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Infection Risks and Antibiotic Stewardship in CAR T-cell Therapy

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the management of refractory hematologic malignancies such as leukemia, lymphoma and multiple myeloma, offering unprecedented remission rates. Yet, complications arising from infections remain a major challenge, particularly in the early post-infusion period and during prolonged immune suppression. This editorial synthesizes recent evidence (2021–2025) on infection epidemiology, risk factors, and stewardship strategies in CAR T-cell recipients. Early infections, especially from bacteria are influenced by neutropenia, prior therapy, and disease biology, while long-term immune suppression of $CD4^+$ T cells help sustain vulnerability. Antibiotic stewardship presents a critical opportunity to reduce unnecessary exposure through biomarker-guided diagnostics and de-escalation protocols. Rising cases of antimicrobial resistance and dysbiosis pose significant challenges, while emerging diagnostic technologies and microbiome-focused interventions offer promise. Future strategies should be focused on integrating clinical vigilance, harmonized prophylaxis, and microbiome-awareness stewardship to optimize both safety and efficacy in CAR T-cell therapy.

Introduction

Chimeric Antigen Receptor T-cell (CAR T-cell) therapy, an innovative form of immunotherapy is becoming the cornerstone of treatment for patients with relapsed and refractory hematologic malignancies such as leukemia, lymphoma, and multiple myeloma [1]. Despite the promises recorded, factors such as early infusion fevers, overlapping inflammatory toxicities and prolonged immune deficits threaten their continued use for treatment [2]. At the end, the physician is faced with a decision; to treat the malignancy (protect the patient) or deal with the consequences of the treatment: confront the case of antimicrobial resistance and microbiome disruption created by the treatment.

Early Infectious Complications

The first month after CAR T-cells infusion is the period most frequently associated with infections (**Figure 1**). In their work, Wittmann Dayagi *et al.* [3] documented 36 infections out of 88 patients treated with CD28-based CD19 CAR T-cells. Reduced neutrophil count (Neutropenia) and lack of response were cited as major risk factors associated with CAR T-cell treatment. Similarly, Mikkilineni *et al.* [4] reported that, 32.7% of patients across five trial studies developed infections within 30 days, with bacteremia and bacterial site infections predominating as potential risk factors. The study of Beyar-Katz *et al.* [5] also observed infections in 45% of the patients with diffuse large B-cell lymphoma, while Garcia-Pouton *et al.* [6] documented 77 infections among 91 adults. Chimeric Release Syndrome resulting from rapid and massive activation of immune cells has been reported to complicate diagnosis, yet studies by Ng *et al* . [7] reports that despite the low bacteremia (2.7%) and CRS recorded among patients, they were still given empiric antibiotics. Based on these observations, it has been suggested that biomarkers including C-Reactive Protein (CRP), D-dimer, and ferritin could offer moderate level of discrimination beyond 14 days for monitoring infection and inflammation.

Long-Term Immune Deficiency

Immune suppression has been reported to persist beyond the acute phase. In their study, Cheng *et al*. [8] demonstrated that patients with multiple myeloma that received CAR T-cell infusion experienced prolonged $CD4^+$ T-cell deficiency and late infections, particularly in bacteremia. In another study, Portuguese *et al.* [9] showed that, extramedullary disease (EMD) was linked to higher toxicity, prolonged neutropenia, increased bacteremia, and worse survival while Masih *et al.* [10] reported on the convergence of serious bacterial infections with HLH-like CRS in pediatric patients, underscoring the complexity of overlapping toxicities.

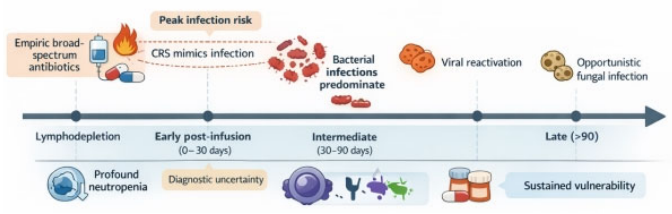

Figure 1. Temporal evolution of infection risk following CAR T-cell therapy.

