Overview of Infections Complicating Pediatric Hematopoietic Cell Transplantation

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KEYWORDS

• Infection • Hematopoietic cell transplantation • Immunocompromised children

KEY POINTS

- Despite improvements in supportive care, infections remain a significant cause of morbidity and mortality both early and late after hematopoietic cell transplantation.
- The complex interplay of host, transplant, and pathogen-related factors determine the risk of infectious complications after hematopoietic cell transplantation.
- Knowledge of the epidemiology and risk factors for infection at each phase after hematopoietic cell transplantation is needed to develop a differential diagnosis and institute optimal diagnostics and therapies.
- Prevention of infection and timely immune reconstitution are key to successful hematopoietic cell transplantation outcomes and are influenced by pretransplant, transplant, and posttransplant factors.

INTRODUCTION

Advances in hematopoietic cell transplantation (HCT) and refinements in supportive care strategies have led to an increasing number of HCT with improved outcomes in recent years in both adults and children.[1] However, infections remain an important cause of morbidity and mortality after HCT.[2] This article provides an overview of the epidemiology and risk factors for infections complicating HCT in children.

THE RISK FOR INFECTION IN CHILDREN AFTER HEMATOPOIETIC CELL TRANSPLANTATION

HCT is used to treat malignant (eg, leukemias, myelodysplastic syndromes, and high-risk solid tumors) and nonmalignant diseases (eg, hemoglobinopathies,

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bone marrow failure syndromes, inborn errors of metabolism, and primary immunodeficiencies). Possible HCT graft cell sources include bone marrow, peripheral blood stem cells, and umbilical cord blood (UCB). The recipient's immune system is altered or ablated by an immunosuppressive conditioning regimen, which may include a combination of chemotherapy, immunotherapy, and irradiation, given 4 to 10 days before intravenous infusion of the hematopoietic cell (HC) graft source (day 0) from either the patient's own previously harvested HC (autologous) or HC from a distinct donor (allogeneic; syngeneic if from twin donor). Immune reconstitution after HCT generally is heralded first by neutrophil engraftment, followed by monocyte and natural killer cell recovery, platelet recovery, and over the subsequent months, by B- and T-cell recovery, first with normalization of numbers, followed by qualitative immune recovery (**Fig. 1**). Many factors affect the success and tempo of immune reconstitution after HCT, including the HC source and presence of graft-versus-host disease (GVHD). For example, in allogeneic HCT recipients without evidence of GVHD, lymphocyte class switching can be seen as early as 6 to 8 months after HCT. Conversely, in patients with GHVD requiring ongoing or augmented immunosuppression, immune dysregulation of the phagocytic, humoral, and cellular arms of the immune system is ongoing and leads to an overall increased risk of infection. Reconstitution of distinct immune cell subsets has been associated not only with risk of infection, but also to HCT outcomes including development of GVHD, relapse, and overall survival.[3]

The risk of infectious complications, type of pathogen, and timing of infections after HCT varies according to type of HCT, with pretransplant, transplant, and posttransplant factors contributing to this risk (**Fig. 2**, **Table 1**). Infections after HCT may represent infections derived from a patient's microbial flora, reactivation of latent infection, or primary infection, the latter more frequently observed in children than adults. In addition, noninfectious HCT complications such as engraftment syndrome, hepatic venoocclusive disease (or sinusoidal obstruction syndrome), GVHD, and transplant-associated thrombotic microangiopathy may mimic infections and further confound the post-HCT period. Knowledge of the epidemiology and risk

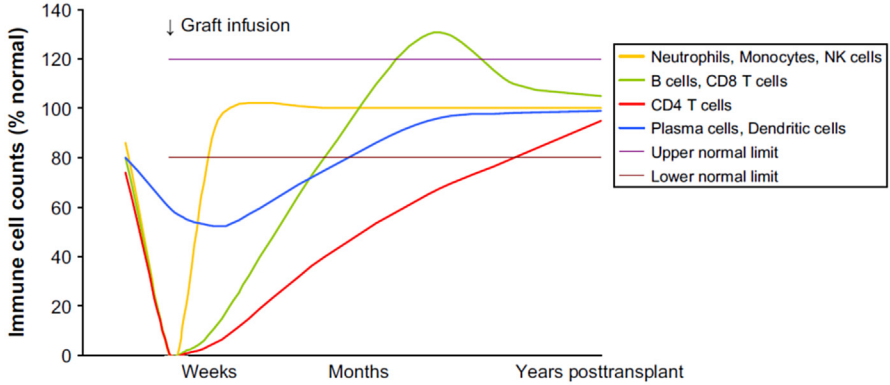

Fig. 1. General timing of immune reconstitution after myeloablative hematopoietic cell transplantation. (*From* Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15(10):1150; with permission.)