DOI: 10.46765/2675-374X.2022V3N2P167

# MANAGEMENT OF INFECTIONS AND VACCINATION IN CAR-T CELL THERAPY

Clarisse Martins Machado[1]

*1 Universidade de São Paulo*

Correspondence to: clarisse martins machado (clarimm@usp.br)

Received: 01 Sep 2022 • Revised: 26 Sep 2022 • Accepted: 13 Nov 2022.

## GOALS

1. Describe the procedures necessary for the clinical and epidemiological evaluation of the chimeric antigen receptor T-cell therapy (CAR-T cell therapy) candidate, classify the infectious risk, define the criteria for the implementation of prophylactic, empirical and preemptive antimicrobial strategies and guide laboratory and clinical monitoring of the infectious events.

2. Define the indications and contraindications of inactivated and attenuated vaccines and propose a vaccination schedule before and after CAR-T therapy.

## INTRODUCTION

As a result of the underlying disease and previous cytotoxic treatments, candidates for CAR-T cell therapy are at increased risk of infections due to the high degree of pre-existing immunosuppression. This immunosuppressive state is aggravated by the lymphodepleting chemotherapy given prior to CAR-T infusion, and later by prolonged cytopenias, due to the "on target, off-tumor" depletion of normal CD19-expressing B cells in most patients, which contributes to hypogammaglobulinemia[1]. Furthermore, despite encouraging results, the currently approved CAR-T cell therapy products have severe toxicities, including cytokine release syndrome (CRS) and immune-effector cell associated neurological syndrome (ICANS)[2,3].

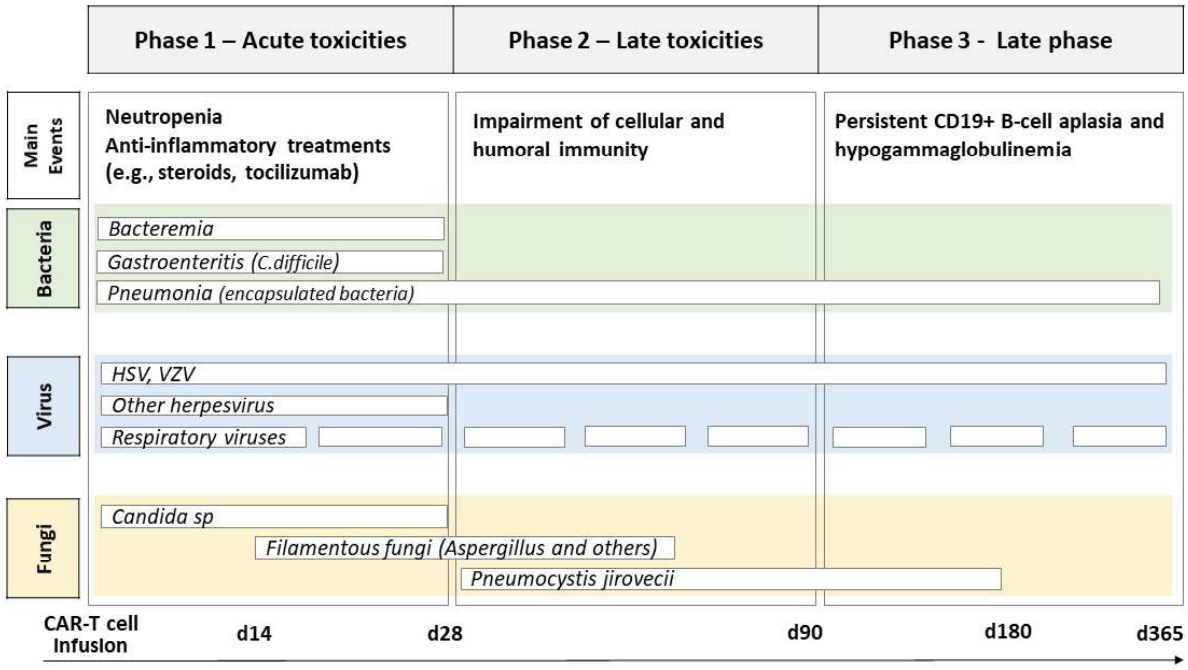
The treatment of these acute complications in addition to the cytopenias may result in deep and long-term immunological deficits, as the CAR-T cells can persist for years[4-6]. Approximately 18% to 34% of patients develop infections within the first 2 months after CAR-T therapy despite antimicrobial prophylaxis[7].

