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TRANSPLANT INFECTIOUS DISEASE

REVIEW ARTICLE

Infectious complications of car T-cell therapy: A longitudinal risk model

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Abstract

Background: CAR T-cell therapy, where a patient's own T cells are re-engineered to express a receptor to a target of interest, is becoming an increasingly utilized cancer-directed therapy. There are significant toxicities that contribute to a novel state of immunocompromise, leading to new patterns of infectious complications that require further detailed study.

Methods: We created a single-center cohort of adult recipients of CD19-directed CAR T-cell therapy and assessed infectious outcomes, supportive care received, toxicities, and markers of immune function up to 2 years following CAR T-cell therapy. Descriptive statistics were used as appropriate for analysis. We additionally conducted time-to-event analysis assessing time-to-first infection with either log-rank testing or Cox regression with univariate analysis, before including significant predictors into a multivariate Cox model of time to infection.

Results: We identified 73 patients who received CD19-directed CAR T-cell therapy who predominantly had diffuse large B-cell lymphoma. Within 30 days of cell infusion, bacterial and *Candida* infections were the most common, with 64% of infections due to these organisms. Between 30 days and 2 years postinfusion, respiratory viruses and pneumonia were the most frequent infections, with 68% of infections due to these etiologies. Receipt of tocilizumab, development of immune effector cell-associated neurotoxicity syndrome (ICANS), or lower neutrophil count were associated with quicker onset of infection in a multivariate Cox model.

Conclusions: Respiratory viruses remain an important infectious complication of CAR T-cell therapy following the first year. The model may be a useful tool to identify patients at the highest risk of infection.

KEYWORDS
CAR T-cell, cellular therapy, infection, model

Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine release syndrome; HSCT, hematopoietic stem cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; IVIG, intravenous immune globulin; LD, lymphodepleting; NHL, non-Hodgkin's lymphoma; RVI, respiratory viral infection.

1 | INTRODUCTION

Outcomes for relapsed or refractory B-cell non-Hodgkin lymphoma (NHL) are poor with traditional chemoimmunotherapy and stem cell transplantation, despite many novel approaches to treatment in the preceding years.[1–7] This high unmet need accelerated the clinical development and eventual regulatory approval of cellular therapies targeting cluster of differentiation (CD)19, a pan-B-cell molecular marker. In chimeric antigen receptor (CAR) T-cell therapy, patients peripheral blood mononuclear cells are first harvested through the process of apheresis.[8–10] These cells are then shipped to the manufacturer's laboratory, where, via transduction with viral vectors or other means, recombinant genes are inserted into the host cell's DNA, leading to the production of the CARs on the T-cell's surface. After laboratory clonal expansion, these cells are then shipped back to the medical center, and the patient is then given a lymphodepleting (LD) course of chemotherapy followed by an infusion of these recombinant T-cells. The CAR T-cells then seek out and destroy cells expressing the specific antigen that the CARs target.

Commercial CD19-directed products have demonstrated impressive and often durable responses in high-risk B-cell NHL.[11,12] CD19-directed CAR T-cells may also demonstrate on-target, off-tumor activity against healthy B cells expressing the CD19 antigen. These B cells are responsible for humoral immunity, and their depletion may lead to hypogammaglobulinemia and an increased risk of infections.[13–17] Specifically, prolonged lymphopenia and hypogammaglobulinemia (including poor mucosal immunity) have been noted following CAR-T infusion.[13,14] An association with hypogammaglobulinemia following cell infusion and delayed viral infections has been reported,[15] as well as an increased total infection risk during the early postinfusion period.[16]

Additionally, patients undergoing CAR T-cell therapy are often profoundly immunosuppressed from prior chemotherapy including possible hematopoietic stem cell transplantation (HSCT). As compared to HSCT or myeloablative regimens for acute leukemia, the initial duration of neutropenia for CAR-T recipients is typically shorter (1–2 weeks), with the highest rate of infection in the first 30 days following infusion.[18] Limited data suggest that bacterial processes predominate in the early postcell infusion period, followed by viral infections in the months following.[18,19]

Following cell infusion, anti-IL-6 therapies and high-dose corticosteroids are often employed for management of CAR T-cell-related toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). These agents may additionally further immunosuppress patients and contribute to the risk of infection.

