# Long-term follow-up and late complications of CAR-T cell therapy

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## ABSTRACT

**Background:** Chimeric antigen receptor T-cell (CAR-T cell) therapy has transformed the treatment landscape for relapsed or refractory hematologic malignancies. As the number of long-term survivors continues to grow, the recognition and management of late complications have become critical clinical priorities. The existing literature remains fragmented, with limited long-term prospective data and a lack of unified follow-up guidelines. **Methods:** A narrative review of the literature was conducted using PubMed, MEDLINE, and Google Scholar databases from inception through April 2026. Key search terms included long-term follow-up, survivorship, late effects, CAR-T cell therapy, chimeric antigen receptor, late complications, delayed cytopenias, hypogammaglobulinemia, secondary malignancies, immune reconstitution, and screening. This review synthesizes available evidence with expert consensus recommendations. **Results:** The review identifies prolonged cytopenias, hypogammaglobulinemia and infectious complications as the most prevalent late effects. Secondary myeloid neoplasms occur with a shorter latency than historically observed after conventional chemotherapy. Neurocognitive deficits following immune effector cell-associated neurotoxicity syndrome generally resolve within six months. Cardiovascular, endocrine, and reproductive late effects are emerging areas of concern with limited specific data. **Conclusion:** Structured, long-term, multidisciplinary follow-up is essential for CAR-T cell therapy recipients. This review provides recommendations for the long-term surveillance and management of these patients. Prospective registries and standardized screening protocols are urgently needed.

**Keywords:** Survivorship; Receptors, Chimeric Antigen; screening protocols.

## INTRODUCTION

CAR-T cell therapy has achieved unprecedented response rates in relapsed or refractory hematologic malignancies by targeting tumor-associated antigens, most commonly CD19 and B-cell maturation antigen (BCMA).[1,2] Multiple products are now approved for B-cell acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma (LBCL), mantle cell lymphoma, follicular lymphoma, and multiple myeloma.[3] Five-year data from pivotal trials such as ZUMA-1 demonstrate durable remissions in a subset of patients,[4] while acute toxicities, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), are well-characterized and effectively managed.[5]

As the population of long-term survivors grows (over 30,000 patients treated globally), attention has shifted to late complications occurring beyond 90 days after infusion.[6] These include prolonged cytopenias, B-cell aplasia and hypogammaglobulinemia, delayed infections, subsequent malignant neoplasms (including T-cell lymphoma from insertional oncogenesis), neurocognitive sequelae, cardiovascular dysfunction, and psychosocial impairment.[1,5,7] Unlike hematopoietic cell transplantation (HCT), which benefits from decades of survivorship guidelines, CAR-T cell therapy lacks[8] standardized long-term follow-up (LTFU) protocols.[8,9]

This narrative review provides a comprehensive, clinically actionable overview of LTFU requirements and late complications of CAR-T cell therapy, with critical appraisal of available evidence and identification of future research priorities.

## METHODS

This narrative review was conducted through a literature search of PubMed, MEDLINE, and Google Scholar databases from inception through April 2026. The search strategy employed combinations of the following key terms: "long-term follow-up," "survivorship," "late effects," "CAR-T cell therapy," "chimeric antigen receptor," "late complications," "screening," "delayed cytopenias," "hypogammaglobulinemia," "secondary malignancies," "immune reconstitution,""neurotoxicity,""cardiotoxicity,""quality of life," and "vaccination." Additional references were identified through manual review of bibliographies of relevant articles and published guidelines.

Eligible publications included clinical trials, observational cohort studies, retrospective analyses, systematic reviews, meta-analyses, case series, expert consensus statements, and clinical practice guidelines reporting on late effects (occurring ≥30–90 days after infusion) in patients who received CAR-T cell therapy for hematologic malignancies. Studies exclusively addressing acute toxicities (CRS, acute ICANS) without follow-up beyond 30 days were excluded. Studies focusing solely on HCT without a CAR-T cell therapy component were excluded, although HCT data were retained when relevant as contextual background or when patients had received prior HCT before CAR-T cell therapy.

This is a narrative review and does not constitute a formal systematic review or meta-analysis. Recommendations presented herein are based on available evidence synthesized with expert consensus where data are limited. The strength of evidence is appraised within each section.

## RECOMMENDED FOLLOW-UP TIMELINE AFTER CAR-T CELL THERAPY

A structured follow-up schedule is essential for the early detection and management of late complications. Regulatory agencies mandate a minimum of 15 years of LTFU for recipients of products manufactured with integrating viral vectors.[10,11] Table 1 presents a comprehensive recommended follow-up timeline integrating recommendations from the EBMT, institutional protocols, and[1,5,8,12] the available literature.[1,5,8,9,12] Recipients of CAR T cell therapy that have received prior HCT or that undergo subsequent HCT should be managed according to published guidelines for this population.[9]

