REVIEW ARTICLE

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Infectious complications, immune reconstitution, and infection prophylaxis after CD19 chimeric antigen receptor T-cell therapy

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CD19-targeted chimeric antigen receptor (CAR) T-cell becomes a breakthrough therapy providing excellent remission rates and durable disease control for patients with relapsed/refractory (R/R) hematologic malignancies. However, CAR T-cells have several potential side effects including cytokine release syndrome, neurotoxicities, cytopenia, and hypogammaglobulinemia. Infection has been increasingly recognized as a complication of CAR T-cell therapy. Several factors predispose CAR T-cell recipients to infection. Fortunately, although studies show a high incidence of infection post-CAR T-cells, most infections are manageable. In contrast to patients who undergo hematopoietic stem cell transplant, less is known about post-CAR T-cell immune reconstitution. Therefore, evidence regarding antimicrobial prophylaxis and vaccination strategies in these patients is more limited. As CAR T-cell therapy becomes the standard treatment for R/R B lymphoid malignancies, we should expect a larger impact of infections in these patients and the need for increased clinical attention. Studies exploring infection and immune reconstitution after CAR T-cell therapy are clinically relevant and will provide us with a better understanding of the dynamics of immune function after CAR T-cell therapy including insights into appropriate strategies for prophylaxis and treatment of infections in these patients. In this review, we describe infections in recipients of CAR T-cells, and discuss risk factors and potential mitigation strategies.

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INTRODUCTION

CD19 chimeric antigen receptor T (CAR) cells have become a major breakthrough treatment for patients with relapsed/refractory (R/R) B lymphoid malignancies in the past several years, providing excellent anti-tumor activity with high response rates and potential long-term disease-free remission [1]. There are currently four CD19 CAR T-cell products approved for various B cell lymphoid cancers [2–7]. In addition, two CAR T-cells products against B cell maturation antigen (BCMA) were also recently approved for patients with refractory multiple myeloma (MM) [8, 9]. Besides their impressive efficacy, CAR T-cells can cause several unique adverse events including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), hypogammaglobulinemia, and prolonged cytopenia [10]. In addition, due to on-target effects, CD19 CAR T-cells result in depletion of B cells and a subset of CD19 + plasma cell whereas BCMA-targeted CAR T-cells lead to plasma cell aplasia [11, 12]. As a result of underlying immune system dysregulation and further disruption by CAR T-cells, patients who undergo CAR T-cell therapy are predisposed to infections. Moreover, underlying hematologic malignancies and immunosuppressive treatment for CAR T-cell-associated toxicities also contribute to the cumulative immunosuppressive state of CAR T-cell recipients. Understanding the characteristics and risk factors of infections including immune kinetics associated with CAR T-cell therapy should lead to better patients' outcomes. This review will focus mainly on infectious complications in patients with R/R non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL) treated with CD19 CAR T-cells but, will also briefly touch on infections after BCMA CAR T-cells in patients with R/R MM.

INCIDENCE AND CHARACTERISTICS OF INFECTION AFTER CAR T-CELL THERAPY

Data on infections following CAR T-cell therapy have been mostly derived from single-center retrospective studies [13–19] in patients treated with CD19 CAR T-cells as well as some information from prospective clinical trials. With the recent approval of BCMA CAR T-cells, there is also emerging data in infectious complications in patients treated with these products. Patients with hematologic malignancies who undergo CAR T-cell therapy can develop infections at several timepoints after treatment. CAR T-cell therapy may be divided into three phases including the initiation of lymphodepletion (LD) chemotherapy, early post-CAR T-cells (day 0 to +30), and late phase after CAR T-cells (day +30 to +365 or beyond) (Fig. 1) [20]. The pattern of infections and dominant causative pathogens during each period varies based on the primary component of immune deficiency state at various time points.

Infections in patients who undergo CD19 CAR T-cell therapy

The incidence of infections in patients receiving CD19 CAR T-cells varies from 18 to 56% in the prospective registration clinical trials and 20–60% in retrospective cohort analyses [2–8, 13–17, 21–30].

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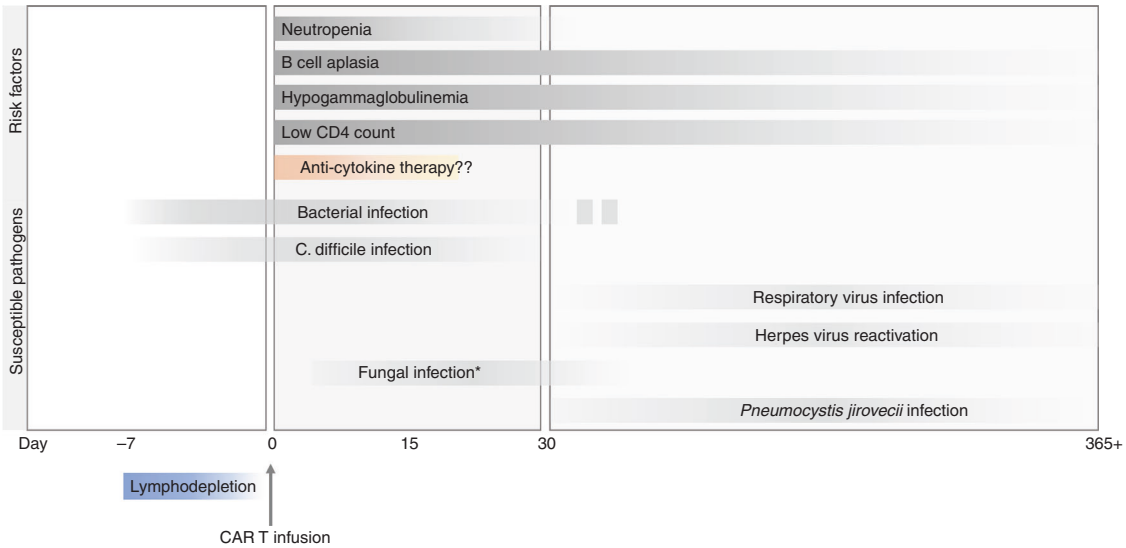

Fig. 1 Potential causative pathogens and immune suppression state by duration after chimeric antigen receptor T-cell therapy.

