identified, screened, excluded, and included in the final synthesis (Jain MD, Smith M, Shah NN).

Data Extraction

The extraction of the data was directed at the complication type, incidence rates, the identified risk factors, the time-to-onset, the principal diagnostic features, the first-line management strategies, the escalation criteria, and the reported outcomes. Where possible, the strengths of guidelines and evidence levels were mentioned (Rejeski K, Greco R, Onida F et al.). Society consensus statements in haematology and oncology were accorded more interpretive importance because of their multidisciplinary system of evidence synthesis.

RESULTS AND EVIDENCE SYNTHESIS

Early Hyperinflammatory Toxicities

Cytokine Release Syndrome

The most common acute complication of CAR-T therapy is the cytokine release syndrome. It typically manifests within the first few days after infusion, but in different cases, the manifestation takes some time, depending on the disease burden and the nature of the CAR constructs (Gandhi AP, Lee CJ). CRS is clinically defined by fever, hypotension, hypoxia, and laboratory findings of systemic inflammation such as increased C-reactive protein and ferritin.

The main issue that internal medicine specialists face is related to the inability to differentiate CRS and bacterial sepsis. The two conditions are characterised by fever and hemodynamic instability. The coincidence in time with the CAR-T infusion and the lack of recognisable infectious agent can be used to suggest a diagnosis of CRS. Empiric broad-spectrum antibiotics are usually justified until infection is excluded (Munshi PN, Olin RL, Wall S et al.).

CRS has grading systems, which classify the severity of the condition according to the respiratory and hemodynamic compromise. Early management entails supportive management such as intravenous fluids and supplemental oxygen. There is a likelihood that, in persistent hypotension or hypoxia, this has to be escalated to vasopressor support or intensive

care observation. Tocilizumab is an interleukin-6 receptor antagonist that is a cornerstone therapy for moderate to severe CRS. The introduction of corticosteroids is done when the symptoms do not improve or the manifestations that threaten life appear (Nunes F, de Gusmão BM, Wiginesk FB et al.). Internal medicine teams must learn that the appropriate administration of these agents does not seem to undermine the long-term oncologic effectiveness.

Immune Effector Cell-Associated Neurotoxicity Syndrome

Immune effector cell-associated neurotoxicity syndrome follows or is sometimes overlapped by CRS but occurs by itself. The symptoms include mild confusion and word-finding difficulty, seizures, and cerebral oedema. Serial cognitive assessment, orientation testing, handwriting assessment, and focal deficit monitoring should also be included in the neurologic assessment of hospitalised patients receiving or having recently received CAR-T therapy.

Metabolic encephalopathy, stroke, infection, and medication effects are all covered under differential diagnosis. In severe cases, brain imaging and electroencephalography is required. A lumbar puncture should be considered when CNS infection or inflammation is suspected (Jain T, Olson TS, Locke FL). Corticosteroids are still the first line pharmacologic treatment of significant ICANS, and tocilizumab has a very limited effect in isolated neurotoxicity. Patients with the rapid development of neurologic status or the presence of signs of increased intracranial pressure should be subject to early neurology consultation and ICU transfer.

Infectious Complications

Neutropenic Fever and Bacterial and Fungal

Cytopenias in CAR-T patients often occur because of the previous chemotherapy, lymphodepleting treatment, and inflammation. The treatment of neutropenic fever among this population should be managed similarly to other high-risk oncology patients, and empiric broad-spectrum antibiotics need to be started immediately after blood cultures (Zuo R, Han M). Internal medicine physicians must observe alertness towards opportunistic infections, especially in patients with a period of neutropenia.

Viral Reactivation and Hypogammaglobulinemia

B-cell–directed CAR-T therapies can cause long-term B-cell aplasia, which causes hypogammaglobulinemia. Such a condition increases the susceptibility of patients to sinopulmonary infections and viral reactivation (Brudno JN, Kochenderfer JN). Common techniques include immunoglobulin level monitoring and intravenous immunoglobulin replacement for patients with frequent infections. Antiviral prophylaxis is needed at the time of herpesvirus reactivation based on the protocols of particular institutions.

Antimicrobial Prophylaxis

There is an agreement of guidance in the prophylaxis of Pneumocystis jirovecii and herpes simplex virus after CAR-T therapy within the initial few months. The prophylaxis period depends on the immunity. It is the responsibility of the internal medicine team to verify lists of medications to avoid the discontinuation of the recommended prophylactic regimens during hospitalisation.

