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The Burden of Infections Prior to Chimeric Antigen Receptor (CAR) Modified T-cell Therapy Predicts Post-CAR-T-cell Infectious Complications

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INTRODUCTION

- Chimeric antigen receptor-modified T-cell (CAR-T-cell) therapy is a novel treatment for B-cell malignancies
- CAR-T-cell patients are at increased risk for infection due to conditioning chemotherapy, neutropenia, infusion-related toxicities, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and their treatments (steroids and tocilizumab, an IL-6 inhibitor)
- Previous studies suggest:
  - Infections are most common in the first month after CAR-T-cell infusion
  - Pre-infusion risk factors for infection:
    - Prior allogeneic hematopoietic stem cell transplant (HSCT), CAR-T-cell dose, malignancy type
  - Post-infusion risk factors for infection:
    - High grade CRS, neutropenia, tocilizumab and steroid receipt
- Prior studies largely focused on clinical trial patients
- Pre-CAR-T-cell risk factors are ill-defined

OBJECTIVE

To determine the epidemiology of and risk factors for infections after CAR-T-cell infusion recipients at our center

METHODS

Study Design and Patients:

- Retrospective cohort study of patients who underwent CAR-T-cell infusion at UPMC Shadyside Hospital from July 2017 to September 2019
- Chart review of 60 consecutive CAR-T-cell recipients was conducted
- Demographic, laboratory, microbiologic, and clinical infection and outcome data were collected for each patient from 6 months pre- and at least 6 months post-CAR-T-cell infusion

Definition of Infections:

- Criteria from CDC/NHSN HAI surveillance definitions and EORTC-MSG invasive fungal infection definitions were used

Statistical Analyses:

- Cox proportional hazard were used to identify factors associated with infection risk
- Significance was defined as a *P*-value ≤ 0.05

RESULTS

CAR-T-cell Recipient Characteristics

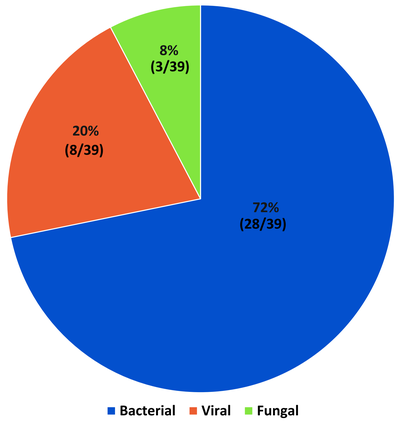
Table 1. Demographics of CAR-T recipients at the time of infusion

Patient Characteristics	All CAR-T Recipients (n=60)
Median age in years (range)	66 (23-84)
Male, no. (%)	31 (52)
White, no. (%)	58 (97)
Type of Malignancy, no. (%)	
Non-Hodgkin Lymphoma	53 (89)
Chronic Lymphocytic Leukemia	5 (8)
Acute Lymphocytic Leukemia	2 (3)
Prior HSCT, no. (%)	15 (25)
Allogeneic	2 (3)
Autologous	13 (22)
Prior lines of therapy, median (range)	3 (1-9)

CRS Grade	Patient No. (%)	ICANS Grade	Patient No. (%)
0	16 (27)	0	33 (55)
1	21 (35)	1	4 (7)
2	23 (38)	2	16 (27)
3	0 (0)	3	7 (12)
4	0 (0)	4	0 (0)
5	0 (0)	5	0 (0)

Infections Prior to CAR-T-cell Therapy

Figure 1. Type of infections in 6 months prior to CAR-T-cell infusion



Infections after CAR-T-cell Therapy

Figure 2. Pathogens causing infections after infusion

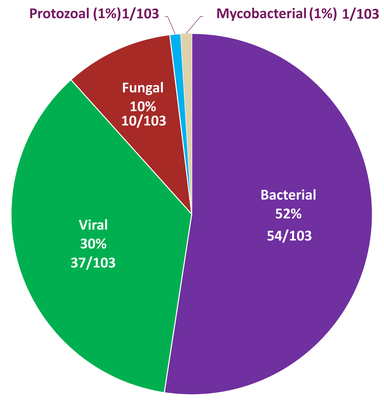


Table 2. Types of infections after CAR-T-cell infusion

Bacterial Infections (N=54)	Number (%)
Pneumonia	16 (30)
Bacteremia	11 (20)
SSTI	7 (13)
Intra-abdominal	6 (11)
HEENT	6 (11)
UTI	3 (6)
BJI (Bone and Joint Infection)	1 (2)
Multi-system	4 (7)