**Table 1.** Summary of recommended follow-up timeline after CAR-T cell therapy.

| Domain | Day +30 | Day +100 | 6 Months | 1 Year | Annually (≥2 years) |
|---|---|---|---|---|---|
| Hematology | CBC with differential; reticulocyte count | CBC; peripheral blood smear if cytopenic | CBC; B-cell count (CD19+ flow cytometry) | CBC; B-cell count; bone marrow biopsy if persistent cytopenias | CBC; peripheral smear; consider CH screening |
| Immunoglobulins | Quantitative IgG, IgA, IgM | Quantitative immunoglobulins; assess need for IVIG | Quantitative immunoglobulins; IVIG if IgG <400 mg/dL with infections | Quantitative immunoglobulins | Quantitative immunoglobulins; reassess IVIG need |
| Infections | Active surveillance; antimicrobial prophylaxis review | Viral reactivation screen (CMV, EBV, HBV); continue antiviral/PJP prophylaxis | Continue prophylaxis if immunosuppressed; IVIG assessment | Reassess prophylaxis based on immune reconstitution | Reassess infection risk; seasonal vaccinations |
| Immune reconstitution | Lymphocyte subsets (CD4, CD8, CD19, NK cells) | Lymphocyte subsets | Lymphocyte subsets; CD4 count | Lymphocyte subsets | Lymphocyte subsets if clinically indicated |
| Neurology | Neurological exam; cognitive screening | Neurological assessment; neuropsychological testing if ICANS history | Repeat cognitive assessment if deficits | Annual neurological exam | Annual screening; referral if new symptoms |
| Cardiovascular | Troponin, BNP if CRS ≥ grade 2; echocardiogram if indicated | Echocardiogram if prior cardiac events | Cardiovascular risk assessment | Annual cardiovascular screening | Lipid panel; BP; metabolic syndrome screening |
| Pulmonary | Chest imaging if symptomatic | Pulmonary function tests (PFTs) if symptomatic | PFTs if prior pulmonary complications | Annual respiratory assessment | As clinically indicated |

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| Domain | Day +30 | Day +100 | 6 Months | 1 Year | Annually (≥2 years) |
|---|---|---|---|---|---|
| Endocrine | — | TSH; fasting glucose | TSH; gonadal hormones if fertility concerns | TSH; HbA1c; gonadal assessment | Annual thyroid, metabolic, and gonadal screening |
| Renal | Creatinine, electrolytes | Creatinine, urinalysis | Renal function panel | Annual renal panel | Annual renal panel |
| Psychosocial | Distress screening | Quality of life assessment; psychosocial referral if needed | Repeat distress screening; assess return-to-work | Annual psychosocial assessment; caregiver burden screen | Annual screening; survivorship care plan |
| Malignancy surveillance | — | Disease restaging | Disease restaging; skin exam | CBC with differential; age-appropriate cancer screening | CBC; consider CH testing; skin surveillance; age-appropriate screening |
| Vaccinations | — | — | Assess readiness for revaccination (B-cell recovery, IVIG status) | Begin revaccination if immune reconstitution adequate | Annual influenza; booster vaccines per protocol |

CBC: complete blood count, CRS: cytokine release syndrome, ICANS: immune effector cell-associated neurotoxicity syndrome, CMV: Cytomegalovirus, EBV: Epstein-barr virus, HBV: hepatitis B virus, PJP: Pneumocystis jirovecii pneumonia, IVIG: intravenous immunoglobulin, PFT: Pulmonary function tests, HBA1c: glycated hemoglobin, CH: clonal hematopoiesis, BP: blood pressure. Source: Elaborated by the authors using data from Rotz et al. (2024).[9]

## HEMATOLOGIC COMPLICATIONS

### Prolonged and delayed cytopenias

Prolonged cytopenias are among the most common late effects of CAR-T cell therapy. Cytopenias persisting beyond 30 days occur in 30–40% of patients, while those extending beyond 90 days are reported in 3–22%.[3,13] The one-year cumulative incidence of hematological toxicity after CD19-directed CAR-T cell therapy has been reported at 58%, with blood count normalization in approximately 15% at three months and 60% at nine months.[14] Grade 3–4 cytopenias persisted in 11% at two years in the axicabtagene ciloleucel pivotal trial.[15]

The pathophysiology is multifactorial. Immune effector cell-associated hematotoxicity (ICAHT), proposed as a distinct entity, involves both an early inflammatory phase driven by CRS and a late phase related to interferon-mediated signaling, impaired stem cell reserve, and clonal hematopoiesis (CH).[16–18] Risk factors include higher-grade CRS, prior allo-HCT, a greater number of prior therapy lines, elevated CAR-HEMATOTOX score, and pre-existing bone marrow dysfunction.[8,19] Pre-existing CH mutations (most commonly in *TP53*, *DNMT3A*, and *TET2*) can expand post-treatment, contributing to persistent cytopenias and secondary myeloid neoplasms.[16,20] The CAR-HEMATOTOX scoring system is useful for baseline risk stratification.[21] Table 2 summarizes screening and management recommendations.

**Table 2.** Recommendations for screening and management of hematologic complications after CAR-T cell therapy.

| Complication | Screening | Management | Frequency |
|---|---|---|---|
| Prolonged cytopenias | CBC with differential, reticulocyte count, peripheral smear | Growth factors (G-CSF), transfusion support; bone marrow biopsy if persistent for ≥ 1 month to exclude MDS/AML | Monthly to day +100; every 3 months thereafter |
| B-cell aplasia | CD19+ B-cell count by flow cytometry | Monitor; clinical significance depends on infection risk | Every 3–6 months for first 2 years |
| Hypogammaglobulinemia | Quantitative IgG, IgA, IgM | IVIG if IgG <400 mg/dL with recurrent infections; individualize threshold | Monthly initially; every 3–6 months long-term |
| Clonal hematopoiesis | Consider targeted NGS panel (TP53, DNMT3A, TET2) in patients with persistent cytopenias | Hematology referral; bone marrow evaluation | At baseline and if new persistent cytopenias |

CBC: complete blood count, IVIG: intravenous immunoglobulin, NGS: next generation sequencing, MDS/AML: myelodysplastic syndrome/ acute myeloid leukemia. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