Hematologic and Coagulation Issues

Prolonged Cytopenias

Refractory anaemia, thrombocytopenia, and neutropenia do not limit its effects to the acute post-infusion period. Differential diagnosis consists of more marrow suppression, immune-mediated, and disease relapse. The support of transfusion is in accordance with the normal thresholds, but clinicians are required to pay attention to the risk of bleeding in thrombocytopenic patients.

Coagulopathy

This results in systemic inflammation during severe CRS, resulting in coagulopathy mimicking disseminated intravascular coagulation (Ferreri CJ, Bhutani M). A high level of D-dimer and a low level of fibrinogen can be seen. Treatment of the underlying inflammatory process and administration of supportive transfusion therapy according to the clinical setting are the concerns of management. This presentation should not be confused with coagulopathy or thrombotic microangiopathy caused by sepsis by internal medicine specialists.

Venous Thromboembolism

Malignancy and systemic inflammation are risk factors for thrombosis. The decisions on anticoagulation need to strike a balance between the necessity of bleeding and considering thrombocytopenia.

Metabolic and Renal Emergencies

Tumor Lysis Syndrome

The tumor lysis syndrome, although uncommon compared to that with conventional chemotherapy in case of higher-burden leukemia or lymphoma, happens following CAR-T therapy, especially in patients who have a huge tumor burden (Bangolo A, Amoozgar B, Mansour C et al.). There is a rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Prevention involves proper hydration and uric acid-lowering in high-risk persons. Rasburicase is used in either established or high-risk situations with increased uric acid.

Acute Kidney Injury

Hypotension during CRS, nephrotoxic drugs, or crystal deposition due to tumour lysis cause acute kidney injury. It should be assessed through evaluation, including volume test, urinalysis, and medication review (Ahmed N, Oluwole O, Mahmoudjafari Z et al.). This should be done with early nephrology intervention in instances of rapidly growing creatinine levels or refractory electrolyte disorders.

Cardiopulmonary Complications

Shock Differential

The differentials to CAR-T recipients with hypotension are CRS-related distributive shock, septic shock, and cardiogenic shock due to inflammatory cardiomyopathy. Bedside echocardiography is useful in differentiating between reduced ejection fraction and vasodilatory states. CRS implicates the use of hemodynamic support and specific anti-inflammatory therapy by the management (Santomasso BD, Gust J, Perna F).

Atrial Fibrillation and Heart Failure

General inflammation can be the cause of abnormal heartbeat or worsen the primary cardiac illness. In patients with severe CRS, it is suitable to use continuous telemetry monitoring. Symptoms of new-onset heart failure should be examined by echocardiography and consultation with a cardiologist.

Rare but Critical Syndromes

HLH/MAS-like Hyperinflammation

Some of the patients can get a hyperinflammatory syndrome that is similar to hemophagocytic lymphohistiocytosis or macrophage activation syndrome. Serious hyperferritinemia, cytopenias, hepatopathy, and coagulopathy can be detected. This disorder involves the multidisciplinary management that is usually based on high-dose corticosteroids and other immunomodulatory drugs.

Delayed neurotoxicity and Secondary Malignancy

Late neurologic effects and fear of secondary malignancy have also been reported, but were rather rare. Care-based components should also include long-term follow-up and collaboration with the oncology domain (Li Y, Mei H).

CAR-T therapy has transformed the prognosis in the case of refractory hematologic malignancies but presents intricate systemic toxicities that often need to be managed beyond specialised oncology units. Internal medicine specialists have to identify time-sensitive inflammatory syndromes like CRS and ICANS, be vigilant with respect to infectious and hematologic complications, and identify overlapping states of shock. Organized evaluation, prompt supportive care, and early consultation with oncology and critical care units are the main elements of patient outcomes maximization. With the extension of CAR-T indications, will competence in the management of these systemic effects become an indispensable part of modern inpatient medicine?

