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TRANSPLANT INFECTIOUS DISEASE

REVIEW ARTICLE

Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies

Eleftheria Kampouri[1,2] | **Jessica S. Little**[3,4] | **Kai Rejeski**[5,6] | **Oriol Manuel**[2] | **Sarah P. Hammond**[4,7] | **Joshua A. Hill**[1,8,9]

[1]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA

[2]Infectious Diseases Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[3]Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[4]Division of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

[5]Department of Medicine III—Hematology/Oncology, LMU University Hospital, LMU Munich, Munich, Germany

[6]German Cancer Consortium (DKTK), Munich site, and German Cancer Research Center, Heidelberg, Germany

[7]Divisions of Hematology/Oncology and Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[8]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA

[9]Department of Medicine, University of Washington, Seattle, Washington, USA

Correspondence
Eleftheria Kampouri, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Eastlake Avenue E 1100, Mail Stop E4-100, Seattle, WA 98109, USA.
Email: kampourie@fredhutch.org

Abstract

Background: Chimeric antigen receptor (CAR)-T-cell therapies have revolutionized the management of acute lymphoblastic leukemia, non-Hodgkin lymphoma, and multiple myeloma but come at the price of unique toxicities, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and long-term "on-target off-tumor" effects.

Methods: All of these factors increase infection risk in an already highly immunocompromised patient population. Indeed, infectious complications represent the key determinant of non-relapse mortality after CAR-T cells. The temporal distribution of these risk factors shapes different infection patterns early versus late post-CAR-T-cell infusion. Furthermore, due to the expression of their targets on B lineage cells at different stages of differentiation, CD19, and B-cell maturation antigen (BCMA) CAR-T cells induce distinct immune deficits that could require different prevention strategies. Infection incidence is the highest during the first month post-infusion and subsequently decreases thereafter. However, infections remain relatively common even a year after infusion.

Results: Bacterial infections predominate early after CD19, while a more equal distribution between bacterial and viral causes is seen after BCMA CAR-T-cell therapy, and fungal infections are universally rare. Cytomegalovirus (CMV) and other herpesviruses are increasingly breported, but whether routine monitoring is warranted for all, or a subgroup of patients, remains to be determined. Clinical practices vary substantially between centers, and many areas of uncertainty remain, including CMV monitoring, antibacterial and antifungal prophylaxis and duration, use of immunoglobulin replacement therapy, and timing of vaccination.

Conclusion: Risk stratification tools are available and may help distinguish between infectious and non-infectious causes of fever post-infusion and predict severe infec-

Eleftheria Kampouri and Jessica S. Little contributed equally to this study.

tions. These tools need prospective validation, and their integration in clinical practice needs to be systematically studied.

KEYWORDS
BCMA, CAR-T-cell therapy, CD19, infections, prediction, prevention, risk stratification

1 | INTRODUCTION

Chimeric antigen receptor (CAR)-T-cell therapies have transformed the landscape of cancer care, inducing durable responses in often heavily pretreated patients with B-cell and plasma-cell hematologic malignancies facing dire prognoses. The first two CD19-targeted CAR-T-cell products were approved by the U.S. Food and Drug Administration (FDA) in 2017, marking a new era for cellular immunotherapies, and several more products and indications for their use followed.[1] Approved CD19-targeted CAR-T-cell products include: tisagenlecleucel (Kymriah; Novartis) for B-cell acute lymphoblastic leukemia (ALL) in children and young adults, large B-cell lymphoma and more recently follicular lymphoma[2–5]; axicabtagene ciloleucel (Yescarta; Kite/Gilead) for large B-cell lymphoma and follicular lymphoma[6,7]; brexucabtagene autoleucel (Tecartus; Kite/Gilead) for mantle cell lymphoma and B-ALL in adults[8,9]; and lisocabtagene maraleucel (Breyanzi; Juno/BMS) for large B-cell lymphoma.[10,11] Indications for use are constantly evolving and their place in therapy is shifting to sooner rather than later, as second line of treatment for B-cell lymphoma refractory or relapsing after first line of chemotherapy.[11–14] Since March 2021, two novel products targeting B-cell maturation antigen (BCMA) became available for relapsed/refractory multiple myeloma: idecabtagene vicleucel (Abecma; Celgene/BMS) and ciltacabtegene (Carvykti; Janssen/Legend).[15–17] Beyond the approved products, more than 300 ongoing trials are investigating novel constructs, targets, and indications,[18] and CAR-T-cell use is rapidly expanding in various hematologic malignancies, solid tumors, and non-oncological indications such as autoimmune diseases and infections.[19–24]

The widespread use of these potent therapies is in part limited by frequent toxicities, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), early immune effector cell-associated hematoxicity (ICAHT),[25] and hemophagocytic lymphohistiocytosis (HLH), in the acute setting. Definitions and grading of acute post-CAR-T-cell toxicities are available by the American Society for Transplantation and Cellular Therapy.[26] Furthermore, cytopenias can be delayed in nature, and the expected "on target off-tumor" effects result in long-term B-cell aplasia and antibody deficiencies (Figure 1).[25,27–32] The risk for infection after CAR-T-cell therapy is high due to these and other factors,[33] creating unique challenges and opportunities for infection prevention.

Several decades of experience with hematopoietic cell transplant (HCT) recipients has taught us that optimizing supportive strategies is essential to prolong survival and improve outcomes. Six years after the first FDA approval, thousands of patients have received these "living drugs."[34] However, despite major advances in CAR-T-cell manufacturing and administration, infection prevention strategies remain disproportionately unevolved and are still based on expert opinion consensus and extrapolated from other patient populations (e.g., autologous HCT recipients). Accurately assessing infections and risk factors is a prerequisite for designing trials to establish evidence-based preventive strategies. However, this is not an easy task due to the heterogeneity in infection data collection and reporting in trials and the often small sample sizes along with various methodologies and inclusion criteria in existing cohorts. Here, we review the risk factors and epidemiology of infections after CD19- and BCMA-targeted CAR-T-cell therapy and the preventive strategies to mitigate these complications. Clinical practice varies between centers; we summarized different approaches and the evidence (or lack thereof) to provide the rationale behind them while highlighting areas of ongoing uncertainty.

2 | INFECTION RISK

A plethora of factors contribute to high infection risk in CAR-T-cell therapy recipients,[33] shaping temporally distinct infection patterns during different periods (early vs. late) post-infusion (Figure 1).