Despite the advent of multiple cellular therapy products, there is scant data to guide the use of prophylactic antimicrobials or the management of infectious complications, following CAR T-cell infusion. A recent report suggests that infectious complications following CAR T-cell therapy were likely underreported in the pivotal trials due to similarities in presentation to known CAR T-cell toxicities, and furthermore, longitudinal infection data are lacking.[20] Which CAR T-cell therapies, co-morbidities, and immunologic markers carry the highest risk for infection in this population remains unclear given disparate descriptions in the available literature.[15,19,21] Therefore, there still exists a need to describe the real-world experience related to the natural history of infections following CAR T-cell therapy and to identify patients most vulnerable to infectious complications.

To address this gap, we performed a single-center retrospective cohort study of patients receiving CAR T-cell products for B-cell NHL, with the goal of creating a model of infectious complications, including timelines, and patient and therapeutic factors associated with such infections.

2 | MATERIALS AND METHODS

2.1 | Study population

This analysis includes adults aged ≥ 18 years who received CD19-directed CAR T-cell products at the University of Chicago either on- or off-clinical protocol prior to September 1, 2021.

2.2 | Experimental design and clinical setting

This is a single-center retrospective cohort study using medical records of adult patients who received CAR T-cell therapy, with the primary objective of developing a model of infectious risk following this novel therapy. Patients who met inclusion criteria underwent manual chart review and extraction of data into an encrypted REDCAP database.[22–24] Data extracted included therapies administered, toxicities, infectious complications, demographics, and markers of immunologic function. CAR T-cell product and patient selection for therapy, the use of bridging therapy, treatment setting (inpatient or outpatient), toxicity management, and response assessment were per the treating physician's discretion and in accordance with institutional practices. Patients were followed for up to 2 years, less if the recipient suffered disease progression, or was lost to follow-up, or died (at which times the data is censored). Planned time points of extraction of clinical data included baseline, 30 days postinfusion, 3 months postinfusion, and then every 3 months through the end points noted above. These time points were chosen as they approximated the standard schedule of hematology follow-up at our center.

CAR T-cell recipients at our center typically receive prophylaxis against pneumocystis (such as trimethoprim-sulfamethoxazole, atovaquone, and dapsone) for at least 6 months and herpesviruses (with acyclovir or valacyclovir) for 6–12 months, depending on Cd4 count. Bacterial (such as levofloxacin or cefdinir) and yeast prophylaxis (such as fluconazole or micafungin) is provided during the initial period of neutropenia following LD chemotherapy. Antifungal coverage was expanded to cover moulds (with posaconazole or isavuconazole) if the patient's absolute neutrophils count (ANC) was less than 1000 for over 7 days, they received dexamethasone at or above 10 mg per day for more than 4 days, they received methylprednisolone at or

above 1 gram per day for more than 2 days, or the patient required additional immunosuppressants beyond tocilizumab or siltuximab and corticosteroids for worsening CRS or ICANS. Replacement with intravenous immunoglobulin (IVIG) is only administered if immunoglobulin G levels are noted to be less than 400 mg/dL and the patient has an active infection.[25] Granulocyte-colony stimulating factor was utilized per institutional protocol for neutropenia. CRS and ICANS are defined and graded in this study as per American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.[26] Where reported, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 definitions were used.

Given that this is a retrospective study based upon chart review, infections that are definitively diagnosed by culture isolation from a sterile site alone (bacteremia & fungemia) or a positive NAAT for a herpesvirus were defined as microbiologically diagnosed. Otherwise, infection type was abstracted from clinical documentation (record of diagnosis and treatment per progress note) in scenarios where lab results alone are unable to differentiate between true infection and colonization (*Clostridioides difficile*, UTI), the diagnosis of infection is typically clinical (pneumonia, cellulitis), or the infection occurred elsewhere and was reported to the hematologist during long-term follow-up (such as presumed viral URI managed by primary care doctor), if incorporated into clinical notes. The 2019 EORTC/MSGERC definitions were used for any mould infection.[27]

Standard-dose corticosteroids were defined as ≤40 mg/day of dexamethasone or equivalent, whereas high-dose steroids were defined as 1000 mg per day of methylprednisolone or equivalent. Where unspecified, steroid use refers to the receipt of either dosing strategy.