However, differences in incidence among studies could be attributed to several factors, including patient-related factors, CAR T-cell-related factors, and the definition and duration of follow up in each study. Table 1 summarizes the incidence and characteristics of infections after CD19 CAR T-cells from phase II/III prospective clinical trials.

In addition, several retrospective cohort studies have reported real-world data on infectious complications and outcomes in patients treated with CAR T-cells (Table 2). In a retrospective report by Hill et al. describing a single-center experience of infectious complications in patients with various B lymphoid malignancies treated with CD19 CAR T-cells, 23% of patients developed infection within the first 28 days after CAR T-cell infusion, which translated into an infection density of 1.19 infections for every 100 days at risk [13]. Patients with B-ALL had a higher infection density compared to other hematologic malignancies. Park et al. reported a 40% incidence of infections during the early phase (day 0–30) in adult B-ALL patients who received CD19–28z CAR T-cell therapy [16]. There were 20 bacterial and 16 viral infections [16]. The incidence of infections in pediatric, adolescent, and young adult patients with B-ALL who received CD19 CAR T-cells was similar to adult patients. According to Vora et al., 54% of patients developed infectious complications within the first 90 days, with most occurring within the first 28 days [18].

In patients with lymphoma, Wudhikarn et al. reported real-world data on infectious complications in 60 consecutive patients with diffuse large B cell lymphoma (DLBCL) treated with axicabtagene ciloleucel or tisagenlecleucel [17]. The 1-year cumulative incidence of infection was 63.3% with bacterial infections being the most common (1-year incidence 57.2%). Other reports also demonstrated similar patterns and incidence of infections in patients with DLBCL treated with CD19 CAR T-cells [18, 28, 31].

Data on infectious complications in patients with MM treated with CAR T-cells are still limited. Unlike CD19 CAR T-cells, viral infection is the most common infectious complication followed by bacterial and fungal infections. In a recent report of 55 patients with R/R MM patients treated with BCMA CAR T-cells, 53% developed infection within the first 6 months (53% viral, 40% bacterial, and 6% fungal) [32]. Approximately half of the infectious events occurred within the first 100 days. Josyula et al. also reported the effect of BCMA CAR T-cells on humoral immunity and risk of infection in patients with R/R multiple MM [33]. The incidence of early infections (<30 days post-CAR T-cell therapy) appeared to be less common than for B lymphoid malignancy treated with CD19 CAR T-cells, whereas late infections were more frequent. In addition, viral infections were more frequent than bacterial infections.

Bacterial infections

Most retrospective data describe a similar pattern of infections after CAR T-cells. During the early post-CAR T-cell period (including LD chemotherapy and the first 30 days after infusion), the most common pathogens are bacteria with neutropenia being a notable risk factor. Bacterial infections account for up to 40–50% of infections and typically occur within the first 2 weeks during the neutropenia period, presenting either as bacteremia or organ-specific infection. Bloodstream infection including central venous catheter-associated infection, gastrointestinal, and respiratory tracts are the three most common sites of infection. Common bacterial infections (especially the first 30 days) include Clostridium infection, gram-negative Enterobacteriaceae, and gram-positive enterococci [15, 17]. These patients are at risk of developing multi-drug resistant nosocomial bacterial infection due to previous history of heavy exposure to broad-spectrum antibiotics, which may predispose them to microbiome alteration and colonization of drug-resistant pathogens. In one study, 4 of 24 bacterial infections during the first 28 days post-CAR T-cell infusion were due to fluoroquinolone-resistant gram-negative bacteria [13].

Viral infections

In contrast to bacterial pathogens, viruses are more common later in the course after CD19 CAR T-cell therapy. After day +30, lymphopenia (either B or T lymphocytes) and hypogammaglobulinemia become two critical components of immune dysfunction. Respiratory viral pathogens are the most common pathogens especially in the later phase of CAR T-cell therapy with most events being mild or moderate in severity with some patients developing severe infection. In addition to B cell aplasia, a significant proportion of patients has profound CD4 lymphopenia, and delayed reactivation of herpes viruses is frequently observed over 6–12 months after CD19 CAR T-cell infusion. Cytomegalovirus (CMV) reactivation (including Herpes virus) was reported in ~1–2% but the real incidence is not known since routine monitoring of CMV varies among centers. Most reported cases presented as CMV viremia whereas CMV disease was uncommon but has been increasingly reported with some fatal cases being described [31, 34, 35].

Table 1. Incidence and characteristics of infectious complications in selected registered studies of patients treated with CD19 chimeric antigen receptor T-cells.