2.1 | Pre-treatment

The immunosuppressive burden is high even before CAR-T-cell infusion; infections can occur in up to half of patients in the 3 months prior to infusion[35,36] and have been associated with a higher risk for post-infusion infection.[36,37] The type of underlying malignancy and prior treatments are key determinants of peri-CAR-T-cell infusion infection risk. B-ALL compared to lymphoma has been associated with higher risk for infection.[38] Furthermore, studies using tisagenlecleucel, report a tendency toward a higher infection rate in patients with ALL, followed by diffuse large B-cell lymphoma and finally follicular lymphoma.[2,4,39] A higher number of prior antitumor regimens,[36,38] previous allogeneic HCT,[35] and bridging chemotherapies for lymphoma[40] have all been identified as risk factors for infection. Finally, hematopoietic reserve pre-CAR-T-cell infusion and, more specifically, severe neutropenia at baseline (<500 cells/mm^3), which likely reflects the burden of disease and prior treatments, as well as baseline inflammation state (elevated C-reactive protein [CRP] levels) may also be associated with increased risk for infection.[36–38,41]

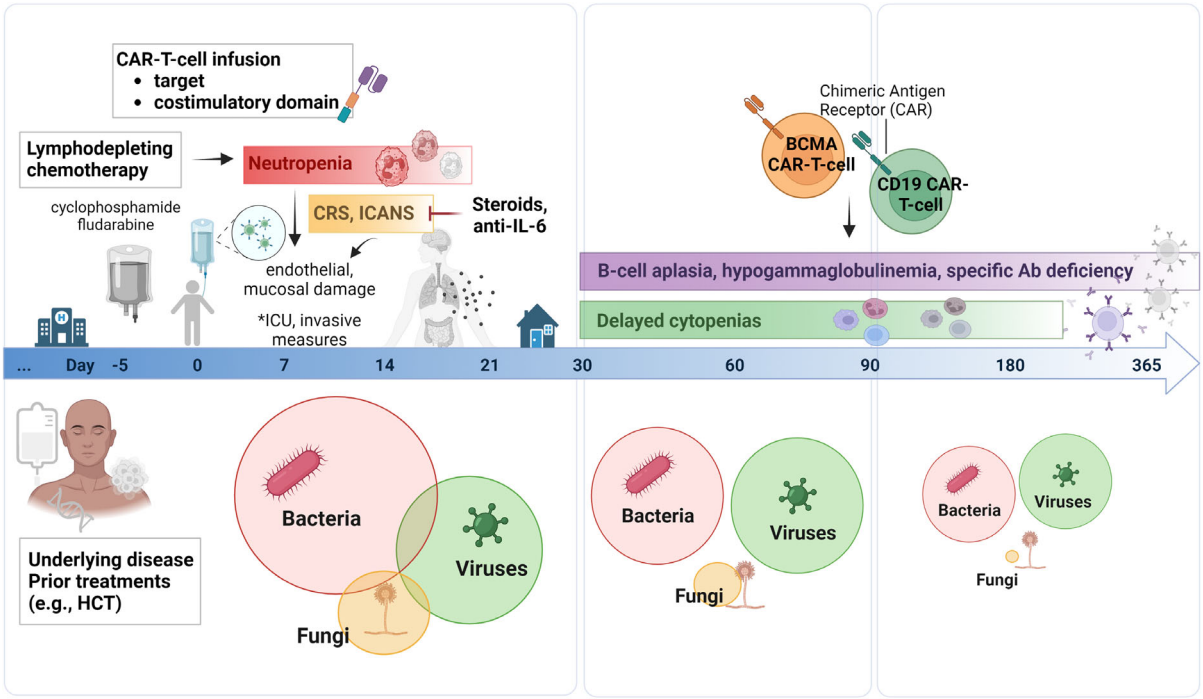


FIGURE 1 Infection risk and epidemiology during different time intervals after chimeric antigen receptor (CAR)-T-cell therapy. The size of the bubble represents the relative approximated frequency for each type of infection (bacterial, viral, and fungal). Neutropenia and delayed cytopenias are now referred to as early and late immune effector cell-associated hematotoxicity (ICAHT). CRS, cytokine release syndrome; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; IL-6, interleukin 6. *Source*: Created with BioRender.com.

2.2 | Early (days 0–30)

Severe neutropenia (<500 cells/mm^3) develops in over 90% of patients after lymphodepleting chemotherapy, with a median duration of 9 days, and can be prolonged (>21 days).[42–45] The severity and duration of neutropenia is a key determinant of the epidemiology of early infections, with most infections being bacterial and occurring during the neutropenic phase (first 10 days after infusion).[38,46] Fungal infections may occur in the setting of treatment with corticosteroids, prolonged neutropenia, or depending on host factors (e.g., ALL) but are rare.[35,36,38,40,46–56]

CRS[38,46] and ICANS[37,38,40,57] are important determinants of infection risk early after infusion. These acute toxicities reflect the robust activation and proliferation of CAR-T cells triggered by their encounter with tumor cells and endogenous immune effector cells, leading to lysis of targeted cells, massive cytokine release, and endothelial damage.[58] In addition to the resulting profound immune dysregulation, their management often relies on immunosuppressive treatments, including steroids and/or anti-interleukin-6 (IL-6) (tocilizumab) and invasive procedures for critically ill patients, further adding to the infection risk.[26] Corticosteroid therapy (especially of longer duration or high dose) is a strong predictor of infection, both early and late after infusion after CD19 CAR-T cells, although data on BCMA CAR-T cells are limited.[36,40,41,49,59] An association between tocilizumab and infection has been reported in some univariate analyses,[38,40] but not upon multivariable analysis.[38,41] However, data from the Center for International Blood and Marrow Transplant Research (CIBMTR) among 391 patients with grade 1 CRS showed no difference in infection between patients treated with tocilizumab or not.[60] The much shorter duration of tocilizumab in the setting of CRS might not impact infection risk in the same way it does in patients with auto-immune diseases,[60] while tocilizumab can be used as steroid-sparing strategy in CRS.[61]