2.3 | Statistical methods

Analyses were carried out in STATA 17.[28] Descriptive statistics were used as appropriate for the assessment of the distribution of data. For the purposes of calculating median values, missing data were not incorporated as a zero. Some graph generation was performed in Microsoft Excel. Time-dependent analyses were undertaken; specifically, time-to-first infection was recorded to eventually create a multivariate Cox regression model. Right censoring occurred at 2 years if no infection occurred, or if death or disease progression occurred before an infection occurred. For binary predictors of time-to-first infection, Kaplan–Meier curves were generated, and log-rank testing was performed. For continuous predictors of time-to-first infection, univariate Cox regression was performed. After multiple predictors of interest were analyzed in univariate analyses (either by Kaplan–Meier or univariate Cox regression as above), the predictors that met criteria for admission into the final model ($p < .1$) were included into a multivariate Cox-regression analysis of time-to-first infection. If there was theoretical concern for confounding with the predictors incorporated into the model, an interaction term was incorporated to assess for significance. One predictor was allowed into the multivariate model per 10 subjects experiencing the outcome of interest. The Biostatistics Core at the University of Chicago assisted in the design of the multivariate Cox model.

2.4 | Ethics

This research was approved by the University of Chicago Institutional Review Board (IRB).

2.5 | Patient consent statement

Given the retrospective and noninterventional nature of the study, waiver of informed consent was obtained.

3 | RESULTS

A total of 73 patients were identified who met the inclusion criteria. The population was primarily males (68.49%) with good performance status (Eastern Cooperative Oncology Group 0–1, 91.78%) (Table 1). Diffuse large B-cell lymphoma (65.75%) and high-grade B-cell lymphoma (19.18%) were the most common malignancies. At the time of referral for consideration of CAR T-cell therapy, disease status was most commonly refractory to most recent therapy (41.10%) or primary refractory (34.25%). Most patients received Axicabtagene ciloleucel (60.27%) or Tisagenlecleucel (35.62%). Only 12 of 73 patients had been receiving any IVIG prior to the CAR T-cell infusion.

At apheresis, the median age in our cohort was 64. Although preapheresis the median absolute neutrophil count was 3330 cells/μL, the median absolute lymphocyte count and IgG at that time point were more borderline at 670 cells/μL and 465 mg/dL, respectively. A total of 51 subjects (69.86%) underwent variable bridging therapy to temporize the disease until cell infusion.

Regarding inflammatory toxicities of CAR T-cell therapy, 65 (89%) patients developed any grade of CRS, which was predominantly grade 1 (40%) or grade 2 (55.38%) (Table 2). Three subjects in total developed grade 3 or 4 CRS. A total of 38 (52%) patients developed any grade of ICANS during the study, including 18 (25%) patients who developed grade ≥3 toxicity. In relation to toxicity management, 54 (74%) patients received tocilizumab. The median number of tocilizumab doses received was 2, with an interquartile range (IQR) of 1–3. Only five patients received siltuximab. Steroids were employed for toxicity management in 32 (43.84%) of patients. Standard-dose steroids (≤40 mg/day of dexamethasone or equivalent) were used in 41.10% of all patients, whereas high dose steroids (1000 mg/day methylprednisolone or equivalent) were used in 10.96% of all patients.

Assessing markers of immunologic function over time, we noted that the median immunoglobulin G levels (465 mg/dL at apheresis) descended between 30 days and 3 months to 347 mg/dL postcell infusion without ever making a full recovery back to baseline levels (Supporting Information Figure S1). Some patients did receive IVIG before (16.44%) or following cell infusion (26.03%) if infection

TABLE 1 Baseline characteristics.

Variables	Frequency ($n = 73$)	Percent (%)
Sex		
Male	50	68.49
ECOG		
0–1	67	91.78
2	5	6.85
3	1	1.37
Disease type		
DLBCL	48	65.75
HBGL	14	19.18
TFL	7	9.59
MCL	2	2.74
PMBCL or ALL	2	2.74
Bridging therapy	51	69.86
Disease status		
Primary refractory	25	34.25
Refractory to most recent therapy	30	41.10
Relapsed	15	20.55
Complete remission	3	4.11
Cell product		
Axicabtagene ciloleucel	44	60.27
Tisagenlecleucel	26	35.62
Brexucabtagene autoleucel	2	2.74
Lisocabtagene maraleucel	1	1.37
Receipt of IVIG before CAR T	12	16.44
Variable	**Median**	**IQR**
Age (years)	64	51–75
Lines of prior therapy (n)	3	3—5
ANC (cells/μL)	3330	2580—4800
ALC (cells/μL)	670	430—910
IgG (mg/dL)	465	364—697

Baseline patient population characteristics as described by frequency (*n*) and percent of total population or median and interquartile range (IQR).
Abbreviations. ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group Performance Score; HGBL, high grade B-cell lymphoma; IgG, immunoglobulin G levels; IVIG, Intravenous immune globulin; MCL, Mantle-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; TFL, transformed follicular lymphoma.