	CD19-positive B cell Non-Hodgkin lymphoma										Acute B-cell Lymphoblastic Leukemia	
	ZUMA-1 (2)	**JULIET (3)**	**TRANSCEND-NHL-001 (4)**	**ZUMA-7 (23)**	**BELINDA (27)**	**TRANSFORM (24)**	**ZUMA-12 (25)**	**ZUMA-2 (5)**	**ZUMA-5 (7)**	**ELARA (26)**	**ELIANA (22)**	**ZUMA-3 (6)**
Clinicaltrials.gov Identifier Number	NCT02348216	NCT02445248	NCT02631044	NCT03391466	NCT03570892	NCT03575351	NCT03761056	NCT02601313	NCT03105336	NCT03568461	NCT02435849	NCT02614066
Patient Population	R/R DLBCL, R/R PMBCL, R/R tFL	R/R DLBCL, R/R HGBL, R/R tFL	R/R DLBCL, R/R tNHL, R/R FL Gr 3, R/R HGBL, R/R PMBCL	R/R DLBCL, R/R PMBCL, R/R tFL	R/R DLBCL, R/R HGBL, R/R tFL	R/R DLBCL, R/R tNHL, R/R FL Gr 3, R/R HGBL, R/R PMBCL	High-risk DLBCL, HGBL	R/R MCL	R/R FL	R/R FL	R/R B-ALL (Age < 25 years)	R/R adult B-ALL
Number of patients	105	111	269	170 in axi-cel arm	162 in tisa-cel arm	92 in liso-cel arm	40	68	148	97	75	71
Median duration of follow-up	15 months	14 months	12.3 months	24.9 months	10 months	6 months	15.9 months	17.5 months	17.5 months	16.6 months	13.1 months	16.4 months
Overall infection												
- Any Grades	38%	34% (<8 wks), 39% (>8 wks)	NR	41%	NR	NR	33%	56%	NR	18.6% (8 wks)	45% (8 wks)	NR
- Grade ≥3	28%	20% (<8 wks), 18% (>8 wks)	12% (5% after day 90)	14%	NR (Grade 5 3.1%)	15%	19%	32% (Grade 5 in 2 pts)	18%	5.2% (8 wks)	24% (8 wks)	25%
Bacterial infection	Any Grades 40%	NR	Grade≥3 10%	NR	NR (3 pts died from bacterial sepsis)	NR	Grade ≥ 3 5%	NR	NR	NR	NR	NR
Viral infection	Any Grades 10%	NR	Grade≥3 1%	NR (1 pt had hepatitis B reactivation, 3 pts had COVID-19 pneumonia (Grade ≥ 3)	NR (2 pts died from COVID-19 pneumonia)	NR	Grade ≥ 3 2%	NR CMV 2% HZV 4% Influenza 4%	NR	NR	NR	NR
Fungal infection	Any Grades 6%	NR	Grade≥3 1%	NR	NR	NR	Grade ≥ 3 1%	NR	NR	NR	NR	NR

R/R relapse/refractory, *DLBCL* diffuse large B cell lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *tFL* transformed follicular lymphoma, *HGBL* high grade B cell lymphoma, *NHL* non-Hodgkin lymphoma, *MCL* mantle cell lymphoma, *ALL* acute lymphoblastic leukemia, *NR* not reported, *CMV* cytomegalovirus, *HZV* Herpes Zoster virus, *pt* patient.

Table 2. Data of infectious complications in patients with B lymphoid malignancy treated with CD19 CAR T-cell from retrospective studies.