The type of CAR-T-cell product and the costimulatory domain (4-1BB vs. CD28) influence the risk for CRS, ICANS, and hematological toxicity.[62,63] Axicabtagene ciloleucel (CD28) was associated with a greater risk for CRS, ICANS, and hematological toxicity in a head-to-head comparison with tisagenlecleucel (4-1BB) among 809 adults with relapsed/refractory (R/R) diffuse large B-cell lymphoma after propensity score matching.[64] This could indirectly lead to a higher theoretical infection risk[62]; however, the relationship with infection is not as straightforward, and post-marketing surveillance data suggested an increased infection risk with tisagenlecleucel compared to axicabtagene ciloleucel, although such studies are predisposed to bias.[65]

2.3 | Late (after day 30)

The engagement of CAR-T cells with their targets on non-malignant cells of the B-lineage, also known as "on-target off-tumor" effects, contributes to the prolonged depletion of B cells and plasma cells, hypogammaglobulinemia, and specific antibody deficits. BCMA and CD19 CAR-T cells induce distinct immune deficits due to the expres-

sion of their targets on normal B-lineage cells at different stages of differentiation.[32,66] CD19 is expressed on B cells at earlier stages (naïve and memory B cells), and is lacking from the long-lived plasma cells which are mostly responsible for maintaining stable concentrations of antigen-specific antibodies against previously encountered pathogens.[67,68] Targeting CD19 thus leads to B-cell depletion and may contribute to hypogammaglobulinemia, but pathogen-specific immunoglobulin G (IgG) levels can be maintained.[40,49,69,70] BCMA is expressed in all plasma cells, so its targeting may lead to more severe hypogammaglobulinemia and a decrease in specific antibody levels.[70]

Hypogammaglobulinemia rates vary greatly between CAR-T-cell products and patient populations but are reported in up to 46%–62% of patients with large B-cell lymphoma treated with axicabtagene autoleucel a year or more after infusion.[40,49,71] In pediatric patients with B-ALL, B-cell aplasia is reported in two-thirds of patients at 12 and 24 months (and even longer) after infusion; hypogammaglobulinemia is likely underestimated due to ample use of immunoglobulin replacement therapy (IGRT) in this population.[72–74] After BCMA CAR-T-cell therapy, hypogammaglobulinemia was present in 53%–75% of patients a year after infusion[55,75] and was severe (IgG < 300 mg/dL) in 41%.[75] It is yet unclear how these deficits influence long-term infection risk, although hypogammaglobulinemia seems to increase infection risk in the pediatric population.[35,72] Importantly, hypogammaglobulinemia does not necessarily reflect pathogen-specific antibody levels and does not preclude antibody response to vaccination. However, these distinct immune deficits highlight the need for different preventive strategies between BCMA versus CD19 and children versus adults.[32]

Cellular immunity is also durably impaired in CD19 CAR-T-cell recipients; CD4+ T-cell counts decrease after infusion and may remain very low, with a median of 155 cells/μL at 1 year[40] and <200 cells/μL in half of patients at 18 months post-infusion.[49] A biphasic temporal course of neutropenia has been described in 52% of patients, with an intermittent recovery in most by 3 weeks after CAR-T-cell therapy followed by a second trough 2 months after infusion.[44] In contrast to early ICAHT, which is closely related to the lymphodepleting chemotherapy in the setting of concurrent underlying immune dysregulation and impaired hematopoietic function,[76,77] delayed cytopenias are independent of systemic myelotoxic therapies, but the exact mechanism is not elucidated. A higher grade of CRS and higher levels of CRS-related cytokines (e.g., IL-6 levels) have been implicated in delayed hematologic recovery post-CAR-T-cell therapy[42,43,45] but not consistently across studies.[44] Finally, the response to treatment of the underlying disease (remission vs. persistence/relapse) will also impact infection risk, particularly in the context of additional anti-tumor therapies. Disease response after CAR-T-cell therapies is further discussed in this issue by D'Angelo et al.

3 | EPIDEMIOLOGY OF INFECTIONS

The epidemiology of infections is distinct in the early and late periods following CAR-T-cell infusion due to the chronological distribution of infection-risk factors (Figure 1). Traditionally, early infections have been characterized as infections prior to day 28 or 30 post-infusion and late infections have been defined as any infection after that point. However, frequently patients with a more complicated post CAR-T-cell therapy course may remain hospitalized on day 30, which can modify their risk compared to patients who have been discharged and are in the community.[38,46] In that setting, day 100 has become another important time point that is used to delineate early versus late infections, particularly as follow-up durations extend to a year or greater.

3.1 | CD19-targeted CAR-T-cell therapy

A rapidly growing body of literature assesses infections after CD19 CAR-T-cell therapy, but the high heterogeneity between studies hinders direct comparisons and generalizable conclusions. A wide range of infection rates is reported depending on the patient population (type of malignancy), study setting (pivotal trials vs. real-world experience), CAR-T-cell product (commercial vs. investigational), preventive/prophylactic practices used, timeframe, and definition of infection (clinically/microbiologically documented infections) (Table S1). In pivotal trials of CD19 products, infections were reported in 19%–69% and severe infections (grade ≥3) in 5%–32% post-CAR-T-cell infusion with variable follow-up time (Table S2).[2,4,6–10,39] A recent meta-analysis reported a pooled incidence rate of 34% after CD19 CAR-T cells (95% confidence interval, 26%–43%) (27 studies with 2450 patients), and a lower incidence for randomized control trials compared to observational studies.[78]

3.1.1 | Early (days 0–30)

Focusing on cohort studies distinguishing between early (<28–30 days) and late (beyond 28–30 days), infection incidence is estimated at 12%–46% within the first month and subsequently decreases during following months (Figure 2).[35–38,40,46,49,50,57,59,79] Infection density within the first month is 0.48–2.89 infections per 100 days at risk.[35,37,38,40,49,50] Bacterial infections predominate during the first month, representing 32%–68% of all events. Furthermore, *Clostridioides difficile* infections are frequently reported but some degree of overdiagnosis is possible when using sensitive polymerase chain reaction (PCR) methods in patients frequently presenting diarrhea of other causes (chemotherapy, CRS, etc.).[40,59] Viral infections constitute 19%–47% of all infections; these include respiratory viruses, but herpesviruses are increasingly being reported, and cytomegalovirus (CMV) was the main viral pathogen in one study.[57] This pattern may vary in favor of more frequent viral infections in specific populations, such as children,[35] adults with large B-cell lymphoma,[49,57] and BCMA CAR-T-cell recipients. Finally, fungal infections are less common (3%–14%) (Figures 2 and 3).