developed in setting of IgG was less than 400 mg/dL in accordance with institutional protocols. The median absolute neutrophil count, on the other hand, decreased sharply from a baseline of 3330 to 1580 cells/μL by 30 days, followed by a rise to 2055 cells/μL by 3 months, and further increases later (Supporting Information Figure S2). The median absolute lymphocyte count decreased slightly from baseline of 670 to 545 cells/μL by 30 days (CTCAE grade 2), but then had a relatively steady increase to above baseline values by 24 months (1085 cells/μL)—an interesting contrast to the change in immunoglobulin levels over time (Supporting Information Figure S3). For our population, the median number days under study was 284, with an IQR of 123–712.

TABLE 2 Tabulation of inflammatory toxicities of CAR T-cell therapy and corresponding treatments by frequency (*n*) and percent (%).

Variables	Frequency (n = 73)	Percent (%)
CRS per ASTCT criteria	65	89.04
Grade 1 CRS	26	40.00
Grade 2 CRS	36	55.38
Grade 3 CRS	2	3.08
Grade 4 CRS	1	1.54
ICANS per ASTCT criteria	38	52.05
Grade 1 ICANS	8	21.05
Grade 2 ICANS	12	31.58
Grade 3 ICANS	10	26.32
Grade 4 ICANS	8	21.05
Use of standard-dose steroids	30	41.10
Use of high-dose steroids	8	10.96
Receipt of tocilizumab	54	73.97
Number of tocilizumab doses		
1	22	40.74
2	17	31.48
3	9	16.67
4—5	6	11.11
Receipt of siltuximab	5	6.85

Percentages in subheadings are in relation to number who experienced the toxicity or received the therapy as opposed to the entire cohort.
Abbreviations. ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine-release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
Standard-dose steroids defined as dexamethasone 10 mg q6 or similar strategy. High-dose steroids defined as methylprednisolone 1 g or dexamethasone 200 mg at any frequency.

With longitudinal follow-up, there were 91 discrete episodes of infection seen within a total of 41 CAR T-cell recipients. Within the first 30 days following CAR T-cell infusion, there was a relatively even distribution of infection types among the 22 observed events (respiratory viruses, pneumonia, UTI, other [as detailed below], bacteremia, fungemia, and *C. difficile*) (Figure 1). Bacteremias, which were polymicrobial, included *Acinetobacter spp.*, *Enterococcus faecium and faecalis*, *Enterobacter cloacae*, *Raoultella spp.*, and *Citrobacter spp.* Fungemia occurred and responsible *Candida* species included *albicans* and *glabrata* (Supporting Information Table S1). Other infections at this time point included sialadenitis, two episodes of cellulitis, probable invasive pulmonary aspergillosis (the only mould infection in this study),[27] and polymicrobial empyema.