### B-cell aplasia and hypogammaglobulinemia

B-cell aplasia is the prototypical "on-target, off-tumor" effect of CD19- and BCMA-directed CAR-T cell therapies, leading to hypogammaglobulinemia and impaired humoral immunity.[7,22] In one study with a median follow-up of 33 months, 51% of LBCL patients had persistent B-cell aplasia beyond six months.[23] Hypogammaglobulinemia (IgG <400 mg/dL) was present in 61.5% at day 90 and 48.3% at two years in a large multicenter cohort;[24] in another series, 78% had hypogammaglobulinemia within six months. IVIG replacement is administered in 22–34% of patients,[24] with higher rates (90.3%) in CLL patients reflecting prolonged CAR-T cell persistence.[25]

Evidence for prolonged cytopenias and hypogammaglobulinemia is robust but limited by heterogeneity in definitions, patient populations (ALL vs. LBCL vs. MM), and CAR-T products. The predictive value of CH screening for secondary myeloid neoplasms remains under investigation, and standardized ICAHT grading criteria are still being refined.[18]

## INFECTIONS AND IMMUNE RECONSTITUTION

Infections are the leading cause of non-relapse mortality (NRM) following CAR-T cell therapy, accounting for over 50% of NRM events.[26,27] Risk factors include prolonged neutropenia, impaired cellular immunity (CD4+ T-cell counts below 200/µL in one-third of patients at one year), B-cell aplasia, and hypogammaglobulinemia.[15,28] Immune reconstitution is characteristically delayed: CD4+ T cells remained deficient throughout the first year (median 162–208/µL at 90–360 days), while CD19+ B cells remained undetectable.[28]

In a multicenter analysis of 582 patients with aggressive lymphoma, bacterial infections occurred in 66.8% (median 6.7 months) and viral infections in 31.2% (median 5.4 months).[24] Hypogammaglobulinemia was significantly associated with increased bacterial infection risk (OR 2.1–2.5), and IVIG administration was associated with improved overall survival.[24] A temporal shift occurs from predominantly bacterial infections early to viral infections in the late phase, with the respiratory tract as the primary focus (~47% of late infections).[28] Beyond one year, 54.8% of patients experienced infections, including opportunistic pathogens such as progressive multifocal leukoencephalopathy and tissue-invasive CMV disease.[29]

Antimicrobial prophylaxis is widely employed (98.4% antivirals, 74.5% PJP prophylaxis).[24] Expert consensus recommends continuing antiviral and PJP prophylaxis for at least 12 months, or longer if CD4 counts remain below 200/µL.[30,31]. Table 3 outlines infection screening and management recommendations.

**Table 3.** Recommendations for infection screening and management after CAR-T cell therapy.

| Complication | Screening/monitoring | Management | Duration |
|---|---|---|---|
| Bacterial infections | Blood cultures if febrile; surveillance cultures as clinically indicated | Empiric broad-spectrum antibiotics for febrile neutropenia | As indicated clinically |
| Viral reactivation (HSV, VZV, CMV, HBV) | Serology at baseline; CMV PCR monitoring if seropositive | Acyclovir/valacyclovir prophylaxis; entecavir for HBV | ≥12 months or until CD4 >200/µL |
| PJP | CD4 count monitoring | TMP-SMX or alternative prophylaxis | ≥12 months; continue if CD4 <200/µL |
| Fungal infections | Clinical monitoring; CT chest if symptomatic | Anti-mold prophylaxis for prolonged neutropenia or use of high-dose steroids. | During prolonged neutropenia or while risk persists |
| Hypogammaglobulinemia-related infections | Quantitative immunoglobulins | Consider IVIG replacement (IgG target >400 mg/dL), especially in anti-BCMA CAR T. | Ongoing until B-cell recovery and IgG stabilization |

HSV: herpes simplex virus, VZV: varicella zoster virus, CMV: Cytomegalovirus, HBV: hepatitis B virus, PJP: Pneumocystis jirovesis pneumonia, TMP-SMX: trimethoprim-sulfamethoxazole. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

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The evidence base for late infections after CAR-T cell therapy is growing, with large multicenter retrospective studies providing valuable data. However, there are no randomized trials evaluating optimal prophylaxis duration, IVIG thresholds, or prophylaxis discontinuation criteria. The multicenter study by Melody et al.[24] provides the most robust real-world data to date, but selection bias and confounding by post-relapse therapies limit causal inference. Prospective studies are needed to refine prophylaxis protocols and identify modifiable risk factors.

## NEUROCOGNITIVE COMPLICATIONS

While acute ICANS is well-recognized and typically resolves within days to weeks, delayed neurocognitive effects following CAR-T cell therapy represent an underappreciated late complication. Approximately 10% of patients develop new neurological findings at one year requiring intervention,[32] and the EBMT has published guidelines specifically addressing non-ICANS neurological complications, including movement disorders, neurocognitive dysfunction, and cranial nerve palsies.[33]

A prospective study of 20 patients assessed before and after CAR-T cell therapy found that patients who experienced acute ICANS had significant declines in executive function, verbal memory, and auditory attention span at one month post-infusion. However, these deficits resolved by six months with no group differences at one year, suggesting complete resolution of the cognitive manifestations of ICANS in most patients.[34] Nonetheless, a systematic review of cancer-related cognitive impairment after CAR-T cell therapy identified a subset of patients with persistent deficits, though prevalence estimates vary widely due to heterogeneous assessment methods.[35]

In the pediatric population, neurocognitive monitoring has been highlighted as a priority, with recommendations for formal neuropsychological assessment at baseline and at defined intervals post-infusion.[36] BCMA-directed CAR-T cell therapies have been associated with distinct delayed neurotoxicities, including a neurocognitive and hypokinetic movement disorder with parkinsonian features, which may emerge weeks to months after infusion.[37,38] Table 4 provides recommendations for neurocognitive screening.

