16 Pneumonia After Hematopoietic Stem Cell Transplantation

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Pneumonia is the most common infection after transplantation, and the infection with the highest mortality. Roughly two thirds of pneumonia observed after HSCT are of infectious origin, and this observation should be a priority leading the investigations. While the infection-related mortality has decreased after HSCT over time [1], it is not sure that the incidence of pneumonia decreased in parallel. Up to 30% of the patients may develop pulmonary symptoms within the first 100 days after allogeneic HSCT [2]. Even in T-cell-depleted allogeneic HSCT where the incidence of pneumonia seems to be low [3], the occurrence of pneumonia significantly impacts on survival. The rates of bacterial, viral, and polymicrobial pneumonia do not seem to be different during the first 3 months after transplant between allogeneic and autologous HSCT recipients, while the rate of invasive fungal disease (IFD) is much higher after allogeneic HSCT [2], due to a more severe and prolonged immune defect which also favors late infectious complications [4].

Factors enhancing the risk of infectious pneumonia are many and include donor and recipient serologies; previous pneumonia, which may warrant secondary prophylaxis; graft source; choice of donor and conditioning; graft-versus-host disease (GVHD); and also environmental factors. One of the main concerns in pneumonia evaluation is to distinguish infectious and noninfectious pneumonia since many noninfectious causes may mimic infection. Additionally, pulmonary coinfections are frequent. This makes that the results of indirect markers, even though extremely useful in practice, should be cautiously considered as it may identify only part of the responsible pathogens. Only a direct investigation of the lung as provided by bronchoalveolar lavage (BAL), combined with the use of well-chosen indirect markers, gives the best chances to identify several causes of pneumonia.

This chapter focuses on the factors that make the lungs particularly susceptible to infections after HSCT, the main specificities of clinical and imaging presentation of pulmonary infections, and the principles of diagnosis and management.

16.1 Altered Pulmonary Defense After HSCT

The lungs of HSCT candidates may have been exposed to toxic insults from their underlying diseases, prior infection, and prior chemotherapy and irradiation which may compromise normal surveillance barriers. Conditioning before transplant and subsequent immunosuppressive therapy and infection all may impair native defenses and increase the risk for pulmonary infection.

The ciliated and squamous epithelium, from nasopharynx to distal bronchioles, is the first line of defense. Significant impairment of the ciliary epithelium has been reported even years after transplant [5]. The respective role of viral or mycoplasma infection or of GVHD or radiation in this finding cannot be precisely determined. However, these abnormalities were found in 17 of 20 long-term allogeneic HSCT survivors and are probably underestimated in routine practice.

Alveolar macrophages act as phagocytes and secrete cytokines and chemokines providing a next level of defense. Their functions may be altered by immunosuppressive agents and viral infection. During prolonged neutropenic phases, the number of alveolar macrophages decreases, and this could favor infection from pathogens, which are normally phagocyted at the alveolar level [6]. Additionally, after allogeneic HSCT, the recipient alveolar macrophages are progressively replaced by cells of donor origin, and this may partly explain the numeric and functional impairment of the alveolar macrophage population during the first months after transplant [7, 8].

16.2 Evolution of the Problem

The occurrence of infectious pneumonia relates to the interrelationship of infectious exposure or reactivation, the condition of the lungs, and the degree of immunosuppression. The changes in many transplant procedures, including various

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prophylaxes, and the availability of new diagnostic tools over the last decade should have changed the incidence of pneumonia after HSCT. However, there is no clear data to support this hypothesis, and one may consider that these changes have more resulted in a change in timing and causes of pneumonia rather than in incidence or mortality. The increasing use of reduced intensity conditioning (RIC) regimens has significantly decreased the formerly high rate of early bacterial pneumonias. However, concomitantly, multidrug-resistant (MDR) bacteria have become a global concern in most hematology wards [9, 10]. The use of RICs has also changed the kinetics of many complications, delaying the onset of GVHD and the subsequent infections [11, 12]. Preemptive and prophylactic strategies of CMV infection have also considerably reduced the incidence of CMV pneumonia which nowadays affects less than 6% of the patients [13, 14]. However, pneumonia due to respiratory viruses has become common. New antifungal agents have improved therapeutic options for *Aspergillus* infection, but non-*Aspergillus* molds, especially mucormycoses, are being seen with increasing frequency [15–18]. Finally, despite significant progresses, the morbidity and mortality of pneumonia after HSCT remains one of the highest of any transplant.