The rapidity of commercialization and use of CAR-T therapies has revealed an unexplored gap in the management of infections in these patients. The recommendations suggested in this manual are based on data from retrospective studies, expert opinion and approaches used in other relevant settings, since to date, there are no randomized controlled trials on infections in recipients of CAR-T therapy.

## PREVALENCE OF POST-CAR-T THERAPY INFECTIONS AND RISK FACTORS

Infections post-CAR-T therapy are distributed with varied frequency in 3 distinct periods, namely: phase 1, up to 30 days after cell therapy infusion, considered the critical period when acute toxicities are expected (CRS, ICANS); phase 2, between 30 and 90 days after infusion, characterized by infectious events that reflect the slow reconstitution of cellular and humoral immunity; and phase 3, after 90 days of CAR-T therapy with infections mainly due to hypogammaglobulinemia and persistent B-cell aplasia. Figure 1 shows the main infectious agents according to the period after CAR-T therapy.

**FIGURE 1.** **Relevant infections according to period after CAR-T therapy[4].**




A growing number of publications has emerged on infections in CAR-T therapy and, therefore, the recommendations described in this manual should be updated as information with a higher level of evidence becomes available.

To date, most infections are caused by bacteria and almost all cases of bacteremia occur within the first 2 weeks after CAR-T cell infusion. Respiratory virus infections are the second in frequency. There are case reports of herpes simplex virus (HSV) and varicella-zoster (VZV) reactivation in patients with poor compliance to acyclovir prophylaxis but infections due to other herpesviruses and double-stranded DNA viruses (adenovirus, polyomavirus BK) seem to be rare, as well as invasive fungal infections[4].

The risk factors for infections reported in some recently published studies are related to both the host and CAR-T therapy. Factors related to the host include the status of underlying disease, previous chemotherapy, cumulative immunosuppression by previous therapies, previous HCT (allogeneic or autologous), basal cytopenia, presence of comorbidities, previous infections and antimicrobial prophylaxis. Regarding to the factors associated with CAR-T therapy are relevant the type of CAR-T therapy (dose, administration schedule, resulting cytopenias and other hematological side effects), the occurrence of serious adverse events that require additional immunosuppression such as, CRS, ICANS, hemophagocytic lymphohistiocytosis and macrophage activation syndrome, the conditioning regimen and the resulting hypogammaglobulinemia[8].

Lower infection rates are observed in patients who used the optimized dose of CAR-T cells, determined by the underlying disease and tumor burden[1]. According to previous studies, the optimized dose of CAR-T cells maintains the same antitumor activity with a reduced risk of severe CRS[9,10]. Therefore, the use of optimized dose of CAR-T cells is an important step in the management of infections in this setting. Table 1 shows some studies published to date reporting infection rates.

**TABLE 1. Recent publications reporting prevalence rates of infections in CAR-T therapy.**

| Author (year) | Time of occurence | N | Frequency | Agents | | | Reference |
|---|---|---|---|---|---|---|---|
| | | | | Bacteria | Virus | Fungi | |
| Hill (2018) | Early (□28 dias) | 133 | 23% | 17% | 8% | 3% | (1) |
| | Late (>28 dias) | 119 | 14% | 7% | 9% | 2% | |
| Park (2018) | Early (□ 30 dias) | 53 | 42% | 30% | 9% | 8% | (6) |
| | Late (>30 dias) | 32 | 31% | 16% | 28% | 3% | |
| Luo (2019) | Up to 30 days | 109 | 17% | 13% | 3% | 2% | (11) |
| Wudhikan (2020) | Up to 12 months | 60 | 63% | 57% | 44% | 4% | (12) |
| Vora (2020) | Early (□28 days) | 83 | 40% | 18% | 19% | 1% | (13) |
| | Late (>28 days) | 48 | 17% | 6% | 11% | 0% | |
| Cordeiro (2020) | After 90 days | 54 | 61% | 12% | 11% | 3% | |
| Logue (2021) | Early (£ 30d) | 85 | 37% | - | - | - | |
| | Late (>30d) | 70 | 44% | - | - | - | |
| Strati (2021) | Up to 24 months | 31 | 77% | 14% | 24% | 6% | (16) |

For a better understanding of the actions to control infections in CAR-T therapy, the steps will be described according to the longitudinal follow-up of patients, namely: 1) Infectious assessment before CAR-T therapy; 2) Antimicrobial prophylaxis and monitoring of infections and 3) Vaccination in candidates and recipients of CAR-T therapy.