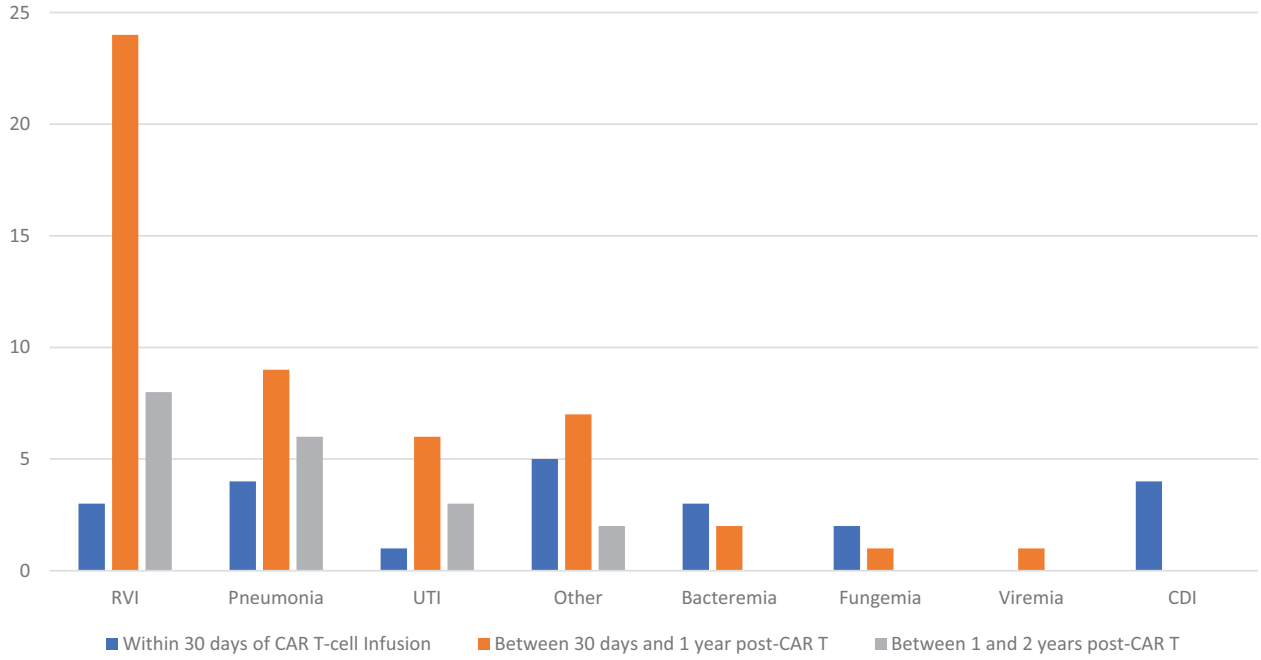

FIGURE 1 Number of episodes of infection following CAR T-cell infusion, stratified by time period. Each episode of infection, even within a single patient, was counted—allowing for multiple infections per patient per time period. Abbreviations—RVI, respiratory viral infection; UTI, urinary tract infection; CDI, *Clostridium dificile* infection; CAR, chimeric antigen receptor. "Other" infections within 30 days of cell infusion include cellulitis, sialadenitis, *Aspergillus pneumonia* and empyema. "Other" infections between 30 days and 1-year postcell infusion included oral HSV, intra-abdominal infection, empyema, conjunctivitis, cellulitis, bacterial sinusitis, and tooth abscess. "Other" infections between 1- and 2-year postcell infusion included shingles and bacterial sinusitis.

After the first 30 days following CAR T-cell infusion and within 1 year, respiratory viruses were the most common infectious complication, with 24 unique instances of infection during this period, out of a total of 50 events during this time. The next most frequent infection type was pneumonia, with nine episodes during this period. Notably, there were no episodes of *C. difficile* diarrhea during this period, but there was one episode of CMV viremia without end-organ disease. Bacteremias occurring during this time included *Acinetobacter spp., E. faecium, and Escherichia coli* (one patient had a polymicrobial process) (Supporting Information Table S2). Other infections during this period included an intra-abdominal infection and polymicrobial empyema, herpes stomatitis, cellulitis, conjunctivitis, bacterial sinusitis, and periapical dental abscess.

Between 1 and 2 years following CAR T-cell infusion, respiratory virus infections continued to be the most predominant infectious complication (eight episodes), again followed by pneumonia (six episodes), out of a total of 19 events. At this timepoint, notably absent were further bacteremias, fungemias, viremias, or *C. difficile* infections (Supporting Information Table S3). Other infections occurring during this time point included bacterial sinusitis and herpes zoster. Although individual susceptibility information was not recorded, overall, for bacterial cultures from sterile specimens, 40 percent would be predicted to be nonsusceptible to typical fluoroquinolone neutropenic bacterial prophylaxis (*Enterococcal* or Gram-positive rod infection).

Time-to-first infection was recorded in our cohort, and univariate time-to-event analyses were conducted (Table 3). Utilizing Kaplan–Meier curves and log-rank testing, we determined that receipt of tocilizumab (*p*-value: .0359) or development of any grade of ICANS (.0207) were associated with a quicker onset of the first infection (Figure 2). Other binary predictors not meeting significance criteria ($p < .1$) for admission into multivariate model included development of any grade of CRS, use of corticosteroids (as defined in Section 2), and receipt of IVIG preinfusion. Continuous predictors of time-to-first infection were initially analyzed by univariate Cox regression. We found that a higher absolute neutrophil count, expressed continuously, at apheresis, appeared protective against time-to-first infection and met criteria for admission into the multivariate model (hazard ratio (HR): 0.86, 95% confidence interval [CI]):.74–1.03, *p*-value: .095). Absolute lymphocyte count at apheresis was not significantly associated with time-to-first infection. We incorporated the significant univariate predictors into a multivariate Cox-regression model of time-to-first infection and found that receipt of tocilizumab (HR: 3.59, 95% CI: 1.04–12.43, *p*-value: .044) and development of ICANS (HR: 5.46, 95% CI: 1.14–26.28, *p*-value: .034) continued to demonstrate increased risk for time-to-first infection, while higher ANC, expressed continuously, appeared protective (HR: 0.82, 95% CI: 0.68–0.99, *p*-value: .038). As patients who developed ICANS may have received tocilizumab, an interaction term was incorporated into the model but was nonsignificant (*p*-value: .091).