The timing of infectious pneumonia follows the timing of other infections according to the type of transplant and occurrence and severity of GVHD which is the main factor prolonging the infectious risk after the neutropenic phase [4]. HSCT recipients are both at risk for nosocomial and community infections according to the phase of transplant. These environmental risks cannot always be prevented, on the contrary of the reactivation risks which must be evaluated before transplant.

16.3 Main Causes of Infectious Pneumonia After HSCT

Although changes in the transplant procedures have impacted on the infectious complications and their timing (see Chap. X), infectious pneumonia after HSCT occurs in predictable risk periods. After allogeneic transplant, early bacterial pneumonia mainly complicates myeloablative transplant, while opportunistic fungal and viral infections may affect the patient irrespectively of the type of conditioning. After autologous transplant, most pneumonias occur during the neutropenic phase, especially in myeloma patients [19], and few of them are of fungal origin [16].

16.3.1 *Bacterial Pneumonia*

Bacterial pneumonia occurring during the initial neutropenia are caused by pathogens common to all neutropenic patients or to those with comparable mucositis in the ward. The clinician should also consider the possibility of streptococcal pneumonia or ARDS related to streptococcal sepsis. These infections are particularly due to *Streptococcus viridans* and have been correlated with the presence of mucositis, the use of prophylactic quinolones, and the administration of high doses of cytarabine (see Chap. 20). The approach to bacterial pneumonias early after transplantation is similar to that in other neutropenic hosts, and it should include coverage for *Pseudomonas* species and eventually MDR in case of previous colonization or infection [20, 21].

Most patients are maintained on indwelling intravenous catheters throughout this period, and seeding of the lungs from bacteremia continues to be a potential risk. After recovery from neutropenia, allogeneic transplant recipients continue to be at risk for any nosocomial infections as long as they stay in the hospital (see Figure 16-1). Bacterial infections occurring in the late posttransplantation period may be favored by persistent immunoglobulin deficiency, which increases the risk of pneumonia caused by encapsulated bacteria.

Invasive pneumococcal infection occurs significantly more often after allogeneic, than after autologous, transplantations and especially in case of chronic GVHD [22–24]. They may be rapidly fatal. In a prospective study from the European Blood and Marrow Transplantation Group [22], no pneumonia developed in seven cases of invasive infection observed before day 100, whereas it was seen in 18 of 44 (41%) cases observed after day 100, and half of the fatal cases of late infection were associated with pneumonia. Early immunization with the 13-valent conjugate vaccine, completed by the 23-valent polysaccharide later, or a fourth dose of the conju-