Antibiotic Stewardship (Figure 2)

Patients on CAR T-cell therapy are vulnerable to immune suppression and infection, often necessitating antibiotic use. In their review of continuous versus intermittent beta-lactam infusion, Alawyia *et al*. [11], reported the benefits of extended infusion in sepsis and Febrile Neutropenia (FN) with Mizuno *et al.* [12] emphasizing adherence to febrile neutropenia (FN) guidelines for better outcome. On the contrary, Lucena *et al.*, [13] reported that cutting back on the use of broad-spectrum antibiotics reduces unnecessary exposure without compromising clinical outcomes. Additionally, studies by Malard and Mohty [14] argued that the use of broad-spectrum antibiotics may impair the efficacy of CAR T-cell therapy, due to the ability of the drugs to disrupt the gut microbiome. Therefore, for effective outcome, only clinically stable patients should be recommended for CAR T-cell therapy while patients already receiving treatment should be managed to mitigate risk of infection [15,16].

Antimicrobial Resistance

The rise in number of antibiotic resistances especially, Extended Spectrum Beta-Lactamase (ESBL) producing and carbapenem resistant gram-negative bacteria, poses a serious global threat to wellbeing of individuals [17]. Fluoroquinolone prophylaxis has been proven to reduce bloodstream infections in immunocompromised patients such as those on CAR T-cell therapy. However, their continuous use increases the risk of resistance, with experts suggesting the selective use of the treatment based on individual assessment. Consequently, Kampouri *et al.* [18] calls for a harmonized practice involving variation in the use of antibiotics and monitoring across centers.

Microbiome and Diagnostics

Microbiome dysregulation is implicated as a risk factor in CAR T-cell therapy. The presence of gut dominant bacteria such as *Lactobacillus rhamnosus* in the bloodstream indicates their potential role in infection risk [19]. CAR T-cell manufacturing process has also been implicated as a source of infection risk, with a study by Ayala *et al.* [20] reporting rapid detection of microbial contaminants during CAR T-cell manufacturing. Therefore, experts advise that infection prevention is key to optimizing CAR T cell therapy outcomes. Emerging microbiome focused trials suggest that antibiotic disruption of the microbiome impairs immune recovery and efficacy of CAR T cell therapy.

Future Directions

Novel CAR T cell therapies targeting antigens beyond CD19, B-cell malignancies and natural killer (NK)-based-therapies, offer new treatment options for the management of refractory malignant cancers due to their ability to affect the immune system differently and potentially introduce new risks of infection [21,22]. To that end, the European Society of Blood and Marrow Transplant (EBMT) recommends the harmonization of supportive care, with precision medicine approach promising a refined stewardship and infection prevention [23].

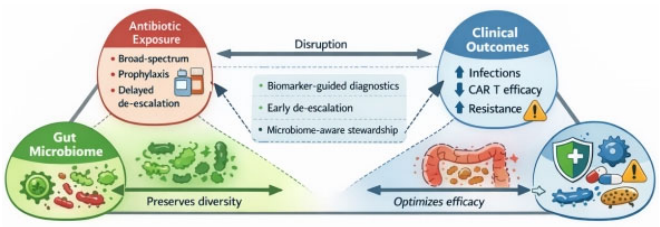

Figure 2. Interplay between antibiotic stewardship, microbiome and CAR T-cell therapy outcomes.

Conclusion

Infections are a frequent ongoing concern after CAR T cell therapy that are influenced by patients' health status, immune recovery and how antibiotic are used by the patient. Antibiotics use should be highly regulated to avoid risk of resistance development by the organism and protect the gut microbiome. Future strategies including integration of biomarker-guided diagnostics to detect infections more precisely, harmonized prophylaxis (standardized preventive treatments), and microbiome-awareness to protect and preserve beneficial bacteria, thereby optimizing both safety and efficacy.

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