**Table 4.** Recommendations for neurocognitive screening after CAR-T cell therapy.

| Domain | Screening tool | Timing | Referral criteria |
|---|---|---|---|
| Cognitive function | Brief cognitive screening (e.g., MoCA); consider neuropsychological battery if ICANS history | Baseline, 1 month, 6 months, 1 year | Persistent deficits at 6 months; new cognitive complaints |
| Neurological exam | Standardized neurological examination | Each follow-up visit | New focal deficits, movement disorders, or cranial nerve abnormalities |
| Psychological symptoms | Self-report (PHQ-9, GAD-7) | Baseline and each follow-up | Moderate-to-severe symptoms; functional impairment |

ICANS: immune effector cell-associated neurotoxicity syndrome. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

Evidence on long-term neurocognitive outcomes is limited by small sample sizes, absence of standardized cognitive batteries, and short follow-up periods in most studies. The distinct neurotoxicity profile of BCMA-directed products underscores the need for target-specific surveillance. Large, multicenter prospective studies with standardized neurocognitive assessments are urgently needed.[34,35]

## CARDIOVASCULAR COMPLICATIONS

Cardiovascular toxicity following CAR-T cell therapy is an emerging concern, particularly in the context of severe CRS, which triggers a cytokine-mediated inflammatory cascade that can cause myocardial injury, arrhythmias,

and hemodynamic instability. Approximately 10% of CAR-T cell therapy recipients may develop new cardiac complications, particularly those with severe CRS.[10] A large propensity-matched cohort analysis using the TriNetX database demonstrated an increased long-term risk of major adverse cardiovascular events (MACE) in hematologic malignancy patients treated with CAR-T cell therapy compared with matched controls.[39]

Mechanisms of cardiotoxicity include direct cytokine-mediated myocardial damage (particularly by interleukin-6 and interferon-γ), troponin elevation during CRS, and pre-existing cardiovascular risk factors exacerbated by treatment-related stress.[40,41] In the CD22 CAR-T cell trial, two of six NRM events were due to treatment-unrelated cardiac events, highlighting that the heavily pretreated patient population carries intrinsic cardiovascular risk.[42] Table 5 outlines cardiovascular screening recommendations.

**Table 5.** Recommendations for cardiovascular screening after CAR-T cell therapy.

| Assessment | Indication | Timing |
|---|---|---|
| Troponin, BNP/NT-proBNP | All patients with CRS ≥ grade 2 | Acute phase; repeat at day +100 if elevated |
| Echocardiogram | Baseline if risk factors; post-CRS if cardiac symptoms | Baseline, post-CRS if needed |
| Cardiovascular risk factor assessment | All patients | Annually |
| Lipid panel, HbA1c, blood pressure | All patients | Annually from 1 year onward |

HBA1c: glycated hemoglobin, CRS: cytokine release syndrome. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

CAR-T-specific cardiovascular data are largely derived from retrospective analyses, pharmacovigilance databases, and single-center case series. Large prospective studies with predefined cardiac endpoints are lacking. It remains unclear whether cardiac injury during CRS leads to lasting structural damage or accelerated atherosclerosis in survivors. Collaboration with cardio-oncology services is recommended for high-risk patients.[39,40,41]

## RESPIRATORY COMPLICATIONS

Pulmonary late effects after CAR-T cell therapy are primarily infectious in etiology. Respiratory infections predominate after day 100, particularly in recipients of BCMA-directed products.[43] In one analysis, the respiratory tract was the focus of approximately 47% of all late infections.[28] Non-infectious pulmonary complications, including organizing pneumonia, pulmonary fibrosis, and bronchiolitis obliterans, have been sporadically reported but are not well-characterized in the CAR-T cell therapy literature.[5]

Patients who experienced severe CRS with associated capillary leak or pulmonary edema during the acute phase may be at risk for persistent pulmonary dysfunction, although this has not been systematically studied. Pulmonary function tests (PFTs) should be considered in patients with ongoing respiratory symptoms.[5]

There is a notable paucity of CAR-T-specific data on non-infectious pulmonary late effects. Most available evidence is extrapolated from the HCT literature or consists of isolated case reports. Prospective longitudinal studies incorporating serial PFTs are needed to define the incidence and natural history of pulmonary complications after CAR-T cell therapy.[5,43]

## ENDOCRINE COMPLICATIONS

Endocrine late effects after CAR-T cell therapy are an emerging area with limited but growing data. Pharmacovigilance analyses have reported thyroiditis, adrenal insufficiency, and hypophysitis in approximately 5–10% of CAR-T cell therapy recipients, often manifesting months after treatment[10]. In a long-term follow-up study of children and young adults after CAR-T cell therapy (median follow-up 6.7 years), endocrinopathies were observed in 62.5% of patients, although many had also received HCT, making attribution to CAR-T cell therapy alone difficult.[44] A case of late-onset invasive aspergillosis with

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pituitary involvement and dysfunction following CD19 CAR-T cell therapy has been reported, illustrating the intersection of infectious and endocrine complications.[45]

The contribution of lymphodepleting chemotherapy (typically fludarabine and cyclophosphamide) to gonadal toxicity and metabolic dysfunction must be considered, as these agents are known to affect endocrine function.[5] Thyroid function screening with thyroid-stimulating hormone (TSH) is recommended at baseline and periodically during follow-up (see Table 1).