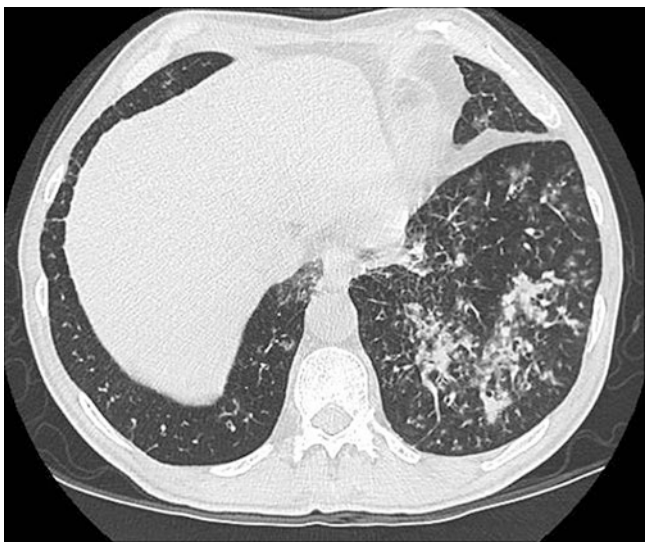

FIGURE 16-1. This 56-year-old patient has received an allogeneic HSCT from an unrelated donor for acute myeloid leukemia. He was smoker and suffered from chronic bronchitis before transplant. He was rehospitalized at 7 months after transplant for severe chronic GVHD and was treated with steroids. He developed febrile pneumonia after 9 days of hospitalization. The lung CT scan showed ground-glass, patchy infiltrates of the left lower lobe. The bronchoalveolar lavage was positive for coronavirus, and the culture of protected aspiration (10^3 CFUs/mL) and the culture of the lavage fluid (10^4 CFUs/mL) were both positive for *Klebsiella pneumoniae.*

gate vaccine in case of GVHD could reduce the incidence of pneumococcal infection over time [25, 26] (see Chap. 48). Similarly, *H. influenzae* may cause pneumonia and sinus infection, usually past the third month after transplantation. Immunization with a conjugate vaccine against type b is recommended from 6 months after transplant.

Pneumonias from *intracellular pathogens* are rarely reported, but they may recur in previously exposed patients. Pneumonia due to *Legionella* species has occasionally been reported in the setting of outbreaks, most often as a nosocomial infection. The radiologic findings may be variable; they may mimic fungal nodules, and they may not be apparent at the onset of high fever and pleuritic pain. Invasive nocardiosis, reported in 0.3–1.7 % after allogeneic transplant, mainly occurs in patients who are not receiving TMP-SMX and is often difficult to differentiate from fungal pneumonia [27, 28].

Mycobacterial infections due to *M. tuberculosis*, *Mycobacterium avium-intracellulare* complex, or other species are rarely reported. Generally, they are diagnosed at 2–18 months after transplantation, but they may develop early when prior infection has occurred (see Figure 16-2) [29, 30].

16.3.2 *Fungal Pneumonia (including pneumocystis pneumonia)*

Fungal pneumonia: *Aspergillus* is the most worrisome cause of IFD after allogeneic HSCT. It reportedly occurs after 0–20 % of transplantations; the most common site is the lung, and GVHD is the main risk factor (see Chap. X). A first peak of incidence occurs during the neutropenic period after myeloablative conditioning regimens, particularly in patients with leukemia. The second incidence peak is generally seen later in patients with acute GVHD and receiving corticosteroids. The availability of antifungal azoles for anti-aspergillus prophylaxis has significantly reduced the incidence [31–33]. However, the mortality of *Aspergillus* remained close to 50 % in recent series. This infection must be considered in any case of fever, particularly in that occurring in the patient on broad-spectrum antibiotics, or of any pneumonia, whether of new onset or a previously diagnosed condition that does not resolve with appropriate therapy (see Figure 16-3). A negative bronchoscopy result, even when combined with testing of galactomannan in the BAL fluid, does not diminish the suspicion for this pathogen. Without secondary prophylaxis eventually combined with surgical removal of the main lesions, the risk of relapse of prior *Aspergillus* infection after HSCT has been estimated around 20 % [34].