	Hill et al. [13]	Park et al. [16]	Logue et al. [15]	Vora et al. [18]	Strati et al. [30]	Cordeiro et al. [28]	Wudhikarn et al. [17]	Baird et al. [14]	Korell et al. [31]	Dayagi et al. [29]
Number of patients	133	53	85	83	31	86	60	41	60	88
Age group	Adult	Adult	Adult	Pediatric	Adult	Adult	Adult	Adult	Adult	Pediatric and adult
Diagnosis										
• NHL	62 (47%)	0 (0%)	85 (100%)	1 (1%)	31 (100%)	43 (50%)	60 (100%)	41 (100%)	49 (82%)	50 57%)
• ALL	47 (35%)	53 (100%)	0 (0%)	81 (98%)	0 (0%)	26 (30%)	0 (0%)	0 (0%)	2 (3%)	38 43%)
• CLL	24 (18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	17(20%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)
Median prior lines of treatment	4 (1-11)	3 (IQR 2-7)	3 (1-8)	NR	3 (1-11)	4 (1-8)	3 (2-9)	3 (2-4)	5 (2-10)	3 (2-more than 5)
Lymphodepletion	Varied	Cyclophosphamide, Fludarabine/ Cyclophosphamide	Fludarabine/ Cyclophosphamide	Varied	Fludarabine/ Cyclophosphamide	Varied	Varied (According to product but mostly Fludarabine/ cyclophosphamide	Fludarabine/ Cyclophosphamide	Fludarabine/ Cyclophosphamide	Fludarabine/ Cyclophosphamide
Previous HCT	50 (38%)	19 (36%)	23 (27%)	46 (55%)	11 (36%)	39 (45%)	17 (28%)	21 (51%)	NR	31 35%)
• Allo HCT	NR	19 (36%)	2 (2%)	46 (55%)	0 (0%)	15 (17%)	5 (8%)	0 (0%)	NR	17 19%)
• Auto HCT	NR	0 (0%)	21 (25%)	0 (0%)	11 (36%)	24 (28%)	12 (20%)	21 (51%)	NR	14 (16%)
Baseline parameters										
• IgG<400 mg/dL	34 (26%)	NR	16 (28%)	13 (16%)	NR	34 (40%)	15 (25%)	4 (24%)	NR	NR
• ALC<200/mm^3	106 (80%)	30 (57%) <300	NR	15 (18%) <300	NR	NR	NR	3 (7%)	NR	NR
• ANC<500/mm^3	16 (12%)	18 (34%)	12 (14%)	28 (34%)	NR	NR	1 (2%)	0 (0%)	NR	NR
CAR T product	NR	CD19-28z CAR T	Axi-cel	Tisa-cel	Axi-cel	NR	Axi-cel, Tisa-cel	Axi-cel	Axi-cel, Tisa-cel, clinical trial CAR T	CD19-28z CAR T
Observation duration	90 days post-CAR-T	180 days post-CAR-T	365 days post-CAR-T	90 days post-CAR-T	2 years post-CAR-T	Minimum 1 year (median 28 months)	1-year post-CAR-T	Minimum 1 year follow up post-CAR-T	180 days post-CAR-T	60 days post-CAR-T
All infection							101 events in 40 pt			45 events in 27 pt
• Early	43 events in 30 pt	26 events in 22 pt	38 events in 31 pt	37 events in 33 pt	71 events in 24 pt	NR	37 events	25 events in 19 pt	8 events during	36 events in 24 pt
• Late	23 events in 17 pt	15 events in 10 pt	32 events in 31 pt	12 events in 11 pt	(combined early and late)	153 events in 33 pt	64 events	48 events	study period	9 events in 7 pt
Bacterial infection										
• Early	24 events in 22 pt	17 events in 16 pt	24 events	20 events in 15 pt	NR	NR	25 events in 20 pt	8 events in 7 pt	8 events during	22 vents
• Late	8 events in 7 pt	5 events in 5 pt	13 events	5 events in 5 pt	NR	23 events	35 events in 16 pt	22 events	study period	6 events
Viral infection										
• Early	13 events in 11 pt	5 events in 5 pt	12 events	16 events	NR	NR	8 events	11 events in 8 pt	3 events during	14 vents
• Late	13 events in 11 pt	9 events in 9 pt	18 events	7 events	NR	10 events	28 events	17 events	study period	1 event
Fungal Infection			2							
• Early	6 events in 4 pt	4 events in 4 pt	2 events	1 event	4 events (combined early	NR	1 event in 1 pt	6 events in 4 pt	5 events during	1 event
• Late	2 events in 2 pt	1 event in 1 pt	0 events	0 event	and late)	4 events	1 event in 1 pt	9 events	study period	1 event
Receipt of GCSF	NR	NR	34 (40%)	NR	31 (100%)	NR	30 (50%)	21 (51%)	NR	NR
IVIG prophylaxis	NR	1 ((2%)	23 (27%)	NR	13 (42%)	NR	19 (53%)	15 (37%)	NR	NR
Antibacterial prophylaxis	Per protocol	0 (0%)	Per protocol	NR	2 (6%)	NR	19 (32%)	Per protocol	Per protocol	NR
Antiherpetic prophylaxis	Per protocol	52 (98%)	Per protocol	29 (35%)	22 (71%)	NR	60 (100%)	Per protocol	Per protocol	NR

Recently, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 or COVID-19) has emerged as one of the major infectious disease threats. Patients with hematologic malignancies including patients who undergo cellular therapy (either stem cell transplant or CAR T-cell therapy) are among the highest risk group of developing severe SARS-CoV-2 infection and having prolonged viral clearance time [36–38]. Viral shedding time of SARS-CoV-2 virus in patients undergoing transplantation and CAR-T cells could be up to 2 months [39]. Data from the European Hematology Association (EHA) reported an incidence of COVID-19 of 4.8% with the median time from CAR T-cell therapy to infection of 169 days [40]. Severe infection was observed in 67% and the COVID-19-related mortality was around 50% highlighting that overall outcome of COVID-19 infection after CAR T-cell therapy was poor [41]. Lymphopenia was an independent factor correlating with degree of COVID-19 severity.

Fungal infections

Fungal infection has been reported sporadically [42]. The most important risk factor for fungal infections is the duration of neutropenia (and in some cases lymphopenia) and prolonged course of systematic corticosteroid for severe CAR T-cell associated adverse reactions. Fungal infections are uncommon with an incidence between 1 and 5% [13, 17, 28, 42, 43]. Fatal cases from severe yeast and invasive mold infection have been increasingly reported [42, 43]. Pneumocystis infection is rarely observed, and this could represent routine use of effective prophylaxis.

In summary, most studies show similar incidences and patterns of infections after CAR T-cell therapy. Infections, especially severe infections and bacterial infections are more common during the first 30 days. After day +30, bacterial infections remain common but become less frequent and less severe. In the later phase, viruses are seen more often and are usually mild to moderate in severity. Other infections, i.e., fungal or pneumocystis infections are less frequently observed likely due to effective prophylactic strategies but can still be seen in patients with prolonged neutropenia or exposure to intensive and extended immunosuppressive treatments for CAR T-cell-associated complications.

RISK FACTORS OF INFECTIOUS COMPLICATIONS IN PATIENTS RECEIVING CAR T-CELL THERAPY

Hill and Seo recently provided an overview of patients with high risk for infectious complications after CAR T-cell therapy [20]. The underlying predisposing factors for infection can be divided into host-related and CAR T-cell-related factors.