CAR-T-specific endocrine data are extremely limited, consisting primarily of case reports and subgroup analyses within larger cohort studies. Most endocrine late effects reported in pediatric populations are confounded by prior HCT or total body irradiation. Dedicated prospective studies evaluating endocrine function in adult CAR-T cell therapy recipients who have not undergone HCT are lacking.[44]

## OCULAR COMPLICATIONS

Ocular adverse events following CAR-T cell therapy are uncommon but increasingly recognized. Data from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) indicate that ophthalmologic events account for approximately 1.97% of all adverse events associated with cellular therapies. Tisagenlecleucel accounted for the majority of reported ocular cases, with the most common events being visual impairment (35.3%), abnormal pupillary response (17.7%), papilledema (11.8%), mydriasis (11.8%), and photophobia (11.8%).[5]

Patients may report floaters, photopsia, or blurred vision without correlating physical examination findings. These symptoms can occur both early and late after infusion. Cases of ocular herpes zoster and acute retinal necrosis have been described, likely secondary to viral reactivation in the setting of immunosuppression. In patients who underwent prior allogeneic HCT, worsening of ocular chronic graft-versus-host disease (cGVHD) has been reported after CAR-T cell therapy.[5] Table 6 summarizes recommendations for ocular follow-up.

**Table 6.** Recommendations for ocular follow-up after CAR-T cell therapy.

| Recommendation | Details |
|---|---|
| Ophthalmologic follow-up | Rigorous monitoring for patients with prior history of ocular cGVHD |
| Nonspecific ocular complaints | Prompt investigation in all CAR-T cell therapy recipients due to increased infection risk |

cGVHD: chronic graft versus host disease. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

## ORAL AND DENTAL COMPLICATIONS

There are currently no published data specifically characterizing oral or dental late effects attributable to CAR-T cell therapy. In the HCT literature, oral cGVHD, xerostomia, and dental caries are well-documented complications; however, these are related to the alloimmune process and are not expected in autologous CAR-T cell therapy recipients. Patients who received prior HCT before CAR-T cell therapy may carry residual oral complications from their transplant.[5]

Lymphodepleting chemotherapy may transiently affect oral mucosa, but long-term oral complications specific to CAR-T cell therapy have not been characterized. Routine dental surveillance as recommended for the general oncology population is appropriate. This is a knowledge gap with no CAR-T-specific evidence. Future studies should include standardized oral assessments in long-term follow-up protocols.[5]

## DERMATOLOGICAL COMPLICATIONS

Dermatological late effects after CAR-T cell therapy are poorly characterized. CAR-T cell therapy-related T-cell malignancies may manifest with cutaneous involvement, and awareness of skin lesions in this population has

been emphasized.[46] New skin lesions, particularly those suggestive of lymphoproliferative disorders, should prompt biopsy and further evaluation. Non-melanoma skin cancer was the second most common second primary malignancy (15.5%) in a systematic review.[47]

In patients with prior allogeneic HCT, CAR-T cell therapy may exacerbate or trigger cutaneous cGVHD. Annual dermatologic examination is recommended, with a low threshold for biopsy of suspicious lesions. Dermatological data are extremely limited and are largely extrapolated from secondary malignancy reports or post-HCT observations. Dedicated dermatologic assessments in CAR-T cell therapy cohorts are needed.[5,46]

## FERTILITY, SEXUALITY, AND PREGNANCY

The impact of CAR-T cell therapy on fertility is a significant concern, particularly for young adults and pediatric patients. The primary gonadotoxic risk is attributed to lymphodepleting chemotherapy (fludarabine and cyclophosphamide), which can impair ovarian and testicular function, rather than to the CAR-T cells themselves.[48] However, given that most patients have received multiple prior lines of therapy including alkylating agents, the incremental contribution of LD chemotherapy is difficult to isolate.

Current recommendations advocate for fertility preservation counseling before initiating CAR-T cell therapy, including sperm cryopreservation, oocyte/embryo banking, and ovarian tissue preservation as appropriate.[5,48] A study assessing sexual health in young adult patients after CAR-T cell therapy identified concerns including decreased libido, fatigue-related sexual dysfunction, and body image changes, highlighting the need for proactive sexual health support.[49] Table 7 provides recommendations for fertility and reproductive health management.

**Table 7.** Recommendations for fertility and reproductive health after CAR-T cell therapy.

| Recommendation | Details |
|---|---|
| Pre-treatment fertility counseling | All patients of reproductive age; discuss cryopreservation options |
| Gonadal function assessment | FSH, LH, estradiol/testosterone at 6 months and 1 year; anti-Müllerian hormone in females |
| Contraception advice | Recommend effective contraception for at least 12 months post-infusion |
| Sexual health screening | Assess at follow-up visits; referral to fertility/sexual medicine specialists |

Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

Evidence is limited to expert recommendations and small observational studies. No prospective studies have systematically assessed gonadal function in CAR-T cell therapy recipients independent of prior therapy. The relative contribution of LD chemotherapy versus prior treatments to gonadotoxicity remains unclear.[48,49]

## SKELETAL COMPLICATIONS

There are no published data on bone mineral density or skeletal complications specifically attributable to CAR-T cell therapy. However, patients may be at risk for bone loss due to prior corticosteroid exposure (both as part of prior therapies and for CRS/ICANS management), prolonged immobility, and gonadal dysfunction. Lymphoma and myeloma patients may also have disease-related bone involvement.[5]

Bone density assessment with dual-energy X-ray absorptiometry (DEXA) should be considered in patients with cumulative corticosteroid exposure or other risk factors for osteoporosis, following general oncology guidelines.[5]