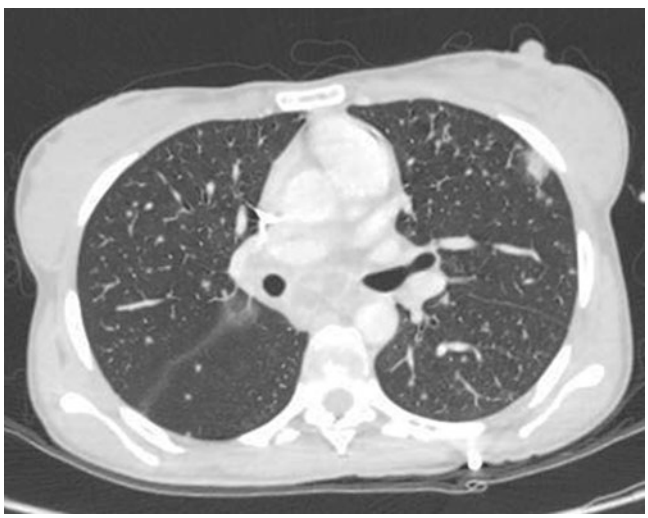

FIGURE 16-2. This 37-year-old woman received an allogeneic HSCT from her HLA-identical brother for poor-risk acute myeloid leukemia. She had a past history of pulmonary tuberculosis 10 years ago, but was intolerant to secondary prophylaxis. Three months after transplant, while she was well with no GVHD, she developed an insidious fever. Chest X-ray was normal. The lung CT scan showed diffuse micronodular infiltrates and a sub-parietal nodule of 1.5 cm in diameter in the upper left lobe. The bronchoalveolar lavage was positive for *M. tuberculosis* in culture.

In addition to being found in the lung parenchyma, *Aspergillus* may be isolated in the tracheobronchial tree where it may be responsible for significant airway obstruction. White, adherent plaques may be seen on bronchoscopy, particularly in the setting of chronic GVHD and steroid use. This infection must be differentiated from worsening bronchiolitis, so that inappropriate and dangerous increases in immunosuppression can be avoided.

Pneumonia due to *Candida* species is rarely reported, partly because no firm criteria for differentiating invasive infection from colonization based on bronchoscopy without biopsy exist. The lungs may be involved in any systemic *Candida* species infection.

Pneumonias due to endemic fungi, such as *Histoplasma* or *Coccidioides* species, particularly in North America, must be considered in these patients, as should the emerging fungi, including *Trichosporon*, *Alternaria*, and *Fusarium* [16].

A special attention should be paid to the possibility of *Mucorales* after allogeneic HSCT (see Chap. 39). Its mortality rate is between 50 and 80 % [18, 35–37]. Mucormycosis shares with aspergillosis common risk factors but usually occurs later, and often after voriconazole administration, although the role of a selection pressure is debated [35]. There is no indirect available marker of mucormycosis except PCR test currently in evaluation [38]. The classical presentation of mucormycosis after transplant mostly mimics aspergillosis, but galactomannan is negative (see Figure 16-4). Differentiating mucor from aspergillus infection is, however, of great importance due to different therapeutic implications. As long as there is a doubt between the two infections, the patient must be treated with liposomal amphotericin B.

Pneumocystis jirovecii Pneumonia (PjP) Historically, the incidence of PjP in patients not receiving prophylaxis in the 1980s was found to be 16 % during the first 6 months after transplant [39, 40]. This incidence has dramatically decreased between 1 and 2.5 % [41, 42] with the use of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, but the mortality in established PjP remains around 50–70 % [43–45].