## 1. CLINICAL AND EPIDEMIOLOGICAL EVALUATION BEFORE CAR-T THERAPY

### 1.1. Serological tests

Serology for HIV, HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), anti-HBc (HBV core antibody), anti-HCV (antibody against the virus of hepatitis C) are mandatory. In case of any positive marker, the nucleic acid tests (NAT) must be carried out. Prior HIV serology is important because some PCR-based screening tests may have false-positive results in post-CAR-T follow-up if lentiviruses were used as vectors to produce the CAR-T cells[17].

Other recommended serologies are: cytomegalovirus (CMV), human T-cell lymphotropic virus type 1 (HTLV-1), Toxoplasma gondii (toxoplasmosis) and Treponema pallidum (syphilis). In children, additional serological screening for herpes simplex virus 1/2 (HSV1/2) and varicella-zoster virus (VZV) may be considered. Candidates who are seropositive for HSV1/2 and/or VZV should receive prophylaxis with acyclovir or valaciclovir. Given the high seroprevalence of HSV and VZV in adults, universal prophylaxis with acyclovir is recommended, without the need for prior serological screening (see prophylaxis).

### 1.2. Assessment of vaccination cards

As part of the pre-CAR-T therapy evaluation, it is recommended to review the patient's vaccination history, and check the status of influenza and pneumococcal vaccines. Influenza vaccine should be administered after leukapheresis and at least 2 weeks before lymphodepletion chemotherapy, and then annually, before the influenza season[4]. The seasonality of influenza in Brazil depends on the latitude, with the highest concentration of cases from January to April in the tropical zone and from May to September in the south temperate zone.

### 1.3. Active infections in the pre-infusion period

Active or uncontrolled infections should be treated prior to infusion of CAR-T therapy. Active infections can be aggravated by lymphocyte-depleted chemotherapy including fludarabine, and by the severe suppression of humoral immunity driven by CAR-T cells. Infections can also result in more severe toxicities due to elevated levels of inflammatory cytokines. About 10% of serious or life-threatening infections after CAR-T therapy were cases of progression of infections diagnosed in the pre-infusion period of cell therapy[1]. Patients with respiratory symptoms

should collect a respiratory panel and await resolution of symptoms to initiate lymphocyte depletion, especially in cases of infection by SARS CoV-2, RSV, PIV 1, 2, 3 and 4, INF A and B, hMPV and ADV[4].

### 1.4. Empirical treatment of strongyloidiasis

Countries in tropical and subtropical regions may have a high prevalence of strongyloidiasis, which may be severe in immunocompromised patients. Given the low sensitivity of serological diagnosis, empirical treatment of *Strongyloides stercoralis* with ivermectin 200mg/kg/day on 2 consecutive days should be considered[18].