TABLE 3 Time-to-event analysis.

	Univariate		Multivariate	
Covariate	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-value
ANC at apheresis	0.868 (0.735–1.025)	.095	0.817 (0.675–0.989)	.038
ICANS by ASTCT		.021	5.464 (1.136–26.285)	.034
Tocilizumab use		.036	3.591 (1.037–12.435)	.044
CRS by ASTCT		.309		
Standard-dose steroid		.114		
High-dose steroid		.917		
IgG at apheresis	1.000 (.999–1.002)	.599		
IVIG pre-CAR T		.428		
ALC at apheresis	0.967 (.663–1.412)	.863		

Abbreviations/units: ALC, absolute lymphocyte count expressed continuously in cells/μL; ANC, absolute neutrophil count expressed continuously in cells/μL; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome, standard dose steroid defined as dexamethasone 10 mg q6 or equivalent , high dose steroid defined as methylprednisolone 1 g or dexamethasone 200 mg; ICANS, immune effector cell-associated neurotoxicity syndrome; IgG, immunoglobulin G expressed continuously in mg/dL; IVIG, intravenous immune globulin.
Event (failure) defined as time-to-first infection. Right censoring occurred at 2 years, death, or disease progression. Binary predictors analyzed using Kaplan–Meier failure curves and log-rank testing (*p*-value only, no hazard ratio) for univariate analysis. Continuous predictors analyzed initially using univariate Cox regression for time to first infection. Predictors meeting significance in univariate analysis ($p < .1$) were admitted into final multivariate Cox-regression model of time to first infection.

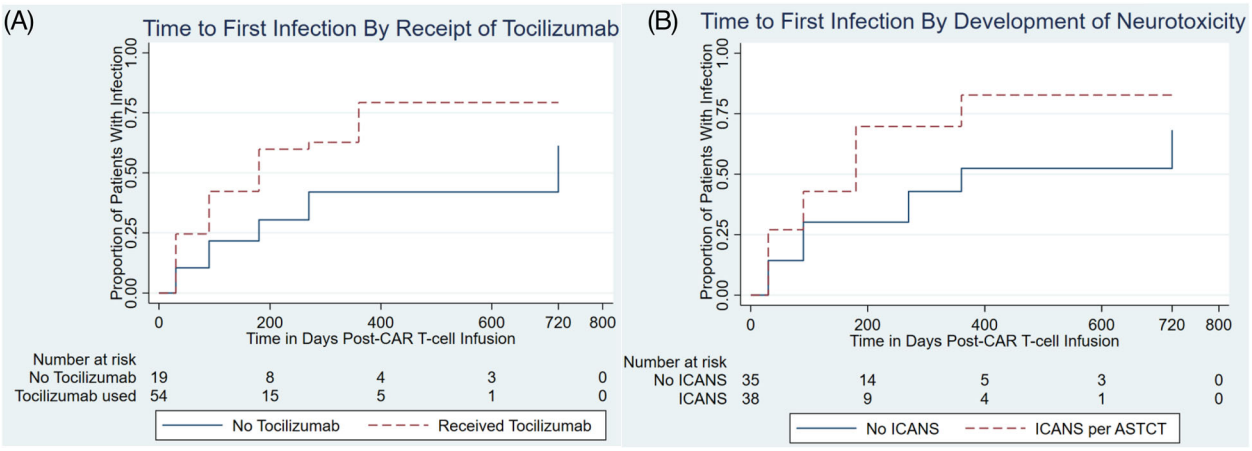

FIGURE 2 Kaplan–Meier failure curves of time-to-first infection following CAR T-cell infusion. Kaplan–Meier failure curves of proportion of patients who developed their first infection (failure) following CAR T-cell infusion by day since cell infusion. Right censoring at two years of follow up, death, or disease progression, whichever came first. (A) Curves separated by receipt of tocilizumab (red dashed line) versus no receipt of tocilizumab (solid blue line) during period of follow-up. Log-rank test $p = .036$. (B) Curves separated by development of CAR T-cell neurologic toxicity (red dashed line), also known as immune effector cell-associated neurotoxicity syndrome (ICANS) as documented by diagnostic criteria from American Society of Transplant and Cellular Therapy (ASTCT) versus no ICANS (solid blue line). Log-rank test $p = .021$.