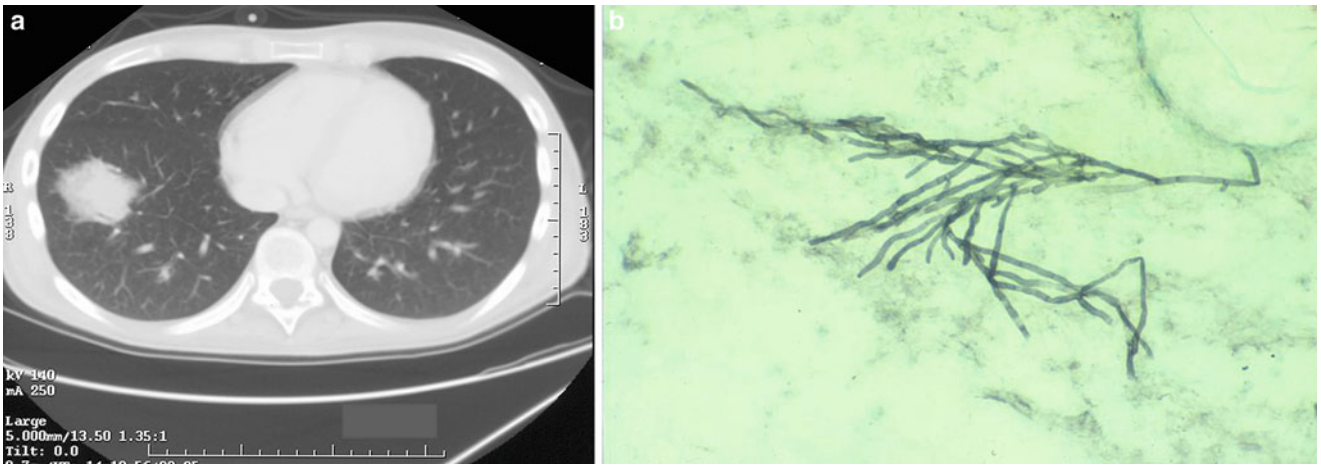

FIGURE 16-3. This young patient, 20 years old, received an allogeneic HSCT from an unrelated donor for acute lymphoblastic leukemia in second remission. He got severe acute GVHD and was not compliant to anti-mold azole prophylaxis. He developed an acute right chest pain with fever. (**a**) Both X-ray and CT scan showed a macronodular and isolated lesion of the right lower lobe. Serum galactomannan assay was negative. (**b**) The bronchoalveolar lavage smears showed hyphae characteristics of aspergillus (Gomori-Grocott stain). The culture of BAL fluid grew to *Aspergillus fumigatus.*

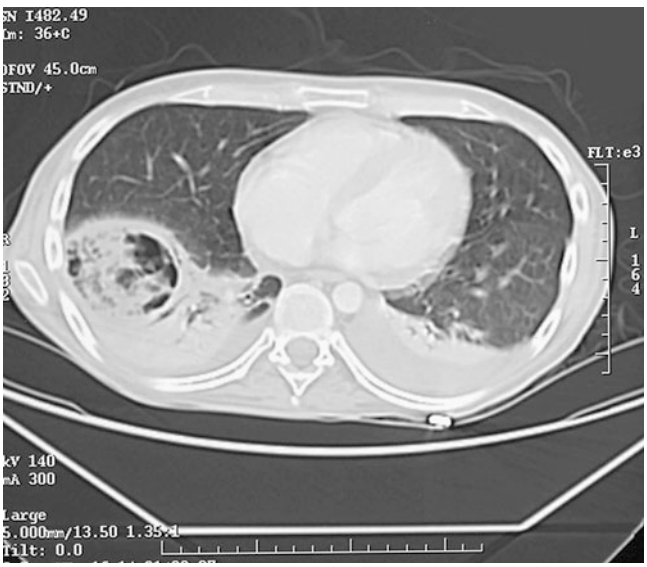

FIGURE 16-4. This 28-year-old patient had received an allogeneic HSCT for acute lymphoblastic leukemia from an unrelated donor. He got severe, cutaneous, and gut GVHD and was treated with steroids. At 4 months after transplant, while still on 0.7 mg/kg of prednisone, he developed a nodular lesion of the right lower lobe. A galactomannan test was positive in serum. He refused fibroscopy and was treated for aspergillus infection with voriconazole. He then did not attend the consultations for 1 month and came back with bilateral thoracic pains and fever. The CT scan showed bilateral pleural effusion and a voluminous round, necrotic lesion surrounded by an area of consolidation in the right lower lobe. Rhizopus grew from the BAL fluid.

However, in patients receiving dapsone prophylaxis, an incidence of 7.2 % was reported after allogeneic HSCT [43]. PjP usually manifests with fever, nonproductive cough, dyspnea, and diffuse interstitial pneumonitis. In HSCT recipients, the presentation of PjP may be extremely abrupt, and the patient may quickly deteriorate and require intensive care unit (ICU) [46–48]. Rarely, the disease may reveal by an isolated low-grade fever and a normal chest X-ray at the beginning. In such cases, if the cause of fever is not rapidly found, a CT scan will show pulmonary ground-glass lesions and prompt a BAL [49]. The elevation of LDH is poorly helpful [46]. Most patients present with nodular infiltrates or other pattern of diffuse interstitial pneumonia. Pleural effusion and pneumothorax are uncommon [44]. Most cases occur between 3 and 24 months after transplant, in patients with acute or chronic GVHD or in relapse of the underlying disease [42, 43, 49, 50]. Most are receiving steroids, especially at a phase of tapering off, or after recent withdrawal, and do not receive, or are not compliant to, TMP-SMX prophylaxis [51]. Whether a low CD4 count is a main risk factor for developing PjP after HSCT is unknown.