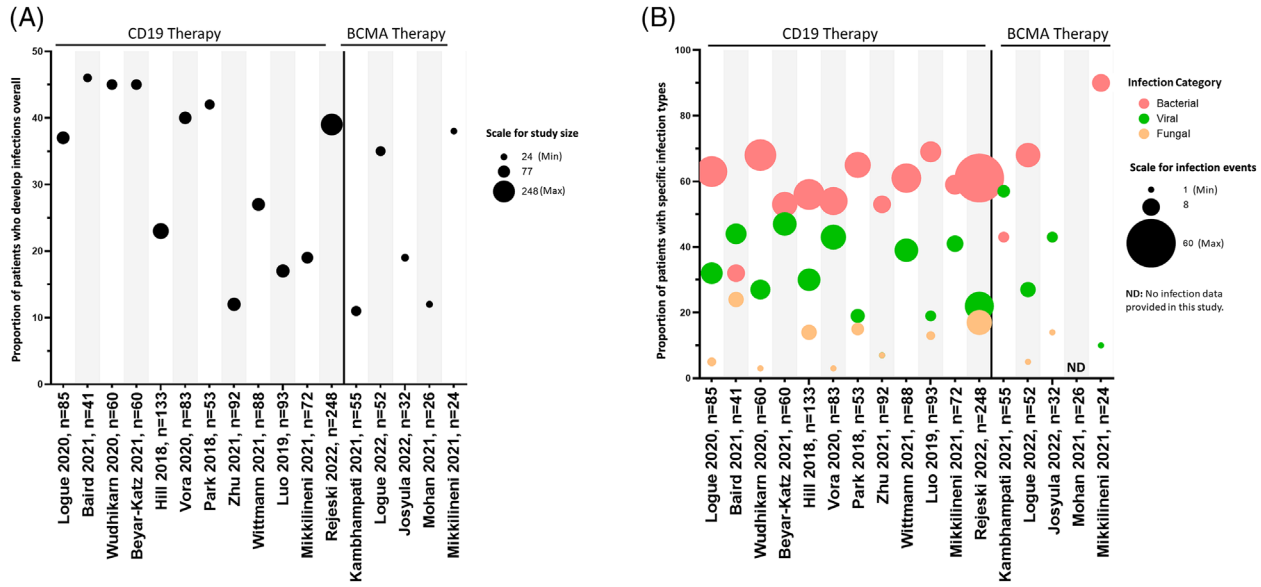


FIGURE 2 Early infections after CD19 and B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T-cell therapy (within 30 days). (A) Rate of infection among all patients. (B) Relative frequency of infection type (bacterial, viral, and fungal) among all infectious events. The diameter of the bubble represents: the number of patients for each study (A) and the number of infectious events (B). Different types of infection are depicted in different colors (pink: bacterial, green: viral, yellow: fungal).

3.1.2 | Late (beyond 30 days)

Infection density universally declines many times (1.8–5.6×) beyond the first month.[35,37,38,40,49,50] After the first month, infections are reported in 10% up to 2 months,[50] 14%–23% up to 3 months,[35,38,59] 6%–40% up to 6 months,[37,46,49] and 44%–53% up to a year after infusion.[40,49]

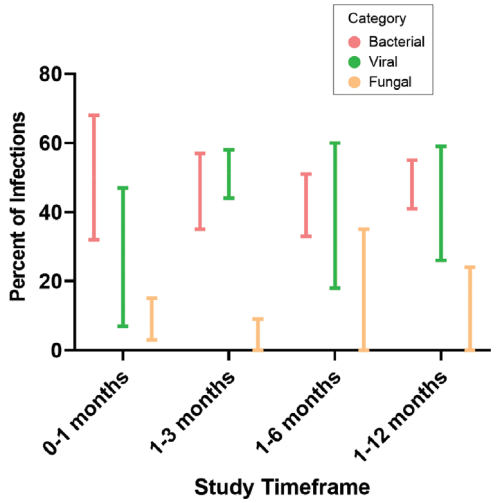
Humoral immune deficits leading to hypogammaglobulinemia and specific antibody deficiencies are likely key risk factors for late infections. Extrapolating from patients with primary immunodeficiencies, severe bacterial infections, especially of the sinopulmonary tract, would be expected. Indeed, bacterial causes represent up to 55% between 1 and 12 months after infusion.[35,37,38,40,46,49,59] Viral infections represent up to ~60% of infections and are mainly due to respiratory viruses (Figure 4).[35,37,38,40,46,49,59] In a study of late events (after 3 months) in patients with at least 12 months of follow-up, hypogammaglobulinemia was the most frequent adverse effect; the most common infectious events were respiratory tract infections (>70%), and among microbiologically documented infections, 60% were bacterial.[48] Fungal infections are rare beyond the first month. In the largest study to date among 280 CAR-T-cell therapy recipients with non-Hodgkin lymphoma, only eight invasive fungal infections were observed up to more than a year post-infusion, despite the lack of antifungal prophylaxis and the high prevalence of severe delayed neutropenia[51] (Figure 3). *Pneumocystis jirovecii* pneumonia occurred in three patients beyond 3 months after infusion and after cessation of anti-*Pneumocystis* prophylaxis, underscoring the prolonged impaired cellular immunity that also occurs in this patient population.[51]

Timeframe	Bacterial cause	Viral cause	Fungal cause	References
0–1 month	32%–68%	7%–47%	3%–15%	35–38,40,49, 50,57,59,79
1–3 months	35%–57%	44%–58%	0%–9%	35,38,59
1–6 months	33%–51%	18%–60%	0%–35%	37,46,49
1–12 months	41%–55%	26%–59%	0%–24%	40,49,59

3.2 | BCMA-targeted CAR-T-cell therapy

Assessment of infectious complications following BCMA-directed CAR-T-cell therapy remains limited by small patient numbers, variable follow-up, and single-center experiences. Multicenter clinical trial data frequently provide incomplete detail on infectious complications for novel oncologic therapies, although they may contribute important information about overall incidence.[80] The incidence of overall infections ranged from 42% to 69% in four major clinical trials, with grade III–IV infections occurring in 6%–24% of patients (Table S3). Information on sites and pathogen types is limited, but viral infections predominated in one study.[15] In addition, six real-world retrospective studies have specifically evaluated infectious complications following BCMA CAR-T-cell therapy (Table S3) with follow-up ranging from 30 days to greater than 1 year. The overall incidence of infections ranged from 53% to 58% in the four largest studies that included >30 patients and from 23% to 38% in the two smaller studies with fewer than 30 patients.[36,53–56,75,81] The majority of infections reported

FIGURE 3 Invasive mold infections following: (A) CD19 and (B) B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T-cell therapy. (A) Invasive mold infections following CD19-directed CAR-T-cell therapy are displayed from left to right in order of oldest published studies to newest published studies. IMI, invasive mold infection; MO, months. (B) Invasive mold infections following BCMA-directed CAR-T-cell therapy are displayed from left to right in order of oldest published studies to newest published studies. *Logue et al. and Wang et al. do not report individual invasive mold infections. Wang et al. reported three fungal infections without specifying site or pathogen type. Logue et al. reported three possible fungal infections ($n = 1$ pneumonia; $n = 2$ skin infections). NR, not reported.