4 | DISCUSSION

Herein, we present data on infectious complications following CAR T-cell therapy up to 2 years following infusion. Infection is the leading cause of nonrelapse mortality in CAR T-cell recipients, and the information presented here has implications for monitoring, prophylaxis, and treatment strategies which could prevent infection or improve clinical outcomes in the future.[29] Importantly, like hematopoietic stem cells and solid organ transplants, the pattern of infections observed following CAR T-cell infusion changes over time. Our data are in keeping with findings from other groups that indicate that early infections within the first 30 days are predominantly due to bacteria and *Candida*. Overall, mould infections and herpes virus infections, although not screened for by institutional practice, were rare. From 30 days post-CAR T-cell infusion up to 2 years, respiratory viral infections (RVIs) and pneumonia become the most prevalent infectious complications. Notably, this suggests that the period of immunodeficiency following CAR T-cell infusion in which patients remain vulnerable to infections may

be longer than 1 year. The marked predisposition to RVIs following the first 30 days after therapy is important as management strategies for many respiratory viruses in immunocompromised patients, including duration of antivirals and use of IVIG, remain unclear. Further exploration is needed to better understand the etiology of respiratory viruses in this population, optimal treatment, prevention strategies, and outcomes of infection.

Our model of time-to-first infection among CAR T-cell patients incorporates a longer duration of follow-up than other models used to risk stratify patients for toxicities of therapy. Developing a time-to-event model for infections in this population is important given the frequency of these complications in our population and in other studies. Some articles report the prevalence of infections as 90% of the subjects under study, meaning that differentiating patients who all demonstrate a similar outcome is challenging. Additionally, these data support the notion that earlier infections postcell infusion may be more acute and clinically severe such as fungemia and bacteremia.[15,19] Our model supports other works that demonstrate that tocilizumab and ICANS are associated with a more rapid development of infection.[30,31] These data allow risk stratification of CAR T-cell recipients for the development of infectious complications and pave the way for further studies evaluating optimal monitoring and/or prophylaxis strategies to prevent these infectious complications. If possible, reductions in rates of CRS or ICANS, and therefore, reductions in the use of additional immunosuppressants, have the potential to also reduce the risk of infection in this population. Newer cellular therapies are being developed with molecular on/off switches, and risk of infection or inflammatory toxicities could play a role in this therapy selection in the future.

In contrast to other predictive scores for toxicity and infection in cellular therapy candidates, baseline laboratory predictors in our model are taken from the period of apheresis as opposed to LD chemotherapy.[29,32] This has the potential benefit in identifying higher-risk groups earlier and altering treatment decisions (what cell product, what prophylaxis, what monitoring) sooner. Typically, LD chemotherapy regimens are tailored to specific cell products, and therefore, potentially waiting until LD chemotherapy and cell infusion to risk stratify patients and make treatment decisions may be too late. Additionally, portions of our model are designed to evaluate cellular therapy candidates based on their status upon referral to a program (around the time of apheresis) and better assess their baseline immunologic function. Many patients following apheresis receive bridging therapies that may be markedly variable (corticosteroids, monoclonal antibodies, chemotherapy, etc.) to prevent disease progression while awaiting cell infusion, and this may impact other models that utilize lab predictors at later time points.

Notable limitations of this study include its retrospective, non-interventional nature, and incorporation of data across years when standards and practices in this population may have evolved. The level of detail is limited to what was documented at the time of the clinical events, which introduces some uncertainty into the analysis. As CAR T-cell therapy expands to new disease indications, and as the management of CAR T-cell therapy-related toxicities evolves over time, it is possible that our findings may become less applicable. Prospective and interventional studies in this population aimed at reducing toxicities and improving clinical outcomes are warranted and should be prioritized.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflict of interest to declare.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190. doi:10.1200/JCO.2010.28.1618
2. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *New Engld J Med*. 2009;333(23):1540-1545. doi:10.1056/NEJM199512073332305
3. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808. doi:10.1182/BLOOD-2017-03-769620
4. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol*. 2014;32(31):3490-3496. doi:10.1200/JCO.2013.53.9593
5. Ardeshna KM, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol*. 2005;130(3):363-372. doi:10.1111/J.1365-2141.2005.05603.X
6. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016;51(1):51-57. doi:10.1038/bmt.2015.213
7. Imhoff W VI, A McMillan, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The ORCHARRD study. *J Clin Oncol*. 2016;35(5):544-551. doi:10.1200/JCO.2016.69.0198
8. National Cancer Institute. CAR T cells: Engineering immune cells to treat cancer—National Cancer Institute. Accessed July 26, 2021. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
9. Styczyński J. A brief history of CAR-T cells: From laboratory to the bedside. *Acta Haematol Pol*. 2020;51(1):2-5. doi:10.2478/AHP-2020-0002