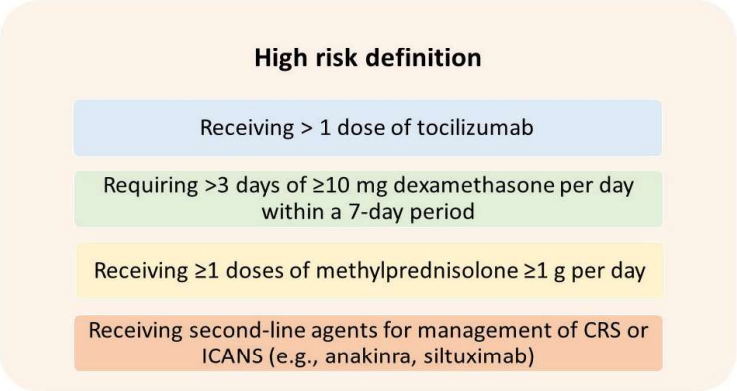
### 1.5. Tuberculosis investigation

In addition to the increased risk of reactivation of latent *Mycobacterium tuberculosis* infection (LTBI) in cancer patients, recipients of CAR-T therapy may need treatment with tocilizumab, an interleukin 6 (IL-6) receptor antagonist that is independently associated with an increased risk of active *M. tuberculosis* infections[19]. Given the high prevalence of tuberculosis in Brazil, investigation of previous tuberculosis in the patient or in close contacts is mandatory. A recent Brazilian study showed LTBI prevalence of 8.7% in HCT candidates. About 10% of the patients reported cases of tuberculosis in their family[20]. Laboratory investigation of LTBI is recommended preferably by the interferon gamma release assay (IGRA) or by the tuberculin skin test (TST). Both tests may be indeterminate in patients with severe lymphopenia. It is recommended to maintain a high level of suspicion for prompt investigation of active TB. In case of proven LTBI, and after exclusion of active TB, prophylaxis with INH should be considered for 6 to 9 months, at a dose of 5 to 10 mg/kg/day up to a maximum dose of 300 mg/day, especially in patients who used tocilizumab.

## 2. ANTIMICROBIAL PROPHYLAXIS AND INFECTION MONITORING

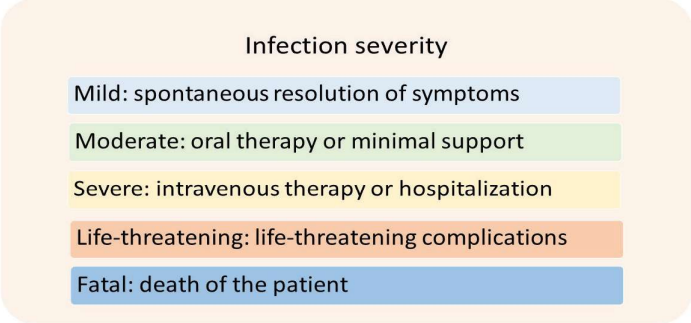
For a better management of infections, it is very important to classify the patient's infectious risk. High-risk patients meet at least one of the criteria described in Figure 2. Evaluation by an infectious disease specialist is recommended for all high-risk patients.

**FIGURE 2.** **High risk definition**




Another important parameter is the classification of infection severity. For the analysis of outcomes, it is important to use the same definitions. The infection is considered: a) mild, if no treatment is needed; b) moderate, if only oral treatment or minimal supportive care is needed; c) severe, if intravenous therapy or hospitalization is required; d) life-threatening; or e) fatal, in the event of the patient's death[21]. The classification of infection severity can be seen in Figure 3.

**FIGURE 3.** **Classification of infection severity[21].**



### 2.1. Bacterial infections

*2.1.1. Prophylaxis*: Levofloxacin 750 mg PO daily should be given during neutropenia (if absolute neutrophil count <500 cells/mm3). Alternative drugs may be considered for patients with contraindications to the use of fluoroquinolones.

*2.1.2. Empirical antibiotic therapy*: In patients with fever, with or without neutropenia, empirical antibiotic therapy should be initiated according to the center guidelines and blood culture routines. If cefepime is the first choice, vancomycin should only be introduced if there is a clear indication for its use, as cefepime has a broad spectrum of activity for gram-positive and gram-negative agents. As cefepime is associated with neurotoxicity in the setting of advanced age and acute kidney injury, alternative drugs with similar spectrum such as ceftazidime plus vancomycin may be considered. The treatment of persistent or refractory CRS or ICANS may mask typical signs and symptoms of infection. In case of doubt whether CRS/ICANS or infection, escalation of therapy to include meropenem and vancomycin should be considered independent of fever. De-escalation of antibiotics can be considered from 48 hours after defervescence and significant improvement in symptoms, always in consultation with the infectious disease specialist.

*2.1.3. Monitoring of bacterial infections*: Blood cultures must be taken according to local recommendations. For patients with CRS or grade ≥2 neurotoxicity, aerobic and anaerobic blood cultures should be taken twice a week, regardless of the occurrence of fever.

### 2.2. Viral infections

*2.2.1. Prophylaxis*: To control HSV-1, HSV-2 and VZV reactivations, prophylaxis with acyclovir/valaciclovir should be started with lymphodepletion chemotherapy and continued for up to 1 year after infusion of CAR-T therapy. Prophylaxis should be discontinued during preemptive use of ganciclovir (GCV) or valganciclovir (vGCV), and resumed after its end.