P. jirovecii is not cultivable in vitro. It may be identified by microscopic detection, direct or indirect immunofluorescence (IF), or nucleic acid tests (NAT) (see Figure 16-5). Several stainings may be used for microscopic detection of trophic forms and cysts in any respiratory sample such as Giemsa to identify trophic forms and toluidine blue O or calcofluor white to detect cysts, without significant difference in their diagnostic performance. IF has a better sensitivity than conventional stainings [52, 53]. The combination of one classical staining and IF allows the detection of both cystic and trophic forms. PCR is the most sensitive diagnostic assay to identify pneumocystis [54–56], although no study defines a clear cutoff of positivity [57, 58].

HSCT recipients, as other non-HIV-infected patients, are known to be infected with low burden of cysts [53, 59, 60]. As there is a decreasing gradient of the pneumocystis burden from upper to lower respiratory airways, this probably explains

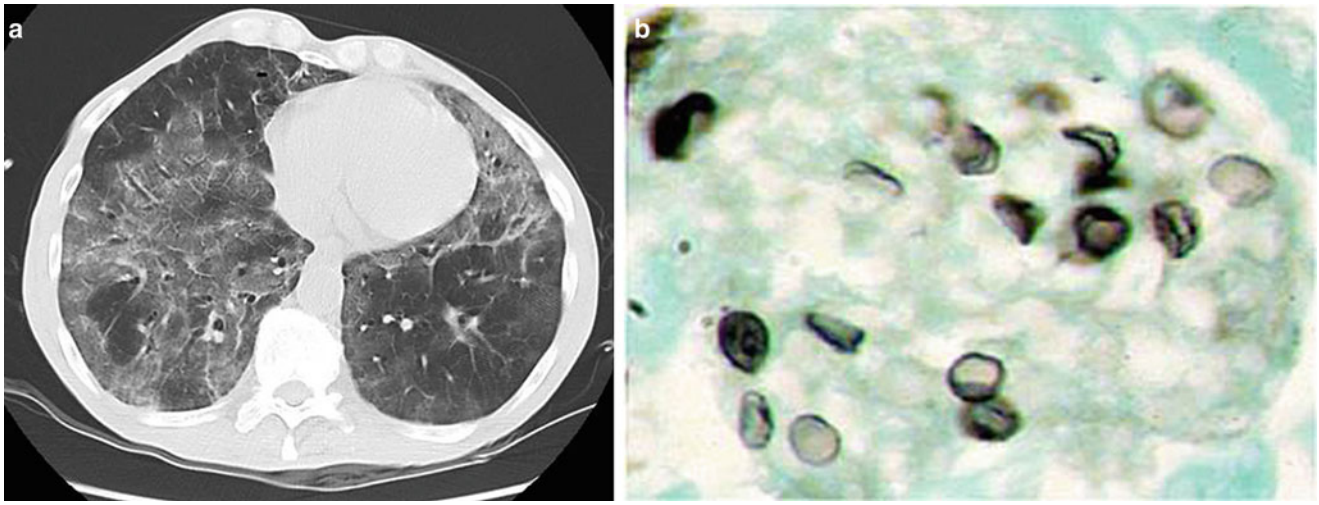

FIGURE 16-5. This 62-year-old patient received an autologous peripheral blood stem cell transplantation for non-Hodgkin lymphoma. He developed a severe rash under trimethoprim-sulfamethoxazole at the end of the first month after transplant. He was therefore switched to atovaquone for *P. jirovecii* prophylaxis. Five months after transplant, he developed fever and rapid respiratory failure with hypoxemia. A chest X-ray showed slight interstitial, bilateral lesions. (**a**) The CT scan showed bilateral ground-glass lesions predominant on lower lobes. (**b**) The bronchoalveolar lavage showed characteristic cysts of *P. jirovecii* on Grocott staining. IF and qPCR were also positive.

the difficulties to identify *P. jirovecii* in induced sputum or other upper respiratory samples with conventional techniques in non-HIV-infected patients. Therefore, BAL fluid is the preferred specimen for the diagnosis of PjP in HSCT recipients. Another argument for BAL is that half of the PjP cases in non-HIV-infected patients are associated with coinfections, especially with bacteria, CMV, and *Aspergillus spp*. [44, 46, 61] which require identification and treatment.

