Hematopoietic Stem Cell Transplant Recipients

Subjects: Transplantation

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Hematopoietic stem cell transplant (HSCT) is a multi-step process with a high risk for complications during marrow ablation, during engraftment, or afterwards. Successful transplantation depends on the selection of the hematopoietic stem cell source, host preparation (conditioning regimen), and modulation of immune cell engraftment to minimize graft-versus-host disease (GVHD).

post-HSCT PERDS DAH IPS bronchiolitis obliterans syndrome

1. Introduction

Hematopoietic stem cell transplant (HSCT) involves replacing a patient's bone marrow with hematopoietic stem or progenitor cells from peripheral blood, bone marrow, or umbilical cord from another person or the same individual to restore immune–hematopoietic function after the underlying disease is eliminated [1]. Pulmonary complications post-HSCT affect between 45% and 60% of recipients [2][3] with a mortality rate exceeding 60% in mechanically ventilated patients after autologous HSCT [4]. This review is intended to form a framework for diagnosing and treating non-infectious and infectious pulmonary complications post-HSCT for the general clinician.

2. Hematopoietic Stem Cell Transplant Overview

Hematopoietic stem cell transplant (HSCT) is a multi-step process with a high risk for complications during marrow ablation, during engraftment, or afterwards [5][6][7]. Successful transplantation depends on the selection of the hematopoietic stem cell source, host preparation (conditioning regimen), and modulation of immune cell engraftment to minimize graft-versus-host disease (GVHD) [7].

Advantages of allogeneic transplant include the ability to correct congenital or acquired defects and the immunologic, anti-tumor effects that can occur in response to persistent disease referred to as the graft versus tumor (GVT) effect [8]. Allogeneic transplant requires that the products be HLA-matched, as poorly HLA-matched products can lead to immune dysregulation and increased risk of GVHD. Furthermore, immune recovery is slower, and opportunistic infections are more common.

After selecting the source of stem cells, the host is prepared via high dose myeloablation therapy, reduced intensity myeloablation, or non-myeloablative conditioning [9]. Once a patient undergoes HSCT, engraftment occurs within a conditioning and host-dependent timeframe.

While there are several definitions of successful engraftment, patients typically develop a neutrophil count greater than 500/mm 3, a platelet count greater than 20,000/microliter without any transfusions for one week, and a hematocrit greater than 25% for at least 20 days without any transfusions [10]. For autologous HSCT, white blood cell recovery typically occurs within two weeks while red blood cell and platelet recovery varies from patient to patient [6]. For allogeneic HSCT, peripheral blood granulocyte counts usually show signs of recovery within three weeks while platelet recovery is often delayed, taking on average 5–7 weeks [6]. Neutrophil engraftment is also dependent on the immunosuppressive regimen used, and recovery can average 10–30 days [11].

3. Timeline of Complications Following HSCT

The diagnosis and management of post-HSCT pulmonary manifestations requires a multidisciplinary approach. Diagnosis can be challenging as post-HSCT syndromes often have nonspecific clinical presentations. Utilizing common timelines of illness presentation post-HSCT (**Figure 1**) in combination with exposures to infectious agents, prior anti-microbial use, and unique radiographic findings aid in the diagnosis. Use of non-invasive tests including upper respiratory cultures, respiratory pathogen PCR, and serologies are useful adjuncts and can take the place of invasive testing to identify infectious pathogens [12]. Timely coordination and open communication between primary service, hematology–oncology, pulmonary, radiology, pathology, and infectious disease specialists is vital to the management of these patients.