Few information is available regarding the management of persistent hepatitis B (HBV) and C (HCV) infections because patients infected with these viruses were excluded from the initial CAR-T studies. Data reported to date suggest that CAR-T therapy is safe in patients with HBV as long as they receive prophylaxis with antivirals such as entecavir. Rare reports of fulminant hepatitis and death have occurred in patients who have stopped entecavir[22].

In a case-control study in China, including 41 HBV-infected patients and 29 controls, no difference was observed in toxicity (CRS or ICANS) or response to CAR-T therapy between groups. HBV reactivation was observed in 17% of HBsAg positive patients and in 3.4% of patients with past HBV infection (anti-HBc positive). Exacerbation of hepatitis was not observed and only one case had an elevation of alanine aminotransferase (ALT)[23]. Strati and colleagues reported two cases of HBV and one case of HCV infected patients who received CAR-T therapy. No patient developed fulminant hepatitis or had viral reactivation or abnormal liver function tests during CAR-T therapy[24].

Based on available information, the risk-benefit of CAR-T therapy in patients with HBV or HCV infection should be evaluated on a case-by-case basis. If CAR-T cell therapy is the option, patients should receive prolonged prophylaxis or suppressive treatment in consultation with an infectious disease specialist or hepatologist.

*2.2.2. Preemptive therapy (CMV)*: The introduction of preemptive therapy should be done with GCV or vGCV according to the established qPCR cut-off, or a positive pp65 antigenemia. vGCV should be administered along with food for better drug absorption, in patients without diarrhea and without significant alterations in liver tests. The duration of preemptive therapy should be at least 14 days, followed or not by maintenance therapy (half dose, once daily for another 2 weeks). In case of neutrophil counts below 1,000/mm$^3$ before starting preemptive therapy, the alternative drug is foscarnet (FOS) 90mg/kg every 12 hours[18].

*2.2.3. Monitoring of CMV reactivation:* Patients with a previous history of HCT should be monitored weekly by CMV quantitative PCR (qPCR) or pp65 antigenemia followed by preemptive treatment with GCV, vGCV or FOS, if necessary, according to SBTMO recommendations for allogeneic HCT recipients[18]. In patients without a history of HCT, there is no need for monitoring, except by high-risk patients (as defined above).

High-risk patients should be monitored for CMV. Monitoring for CMV reactivation should be done weekly for up to 30 days after the last day of dexamethasone (or equivalent) ≥ 10 mg, or other cytokine therapies such as tocilizumab and anakinra, whichever occurs later. In case of reactivation and preemptive therapy, monitoring should be done weekly up to 30 days after discontinuation of preemptive therapy or 2 consecutive negative tests

(whichever occurs later). Differential blood count should be evaluated within 24 hours of starting treatment, and repeated 2-3 times a week during treatment with vGCV, GCV, or FOS. Renal function tests should be measured at least once a week for proper adjustment of antiviral doses.

### 2.3. Fungal infections

*2.3.1. Prophylaxis:* Fluconazole should be administered during neutropenia (absolute neutrophil count <500/mm3) at a dose of 200 mg orally or IV daily. Treatment should be continued until neutropenia resolves. Micafungin 50 mg IV daily can be used as an alternative for patients with contraindications to fluconazole therapy. Posaconazole prophylaxis should be used in high-risk patients (defined above), or if the patient remains neutropenic (<500/mm3) for more than 20 days. The dose of posaconazole on the first day is 300mg PO twice a day, followed by 300mg PO once a day. Prophylaxis should be continued for up to 30 days after the last day of dexamethasone (or equivalent) above 10 mg, or other cytokine therapies such as tocilizumab and anakinra, whichever occurs later. Posaconazole can be discontinued if the absolute neutrophil count is ≥ 500/mm3 without G-CSF for 3 consecutive days. If possible, monitoring the serum level of posaconazole is recommended 7 to 10 days after starting prophylaxis, then weekly, maintaining therapeutic posaconazole levels above 0.7 mg/mL. Voriconazole should be avoided after CAR-T therapy if possible, due to the risk of neurotoxicity. Isavuconazole is not routinely used for prophylaxis[4].