In case a BAL cannot be done, upper respiratory tract (URT) specimens, like induced sputum, oral washings, nasal swabs, or nasopharyngeal aspirates, can be used, but with a lower expected diagnostic value than with BAL. Serum (1-3) β(beta)-D-glucan is a major cell wall component of *P. jirovecii*. Two meta-analyses [62, 63] have shown its excellent sensitivity, but due to its panfungal nature and the frequency of other IFD after HSCT, it can be only a screening tool for PjP. On the other hand, its use in BAL fluid is not recommended, due to a poor sensitivity and reproducibility [64, 65]. The recent guidelines of the fifth European Conference on Infections in Leukemia [66] propose a practical algorithm for the diagnostic of PjP in non-HIV-infected patients, based on the examination of BAL fluid with IF and qPCR. The positivity or negativity of both techniques signs the presence or absence of PjP. When IF is positive, and qPCR negative, this should reflect a technical problem, mainly of qPCR. When qPCR is the only positive assay, although no quantitative cutoff can be uniformly proposed, a high fungal burden favors a diagnosis of PjP. The concomitant positivity of serum (1-3) β(beta)-D-glucan is an additional argument favoring PjP. When BAL is not possible because the patient is too hypoxemic or refuses the procedure, serum (1-3) β(beta)-D-glucan can be helpful in conjunction with URT samples. When the clinical suspicion of PjP is high and the BAL cannot be done immediately, an empirical treatment with TMP-SMX should be started as soon as possible since it will not impair the diagnostic yield of investigative procedures before at least several days. TMP-SMX at the dose of 15–20 mg/kg of TMP plus 75–100 mg/kg of SMX, by oral or preferably IV route, is the first choice for treatment [67], even in patients who were supposed to take TMP-SMX prophylaxis as the presence of dihydropteroate synthase mutations does not significantly affect the treatment efficacy [68]. The addition of steroids for the more hypoxemic patients (PaO2 while breathing room air <70 mmHg), although well established in HIV-infected patients [69], is debated in others.

PjP prophylaxis is strongly recommended from engraftment for at least 6 months after allogeneic HSCT and longer as far as any immunosuppressive drugs are administered [70, 71] and for at least 3–6 months after autologous HSCT [70]. No large prospective series compare the respective prophylactic efficacy of TMP-SMX with alternatives in HSCT recipients. However, strong arguments from both acquired immunodeficiency syndrome prospective studies and HSCT retrospective series suggest that TMP-SMX is the best prophylactic regimen [43, 72], any alternative to TMP-SMX—dapsone, atovaquone, or pentamidine—being inferior [71].

16.3.3 Viral Pneumonia

During the neutropenic phase of transplant, the incidence of herpes simplex virus (HSV) reactivation and disease—including pneumonia—has fallen sharply with the wide use of prophylactic acyclovir or valaciclovir [73].

Until the beginning of the 1990s, CMV was the most significant pathogen for pneumonia after allogeneic transplant, affecting 15 % of the recipients. Preemptive and prophylactic strategies have greatly decreased its incidence, currently in the range of 1–5 % [14, 74–76]. It is generally a febrile disease in which the radiographic patterns are primarily interstitial but sometimes alveolar. Coinfections are frequent. The optimal approach to identify the virus in the lungs is the combination of IF and rapid culture of BAL fluid. The identification of CMV through PCR on BAL fluid has been shown to have limited correlation with the development of CMV pneumonia and therefore is not considered as criteria for CMV pneumonia [77] (see Chap. 24). Therefore, as most of the laboratories abandon IF assays to more automated qPCR techniques, a careful examination of the BAL smears by an experimented cytologist is important to detect the cytological hallmarks of CMV pneumonia, knowing that the identification of the characteristic inclusions in alveolar cells is a sign of advanced infection [78] (see Figure 16-6).