Timeframe	Bacterial cause	Viral cause	Fungal cause	References
0–1 month	32%–68%	7%–47%	3%–15%	35-38,40,49, 50,57,59,79
1–3 months	35%–57%	44%–58%	0%–9%	35,38,59
1–6 months	33%–51%	18%–60%	0%–35%	37,46,49
1–12 months	41%–55%	26%–59%	0%–24%	40,49,59

FIGURE 4 Relative frequency of infection types (bacterial, viral and fungal) as percentage of all infections after CD19 CAR-T-cell therapy during different time intervals. The percentages and references are included in the table given below the figure.

in these studies have been mild to moderate in severity with few infection-related deaths described.[56,75] In contrast to CD19 CAR-T-cell therapy where bacterial infections appear to be most common, the predominant pathogen type has varied in the largest studies of BCMA-directed CAR-T-cell therapy, with several reporting a higher incidence of viral infections in particular herpesvirus and respiratory viral infections, although importantly this outcome may vary based on the follow-up duration.[38,46,54,56] Incidence of fungal infections remains low across all studies despite variation in the use of prophylaxis as well as inclusion of possible invasive fungal infections in some studies (Figure 3).[51,54,56,75] Assessment of infections by site has not been consistent across studies, but notably in those that delineate infection site, respiratory infections have predominated comprising 59%–73% of infectious events.[55,56,75] This was confirmed recently in the largest study to date among 99 BCMA CAR-T-cell therapy recipients showing that respiratory infections predominate, particularly after day 100.[82] This is an important epidemiologic finding that may have implications for prevention strategies.

3.2.1 | Early (days 0–30)

The temporal distribution of infections following BCMA CAR-T-cell therapy varies somewhat between studies, likely related to variable study follow-up, with 11%–38% of infections reported prior to day 30 (Figure 2).[54,56,75] In the largest study by Kambhampati et al., there was a surprisingly low number of early infections recorded with only seven of 47 infectious events (43% bacterial; 57% viral) occurring before day 30, whereas in another study by Logue et al., 22 of 46 events were reported between days 0 and 30 (68% bacterial; 27% viral; and 5% fungal).[56,75] Importantly, while serious infections, including bloodstream infections are rare overall, they occur most often prior to day 30.[55] In a study by Josyula et al., seven early infections (days 0–28) accounted for 75% of bacterial bloodstream infections and 67% of serious infections.[54] *C. difficile* colitis is also seen predominantly in the early period likely related to hospitalization and antimicrobial administration similar to what has been reported in the context of CD19 CAR-T-cell therapy[40,56] (Figure 2) Risk factors for infection such as CRS, ICANS, or use of high-dose corticosteroids have not been identified following BCMA CAR-T-cell therapy as they have with CD19 CAR-T-cell therapy, but specific analyses of early and late risk periods remain limited. However, severe hematotoxicity has been associated with infection in BCMA CAR-T-cell therapy recipients.[83]

3.2.2 | Late (beyond 30 days)

While data are scarce, some understanding of the epidemiology of late infections after BCMA CAR-T-cell therapy can be gleaned from small studies published thus far. In one study to date with 55 patients and 12 months of follow-up, most infections (85%) occurred after day 30, with close to half of those occurring between days 31 and 100 and approximately half after day 100.[75] In terms of pathogen type, bacterial and viral infections were evenly distributed between days 31 and 100, and viral infections predominated after day 100. While the specific late bacterial infections are not well described, the authors did report that respiratory infections predominate overall, comprising 68% of all infections. Notably, all three fungal infections in the study occurred after day 100.[75] In another large study by Logue et al. with 100 days of follow-up, 51% of infections occurred after day 30, with a fairly equal impact of bacterial (mostly sinusitis and pneumonia) and viral infections (respiratory viral infections), demonstrating the importance of respiratory infections in the late period.[56] Two of three possible fungal infections occurred after day 30.[56] Wang et al. evaluated infections from day 0 to 60 and then at varying time intervals after day 60; 57% of infectious events occurred after day 60, the majority of which were respiratory (80%), and two-thirds of reported fungal infections occurred after day 60.[55]

Infections are common after day 30 following BCMA CAR-T-cell therapy, although few studies have evaluated incidence and risk compared to standard anti-myeloma therapy regimens or to novel emerging therapies such as bispecific antibody therapies.[36,53] Late infections are less commonly severe or life threatening. Bacterial and viral infections appear to occur at similar rates from day 30 to 100 and viral infections predominate thereafter. Further granularity is needed on the site-specific bacterial infections occurring after day 30; however, bloodstream infections appear rare, while respiratory infections,

including pneumonia and sinusitis, are common.[54,56] Risk factors for late infections have not yet been characterized, but are key to identify in the future in order to inform preventative strategies and improve quality of life in patients who are otherwise doing well late after BCMA CAR-T-cell therapy.

4 | INFECTION PREVENTION FOLLOWING CAR-T-CELL THERAPY

Best practice recommendations on management and prevention of infectious complications are available from the European Society for Blood and Marrow Transplantation and European Haematology Association,[84] the Spanish Infection Prevention in CAR-T-cell Study Group,[85] the Société de Greffe de Moelle et de Thérapie cellulaire,[86] and a number of expert opinion papers.[32,59,87,88] In the absence of efficacy trials assessing prevention strategies, recommendations mainly rely on limited, mostly retrospective single-center experience. As such, a variety of approaches are utilized (Table 1); the inter-center (and inter-study) heterogeneity in practices was highlighted in a recent meta-analysis[78] and an international survey focusing on hematologic toxicity management practices.[25]

Careful assessment of pre-CAR-T-cell therapy immunologic status and infectious history is key as monitoring or intervention may be tailored to the individual patients' epidemiologic risk, disease state, and prior therapies. More prior lines of therapy[36,38] and prior allogenic HCT[35] in particular have been associated with increased infection risk. For patients who previously received an HCT, relevant infection prevention practices should continue to be followed.