*2.3.2. Pneumocystis jirovecii prophylaxis*: Patients taking trimethoprim-sulfamethoxazole for *P.jirovecii* prophylaxis can maintain prophylaxis during neutropenia post-CAR-T therapy. One double-dose tablet is recommended orally, 3 times a week. If there is concern about potential myelosuppression, trimethoprim-sulfamethoxazole can be started after absolute neutrophil counts above 0.5 x $10^9$/L is reached and maintained for at least 6 months[25]. *P.jirovecii* prophylaxis should be started in all patients on the 28$^{th}$ day after CAR-T cell infusion. Alternative drugs in case of sulfa allergy or prolonged cytopenias are aerosolized pentamidine (300 mg once a month), dapsone (100 mg PO/day) or atovaquone (1500 mg PO/day).

## 3. VACCINATION IN CAR-T THERAPY CANDIDATES AND RECIPIENTS

CAR-T therapy targets cells that express CD19, present on both malignant and non-malignant B cells. However, terminally differentiated B cells such as long-lived plasma cells have low expression of CD19 and can survive after lymphodepletion chemotherapy and CAR-T therapy[26]. Experimental studies have shown that, unlike memory B cells, mature plasma cells in general do not participate in the processing and presentation of antigens, and their main function is to secrete large amounts of specific antibodies for long periods[26].

In adults who had sustained complete response for 6 months after CAR-T therapy, Hill et al. demonstrated a small decrease in serum total IgG concentrations, with preservation of virus-specific antibody concentrations[27]. These data suggest a small impact of CAR-T therapy on preexisting humoral immunity for up to 1 year in adults, and raise an important question about the current recommendation for intravenous immunoglobulin prophylaxis. It is noteworthy that these observations may not be valid for children due to the lower number of established plasma cell clones.

Therefore, it is still unclear whether there is a need for vaccination after CAR-T therapy[7]. Given the paucity of evidence for or against, vaccination is recommended in patients with a complete response for ≥ 6 months (28).

### 3.1. General recommendations

In general, priority is given to the inactivated influenza vaccine, 13-valent pneumococcal conjugate vaccine, and *Haemophilus influenzae* type b conjugate vaccine. According to expert opinion (EBMT and ASTCT), vaccination schedules similar to post-HCT revaccination program may be necessary[28].

Inactivated vaccines can be administered after ≥ 6 months of CAR-T therapy and ≥ 2 months after the last dose of IVIg. Attenuated vaccines can be administered after ≥ 1 year of CAR-T therapy. Figure 4 summarizes the contraindications for the use of inactivated and attenuated vaccines.

**FIGURE 4.** **Contraindications for the use of inactivated and attenuated vaccines.**

| Contraindications for inactivated vaccines | Contraindications for attenuated vaccines |
|---|---|
| • Supplemental immunoglobulins within the past 2 months<br>• Receiving immunosuppressive therapy that reduces T-cell or B-cell function or active symptoms of graft-versus-host-disease that requires treatment<br>• Administration of anti-CD20 or anti-CD19 agent within the past 6 months<br>• Actively receiving chemotherapy* | • Administration of anti-CD20 or anti-CD19 agent within the past 6 months<br>• ≤1 year post CAR–T-cell therapy<br>• ≤2 years post autologous or allogeneic HSCT<br>• ≤1 year off systemic immunosuppressive therapy<br>• ≤8 months after last dose of supplemental immunoglobulins<br>• Absolute $CD4^+$ T-cell ≤200 cells/$mm^3$<br>• Absolute $CD19^+$ or $CD20^+$ B-cell ≤20 cells/$mm^3$<br>• Actively receiving chemotherapy* |

(*Vaccination may be considered in certain therapies that do not suppress T-cell or B-cell responses, such as checkpoint inhibitors, immunomodulatory agents (eg, lenalidomide), tyrosine kinase inhibitors, and select other agents)