10. National Cancer Institute. Definition of CAR T-cell therapy—NCI dictionary of cancer terms—National Cancer Institute. Accessed July 29, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy
11. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New Engld J Med*. 2017;377(26):2531-2544. doi:10.1056/NEJMOA1707447
12. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *New Engld J Med*. 2018;380(1):45-56. doi:10.1056/NEJMOA1804980
13. Isaac McGraw B, Sweeney C, Savaşan S. Recurrent urinary tract infections and low secretory IgA following CD19-directed CAR T-cell therapy for relapsed acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65(1):e26739. doi:10.1002/pbc.26739
14. Hill JA, Giralt S, Torgerson TR, Lazarus HM. CAR-T– and a side order of IgG, to go?—Immunoglobulin replacement in patients receiving CAR-T cell therapy. *Blood Rev*. 2019;38:100596. doi:10.1016/j.blre.2019.100596
15. Wudhikarn K, Palomba ML, Pennisi M, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. *Blood Cancer J*. 2020;10(8):79. doi:10.1038/s41408-020-00346-7
16. Vora SB, Waghmare A, Englund JA, Qu P, Gardner RA, Hill JA. Infectious complications following CD19 chimeric antigen receptor T-cell therapy for children, adolescents, and young adults. *Open Forum Infect Dis*. 2020;7(5):ofaa121. doi:10.1093/ofid/ofaa121
17. Fishman JA, Fishman JA, Hogan JI, Maus M V. Clinical infectious diseases inflammatory and infectious syndromes associated with cancer immunotherapies. *Clin Infectious Dis*. 2018;69(6):909-920. doi:10.1093/cid/ciy1025
18. Fishman JA, Hogan JI, Maus M V. Inflammatory and infectious syndromes associated with cancer immunotherapies. *Clin Infectious Dis*. 2019;69(6):909-920. doi:10.1093/cid/ciy1025
19. Park JH, Romero FA, Taur Y, et al. Cytokine release syndrome grade as a predictive marker for infections in patients with relapsed or refractory b-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. *Clin Infect Dis*. 2018;67(4):533-540. doi:10.1093/cid/ciy152
20. Syed TIS, Abdullah SM, Rehan T, et al. Infections associated with CAR T therapy for treatment of hematological malignancies. *Blood*. 2019;134(1):4442-4442. doi:10.1182/blood-2019-127452
21. Frigault MJ, Nikiforow S, Mansour MK, et al. Tocilizumab not associated with increased infection risk after CAR T-cell therapy: implications for COVID-19? *Blood*. 2020;136(1):137-139. doi:10.1182/blood.2020006216
22. Obeid JS, McGraw CA, Minor BL, et al. Procurement of shared data instruments for Research Electronic Data Capture (REDCap). *J Biomed Inform*. 2013;46(2):259-265. doi:10.1016/J.JBI.2012.10.006
23. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/J.JBI.2019.103208
24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/J.JBI.2008.08.010
25. Derman BA, Schlei Z, Parsad S, Mullane K, Knoebel RW. Changes in intravenous immunoglobulin usage for hypogammaglobulinemia after implementation of a stewardship program. *JCO Oncology Practic*. 2020;17(3):e445-e453. doi:10.1200/OP.20.00312
26. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758
27. Peter DJ, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. *Clin Infectious Dis*. 2020;71(6):1367-1376. doi:10.1093/cid/ciz1008
28. StataCorp. Stata Statistical Software: Release 17. Published online 2021. https://www.stata.com
29. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. *J Immunother Cancer*. 2022;10(5):1-14. doi:10.1136/jitc-2021-004475
30. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood*. 2018;131(1):121-130. doi:10.1182/blood-2017-07-793760
31. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica*. 2020;106:(4):978-986. doi:10.3324/haematol.2019.238634
32. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: A model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood*. 2021;138(24):2499-2513. doi:10.1182/blood.2020010543

SUPPORTING INFORMATION

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

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