4.1 | Pre-CAR-T-cell therapy infection prevention

Infection screening is an important component of pre-CAR-T-cell therapy risk assessment. All patients should be screened for human immunodeficiency virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) with serologic testing.[85,87,89] Serologic screening for herpes simplex virus (HSV) and varicella zoster virus (VZV) is helpful to guide the use of antiviral prophylaxis with val/acyclovir, which is recommended through 6–12 months post-CAR-T-cell therapy, and for future consideration for VZV vaccination.[90,91] CMV serologic screening can also be considered before CAR-T-cell therapy and is discussed in detail in Section 5. Assessment of other latent infections can be considered for individual patients based on history and epidemiologic risk factors, including *Mycobacterium tuberculosis*, human T-cell lymphotropic virus type 1, and *Strongyloides stercoralis*.

Immunization is another key aspect of pre-CAR-T-cell therapy assessment and is discussed in Section 4.3.1.

4.2 | Peri-CAR-T-cell therapy infection prevention

Current guidelines and local practices at the authors' centers are summarized in Table 1. Notably, the use of fluoroquinolone prophylaxis during periods of neutropenia varies by center and region depending on rates of fluoroquinolone resistance, as well as an evolving understanding of the risks and benefits of this approach.[84,85] Viral monitoring and prophylaxis are discussed in more detail in Section 5.

Antifungal prophylaxis practices also vary widely across institutions, and the utility remains uncertain given the relatively low incidence after CAR-T-cell therapy overall (Figure 3), although incidence may be enriched in certain patients requiring post-CAR-T-cell therapy immunosuppression.[35–38,40,46,47,49–52,54–56,59,79,92]

Pneumocystis jirovecii prophylaxis is widely recommended across guidelines and institutions for at least 6 months after cell infusion, although optimal duration remains unknown.[84,87] Late cases of *P. jirovecii* pneumonia have been reported in multiple studies after cessation of prophylaxis, suggesting that there may be delayed reconstitution of cellular immunity >6 months after cell infusion.[49,51]

4.3 | Late post-CAR-T-cell therapy infection prevention

4.3.1 | Vaccination

Vaccination following CAR-T-cell therapy is an important intervention to prevent serious infections. Vaccination schedules have been published in expert opinion papers.[87,93] However, the timing of reconstitution of cellular and humoral immunity after CAR-T-cell therapy can vary widely and there is limited knowledge on vaccine immunogenicity in this setting.[85,87,94] Recommendations typically suggest pre-CAR-T-cell vaccination with inactivated vaccines targeting particularly high-risk pathogens in this patient population, such as influenza, SARS-CoV-2, and possibly *Streptococcus pneumoniae*.[85,87,89–91] Revaccination after CAR-T-cell therapy is widely recommended regardless of hypogammaglobulinemia or ongoing B-cell aplasia.[84–86] Inactivated vaccines should be administered at least 3–6 months following cell infusion, and live vaccines are typically recommended ≥12 months after cell infusion.[84–86] Evidence of immune reconstitution, such as recovery of B cells and immunoglobulins, could be used to guide the timing of vaccination but is not well established. The advent of mRNA vaccines has led to reasonable response rates for SARS-CoV-2 with vaccination as early as 3 months post-HCT, providing the rationale for consideration in CAR-T-cell therapy recipients as well.[95] The mRNA platform may allow for rapid expansion of highly immunogenic vaccines for other pathogens as well, especially those targeted toward respiratory viruses which have a major impact on CAR-T-cell recipients.[96]

4.3.2 | Immunoglobulin replacement therapy

Immunoglobulin replacement therapy (IGRT) is a well-supported strategy to mitigate serious bacterial infections, mostly with encapsulated bacteria of the sinopulmonary tract, in the setting of primary immunodeficiencies.[32,97,98] Its role in other infections and settings, including in hematological malignancies, is controversial.[98–100]

TABLE 1 Guidelines and local practices for infection prevention in chimeric antigen receptor (CAR)-T-cell therapy recipients at the authors' centers and from published guidelines.

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antibacterial prophylaxis	NR	NR	NR	FQ during neutropenia[a]	Levofloxacin 500 mg/day during neutropenia[a]	NR	Risk adapted[b]; FQ during neutropenia[a]
Antifungal prophylaxis	Consider fluconazole, posaconazole,[c] or micafungin if severe or prolonged >14 days neutropenia,[a] and/or long-term or high dose (>3 days) of steroids or post-allo-HCT	Fluconazole (400 mg/day) during neutropenia[a]	Consider fluconazole or micafungin if severe neutropenia[a] >14 days, steroids >3 days, post-allo-HCT	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis
Anti-mold prophylaxis	See above	Posaconazole 300 mg/day,[c] nebulized liposomal amphotericin B or micafungin if ≥4 lines of prior treatment, pre-CAR-T-cell infusion severe neutropenia[a], higher dose of CAR-T-cells (>2×10^7), previous IFI, tocilizumab, and/or steroids	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Posaconazole (300 mg/day[c]) if neutropenia[a] >20 days or steroids >3 days for at least 4 weeks after last dose of steroid (and after neutropenia resolution[a])	No anti-mold prophylaxis	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Risk-adapted[b] (posaconazole[c] or micafungin during neutropenia[a] or extended steroid exposure)
Anti-PjP prophylaxis	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 3×/week Start 1 week pre-infusion (pause during neutropenia), continue until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 2×/day on 2 consecutive days/week Start 21–28 days post-infusion, continue for at least 6 months	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3

(Continues)

TABLE 1 (Continued)