**TABLE 2.** **Proposal for a vaccination schedule in CAR-T therapy for adults.**

| Vaccines | Time after CAR T therapy | | | | | | Obs |
|---|---|---|---|---|---|---|---|
| Inactivated | Pre CAR-T | >6mo | >7mo | ≥8moo | >12m | >18m | |
| Influenza | INF | INF | | | | | Annually |
| PCV13 | | PCV13 | PCV13 | PCV13 | | | |
| PPV23 | | | | | | PPV23 | |
| HiB | | HiB | HiB | HiB | | | |
| DTaP | | DTaP | DTaP | DTaP | | | |
| Hepatitis A | | | | | HAV | HAV | Serology before |
| Hepatitis B | | HBV | HBV | | HBV | | |
| MCV ACWY* | | MCV | | MCV | | | |
| IPV* | | IPV | IPV | IPV | | | |
| HPV* | | HPV | | HPV | HPV | | 9-45 years |
| Live attenuated | ≥12-24 mo | | | | | | |
| MMR | MMR | | | | | | Serology before |
| VZ (Shingrix®) | VZ | | | | | | ≥50 years, VZVÅ |

### 3.2. Vaccination Schemes in CAR-T Therapy

Many centers wait for the resolution of B cell aplasia before restarting vaccination. The decision to initiate vaccination should be made individually or based on institutional guidelines. Tables 2 and 3 show suggested vaccination schedules for adults and children, respectively.

**TABLE 3. Suggested vaccination schedule in CAR-T therapy for children.**

| Vaccines | Time after CAR T therapy | | | | | | Obs |
|---|---|---|---|---|---|---|---|
| Inactivated | Pre CAR-T | >6mo | >7mo | ≥8mo | >12mo | >18mo | |
| Influenza | INF | INF | | | | | Annually |
| PCV13 | | PCV13 | PCV13 | PCV13 | | | |
| PPV23 | | | | | | PPV23 | |
| HiB | | HiB | HiB | HiB | | | |
| DTaP | | DTaP | DTaP | DTaP | | | |
| Hepatite A | | | | | HAV | HAV | Serology before |
| Hepatite B | | HBV | HBV | | HBV | | |
| MCV ACWY* | | MCV | | MCV | | | |
| IPV* | | IPV | IPV | IPV | | | |
| HPV* | | HPV | | HPV | HPV | | 9-45 years |
| Live attenuated | ≥24 mo | ≥25 mo | | | | | |
| MMR | MMR | MMR | | | | | Serology before |
| VV (Varivax®) | VV | VV | | | | | VZV negative |

(*Can be postponed after 12 months. PCV13=13-valent conjugate pneumococcal vaccine; PPV23=23-valent polysaccharide pneumococcal vaccine; HiB=Hemophilus influenza type B vaccine; DTaP=Diphtheria, tetanus and acellular pertussis vaccine; MCV=tetravalent conjugate meningococcal vaccine; IPV=inactivated poliomyelitis vaccine; HPV=papillomavirus vaccine; MMR=measles , mumps, rubella vaccine; VV=varicella vaccine; VZ=recombinant herpes zoster vaccine).