Viral Infections (N=37)	Number (%)
Respiratory viral infections	20 (54)
Herpesviridae infections	16 (43)
CMV viremia	10
CMV colitis	1
VZV	2
HSV	3
BK viremia	1 (3)

Fungal Infections (n=10)	Number (%)
Yeast	6 (60)
Mold	3 (30)
PJP pneumonia	1 (10)

Figure 3. Time-to-event curve for infection type occurring in the first 6 months after CAR-T-cell infusion

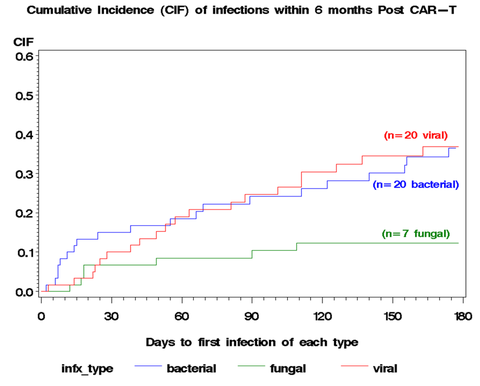
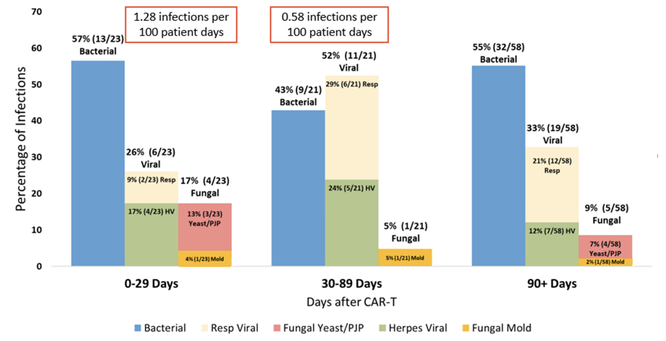


Figure 4. Type of Infection in Early, Intermediate, and Late Post-CAR-T Periods with Infection Density



Infection-related Mortality after CAR-T-cell Therapy

- Infection-related mortality occurred in 9/60 (15%) of patients
- 2/10 (20%) of patients who developed fungal infections died secondary to the following infections
  - *Candida tropicalis* blood stream infection
  - Invasive mucormycosis

Infection Risk Factor Analysis

Table 3. Selected risk factors for any infection after CAR-T infusion by Cox regression analysis

Risk Factor	Hazard Ratio (CI); p-value
Infection 6 mo. pre-CAR-T	**1.62 (1.10-2.38); 0.015**
CRS grade >0	1.87 (0.77-4.53); 0.17
ICANS	1.28 (0.53-3.09); 0.095
Prior lines of therapy last 6 mo.	**1.50 (1.01-2.27); 0.04**
Prior HSCT	
Autologous	0.08 (0.38-2.05); 0.88
Allogeneic	**5.96 (1.34-26.47); 0.019**

*Statistically significant risk factors highlighted in red

CONCLUSIONS

- **Infections after CAR-T-cell therapy were common**
- **Early (0-29 days) infections were primarily bacterial**
- **Fungal infections were less common, but associated mortality was high**
- **CRS/ICANS grade were not associated with infection after CAR-T-cell infusion**
- **Infection prior to CAR-T-cell infusion and prior rounds of therapy were associated with risk of infection after CAR-T-cell therapy**
- **Further studies are warranted to optimize CAR-T patient selection to minimize infectious risk after infusion**

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