Preventing Infections in TCEs: Risk Stratification and Prophylaxis

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T-cell–redirecting therapies, including bispecific T-cell engagers (TCEs) and chimeric antigen receptor (CAR) T-cell products, have transformed the treatment landscape of hematologic malignancies. However, by inducing profound immune modulation and cytopenias, these therapies carry a significant risk of infectious complications that can compromise efficacy and survival. Infection-related morbidity and mortality have emerged as key challenges in patients treated with TCEs, highlighting the need for systematic prevention strategies grounded in risk stratification and tailored prophylaxis.

The pathogenesis of infection risk in TCE-treated patients is multifactorial. Rapid and sustained B-cell depletion leads to humoral immunodeficiency and hypogammaglobulinemia, while prior therapies often result in T-cell dysfunction and prolonged neutropenia. The use of corticosteroids or tocilizumab to manage cytokine release syndrome (CRS) or immune effector cell–associated neurotoxicity syndrome (ICANS) further augments susceptibility. In addition, cytokine-driven mucosal barrier disruption and microbiome alteration contribute to bacterial and fungal invasion. Together, these mechanisms create a complex and dynamic immunocompromised state that demands vigilant monitoring and proactive prevention.

Risk stratification should incorporate host-, therapy-, and disease-related factors. Host characteristics—such as age, comorbidities, baseline immune function, and vaccination history—define inherent vulnerability. Therapy-related elements, including target antigen (e.g., CD19 vs. BCMA), magnitude of cytokine release, and cumulative immunosuppressive exposure, dictate the temporal profile of risk. Disease factors such as tumor burden and marrow reserve also modulate infectious susceptibility. Categorizing patients into low-, intermediate-, or high-risk strata facilitates individualized prophylactic planning.

Preventive measures should follow a multimodal, risk-adapted approach. Antibacterial prophylaxis with fluoroquinolones or trimethoprim-sulfamethoxazole is recommended during prolonged neutropenia or in patients with recurrent infections. Antiviral prophylaxis with acyclovir or valacyclovir effectively prevents herpesvirus reactivation, while cytomegalovirus (CMV) monitoring should be considered in high-risk individuals. Antifungal prophylaxis, such as with posaconazole or fluconazole, is appropriate for those with persistent neutropenia or receiving high-dose corticosteroids. Pneumocystis jirovecii pneumonia prophylaxis should be maintained for at least six months following initiation of TCE therapy. Immunoglobulin replacement is indicated in patients with persistent hypogammaglobulinemia (<400 mg/dL) or recurrent sinopulmonary infections. Vaccination strategies, including revaccination after immune reconstitution and early immunization of close contacts, provide an additional safeguard against preventable infections.

Continuous monitoring is essential to detect evolving immune deficits and opportunistic pathogens. Routine assessment of complete blood counts, immunoglobulin levels, and pathogen surveillance should be integrated into clinical follow-up. Emerging approaches, such as T-cell functional assays and immune repertoire profiling, may refine risk prediction and enable dynamic adjustment of prophylactic intensity. As TCEs move into earlier disease settings and combination regimens, infection risk profiles may evolve, necessitating ongoing reassessment of prevention frameworks.

In conclusion, infection prevention in patients receiving T-cell engagers requires a shift from reactive management to precision-based prophylaxis. A comprehensive risk stratification model combined with individualized, evidence-driven prophylaxis can minimize infection-related complications, sustain therapeutic efficacy, and improve patient outcomes. Collaborative efforts to standardize infection prevention protocols across trials and practice settings will be critical to ensuring the safe and effective integration of TCEs into routine clinical care.