## RENAL COMPLICATIONS

Renal complications may arise from tumor lysis syndrome during CAR-T cell expansion, CRS-associated hemodynamic instability, nephrotoxic medications, and contrast exposure during imaging surveillance. There is limited CAR-T-specific literature on chronic kidney disease (CKD) as a late effect.[5]

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Baseline and periodic assessment of renal function (serum creatinine, estimated glomerular filtration rate, electrolytes, urinalysis) is recommended as part of routine follow-up (see Table 1). Patients with pre-existing renal impairment or those who experienced renal injury during the acute phase should undergo more frequent monitoring.[5]

## PSYCHOSOCIAL HEALTH AND QUALITY OF LIFE

Psychosocial late effects are increasingly recognized in CAR-T cell therapy survivorship, including persistent fatigue, anxiety, depression, post-traumatic stress, and difficulty returning to work,[5,36,50,51] While overall quality of life (QoL) in long-term survivors is generally comparable to the general population, a meaningful subset reports persistent fatigue, cognitive complaints, and emotional distress.[52] Despite disease remission, many patients face ongoing functional limitations, reduced social participation, and unmet needs including inadequate psychological support and financial toxicity.[53,54]

Caregiver burden is substantial, with high rates of anxiety and role strain.[36,54] Remote monitoring programs such as the CARAMA nurse-led initiative have shown promise in managing late complications while reducing burden.[55] Table 8 presents recommendations for psychosocial screening.

**Table 8.** Recommendations for psychosocial screening and support after CAR-T cell therapy.

| Domain | Screening tool | Timing | Intervention |
|---|---|---|---|
| Psychological distress | Distress Thermometer; PHQ-9; GAD-7 | Baseline, day +100, 6 months, 1 year, annually | Referral to psycho-oncology; cognitive behavioral therapy |
| Fatigue | FACIT-Fatigue; PRO-CTCAE | Each follow-up visit | Exercise programs; sleep hygiene; fatigue management |
| Return-to-work | Functional assessment | 6 months, 1 year | Vocational rehabilitation; occupational therapy |
| Caregiver burden | Caregiver Strain Index | 1 month, 6 months, 1 year | Support groups; respite care; psychological support |

PRO data are growing but limited by cross-sectional designs, small samples, and heterogeneous instruments. The finding that QoL is comparable to the general population[7] may reflect survivorship bias. Longitudinal prospective assessments with standardized instruments are needed. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

## SUBSEQUENT MALIGNANT NEOPLASMS

The risk of subsequent malignant neoplasms (SMNs) after CAR-T cell therapy has emerged as one of the most scrutinized late effects.[47,6,27]

### Secondary myeloid neoplasms

Treatment-related myeloid neoplasms (tMN), encompassing MDS and AML, are the most common SMN after CAR-T cell therapy. In an aggregated dataset of 1,542 lymphoma patients (median follow-up 24 months), secondary hematologic malignancies occurred in 3.4% (2.45% per patient-year), predominantly MDS (75%) and AML (26%).[6] A French bicentric analysis reported cumulative tMN incidences of 1.4% at one year, 4.2% at two years, and 7.1% at three years.[56]

Time to onset is notably shorter after CAR-T cell therapy (median 16–20 months) compared with autologous transplantation (~57 months) or standard chemotherapy (~62 months).[57,58] Molecular characterization reveals high frequencies of *TP53* mutations (40–47%), chromosome 7 deletions, and[57–59] complex karyotypes.[57–60] Pre-existing CH mutations, particularly in *TP53*, expand dramatically post-infusion, suggesting clonal selection rather than de novo mutagenesis.[20] Risk factors include older age, more prior therapy lines, high CAR-HEMATOTOX score, and persistent cytopenias.[56,61] Prognosis is poor, with median overall survival of 5.5–9.2 months.[56–58]

### T-cell lymphoma and insertional oncogenesis

The FDA issued a boxed warning in 2024 regarding T-cell malignancies in CAR-T cell therapy recipients, raising concerns about insertional oncogenesis.[3] Cases of T-cell lymphoma containing the CAR construct within the malignant clone have been documented,[62,63] with real-world incidences of 1.04% for tisagenlecleucel and 2.56% for axicabtagene ciloleucel.[64] However, the absolute risk appears very low: in the aggregated trial dataset, T-cell malignancy occurred in only one of 1,542 patients, and a meta-analysis of 7,604 patients found no attributable deaths.[6,27]

### Solid tumors

Solid SMNs have been reported, including skin cancer (15.5% of SMNs), prostate cancer, and lung cancer.[47] In the pediatric follow-up, 8% developed new primary cancers at a median of 6.7 years.[44] Table 9 outlines surveillance recommendations.

**Table 9.** Recommendations for secondary malignancy surveillance after CAR-T cell therapy.

| Malignancy type | Screening | Timing |
|---|---|---|
| Myeloid neoplasms (MDS/AML) | CBC with differential; peripheral blood smear; consider CH panel (TP53, DNMT3A, TET2) | Every 3 months for 2 years; annually thereafter; BM biopsy if new cytopenias |
| T-cell lymphoma | Clinical vigilance; PET-CT or biopsy of suspicious lymphadenopathy or skin lesions | At each follow-up; low threshold for biopsy |
| Solid tumors | Age-appropriate cancer screening per general population guidelines; skin examination | Annually |

MDS/AML: myelodysplastic syndrome/ acute myeloid leukemia, CH: clonal hematopoiesis, BM: bone marrow. Source: Elaborated by the authors using data from Rotz et al., (2024).[9]