TABLE-I summarizes the major systemic complications of CAR-T therapy, their typical onset patterns, key diagnostic considerations, and first-line management principles relevant to internal medicine practice

TABLE-I

Systemic complications of CAR-T cell therapy relevant to internal medicine practice

Complication	Typical Onset After Infusion	Hallmark Clinical Features	Key Initial Diagnostic Tests	First-Line Management Principles
Cytokine Release Syndrome (CRS)	Day 1–7 (most common in first 3–5 days)	Fever, hypotension, tachycardia, hypoxia, elevated CRP/ferritin	CBC, CMP, CRP, ferritin, lactate, blood cultures, chest imaging	Supportive care (IV fluids, oxygen), broad-spectrum antibiotics until infection excluded, tocilizumab for moderate–severe cases, corticosteroids if refractory
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Day 2–10 (follow CRS)	Confusion, aphasia, tremor, seizures, decreased consciousness	Neurologic exam, brain MRI (if severe), EEG, CMP, inflammatory markers	Close neuro monitoring, corticosteroids for ≥ grade 2 symptoms, ICU transfer if seizures or decreased airway protection
Bacterial Infections / Neutropenic Fever	Days–weeks (especially with prolonged cytopenia)	Fever, hypotension, focal infection signs	Blood cultures, urine culture, chest imaging, CBC with differential	Immediate empiric broad-spectrum IV antibiotics, ID consultation in persistent cases
Viral Reactivation / Hypogammaglobulinemia	Weeks–months	Recurrent respiratory infections, low IgG levels	Serum immunoglobulins, viral PCR (if indicated)	IVIG replacement in recurrent infections, antiviral prophylaxis continuation
Prolonged Cytopenias	Weeks–months	Anemia, thrombocytopenia, neutropenia	CBC with differential, bone marrow evaluation if persistent	Transfusion support, growth factors in selected cases, hematology follow-up
Coagulopathy / DIC-like Syndrome	During severe CRS	Elevated D-dimer, low fibrinogen, bleeding tendency	Coagulation profile, fibrinogen, platelet count	Treat underlying inflammation, blood product support as indicated
Tumor Lysis Syndrome (TLS)	Early (especially high tumor burden)	Hyperkalemia, hyperphosphatemia, hyperuricemia, AKI	Electrolytes, uric acid, creatinine, LDH	Aggressive IV hydration, rasburicase if high uric acid, nephrology consult if worsening renal function
Acute Kidney Injury (AKI)	Variable	Rising creatinine, decreased urine output	CMP, urinalysis, volume assessment	Optimize hemodynamics, avoid nephrotoxins, nephrology consultation if severe
Cardiopulmonary Complications	During CRS or later	Hypotension, arrhythmias, reduced ejection fraction	ECG, troponin, BNP, echocardiography	Hemodynamic support, telemetry monitoring, cardiology consultation
HLH/MAS-like Hyperinflammation	Rare, early or overlapping CRS	Very high ferritin, cytopenias, liver dysfunction, coagulopathy	Ferritin, triglycerides, fibrinogen, liver function tests	High-dose corticosteroids, specialist-directed immunomodulatory therapy, ICU management

Practical Management Framework for Internal Medicine

The increasing CAR-T therapy application has transferred the oncology services of acute care and long-term complication care to other parties. The primary clinicians who assess patients with suspected CAR-T-associated toxicities are often internal medicine physicians in emergency departments, on general wards, and in intensive care units (Gatwood KS, Dholaria BR, Lucena M et al.). This means a system-based, structured format to prevent delays in considering and escalation. The section offers a practical way of triage, monitoring, consultation paths, and drug options specific to inpatient medical practise. Figure-1. Triage and management algorithm for suspected CAR-T cell therapy–related toxicity. Source: Developed by the authors based on synthesized literature (2020–2026).

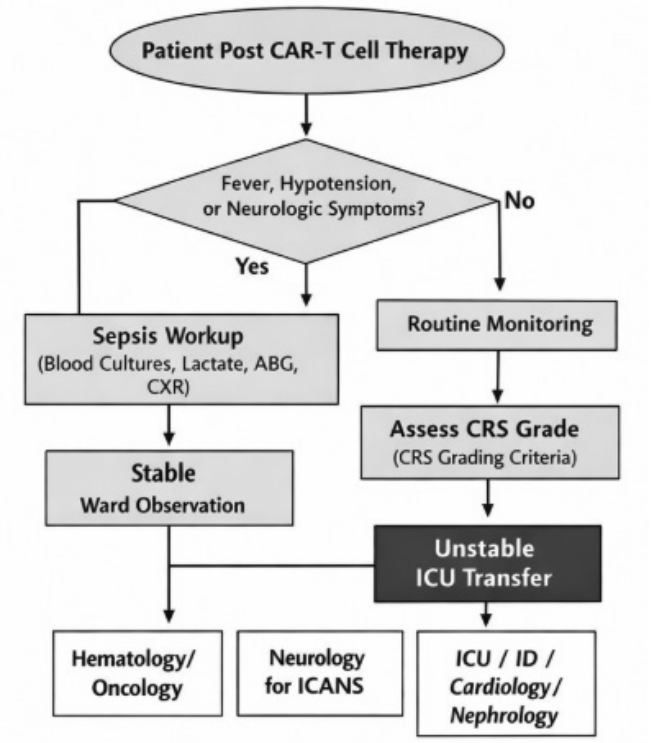
Triage Algorithm: Emergency Department to Ward to Intensive Care