1. *Host-related factors:* Patients who undergo CAR T-cell therapy typically have relapsed/refractory disease and have received several lines of therapy. The extent of prior therapy along with the impact on the immune system of the primary malignancy can lead to varying degrees of immune exhaustion, decreased bone marrow reserve with preexisting cytopenia, and delays in post-treatment immune recovery. Several studies demonstrated that a significant proportion of patients had baseline leukopenia and hypogammaglobulinemia even before CAR T-cell therapy. The underlying primary hematologic malignancy may also play a role in the risk of infection. For example, among B cell lymphoid neoplasms treated with CD19 CAR T-cells, there was evidence showing that patients with B-ALL tended to carry a higher risk of infection post-CAR T-cell therapy than CLL and B-NHL [13]. In addition, history of previous infection prior to CAR T-cell therapy has been shown in many studies to be strongly associated with increased risk of infection after CAR T-cells [17, 18, 44]. Age may also impact the patterns and incidence of infections [29]. In adult B-ALL, Park et al. reported an infection incidence of 42% during the first

Table 2. continued

	Hill et al. [13]	Park et al. [16]	Logue et al. [15]	Vora et al. [18]	Strati et al. [30]	Cordeiro et al. [28]	Wudhikarn et al. [17]	Baird et al. [14]	Korell et al. [31]	Dayagi et al. [29]
Antifungal prophylaxis	Per protocol	42 (79%)	Per protocol	42 (51%)	0 (0%)	NR	48 (80%)	Per protocol	Per protocol	NR
Antipneumocystis prophylaxis	Per protocol	46 (87%)	Per protocol	83 (100%)	13 (22%)	NR	55 (92%)	Per protocol	Per protocol	Per protocol

NHL non-Hodgkin's lymphoma, *ALL* acute lymphoblastic leukemia, *CLL* chronic lymphocytic leukemia, *HCT* hematopoietic cell transplant, *IgG* immunglobulin G, *IVIG* intravenous immunoglobulin, *ALC* absolute lymphocyte count, *ANC* absolute neutrophil count, *CAR* chimeric antigen receptor, *NR* not reported, *pt* patient

30 days with bacteria being the most common pathogen (30%) [16]. In contrast, in another retrospective study in pediatric and young adult B-ALL treated with CD19 CAR T-cells, viral infections were as common as bacterial infections during the first 28 days [18]. Receipt of bridging therapy, impaired performance status, history of prior HCT, underlying medical co-morbidities, and preexisting hypogammaglobulinemia were shown to be risk factors for infections after CAR T-cells in some studies [18, 45, 46].

2. *CAR T-associated factors:* As noted above, a proportion of patients develop profound and prolonged neutropenia after CAR T-cell therapy, which will place them at increased risk of bacterial infection. Aside from LD chemotherapy, CRS and ICANS represent two well-established CAR T-cell-associated complications that can lead to immune dysregulation. Several studies have shown that both severe CRS and ICANS are associated with infections, severe infections, and bloodstream infections both in ALL and B-NHL patients [13, 15, 16]. Severe CRS and ICANS are risk factors for prolonged or recurrent cytopenia, which in turn results in increased risk of infections [47–49].

Moreover, as the management of severe CRS generally involves cytokine-directed therapy such as tocilizumab and systemic corticosteroid, this may impact the ability of the host immune system to mount appropriate response to pathogens. Initial data from a small single-center retrospective study and data from rheumatoid arthritis suggested an association between tocilizumab and increased risk of infection [15, 50]. However, recent findings from a CIBMTR study did not support an association between tocilizumab use and infection in patients who were treated with CD19 CAR T-cell therapy [51]. The impact of systemic corticosteroid, either cumulative dose or duration, on the risk of infectious complication and outcomes after CAR T-cells has been heavily investigated. Several studies showed that steroid exposure is a major risk factor for infectious complications and inferior survival after CAR T-cell therapy [15, 17, 52, 53]. However, there are conflicting results on the effects of tocilizumab and corticosteroid on infection risk, which may be attributable to the definition of infections, antimicrobial prophylaxis, underlying diagnosis, and selection bias among studies. Duration of neutropenia and lymphopenia are other potential predisposing factor for fungal infection [54]. Whether other cytokine-directed therapy for CRS, i.e., anti-IL1 inhibitor would increase the risk of infection is not yet known.

Other factors associated with infections include CAR T-cell dose and target of CAR T-cell product. Higher CAR T-cell dose has been associated with a higher risk of infections in some studies [13]. B-cell aplasia, plasma cell depletion, and resultant hypogammaglobulinemia are inevitable side effects of CD19/BCMA CAR T-cells and could predispose patients to infectious complications [55, 56]. Walti et al. demonstrated that BCMA-targeted CAR T-cells may develop more profound hypogammaglobulinemia and low level of pathogen-specific immunoglobulin including poorer response to immunization compared to CD19 CAR T-cell products [57, 58]. In conclusion, both patients and CAR T-associated factors lead to a cumulative immunosuppressive state, which predisposes CAR T-cell recipients to infections.

HEMATOLOGIC AND IMMUNE RECOVERY AFTER CAR T-CELL THERAPY

Although our knowledge of immune reconstitution in hematopoietic stem cell transplant (HSCT) has been well established, similar data after CAR T-cell therapy is still very limited. Most available data have been derived from patients treated with CD19 CAR T-cells. Besides B cell and plasma cell depletion secondary to on-target off-tumor effects, cytopenia of other cell lineages is a well-documented CAR T-cell-related adverse event. Several studies have demonstrated high incidence of cytopenia after CAR T-cells [14, 42, 47, 59–62]. The mechanism of cytopenia is multifactorial and not yet well understood [63, 64]. Rejeski et al. characterize the pattern of hematologic recovery in patients with R/R DLBCL after axicabtagene ciloleucel into three different categories: quick recovery, intermittent recovery, and aplastic. In this study, the authors reported profound neutropenia (ANC < 100) in 72% of patients and prolonged (21 days or longer) neutropenia in 64% of patients [48]. Intermittent hematologic recovery was the dominant phenotype of patients in this cohort. In another study, Fried et al. also demonstrated the commonly observed biphasic nature of hematologic toxicities in patients with B cell lymphoid malignancy treated with CD19 CAR T-cells [60]. Results from clinical trials showed an incidence of delayed neutropenia after day +28 post-CAR T-cell ranging between 20 and 80% [2–4, 65]. In a retrospective single-center study from the Memorial Sloan Kettering, Jain et al. highlighted the characteristics and risk factors of cytopenia including patterns of hematologic recovery after various types of CAR T-cells in different hematologic malignancy diagnoses [47]. In this study, ~30% recovered white blood count (WBC) and neutrophil count at 1-month post-CAR T infusion. In addition, only 13% and 30% of patients had WBC and neutrophil normalization, respectively, at 1 year after CAR T-cell therapy. Risk factors for delayed hematologic recovery beyond 30 days after infusion were severe CRS and ICANS. Other predisposing factors for prolonged/delayed cytopenia include baseline pre-CAR T cytopenia, early-onset CRS, higher grade CRS, a recent history of HSCT prior to CAR T-cell therapy, higher ferritin/CRP level, and decreased SDF-1 level [47, 60, 66, 67].

