Life-Threatening Infection in Transplant Recipients

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KEYWORDS

• Transplant infection • Critical care • Immunosuppression • Opportunistic infection
• Microbiological diagnosis

KEY POINTS

- Transplant patients represent a heterogeneous and rapidly growing patient group requiring a high index of suspicion for infection.
- Infection is a major posttransplant cause of morbidity and mortality, and new threats continually emerge.
- Individualized assessments of net state of immunosuppression and infection risk are important.
- Aggressive pursuit of an early microbiological diagnosis is crucial; invasive procedures should be used if necessary.
- In the setting of life-threatening infection, reduction or cessation of immunosuppressive therapy whenever possible is an important adjunct to therapy.

INTRODUCTION

Transplant recipients constitute an increasingly diverse and complex patient cohort. They comprise a heterogeneous patient group undergoing solid organ transplantation (SOT), hematopoietic stem cell transplantation (HSCT), or pancreatic islet cell transplantation, and now also include the emerging group of individuals undergoing vascularized composite allotransplantation, such as limb transplants. Infection remains a major cause of morbidity and mortality in transplant recipients; for example, approximately 17% to 20% of the mortality following allogeneic HSCT can be attributed to infection.[1–3]

In SOT where immunosuppressants are prescribed indefinitely, transplant physicians and their patients perpetually negotiate the delicate balance between the risk of graft rejection and infection. Advances in techniques and in modern immunosuppression have improved graft survival but continually unveil new infection challenges

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for the patient.[4–6] The pharmacology of immunosuppression has evolved dramatically in recent years with a plethora of agents now available for physicians to use (**Box 1**).[7] Specific agents vary greatly in their mode, intensity, and duration of immunosuppression, adding yet another layer of complexity to the management and prevention of infectious morbidity and mortality in transplant recipients.[8]

The risk of infection in transplant recipients is a dynamic process and numerous influencing factors must be considered during the evaluation of patients (**Box 2**). The net state of immunosuppression is a central concept in transplantation medicine and represents a key determinant of infectious risk.[1,9] The net state is a measure of an individual's unique susceptibility to infection and incorporates assessment of several important contributing factors

- Pretransplant diagnosis or treatment (eg, myeloablative conditioning before HSCT)
- Induction therapy used at time of transplantation
- Nature of organ or stem cell transplant received (eg, lung vs liver organ transplant or umbilical cord blood, T-cell-depleted stem cell transplants)
- Dose, duration, and choice of maintenance immunosuppression
- Comorbidities (eg, viral coinfection [hepatitis C virus (HCV), cytomegalovirus (CMV)], malnutrition, end-organ failure [cirrhosis, chronic kidney disease])
- Breaches of the mucocutaneous barrier: indwelling devices, mucositis

The time after transplant is also of key importance (**Fig. 1**, **Table 1**). It directly influences the potential pathogens from which an individual patient is at risk.[1] Following periods of intensification of immunosuppression (eg, due to graft rejection or flare of Graft-versus-host disease [GVHD]) the patient's infection risk is adjusted to reflect earlier time points again after transplantation. In the absence of chronic GVHD requiring ongoing immunosuppression in HSCT recipients, immune restitution can in general be considered complete at 2 years after stem cell transplant.[3]

The authors' learning objective is to review significant posttransplant infections that can necessitate critical care support. For ease of description this discussion is divided into infections presenting early after transplantation and those occurring later after transplantation. A more detailed discussion of specific pathogens will then follow.

Early infections are classified here as

- SOT: those encountered between the transplant procedure and 4 weeks after transplantation
- HSCT: infection occurring in the preengraftment phase

Box 1
Immunosuppressant therapies and mechanism of action

Corticosteroids—multiple anti-inflammatory effects

Anti-proliferative agents: mycophenolate mofetil—inhibit nucleotide synthesis and prevent T-cell and B-cell proliferation

Calcineurin inhibitors: cyclosporine, tacrolimus—inhibits T-cell activation

mTor inhibitors: sirolimus—inhibits T-cell activation and proliferation

Monoclonal antibodies: basiliximab (IL-2 receptor antagonist), alemtuzumab (anti-CD52: prolonged T-cell, B-cell depletion), belatacept (binds CD80/86 to prevent T-cell costimulatory signal)

Antilymphocyte antibodies: anti-thymocyte globulin—prolonged T-cell depletion