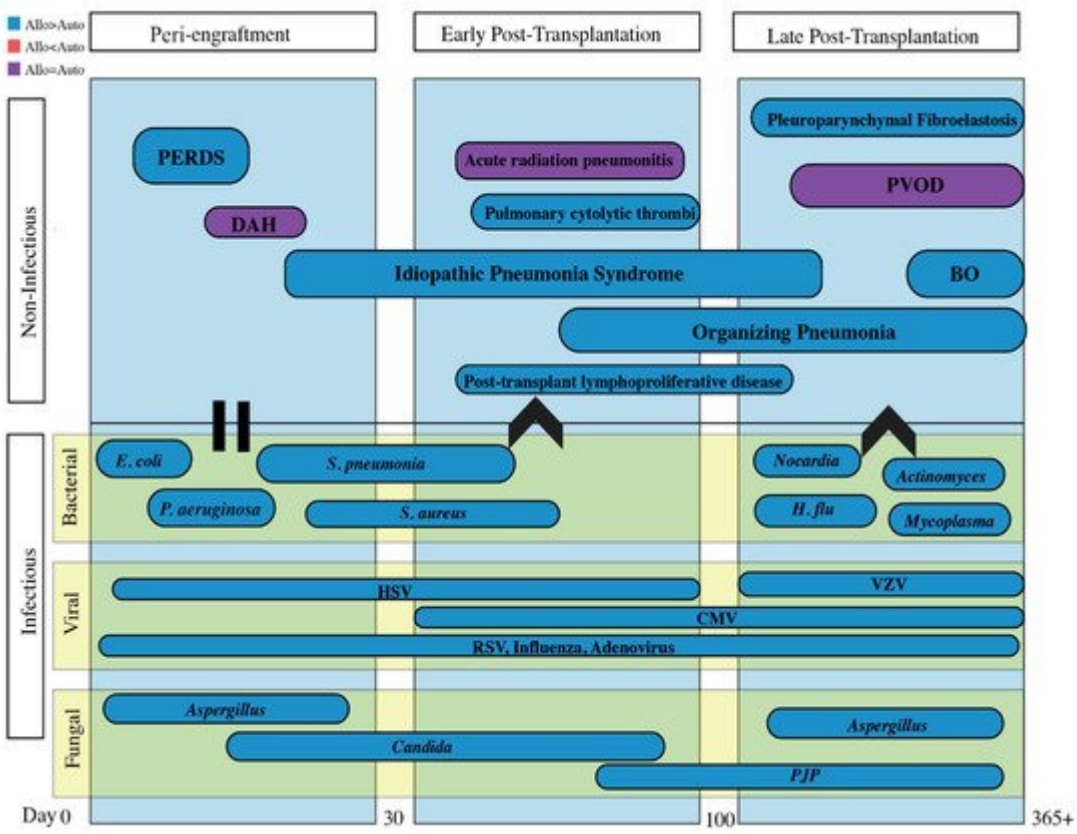

Figure 1. A timetable organized by peri-engraftment, early post-transplantation and late post-transplantation periods encompassing both infectious and non-infectious pulmonary complications. Important to note that all of the

above vary in time of presentation and can often overlap. For example, the increase in non-myeloablative conditioning can make this timeline less reliable. Infectious and non-infectious complications tend to occur more commonly in allogeneic transplants are typically secondary to chronic graft-versus-host disease and prolonged immunosuppressive medications. Abbreviations: PERDS = peri-engraftment respiratory distress syndrome; DAH = diffuse alveolar hemorrhage; PVOD = pulmonary veno-occlusive disease; BO = bronchiolitis obliterans; HSV = herpes simplex virus; VZV = varicella zoster virus; RSV = Respiratory syncytial virus; CMV = cytomegalovirus; PJP = Pneumocystis jirovecii.

Infectious and non-infectious pulmonary complications are classified by etiology and temporality in reference to HSCT, as it reflects the immunologic state of the patient. The often-cited time course for non-infectious entities consists of the pre/peri-engraftment phase (first 30 days), early post-transplantation phase (30–100 days), and the late post-transplantation phase (after 100 days). Infectious complications will be discussed separately.

4. Infectious Complications

The peri-engraftment phase is hallmarked by mucositis due to conditioning therapy and prolonged neutropenia due to non-functional transplanted marrow [13]. The risk of infection is highest when absolute neutrophil count (ANC) is less than 500 and increases with increasing duration of neutropenia before engraftment [14]. During the early post-transplantation phase, infections are related to the defects in cellular immunity caused by immunosuppressive and conditioning regimens [13]. In the late post-transplantation phase, infection rates decline as immunosuppressant medications are tapered unless needed for cGVHD. Because of differences in immune recovery, autologous HSCT recipients are at higher risk of infectious complications during the peri-engraftment and early post-transplantation phase while allogeneic HSCT recipients are at higher risk of infection throughout the late post-transplantation phase due to cGVHD and prolonged immunosuppressive therapy [15][13].