Patients who start with mild symptoms but come to see them only after a period following the recent CAR-T infusion (usually within the first 30 days but occasionally later) must be regarded as high-risk. Triage involves determining the time between CAR-T therapy and observing the infusion date, the patient's present state of a malignancy, and recent events of cytokine release syndrome or immune

effector cell-associated neurotoxicity syndrome.

FIGURE-1

Triage and management algorithm for suspected CAR-T toxicity



At the emergency department, all patients presenting with fever, hypotension, hypoxia, new confusion, or having laboratory findings of inflammation need to be considered in a manner that is consistent with the possibility of early cytokine release syndrome, and a sepsis workup should be initiated. Initial management of febrile or hypotensive patients includes airway assessment, intravenous access, blood tests, empiric broad-spectrum antibiotics, and supplemental oxygen (Li Y, Ming Y, Fu R et al.). Infection cannot be eliminated at presentation, even when cytokine release syndrome is highly suspected. Hemodynamic and volume status should be assessed to distinguish distributive from cardiogenic physiology.

Patients with persistent fever without hypotension, mild hypoxia that responds to low-flow oxygen, or low-grade neurologic symptoms but no focal deficits should be admitted to a monitored medical ward. Such patients need to be re-assessed regularly because they can deteriorate in just a few hours (Zuo R, Han M). The haematology-oncology service should be notified early, and admission to a ward should be arranged.

Transport to an intensive care unit is necessary immediately in the case of vasopressor-dependent hypotension, increasing oxygen demands above low-flow ventilatory support, altered mental status with poor airway defence, seizures, or suspected elevated intracranial pressure. Any laboratory deterioration, such as rising lactate, a rapid increase in ferritin, deteriorating coagulopathy, or the signs of acute kidney failure in the presence of hemodynamic instability, should reduce the threshold of ICU escalation. Definitive grades of toxicity should not be required to make the decision, because timely supportive care is a direct determinant of outcome.

Monitoring Strategy in Hospitalized Patients

A well-organised monitoring, which is in line with the expected time-course of CAR-T related toxicities, is needed to manage inpatients effectively. The first two weeks after infusion, vital measurements should be measured at least every four hours on stable ward patients and continuously on patients with moderate inflammatory characteristics. Of the greatest importance are temperature trends due to the fact that fever is frequently the first symptom of cytokine release syndrome (Gandhi AP, Lee CJ). The blood pressure monitoring must not be limited to absolute hypotension but also to dynamic changes compared to baseline, particularly in elderly patients or those with chronic hypertension.

Daily complete blood count with differential to examine cytopenias, complete metabolic panel to examine the renal and hepatic functions of the body, and inflammatory markers, including C-reactive protein and ferritin, should be part of laboratory surveillance. No single biomarker can be said to diagnose cytokine release syndrome, but an increase in ferritin and C-reactive protein is frequently accompanied by a worsening of the clinical situation (Jain MD, Smith M, Shah NN). The values of coagulation parameters, such as fibrinogen and D-dimer, are useful when patients have severe systemic inflammation or when there is the possibility of coagulopathy.

Monitoring of the neurology should be preventive

and not curative. Early, subtle immune effector ellassociated neurotoxicity syndrome can be identified by daily cognitive screening using structured orientation questions and simple writing or naming. Training of the nursing staff should be done to record changes in handwriting, fluency of speech, or attention. Neurologic testing at least once a shift or even more often is suitable in patients with moderate to severe inflammatory characteristics (Qureshi Z, Altaf F, Jamil A et al.). Acute confusions, focal neurologic deficits, aphasia, or seizure activity is an indication to urgently order imaging and clinical consultation.