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antiviral prophylaxis	Acyclovir 800 mg 2×/day or valacyclovir 500 mg 2×/day Start at LD chemotherapy, continue for 1 year and until CD4 >200 cells/mm^3	Acyclovir 400–800 mg 2×/day At least 60–100 days after infusion	Acyclovir 800 mg 2×/day or valacyclovir 500 mg 2×/day Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	Acyclovir 800 mg 2×/day or valacyclovir 500 mg 2×/day Start at lymphodepleting chemotherapy, continue for at least 1 year	Acyclovir 400 mg 3×/day or valacyclovir 500 mg 2×/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	Valacyclovir 500 mg 2×/day for 6–12 months	Acyclovir 400 mg 2×/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3
CMV monitoring	As clinically indicated	NR	Consider in CMV seropositive patients at high risk Weekly monitoring	Patients treated with >3 days of steroids Weekly until 1 month after last dose of steroid	Strongly consider monitoring for patients receiving >5 doses dexamethasone	Consider in CMV seropositive patients at high risk Weekly/biweekly monitoring	NR
Preemptive threshold	–	NR		150 IU/mL (plasma)	None	None	None

Abbreviations: Allo-HCT, allogeneic hematopoietic cell transplant; CHUV, Lausanne University Hospital; CMV, cytomegalovirus; DS, double strength; EBMT, European Society for Blood and Marrow Transplantation; FQ, fluoroquinolone (levofloxacin 750 mg PO daily); IFI, invasive fungal infection; LD, lymphodepleting; LMU, Ludwig Maximilian University of Munich; NR, not recommended; PjP, *Pneumocystis jirovecii* pneumonia; SFGM-TC, Société de Greffe de Moelle et de Thérapie Cellulaire; SS, single strength; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]Neutropenia defined as absolute neutrophil count <500 cell/mm^3; resolution: first of 3 days ≥500 cell/mm^3.

[b]Adapted to baseline CAR-Hematotox score or other pertinent risk factors for prolonged severe neutropenia (absolute neutrophile count <500 cell/mm^3 for ≥7 days) such as underlying bone marrow infiltration.

[c]Posaconazole 200 mg every 12 h on first day then 300 mg/day.

However, based on the physiopathology of humoral immunodeficiencies post-CAR-T cells, the increased infection risk even late after CAR-T-cell infusion, and extrapolating from other populations (primary immunodeficiencies), there is consensus that IgG levels should be monitored pre-infusion and monthly post-infusion for 3 months (or longer).[84,85] The benefits of universal prophylaxis with IGRT in the setting of asymptomatic hypogammaglobulinemia are unclear. Important criteria that may be most relevant to prompt IGRT include serious or recurrent bacterial infections in the context of a total serum IgG level <400 mg/dL.[32,66,84] BCMA CAR-T-cell therapy recipients[32] and pediatric patients[101,72] appear to have more profound humoral deficits and a theoretically higher benefit from the more liberal use of IGRT. Prospective controlled trials are needed to identify patients who will benefit the most, along with the optimal timing, schedule, duration, and modality of IGRT.

4.3.3 | Novel therapies

Novel therapies, including pathogen-targeted monoclonal antibodies, cytotoxic T-cell and natural killer (NK) cell-based immunotherapies are emerging and may play a role in future prevention and treatment strategies.[102–107]

5 | SPECIAL CONSIDERATIONS

5.1 | Coronavirus disease 2019

Coronavirus disease 2019 (COVID-19) in CAR-T-cell therapy recipients is separately reviewed in this article series by Kampouri et al.[108]

5.2 | Cytomegalovirus

The epidemiology of CMV after CAR-T-cell therapy is not well elucidated due to the absence of routine clinical monitoring and the small size and retrospective design of existing studies.[57,109–111] In CD19 CAR-T-cell therapy recipients with lymphoma, CMV viremia has been reported in 17%–44% with variable frequency of testing, duration of follow-up and inclusion criteria (CMV seropositive vs. seronegative).[57,109–111] In the largest study to date by Márquez-Algaba et al. among 95 CMV-seropositive patients, 42 patients (44%) developed at least one positive CMV PCR test after infusion and 22% had a CMV viral load ≥1000 IU/mL (whole blood samples).[109] There was no evidence of CMV disease in any patient,[109] which is in agreement with most other studies.[57,110] On multivariable analysis, prior use of dexamethasone was associated with an increased risk for CMV viremia ≥1000 IU/mL.[109]

Even less is known about the epidemiology of CMV after BCMA CAR-T-cell therapy. In one study of 61 BCMA CAR-T-cell recipients in China where routine CMV screening was performed at multiple time points before and after infusion, six patients (10%) developed CMV viremia. All six patients were treated with ganciclovir per institutional protocol, although half were asymptomatic and there were no cases of CMV disease.[112]

Thus, while the incidence of CMV viremia may be underestimated, the clinical relevance of these events remains unclear with most patients improving, even without preemptive antiviral therapy. Cases of CMV end-organ disease have been described,[36,38,111,113–116] but are overall rare considering the widespread use of CAR-T-cell therapy in the United States and globally. However, few studies have evaluated CMV viremia in a systematic fashion in this population and the clinical relevance of asymptomatic reactivation remains unknown. In general, routine CMV monitoring is not recommended, but testing should be considered as clinically appropriate or in potentially high-risk patients, such as those receiving >3 days of corticosteroids for management of CRS and/or ICANS,[84,87,117] while specific treatments such as daratumumab-combination regimens for multiple myeloma prior to BCMA CAR-T cell have also been associated with CMV risk.[118,119] Prospective studies are needed to determine whether and in whom to perform CMV monitoring, which may further inform the potential utility of prophylactic therapies such as letermovir in some patient subgroups.

5.3 | Human herpesvirus-6 and Epstein–Barr virus

Human herpesvirus-6 (HHV-6) reactivation and encephalitis have been reported after CAR-T-cell therapy,[49,57,120–123] although this seems to be relatively rare (<1%) even with systematic testing.[117] Of note, diagnosis of HHV-6 encephalitis is challenging due to overlapping manifestations with ICANS, and CSF analysis is infrequently performed outside of the context of refractory or atypical symptoms of ICANS.[123] For Epstein–Barr virus (EBV), one case of viremia and detection in the CSF has been reported in a patient with CRS grade 4 after CD19 CAR-T-cell therapy,[38] while four cases were reported in another study with long-term follow-up post-investigational BCMA CAR-T cells.[112] Similar to HHV-6, EBV reactivation appears to be rare and of unclear clinical significance.[38,112] For both of these viruses, systematic evaluation in large patient cohorts will be needed to better understand the epidemiology of reactivation and end-organ disease. Routine monitoring of HHV-6 or EBV is not recommended given the rare occurrence and unknown significance of asymptomatic viremia.