In addition to neutropenia, lymphopenia especially B cell aplasia are hallmarks of CD19-targeted CAR T-cells. The duration of B lymphopenia may be a surrogate of CAR T-cell persistence and can vary depending upon several factors [55, 68]. Lastly, low CD4 count is a common finding, with documented suppression for up to 1-year or longer post infusion [14, 15, 17]. However, some studies showed that, although low CD4 lymphocyte count was common, it was not associated with increased risk of severe infection [15].

Hypogammaglobulinemia is a known sequelae of CAR T-cell therapy due to depletion of CD19 + B lymphocytes and BCMA+/CD19 + plasma cells. The incidence of hypogammaglobulinemia varies between 20 and 90% [2–4, 22, 56, 69–71]. Up to 40% of patients who undergo CAR T-cell therapy have pre-existing hypogammaglobulinemia secondary to prior treatments. CAR T-cells can further worsen immunoglobulin deficit both qualitatively and quantitatively. The severity and duration of hypogammaglobulinemia have been closely correlated with the degree and duration of B lymphocyte/plasma cell depletion. However, the real incidence, duration, and severity of hypogammaglobulinemia can vary according to practice patterns of immunoglobulin replacement therapy. Moreover, the kinetics of IgG levels may also differ between underlying diagnosis and targets of CAR T-cells. In one report, patients with B-ALL had the most significant change in IgG levels between pre- and post-CAR T-cell therapy compared to patients with DLBCL and CLL [13, 72]. To date, there is also evidence indicating that total IgG may not reflect infection risk. Hill and colleagues demonstrated that specific IgG level to certain organisms can be independent and not correlate with total IgG level. The changes in pathogen-specific IgG level can vary among different pathogens with data suggesting that viral hepatitis, encapsulated bacteria, and Bordetella pertussis are most affected, whereas other viral or bacterial-specific antibodies are preserved (i.e., measles) [72]. Bhoj et al. showed that CD19 negative long-lived plasma cells might be preserved after CD19 CAR T-cell therapy and might explain the persistence of pre-existing humoral immunity against certain organisms in CD19 CAR T-cell recipients [73].

Lastly, BCMA-targeted CAR T-cells may also have more negative effect on post-CAR T pathogen-specific antibody level compared

to CD19 CAR T-cell products [57]. Joshyula et al. reported a cohort of 32R/R MM patients treated with BCMA CAR T-cell and observed that most patients had low IgG level and lost measles-specific IgG [33]. Besides the quantitative effect on IgG level, CAR T-cells against different targets also result in different impacts on the diversity of IgG. Patients with RR multiple myeloma who were treated with BCMA-targeted CAR T-cells also lost the diversity of immunoglobulin against microorganism [74]. These patients can have prolonged and profound hypogammaglobulinemia due to the depletion of all subsets of plasma cell populations.

ANTIMICROBIAL PROPHYLAXIS AND IMMUNOGLOBULIN REPLACEMENT IN CAR T-CELL THERAPY

There are several professional organizations and expert opinion statements that provide recommendations on prophylactic and management strategies for infection post-CAR T-cell therapy, mostly adopted from practice guidelines used in hematopoietic stem cell transplant recipients [20, 75, 76]. Here, we highlight approaches for CD19 targeted CAR T-cell therapy.

1. *Antibacterial prophylaxis:* As risk of bacterial infection inversely correlates with the degree and duration of neutropenia, most guidelines recommend initiating antibacterial prophylaxis during the severe neutropenia period with absolute neutrophil counts (ANC) lower than 0.5×10^9/L and continue until ANC stays sustained above this level. Fluoroquinolones (i.e., levofloxacin) are most commonly used, but extended-spectrum beta-lactam antibiotics (i.e., amoxicillin/clavulanic acid) or nonabsorbable antibiotics (i.e., rifaximin) may be a reasonable alternative depending upon the antimicrobial sensitivity pattern in each region, allergy profiles of the patients, and practice patterns at each center.

   In addition to antibiotic prophylaxis, the role of granulocyte colony-stimulating factors to decrease risk of bacterial infection by shortening the duration of neutropenia has been a debated topic. There were some concerns that G-CSF might affect CAR T-cell response or worsen CRS or ICANS via the activation of myeloid-related cytokines [77, 78]. Overall, the data on the G-CSF are still conflicting, and some studies did not support this concern or suggested that G-CSF administration after the acute phase of CAR T-cell may shorten the duration of neutropenia and decrease the risk of infection in CAR T-cell recipients [79–82]. However, the finite role and effect of G-CSF require further studies. Currently, most experts recommend considering G-CSF in patients with prolonged neutropenia [83, 84]. The administration of G-CSF for prolonged cytopenia beyond 14–21 days after CAR T-cell infusion appeared safe and did not exacerbate CRS [79, 85].
2. *Antiviral prophylaxis:* Prophylactic acyclovir is recommended from the initiation of LD chemotherapy for herpes viral prophylaxis. The duration of antiviral prophylaxis is varied between institutions. Some institutions adopt fixed duration approach for at least 3–6 months after CAR T-cell therapy [17]. However, delayed herpetic and zoster viral reactivation has been reported [14]. Thus, most experts now recommend maintaining acyclovir prophylaxis for an extended period or adopt CD4 guided approach to continue anti-viral prophylaxis until CD4 lymphocyte counts are higher than 200/μL.