Monitoring of fluid balance and urine output is vital since the acute kidney injury can be caused by hypotension, tumour lysis syndrome, or nephrotoxic drugs. Rigid input and output recordings are helpful in the differentiation between prerenal azotemia and intrinsic renal damage. Patients with moderate and severe cytokine release syndrome or living with underlying cardiac disease should be monitored with telemetry because arrhythmias can occur in the circumstances of systemic inflammation.

Consultation Pathways and Multidisciplinary Coordination

Formal and prompt consultation enhances the results of CAR-T recipients having systemic complications. Any suspected toxicity of the therapy should be communicated urgently to the haematology-oncology team, even when the symptoms are mild. Their contribution plays a significant role in terms of implicit leadership of severity and ascertaining the necessity of immunomodulatory treatment (tocilizumab or corticosteroids).

The intensive care consultation must be provided as soon as hemodynamic instability or rapid progressive respiratory incapacity is observed. The internal medicine team is not supposed to postpone the ICU intervention until the diagnostic picture is clear. Collaborative evaluation at an early stage allows effective mobilization of resources (advanced hemodynamic monitoring or mechanical ventilation when necessary) (Zuo R, Han M).

The patient with moderate or severe impaired cognitive function, seizures, focal neurologic symptoms, and those suspected of having high intracranial pressure indicate the need for neurology consultation. In patients who have continued encephalopathy, electroencephalography is necessary to rule out nonconvulsive seizures. In the cases of focal appearance or acute deterioration, neuroimaging is mandatory.

The consultative service of infectious diseases is especially important in a patient experiencing long-term neutropenia, persistent fevers despite taking broad-spectrum antibiotics, possible opportunistic infections, or viral reactivation. Expert advice is valuable when making new decisions on continuing or escalating antimicrobial prophylaxis administrations in individuals and taking into account recent changes in resistance patterns (Deschenes-Simard X, Santomasso BD, Dahi PB).

In patients with new arrhythmias, lower ejection fraction on bedside echocardiography, higher cardiac biomarkers, or inexplicable persistent shock, involvement of cardiology should be sought. Nephrology consultation should be used in cases of refractory electrolyte imbalances, increasing creatinine at a rapid pace, or when renal replacement therapy should be considered.

Medication Considerations and Cautions

Management of CAR-T-related complications commonly involves immunosuppressive agents, vasopressors, antimicrobials, and transfusion assistance. Internal medicine physicians are required to be cautious in terms of possible interactions and cumulative toxicities. Although corticosteroids are good in dealing with severe inflammatory complications, they risk infection and worsen hyperglycemia (Jain T, Olson TS, Locke FL). Closely monitored should be the glycemic control, especially in those patients who are already diabetic.

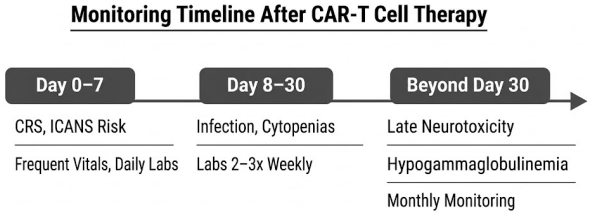
Tocilizumab can conceal infection symptoms by lessening fever and inflammatory indicators. Even in the case of clinical improvement, clinicians need to be aware of the continued process of infection. The empiric antibiotic therapy should not be discontinued just because the inflammatory markers reduce after immunomodulatory treatment (Bangolo A, Amoozgar B, Mansour C et al.).

Neutropenia, previous colonisation with resistant organisms, and kidney function should be considered during the selection of antimicrobials. Dose modifications are required in patients with acute kidney injury. Prophylaxis against Pneumocystis jirovecii and herpesviruses should not be interrupted and should be maintained unless contraindicated, and medications should be reconciled upon admission.

Transfusion thresholds should be individualised. Following CAR-T therapy, anemia and thrombocytopenia are typical. Higher thresholds of platelet transfusion can be needed in actively bleeding patients or scheduled invasive operations. Severe inflammatory states can be linked to coagulopathy, and this requires the use of fibrinogen. Anticoagulation choices in cytopenic patients who are in danger of developing venous thromboembolism should be based upon a balance between thrombosis risks and bleeding risks. Figure-2. Monitoring timeline after CAR-T cell therapy (Day 0–30 and beyond). Source: Developed by the authors based on synthesized literature (2020–2026).