Zygomycosis is the second most common mold infection in HSCT with an increasing incidence over the past few decades [16]. Rare infections with fusarium and scedosporium can occur as well [17]. Invasive fungal infections with mucormycosis generally occurs > 3 months post-transplant and can make up to 8% of fungal infections in this patient population [18]. Although there are various imaging appearances of mucormycosis, one nearly pathognomonic imaging manifestation is the “bird’s nest” sign (**Figure 2** e) [19]. While mucormycosis infections are rare, they are frequently fatal and require early, aggressive management. Treatment involves combination of medical (with amphotericin B for zygomycosis) and surgical therapy [17].

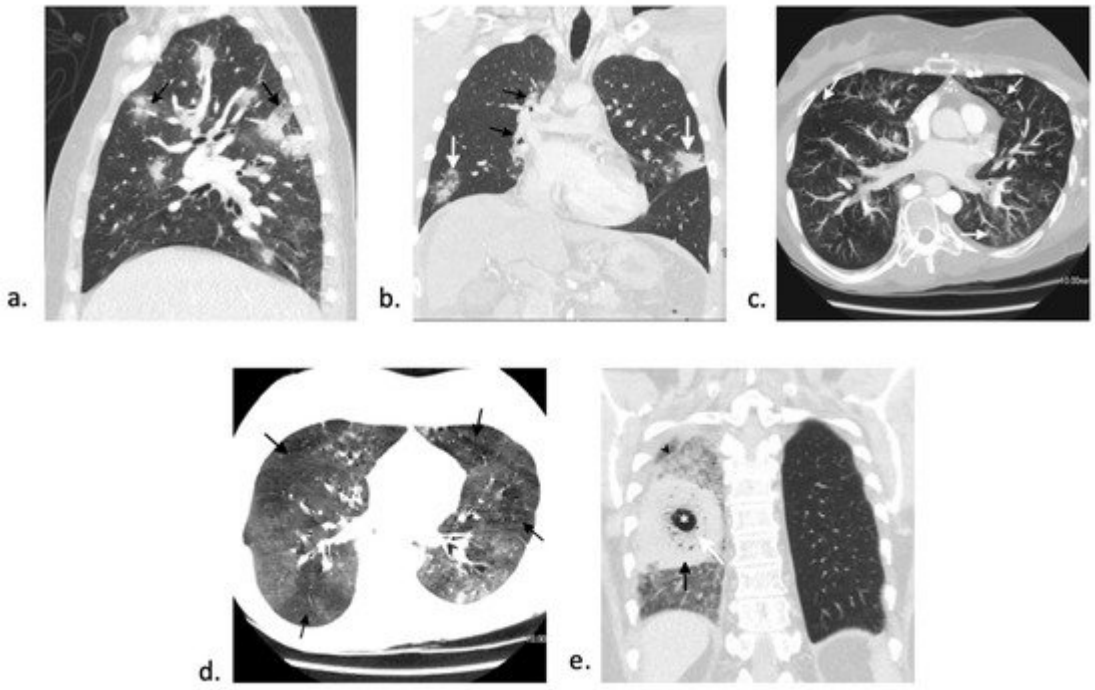

Figure 2. CT findings in early and late infectious complications. (**a**)Angioinvasive aspergillus in a 37-year-old woman status post-autologous HSCT for acute myeloid leukemia (AML). Sagittal chest CT shows numerous areas of nodular consolidation with surrounding ground-glass halos (black arrows) consistent with an angioinvasive infection. Aspergillus was confirmed on bronchoscopy. (**b**) Streptococcus pneumoniae infection in a 34-year-old man status post-autologous HSCT for Hodgkin lymphoma. Coronal chest CT shows nonspecific areas of consolidation in the left upper lobe and right lower lobe (white arrows). Streptococcus pneumoniae infection was confirmed on bronchoscopy. Paramediastinal fibrosis in the right lung (black arrows) due to radiation therapy for HL can be seen. (**c**,**d**) Nontuberculous mycobacterial infection (NTM) and bronchiolitis obliterans syndrome (BOS) in a 51-year-old woman three years after autologous stem cell transplant for acute lymphoblastic leukemia. (**c**) A 5 mm thick maximum intensity projection image (MIP) shows bronchial wall thickening and multifocal tree-in-bud nodularity (white arrows) due to NTM infection. (**d**) Corresponding 5 mm thick minimum intensity projection image (MinIP) at the same level nicely shows the pronounced mosaic attenuation (black arrows) due to BOS. (**e**) Mucor infection in a 49-year-old man nine months after autologous HSCT. Coronal image from a chest CT shows a mass-like lesion with dense circular consolidation (black arrow) with central necrosis manifesting as “bubbly”-appearing areas of ground-glass opacity (white arrow) and cavitation (asterisk). This “bird’s nest” sign is highly suggesting of mucormycosis. Surrounding ground-glass opacity with a “crazy paving” pattern (black arrowhead) is due to hemorrhage.