   Patients who are hepatitis B carriers (HBs Ag positive) or have previous history of hepatitis B infection (HBs Ag negative, Anti-HBc Ab IgG positive) should receive prophylaxis with entecavir for at least 6 months along with surveillance by checking liver function test or HBV DNA. Patients with chronic active hepatitis B (HBsAg positive) with HBe Ag have a higher risk of reactivation than patients with anti-HBc Ab but negative HBs Ag with some fatal cases being reported [86, 87]. Patients with chronic hepatitis B infection should have suppressed HBV DNA level before undergoing CAR T-cell therapy. With entecavir prophylaxis and close surveillance, CAR T-cell therapy is feasible and safe in patients with evidence of previous or chronic hepatitis B infection [88–91].

   As SARS-Co-V-2 virus has emerged as a major infectious disease threat over the past 2 years, patients with hematologic malignancies receiving active anti-cancer treatments are at risk of developing severe infection [92]. Although there is no evidence for antiviral prophylaxis for SARS-Co-V-2 infections, many centers are using pre-exposure prophylaxis with long-acting monoclonal antibody tixagevimab/cilgavimab to prevent the occurrence of symptomatic infection [93]. A recent report from MSK supports the use of 300 mg dose, as recommended by the US FDA, but also highlights the fact that the antibody appears less effective against the emerging Omicron variants [94].
3. *Antifungal prophylaxis:* Although fungal infection is uncommon in patients undergoing CD19 CAR T-cell therapy, antifungal prophylaxis should be considered in some patients with prolonged cytopenia or prolonged systemic corticosteroid treatment for CAR T-cell-associated adverse events [20, 95]. In patients who are not high risk for fungal infection and do not have previous history of active fungal infection, fluconazole should be continued until the resolution of neutropenia. However, in patients with prolonged neutropenia, a history of prior mold infection, or higher grade of CAR T-cell associated complications requiring intensive immunosuppressants, later generation of mold active azoles and infectious disease consultation may be indicated [20, 75, 95].

   For prophylaxis of pneumocystis infection, most available guidelines recommend trimethoprim/sulfamethoxazole to be initiated at around 1 month post-CAR T infusion if blood count recovery allows, otherwise less myelosuppressive alternatives such as inhaled pentamidine, dapsone or atovaquone should be considered. Prophylaxis against pneumocystis infection is recommended by most experts to be extended until recovery of CD4 above 200/μL due to potential infection in early discontinuation reported by some previous studies [14, 17].
4. *Immunoglobulin replacement:* Data on immunoglobulin replacement in CAR T-cell therapy is extrapolated from patients with hematologic malignancy who receive anti-CD20 monoclonal antibody and patients who undergo allogeneic HSCT [96–99]. Therefore, it is unclear if IVIG replacement alters the overall post-CAR T-cell IgG level or improves survival outcomes [96, 100]. Wudhikarn and colleagues showed that IVIG replacement had no correlation with the incidence of infection in patients treated with CD19 CAR T-cells [17]. Similarly, Baird et al. reported no difference in IgG level during post-CAR T-cell follow-up irrespective of IVIG replacement [14]. As described earlier, the effect of CAR T-cell on humoral immunity against certain microorganisms is highly different therefore the benefit of IVIG replacement on the prevention of certain types of infection may not be equal. Practice patterns around IVIG replacement can vary widely among practicing providers and institutions. Most guidelines and recommendations from expert opinion suggest giving IVIG replacement to patients with IgG level below 400 mg/dL or 400–600 mg/dL who have history of recurrent infection [20, 74, 101, 102].

IMMUNIZATION IN PATIENTS AFTER CAR T-CELL THERAPY

Patients who undergo CAR T-cell therapy have significant immune dysregulation, affecting innate immunity during the early phase, as well as both humoral and cellular adaptive immunity in the

Table 3. Vaccination for adult patients after CD19 chimeric antigen receptor T cell therapy (modified from Hill and Seo [20]).

Killed/inactivated vaccines[a]	**Pre-CAR**	**3 m**	**4 m**	**6 m**	**6 + m**	**7 + m**	**8 + m**	**10 + m**	**12 + m**	**18 + m**	**20 + m**	**22 + m**	**24 + m**	**26 + m**	**27 + m**	**Time between doses**
SARS-Co-V-2 vaccine (mRNA-based)		X	X	X			X									Primary vaccination: 3 doses of mRNA-based vaccine with 3–4 weeks between 1st, 2nd dose. 3rd dose. Booster vaccine to be given at least 3 months after 3rd dose
Influenza (inactivated)	X				X											
Pneumococcal conjugate				Titer	X	Titer[c]	X	X								1–2 m
Pneumococcal polysaccharide				Titer		Titer[c]				X	Titer[c]					
Diphtheria/ Tetanus/acellular Pertussis				Titer	X	Titer[c]	X	X	Titer[c]							1–2 m
Hemophilus influenza type B				Titer	X	Titer[c]	X	X		Titer[c]						1–2 m
Hepatitis A				Titer	X	Titer[c]			X	Titer[c]						6 m
Hepatitis B				Titer	X	Titer[c]	X		X	Titer[c]						2 m
Live and non-live adjuvant Vaccines[b]					**Pre-CAR**	**6 m**	**6 + m**	**7 + m**	**8 + m**	**10 + m**	**12 + m**	**18 + m**	**20 + m**	**22 + m**	**24 + m**	**26 + m**	**27 + m**	**Time between doses**
MMR												X		X			Titer[c]	
Varicellar-Zoster (live); Seronegative												X		X				1 m
Varicellar-Zoster (non-live adjuvant) in VZV seropositive patients, >50 years												X		X				1–2 m