FIGURE-2

Monitoring timeline after CAR-T cell therapy



DISCUSSION

Complications Commonly Missed by Non-Oncology Teams

Non-oncology clinicians need to be aware of some of the complications of CAR-T therapy, even though these complications are becoming more familiar. Mild confusion or word-finding difficulty is the initial symptom of early immune effector cell-associated neurotoxicity syndrome and is confused with drug effects or metabolism (Bangolo A, Amoozgar B, Mansour C et al.). The inability to identify the initial neurologic alterations can delay the administration of corticosteroids and increase the chances of developing severe cerebral edema.

Delayed hypogammaglobulinemia resulting in frequent infections months after treatment is the other issue that is often neglected. Recurrent sinopulmonary infections may occur in the absence of neutropenia. The immunoglobulin deficiency should be included in the differential diagnosis of internal medicine physicians, and the corresponding tests should be organised.

Severe cytokine release syndrome-induced coagulopathy is similar to disseminated intravascular coagulation caused by sepsis. Failure to recognise the inflammatory setting results in the inappropriate classification of the aetiology and the postponement of specific immunomodulatory therapy (Ahmed N, Oluwole O, Mahmoudjafari Z et al.). On the same note, cardiomyopathy caused by systemic inflammation can also be confused with ischemic heart disease when tested without taking into account recent CAR-T therapy.

Evidence Gaps and Heterogeneity

There is still an ongoing development of evidence-based to CAR-T based systemic complications. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome grading systems have been refined; there is still variability between research and institutions. Rates of incidence vary according to constructs of CAR, patient characteristics, and disease burden (Nunes F, de Gusmão BM, Wiginesk FB et al.). A number of managerial recommendations are based on consensus statements and not randomised controlled trials.

The long-term results of immunomodulatory therapy for severe toxicities are not well defined. There are still unanswered questions on the best steroid dosing regime, the length of time taken to achieve prophylaxis with antimicrobial agents, and immunoglobulin replacement levels. The ability of the CAR-T products to be heterogeneous also complicates the standardization of management algorithms.

Implementation Strategies in Hospital Systems

Hospitals ought to establish standardised order

sets of suspected CAR-T-related toxicities in order to enhance patient safety. Such sets of orders can contain prescribed laboratory testing, imaging studies, and consultation criteria. Education of nurses is essential, especially with respect to the neurologic monitoring and prompt identification of hemodynamic instability.

Early warning scores should be incorporated into the electronic medical records, which will help to promptly escalate (Gatwood K, Mahmoudjafari Z, Baer B et al.). Combinations of fever, hypotension, and recent CAR-T therapy have automated warning systems that help to serve as a quick response team assessment. Simulation training exercises using a multidisciplinary approach can also help increase the readiness to severe inflammatory syndromes.

Documentation on the status of CAR-T therapy within the medical record, infusion date, and previous toxicities must be clearly documented to ensure that it is immediately evident to emergency clinical staff and ward staff. Discharge patient education must also focus on when they require urgent care, since the consequences of the delay arise even beyond the oncology units.

LIMITATIONS

The review is founded upon secondary evidence in published literature of the past six years (2020-2026). In that way, it is prone to publication bias, especially the exaggeration of severe/ unusual cases. New products and combination regimens can replace some of these recommendations as therapeutic protocols rapidly evolve and their range of indications grows to incorporate CAR-T therapy.

The heterogeneity of CAR constructs, patient groups, and institutional practises restricts the generalizability. Numerous management methods are based upon the professional opinion and not the comparative trials on high level. There is also a possibility of real-life performance of community hospitals that is different from what is being reported at the specialised centres.

CONCLUSIONS

CAR-T therapy has presented a paradigm shift in patient therapy who have reached refractory hematologic malignancies but has a unique signature of systemic complications that often manifest in general medical practise. Specialists in internal medicine should be able to identify early inflammatory syndromes, distinguish them from sepsis and cardiogenic shock, and provide immediate supportive treatment, even involving multidisciplinary teams. Strict surveillance, well-spelt-out escalation events, and sensitivity to delayed immunologic events are needed. CAR-T applications are expected to increase in the future, and a standardised set of hospital guidelines and clinician training is essential in order to achieve safe and effective inpatient care.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Öznur Sarı:** Conception, design, data analysis, writing.
2	**Mehmet Polat:** Interpretation, literature search, critical revisions.