## REFERENCES


1. Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131(1):121–30.
2. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev. 2019;34:45–55.
3. Hansen DK, Dam M, Faramand RG. Toxicities associated with adoptive cellular therapies. Best Pract Res Clin Haematol. 2021;34(3):101287.
4. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood. 2020;136(8):925–35.
5. Cappell KM, Sherry RM, Yang JC, Goff SL, Vanasse DA, McIntyre L, et al. Long-Term Follow-Up of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. J Clin Oncol. 2020;38(32):3805–15.
6. Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):449–59.
7. Jain T, Bar M, Kansagra AJ, Chong EA, Hashmi SK, Neelapu SS, et al. Use of Chimeric Antigen Receptor T Cell Therapy in Clinical Practice for Relapsed/Refractory Aggressive B Cell Non-Hodgkin Lymphoma: An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25(12):2305–21.
8. Gudiol C, Lewis RE, Strati P, Kontoyiannis DP. Chimeric antigen receptor T-cell therapy for the treatment of lymphoid malignancies: is there an excess risk for infection? Lancet Haematol. 2021;8(3):e216–28.
9. Turtle CJ, Hanafi L-A, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8 + and CD4 + CD19-specific chimeric antigen receptor–modified T cells. Sci Transl Med. 2016 Sep 7;8(355):100–106.
10. Turtle CJ, Hanafi L-A, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123–38.
11. Luo H, Wang N, Huang L, Zhou X, Jin J, Li C, et al. Inflammatory signatures for quick diagnosis of life-threatening infection during the CAR T-cell therapy. J Immunother Cancer. 2019;7(1):1–11.
12. Wudhikarn K, Palomba ML, Pennisi M, Garcia-Recio M, Flynn JR, Devlin SM, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. Blood Cancer J. 2020 Aug 5;10(8):79.
13. Vora SB, Waghmare A, Englund JA, Qu P, Gardner RA, Hill JA. Infectious Complications Following CD19 Chimeric Antigen Receptor T-cell Therapy for Children, Adolescents, and Young Adults. Open Forum Infect Dis. 2020 May 1;7(5):1–9.
14. Cordeiro A, Bezerra ED, Hirayama A V., Hill JA, Wu Q V., Voutsinas J, et al. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. Biol Blood Marrow Transplant. 2020 Jan;26(1):26–33.
15. Logue JM, Zucchetti E, Bachmeier CA, Krivenko GS, Larson V, Ninh D, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. Haematologica. 2021;106(4):978–86.
16. Strati P, Varma A, Adkins S, Nastoupil LJ, Westin JR, Hagemeister FB, et al. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. Haematologica. 2021;106(10):2667–72.
17. Laetsch TW, Maude SL, Milone MC, Davis KL, Krueger J, Cardenas AM, et al. False-positive results with select HIV-1 NAT methods following lentivirus-based tisagenlecleucel therapy. Blood. 2018;131(23):2596–8.
18. Maiolino MG, Carlesse F, Ramos JF, Machado CM. Prevention and treatment of infectious complications post-HSCT. JBMTCT. 2021 Mar 11;4(1):197–217.
19. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther. 2011;13(5):R141.

20. de Oliveira Rodrigues M, de Almeida Testa LH, dos Santos ACF, Zanetti LP, da Silva Ruiz L, de Souza MP, et al. Latent and active tuberculosis infection in allogeneic hematopoietic stem cell transplant recipients: a prospective cohort study. Bone Marrow Transplant. 2021 Sep 8;56(9):2241–7.

21. Young JH, Logan BR, Wu J, Wingard JR, Weisdorf DJ, Mudrick C, et al. Infections after Transplantation of Bone Marrow or Peripheral Blood Stem Cells from Unrelated Donors. Biol Blood Marrow Transplant. 2016 Feb;22(2):359–70.

22. Bupha-Intr O, Haeusler G, Chee L, Thursky K, Slavin M, Teh B. CAR-T cell therapy and infection: a review. Expert Rev Anti Infect Ther [Internet]. 2021;19(6):749–58. Available from: https://doi.org/10.1080/14787210.2021.1855143

23. Wang Y, Liu Y, Tan X, Pan B, Ge J, Qi K, et al. Safety and efficacy of chimeric antigen receptor (CAR)-T-cell therapy in persons with advanced B-cell cancers and hepatitis B virus-infection. Leukemia. 2020 Oct 27;34(10):2704–7.

24. Strati P, Nastoupil LJ, Fayad LE, Samaniego F, Adkins S, Neelapu SS. Safety of CAR T-cell therapy in patients with B-cell lymphoma and chronic hepatitis B or C virus infection. Blood. 2019 Jun 27;133(26):2800–2.

25. Maertens J, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, et al. ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71(9):1–8.

26. Bhoj VG, Arhontoulis D, Wertheim G, Capobianchi J, Callahan CA, Ellebrecht CT, et al. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. Blood [Internet]. 2016;128(3):360–70. Available from: http://dx.doi.org/10.1182/blood-2016-01-694356

27. Hill JA, Krantz EM, Hay KA, Dasgupta S, Stevens-Ayers T, Bender Ignacio RA, et al. Durable preservation of antiviral antibodies after CD19-directed chimeric antigen receptor T-cell immunotherapy. Blood Adv. 2019;3(22):3590–601.

28. Kansagra AJ, Frey N V, Bar M, Laetsch TW, Carpenter PA, Savani BN, et al. Clinical Utilization of Chimeric Antigen Receptor T Cells in B Cell Acute Lymphoblastic Leukemia: An Expert Opinion from the European Society for Blood and Marrow Transplantation and the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019 Mar;25(3):e76–85.