5.4 | Herpes simplex virus and varicella zoster virus

Reports of HSV infection and VZV after CAR-T-cell therapy are infrequent given the widespread use of val/acyclovir prophylaxis for 6–12 months following cell infusion.[59,85] HSV and VZV reactivation has been described in CAR-T-cell therapy recipients after prophylaxis cessation or in the setting of non-adherence.[35,46,48,112] Cases of breakthrough infection while on HSV/VZV prophylaxis have rarely been reported.[59]

End-organ disease due to HSV or VZV is uncommon although one fatal case of HSV pneumonia has been described following BCMA CAR-T-cell therapy in a patient with severe CRS and acyclovir resistance.[59,113] Routine antiviral prophylaxis with acyclovir or valacyclovir for human HSV and/or VZV seropositive patients is recommended in both BCMA and CD19 CAR-T-cell therapy; duration is less well defined and ranges from at least 100 days[85] to >1 year after CAR-T-cell therapy.[84,87]

5.5 | Hepatitis B virus

Several studies have thus far described HBV reactivation in patients receiving CD19 and BCMA CAR-T-cell therapy, demonstrating a low overall risk of reactivation for those with chronic HBV on prophylaxis with entecavir or tenofovir, although a few fatal cases of HBV reactivation have been reported in patients despite the use of antiviral therapy.[124–127] Wang et al. evaluated 61 patients receiving BCMA CAR-T-cell therapy demonstrating HBV reactivation in 2/4 (50%) of the patients with chronic HBV (HBsAg+) despite entecavir prophylaxis.[112] The need for antiviral prophylaxis in patients with resolved HBV remains unclear with one study demonstrating no cases of reactivation among 37 patients with resolved HBV (HBsAg−/HBcAb+) despite only two who received prophylaxis, in contrast with other sporadic cases in the literature of HBV reactivation following CAR-T-cell therapy in patients with resolved infection.[112,125,127,128] Thus, patients undergoing either CD19 or BCMA CAR-T-cell therapy with a history of both chronic (HBsAg+) and resolved HBV (HBsAg−/HBcAb+) should receive antiviral prophylaxis with entecavir or tenofovir for at least 6 months after CAR-T-cell therapy.[128,129] If antiviral prophylaxis is not used, close monitoring of HBV viral load with preemptive HBV therapy is critical.

6 | ROLE OF PREDICTIVE SCORES AND IMMUNE MONITORING

Aside from established clinical risk factors as discussed above, a few studies assess the role of individual biomarkers for predicting infection risk. CRP peak tended to be higher on the day of diagnosis of CRS grade ≥2 versus infection in one study,[130] while an increase in CRP prior to fever onset was associated with infection in another.[57] A higher procalcitonin level within 48 h from fever was also associated with infection.[131] Finally, cytokine levels, including higher levels of IL-8 and IL-1β, lower interferon-γ, and a double peak of IL-6 were associated with severe bacterial infections,[79] while cytokine levels did not differ between patients with and without infection in another study.[46] In children receiving CD19 CAR-T cells for B-ALL and admitted to the ICU, interferon-γ and IL-1β could differentiate sepsis from CRS.[132]

A recently validated score, the CAR-Hematotox, used a combination of five readily available pre-lymphodepletion biomarkers evaluating hematopoietic reserve (platelet count, absolute neutrophile count, hemoglobin) and systemic inflammatory state (CRS, ferritin) to predict post-CAR-T-cell hematotoxicity.[44] Real-world evidence from 248 adults with lymphoma treated with CD19 CAR-T cells in six centers showed that a high score performed well as a predictor of severe infection during the first 90 days.[25] Fluroquinolone prophylaxis was used equally frequently (~60%) in the high- and low-score patient groups. Importantly, antibacterial prophylaxis led to a significant reduction in the cumulative incidence of bacterial infections in the high-risk group but did not influence infection in the low-risk patients.[25] These findings suggest that prophylaxis might have some benefits in preventing severe infection in a carefully selected subgroup of patients. Thus, the score may be utilized to better tailor antibacterial prophylaxis—still used in many centers during neutropenia—to patients who may benefit from it, while preventing unnecessary antibiotic exposure in low-risk candidates.[41] This could be of great interest in CAR-T-cell therapy recipients given the recent evidence highlighting the role of gut microbiome in clinical responses after therapy.[133,134] Importantly, the score has also been validated in the context of CAR-T-cell therapy for mantle cell lymphoma and multiple myeloma.[135,83]

More recently, the combination of a high CAR-Hematotox score with a high procalcitonin (≥1.5 μg/L) on the day of first fever identified patients who went on to develop severe infections during the phase of coincident CRS.[130] Finally, important risk stratification tools from the transplant setting (both solid organ and HCT), including CMV immune monitoring should be studied in this population. Future prospective studies will need to integrate these tools to validate and determine their place in clinical practice, best timing to implement them and optimal cutoffs.

7 | GOING BEYOND

Despite the great advances in the field, important gaps in our understanding of infections and high uncertainty regarding optimal prevention practices remain.[25,33] As a first step to limit the uncertainty, we need to continue to accurately and uniformly (and ideally prospectively) assess the epidemiology of infections, including atypical pathogens. Frequent reassessment may be needed as CAR-T-cell targets and patient populations evolve. Importantly, we need higher transparency and quality of infection data collection and reporting both from post-marketing studies and trials primarily designed for primary oncology outcomes. Technical guidelines based on consensus from an expert panel are available for the diagnosis and grading of infectious diseases in related patient populations from the Blood and Marrow Transplant Clinical Trials Network and represent best practice;[136] a consensus statement for standardised reporting of infections in immunocompromised patients across study types was also recently published (Please add this reference: PMID:37683684, published in Lancet Infectious Diseases in Sep 2023, BW Teh et al). Systematically generated data can in turn inform the design of clinical trials assessing the efficacy of different practices (e.g., IGRT, vaccination) specifically in the CAR-T-cell population, which are a prerequisite to move from "expert consensus" to recommendations based on high level of evidence. At the same time, the field should continue to evolve away from "one size fits all" approaches as we strive to develop precision-medicine strategies to optimize health care utilization and

resource allocation. Implementation and assessment of the role of available and new risk stratification tools based on biomarkers and immune monitoring will be an important step in that direction.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Eleftheria Kampouri https://orcid.org/0000-0001-8019-3073
Oriol Manuel https://orcid.org/0000-0001-7607-0943

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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