Multiple large retrospective cohorts and aggregated trial data are now available, but limitations include inability to disentangle the contribution of CAR-T cell therapy from prior genotoxic therapies, short follow-up, and potential reporting bias. The 15-year LTFU requirement is appropriate, but optimal screening strategies require prospective validation. Pre-treatment CH screening as a risk-stratification tool is promising but not yet validated for clinical decision-making.[6,56,27]

## IMMUNIZATIONS

Revaccination after CAR-T cell therapy is critical given the prolonged humoral immune deficiency from B-cell aplasia and hypogammaglobulinemia.[65] CD19-directed CAR-T cell therapy recipients maintained seroprotection rates comparable to the general population, while BCMA-directed recipients had significantly fewer pathogen-specific antibodies (prevalence ratio 0.47).[65] Influenza vaccine immunogenicity is reduced but measurable, supporting vaccination regardless of B-cell aplasia.[66,67]

Expert consensus and EBMT guidelines suggest initiating revaccination 3–6 months after infusion once immune reconstitution is evident.[2,12,68,69] Inactivated vaccines are considered safe; live vaccines should be considered after 2 years post-infusion in patients with adequate immune reconstitution. Annual influenza vaccination is recommended for all recipients and household contacts.[69,70] The Brazilian Immunization Society (SBIm) provides regularly updated vaccination calendars tailored for immunocompromised patients, including post-CAR-T cell therapy recipients.[71] Table 10 presents a suggested revaccination schedule for children aged ≥ 7 years and adults.

Vaccination data are limited to small observational studies. No randomized trials have evaluated optimal timing or correlates of protection. Current schedules are largely extrapolated from HCT literature and require prospective validation in CAR-T cell therapy recipients.[65,66,69,70]

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**Table 10.** Recommended immunizations following CAR-T cell therapy (children aged ≥ 7 years and adults).

| Inactivated Vaccines | Interval to Start Revaccination After HCT | Dose Schedule, Considering Post-HCT Interval | Comments | Availability CRIE / Private Clinics |
|---|---|---|---|---|
| Influenza | Ideal: 6 months<br>Minimum: 3 months | Children 7 to 8 years: two doses with a 30-day interval.<br>Children younger than 9 years should receive two doses with a one-month interval. | People over 60 should preferably receive the high-dose vaccine (HD).<br>Vaccinate household contacts. | YES – 3V in CRIE for patients and contacts.<br>YES – 3V, 4V and HD in Private Clinics. |
| COVID-19 | 6 months | Access updated data on groups covered by the PNI, vaccine availability, and schedules at: https://www.gov.br/saude/pt-br/assuntos/covid-19 | | YES – in CRIE and BHU. |
| RZV | 2-12 months | Two doses with an interval of 1-2 months.<br>For autologous transplants - vaccinate between 2 and 6 months after HCT.<br>For allogeneic transplants (fewer data on efficacy) - vaccinate between 6 and 12 months after HCT, in the absence of GVHD or off immunosuppressive therapy. | For seropositive individuals aged 18 years and older. | YES – in private clinics. |
| DTaP/IPV | 7 months | Three doses: 7 - 9 - 11 months. | If DTaP/IPV vaccine is not available, administer DTaP and IPV separately. | YES – DTaP/IPV in private clinics.<br>YES – DTaP and isolated IPV in CRIE. |
| PCV20, PCV15 or PCV13 | 6 months | PCV20: four doses, 6 - 8 - 10 months and a booster 6 months after D3 (at least 12 months after HCT).<br>OR: Sequential schedule PCV15/13 and PPSV23: 3 doses PCV at 6 - 8 -10 and PPSV23 one dose six months after D3 (at least 12 months after HCT). If GVHD occurs, swap this dose of PPSV23 for PCV15/13. | If PCV20 is used, PPSV23 is not recommended.<br>If PCV15 or PCV13 is used, it is necessary to follow the sequential schedule with PPSV23. | YES – PCV20, PCV15 and PCV13, in private clinics and PCV13 in CRIE. |
| Hib | 7 months | Three doses: 7 - 9 - 11 months. | | YES – in CRIE and private clinics. |
| PPSV23 | 2 months after the last dose of PCV15 or PCV13. | Two doses. The first dose should be administered from 12 months after transplantation. The second dose five years after the first. | The first dose must be applied at least two months after the last dose of PCV13 or PCV15.<br>If PCV20 is used, PPSV23 is not recommended. | YES – in CRIE and private clinics. |
| MenACWY or MenC | 6 months | Two doses: 10 - 12 months. | | YES – in CRIE and private clinics. |
| Men B | 6 months | Two doses: Bexsero® 10-12 months, Trumenba® 10-16 months. | Bexsero® licensed up to 50 years. Trumenba® licensed from 10 to 25 years. Not interchangeable. | YES – in private clinics. |
| Hep A | 6 months | Two doses: 11 - 17 months. | | YES – in CRIE and private clinics. |
| Hep B | 6 months | Three doses: 11 - 12 - 17 months. | It is necessary to request serology for Hepatitis B 30 to 60 days after the last dose of the schedule. Immunity is considered present if anti-HBs is ≥ 10 mUI/mL. If serology is negative, repeat the three-dose vaccine schedule once more. | YES – in private clinics, in the combined Hepatitis A+B form. |
| HPV4 and HPV9 | 6 months | Three doses: 11 - 13 - 17 months. | Two vaccines are available in Brazil, HPV4 and HPV9. Prefer HPV9 to expand protection; if not available, HPV4 can be used. | YES – HPV4 in CRIE, for women and men up to 45 years.<br>YES – HPV9 in private clinics. |