[a]For inactivated virus vaccines, vaccines should be given at least 2 months post last dose of IVIG.
[b]For lived attenuated or non-live adjuvant vaccines will not be given until 1-year post-CAR T-cells (and at least 2 years post-HSCT if patients had HSCT prior to CAR T-cell therapy), at least 5 months after last dose of IVIG, absolute CD4 count >200/μL.
[c]If patients do not develop response after a given dose of vaccination, additional vaccination should be deferred until there are evidence of immune reconstitutions: Detectable serum IgA, and CD19 B cell count >20/μL and CD4 + T cell count >200/μL (all of which should be fulfilled).

later phases. Duration of B cell aplasia, hypogammaglobulinemia, and CD4 lymphopenia can be widely different and may not correlate to each other. Most data indicate that CD4 lymphocyte will gradually recover after 3–6 months after CAR T-cell therapy but in certain occasions can be delayed and suppressed over 12 months. However, factors that determine the ability to mount immune response to vaccination after CAR T-cell therapy are not well understood. In a recent study, neither B cell aplasia or low IgG predicted vaccine immunogenicity and thus should not preclude vaccination after CAR T-cells [58]. While patients treated with CAR T-cells had lower rate of seroprotection after vaccinations, some patients could develop adequate immune responses. In addition, a proportion of patients who had vaccination pre-CAR-T cell therapy developed antibody response to vaccines after post-CAR-T cell boost or had persistent seroprotective antibody level for up to 3 months post-CAR T-cell therapy [72].

Most professional societies including ASH, ASTCT, and EBMT issued guidelines adopted from recommendations in alloHCT [103, 104]. In general, it is recommended to start immunization with inactivated/killed pathogen vaccines after 3–6 months and consider giving live attenuated virus vaccine at least 12 months post-CAR T-cell (or until CD4 count >200/μL), respectively. Physicians may incorporate the pathogen-specific IgG level and post-immunization immune response to guide decision for vaccination in these patients.

Regarding SARS-CoV-2 vaccine, the current guidelines recommended that patients who are scheduled to undergo CAR T-cell therapy should complete primary series of SARS-CoV-2 vaccines at least two weeks before the initiation of LD chemotherapy to allow memory T cell formation if feasible. In addition, patients who had COVID-19 vaccination before CAR T-cell therapy also should have repeated COVID-19 vaccination series [105]. Currently, ASH/ASTCT currently recommends a complete series of mRNA-based COVID19 vaccines including a booster starting at 3 months after CAR T-cell therapy [106]. The primary series of COVID-19 vaccination could be either 3 doses of mRNA-based vaccine or a dose of the adenovirus vector-based vaccine followed by a second dose of the mRNA-based vaccine. The booster dose could be given ~2–3 months after the primary vaccination according to the most recently updated guideline of COVID-19 vaccination for patients with moderate or severe immunocompromised states. Data on the response to COVID-19 vaccination are conflicting. Abid et al. reported the overall response rate of 31% to SARS-CoV-2 vaccine in CAR T-cell therapy recipients [107]. Dhakal et al. also reported a single-center experience showing a low rate of humoral immune response (21%) after COVID-19 vaccination in patients treated with CD19 CAR T-cells [108]. However, in another study, Tamari et al. reported that 77% of patients achieved positive neutralization activity 3 months after COVID-19 vaccination [109]. Jarisch et al. also demonstrated a robust T cell response, especially in CD4 lymphocyte subset, in eight lymphoma patients who received CD19 CAR T-cells [110]. Moreover, Parvathaneni et al. showed that despite lower humoral response to SAR-CoV2 vaccines, spike-specific T-cell response to mRNA-based vaccines (BNT162b2 and mRNA-1273) in 12 patients treated with CD19 CAR T-cells was comparable to healthy control [111]. Further larger prospective studies are required to help physicians better understand and provide appropriate vaccination to CAR T-cell recipients. Table 3 summarizes the recommendation for vaccination in patients treated with CAR T-cells [20].

CONCLUSION

Infectious complications are common in patients who undergo CAR T-cell therapy. As CAR T-cell therapy increasingly becomes a critical treatment component of hematologic malignancy, better understanding of the natural history of infection and the kinetics of immune reconstitution in these patients will provide treating physicians more insight to provide proper management for the patients.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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AUTHOR CONTRIBUTIONS

KW generated the concept of the study, conducted the literature search, reviewed the literature, and draft the initial manuscript. MAP contributed to writing the manuscript and provided feedback on the manuscript. All authors reviewed and approved the final version of the manuscript.

COMPETING INTERESTS

M-AP reports honoraria from Abbvie, Allovir, Astellas, Bristol-Myers Squibb, Celgene, Equilium, Exevir, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros, OrcaBio, Takeda, and VectivBio AG, Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, Sellas Life Sciences, and Servier, and the scientific advisory board of NexImmune. He has ownership interests in NexImmune and Omeros. He has received institutional research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis. KW declares no relevant conflict of interest.

ADDITIONAL INFORMATION

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