Viral pneumonia from reactivation is common during the peri-engraftment phase and should be closely monitored while patients are immunosuppressed. Viral infection from herpes simplex virus (HSV)-1 and -2 occur in peri-engraftment and early post-transplantation phase, those from cytomegalovirus (CMV) and human herpes virus-6 (HHV-6) are often present in early post-transplantation phase, and infection from varicella zoster virus (VZV) is more common in the late post-transplantation phase [20]. The incidence of reactivation of viruses such as HSV, CMV, and VZV has drastically decreased since prophylaxis became routine.

RSV is one of the more common CARV that is associated with high mortality rate. In a single center retrospective study of 280 allo-HSCT recipients with RSV infection, 29% had progression to lower respiratory tract infection [21]. Older age, smoking history, conditioning with high-dose total body irradiation, and lymphopenia were associated with an increased risk of progression from upper respiratory to lower respiratory tract infection [21][22]. RSV is associated with a wide mortality rate, ranging from 5% to 43%, in HSCT patients [23][21][24][25][26]. Older age, male gender, bone marrow or cord blood as transplant source, corticosteroid use, lower respiratory tract infection, and oxygen requirement are all associated with increased overall mortality [21][25][26][27].

5. Diagnostic Tools

Open communication between these primary services and these subspecialists is necessary for the initial evaluation of these patients. There are multiple diagnostic tools available if non-invasive methods do not yield a diagnosis. The most frequently utilized and widely considered safest diagnostic tool is flexible bronchoscopy. Bronchoscopic findings result in identification of infectious pathogens in 31–71% cases and change in therapy in 24–52% of patients [28][29]. Although yield is higher if performed early on and prior to initiation of anti-microbials, bronchoscopy may yield a treatment-altering diagnosis in up to half of cases, [30][31] even while patients are receiving empiric antimicrobial therapy [6]. Bronchoscopy with BAL can also identify organisms not evident on non-invasive testing and proves to be an important complementary strategy in the work-up of pulmonary complications in this population [32]. Furthermore, BAL cellularity can also help with the diagnosis of non-infectious entities including DAH. However, bronchoscopy becomes higher risk in those with hypoxemia, neutropenia and/or thrombocytopenia [33]. Most complications are reported as mild and self-limiting, but more severe adverse events like respiratory failure, arrhythmias, shock, and severe bleeding occurred at a rate of ≤5% [34].

While prior studies have shown that transbronchial biopsies (TBBx) can increase the diagnostic yield compared to bronchoscopy alone [35], more recent studies note that the addition of TBBx is not associated with a change in antibiotic therapy. However, positive results did increase the odds of a change in corticosteroids, suggesting a utility in non-infectious etiologies [36]. Not surprisingly, transbronchial biopsy confers an increased rate of complications and procedural mortality compared to bronchoscopy alone [36]. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has been demonstrated to be a safe and effective diagnostic method in sampling peripheral ground-glass opacities with high suspicion for primary malignancy [37][38], although the study of this technique as a diagnostic tool for infectious or non-infectious complications has been limited in immunocompromised patients [39]. However, limited data does demonstrate increased yield utilizing EBUS-TBNA compared to BAL alone in this pediatric population [39]. More research is required to elucidate the benefits and risks of EBUS-TBNA in the adult HSCT population. Trials comparing yield and safety of newer bronchoscopic interventions such as cryobiopsy to traditional TBBx in HSCT patients are lacking.

The use of other more invasive modalities is controversial [40]. Percutaneous CT-guided transthoracic lung biopsy has been performed in the past [41]. Surgical lung biopsy, either by video-assisted thoracoscopic surgery (VATS) or open thoracotomy [42][43], is now rarely performed due to risk of increased post-operative procedural complications and procedure-related mortality. The utility of these more invasive techniques has decreased over the past decade

as other non-invasive diagnostic tests have improved [40]. Overall, the choice of invasive modality is individualized based on risks and benefits of the procedure for the patient [44]. The decision for and mode of bronchoscopic evaluation is institution- and practitioner-specific [44].

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