| Inactivated Vaccines | Interval to Start Revaccination After HCT | Dose Schedule, Considering Post-HCT Interval | Comments | Availability CRIE / Private Clinics |
|---|---|---|---|---|
| RVS | 12 months | Single dose. From 12 months, at any time, independently of seasonality. | Recommended from 50 years of age.<br>Two vaccines are available: Arexvy® (GSK) and Abrysvo® (Pfizer). | YES – in private clinics. |
| Attenuated Vaccines | Interval to Start Revaccination After HCT | Dose Schedule, Considering Post-HCT Interval | Comments | Availability CRIE / Private Clinics |
| Dengue | 24 months | Two doses: 25 and 28 months | Dengue vaccine should be administered with an interval of 30 days from any other attenuated vaccine.<br>Licensed for people aged 4 to 60 years.<br>If the epidemiological risk and immune status permit, it can be administered from 12 months onward. Otherwise, wait 24 months or until there is evidence of immune system reconstitution. | BHU 10-14 years and private clinics from 4 years. |
| MMR | 12 - 24 months | Two doses: 24 - 25 months. | Vaccinate household contacts. | YES – in CRIE for patients and contacts and private clinics. |
| Varicella | 24 months | Two doses: 24 - 25 months. | Vaccinate seronegative <50 years.<br>Low efficacy in preventing shingles in seropositive individuals.<br>Vaccinate household contacts. | YES – in CRIE for patients and contacts and private clinics. |
| Yellow Fever | 24 months | Two doses: first 24 months and second 10 years later. | | YES – in CRIE and private clinics. |

HCT (Hematopoietic Cell Transplantation), HD (High-Dose, for Influenza vaccine), PNI (Programa Nacional de Imunização), CRIE (Centros de Referência para Imunobiológicos Especiais), BHU (Brazil's Basic Health Units), RZV (Recombinant zoster vaccine), GVHD (Graft-versus-Host Disease), dTpa/IPV (Diphtheria, Tetanus, acellular Pertussis / Inactivated Polio Vaccine), PCV20, PCV15, PCV13 (Pneumococcal Conjugate Vaccine, 20-valent, 15-valent, and 13-valent) PPSV23 (Pneumococcal Polysaccharide Vaccine, 23-valent), Hib (Haemophilus influenzae type b), MenACWY, MenC, MenB (Meningococcal Conjugate Vaccines), Hep A, Hep B (Hepatitis A and B), HPV4, HPV9 (Human Papillomavirus Vaccine, 4-valent and 9-valent), RSV (Respiratory Syncytial Virus), GSK and Pfizer (pharmaceutical companies), and MMR (Measles, Mumps, Rubella). Source: Adapted from SBIm, (2025).[71]

## KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite the expanding literature, critical gaps persist:

- Prospective data: Most evidence derives from retrospective cohorts with heterogeneous populations and variable follow-up. Multicenter prospective registries with standardized data collection. (including immune reconstitution, neurocognitive assessments, cardiac biomarkers, PROs, and fertility outcomes) are urgently needed.[36,72]
- Etiology attribution: Disentangling late effects of CAR-T cell therapy from those of LD chemotherapy, prior therapies, or the underlying disease remains a fundamental challenge. Patients treated in earlier lines may help isolate CAR-T-specific effects.[42]
- Clonal hematopoiesis: The role of pre-existing CH in driving tMN, and whether pre-treatment screening should influence decisions, remain open questions.[20,59]
- Organ-specific effects: Data on cardiovascular, pulmonary, endocrine, renal, skeletal, ocular, oral, and dermatological late effects specific to CAR-T cell therapy are absent or extremely limited.[5,10]
- Vaccination: Optimal revaccination timing, vaccine type, need for live vaccines, and correlates of protection remain poorly defined.[65,66,67]

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- Psychosocial care and PROs: Standardized longitudinal assessments are needed to understand QoL recovery trajectories and identify patients at risk.[52,54]
- Pediatric considerations: Long-term effects on neurodevelopment, growth, endocrine function, and educational attainment are particularly underexplored[36,44]
- Novel constructs: As CAR-T cell therapy expands to new targets (CD22, GPRC5D) and indications (autoimmune diseases), novel late-effect profiles may emerge, requiring dedicated surveillance programs.[72]

## CONCLUSION

The most prevalent late effects include prolonged cytopenias, hypogammaglobulinemia, and infectious complications from impaired immune reconstitution. Secondary myeloid neoplasms carry a poor prognosis, while T-cell lymphoma from insertional oncogenesis, though rare, warrants vigilance. Neurocognitive deficits generally resolve within six months, and cardiovascular, endocrine, and reproductive late effects remain emerging areas with limited data.

Structured, multidisciplinary LTFU is essential. The timeline in Table 1 provides a practical framework requiring prospective validation. Priorities include development of prospective registries, standardized screening protocols, integrated survivorship care plans, and collaborative international efforts to optimize outcomes for CAR-T cell therapy survivors.[9,36]

## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

## AUTHOR'S CONTRIBUTIONS

**Conceptualization:** Fatobene G. **Investigation:** Barroso KSN. **Methodology:** Fatobene G. **Formal Analysis:** Barroso KSN. **Data Curation:** Barroso KSN. **Project Administration:** Barroso KSN. **Funding Acquisition:** Not applicable. **Writing:** Barroso KSN. **Supervision:** Fatobene G. **Final Approval:** Fatobene G.

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## DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that they did not use Artificial Intelligence tools at any stage of the preparation, correction, or evaluation of this work.

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