Other herpesviruses, including varicella-zoster virus, EBV, and *Human herpesvirus* 6 (HHV-6), have been reported as causes of pneumonia in HSCT recipients. High levels of HHV-6 DNA have been found in the lung tissue of patients with idiopathic or CMV interstitial pneumonitis [76]. However, the clinical significance of this finding, and the need for specific therapy, is still unclear.

Pneumonia caused by respiratory viruses has become a main concern in HSCT recipients. The list regularly enlarges [79, 80]. The main risk factors for death are the early onset after transplant, neutropenia, lymphopenia, GVHD, steroid administration, and older age [79, 81–83]. Recently, an immunodeficiency scoring system has been proposed to predict poor outcomes and better identify patients infected by respiratory syncytial virus and who should benefit the most from antiviral therapy [83]. The incidence is lower after autologous than after allogeneic transplant [84]. Identification by NAT in respiratory samples is the recommended technique and may be performed on nasopharyngeal or throat swabs, bronchial aspiration, or BAL fluid [79, 85, 86] with multiplex assays. Diagnosing these patients early has several benefits: [1] some of these infections may be efficiently treated (e.g., oseltamivir in influenza infection or ribavirin for respiratory syncytial virus); [2] all of them imply isolation and barrier measures to prevent transmission to other patients or staff; [3] respiratory viral infections early after allogeneic transplant predict the development of alloimmune lung syndrome, including bronchiolitis obliterans and idiopathic interstitial pneumonia [79, 87, 88]. When respiratory viruses are detected before transplant, delaying the transplant should be considered [89].

Measles pneumonia has rarely been reported after HSCT but may be an expected event in the setting of outbreaks [90] and may occur without a rash. Adenovirus pneumonia is a very rare but potentially life-threatening event occurring in the setting either of disseminated adenovirus infection or of usually upper and then lower respiratory tract infections [91] (see Chap. 33) and occur more frequently in children than in adults and in unrelated transplants or after T-cell depletion.

16.3.4 Other Causes

Reports of pulmonary *toxoplasmosis* are rare; it is usually seen in the setting of disseminated infection resulting from reactivation, during the first year after transplantation in seropositive recipients not receiving TMP-SMX. The pattern is usually a diffuse interstitial disease, and neurologic symptoms may be absent. *Toxoplasmosis* may be identified in BAL fluid and blood by IF and qPCR. A prospective screening by qPCR in the patients at risk may allow a preemptive therapy [92].

16.4 Differential Diagnosis to Infectious Pneumonia: The Main Noninfectious Processes Affecting the Lungs After HSCT

The lung is the site of numerous noninfectious injuries causing one third of pulmonary infiltrates after HSCT. This needs to be considered because they may require specific treatments. Pulmonary edema, pulmonary embolism, and acute respiratory distress syndrome may occur at any time, but more often during the early phase of transplant, without any special presentation in transplant recipients and will not be detailed here. Other noninfectious processes affecting the lung deserve specific consideration as they are either frequent or specifically observed in HSCT recipients. These noninfectious processes may be associated with infections, increasing the difficulty to propose optimal treatment. The best identification is however of crucial importance since steroids may be indicated in several noninfectious processes while they will be deleterious in most infections. The probability of their occurrence may vary by time after transplantation and type of transplant.

Alveolar hemorrhage (AH) is a frequent noninfectious process affecting the lung after any HSCT, with an incidence rate of 6–41 % [93–95]. AH is diagnosed on the basis of either a bloody aspect of the BAL fluid—usually transient—or the presence of ≥20 % of siderophages among alveolar macrophages (see Figure 16-7) [96]. AH after HSCT may be an autonomous process favored by thrombocytopenia, other coagulation disorders, or renal failure [96] and by any rupture of the alveolar-capillary barrier such as in pulmonary edema, but it may also be associated with infections, like aspergillus or CMV, in two thirds of the cases [94, 97].

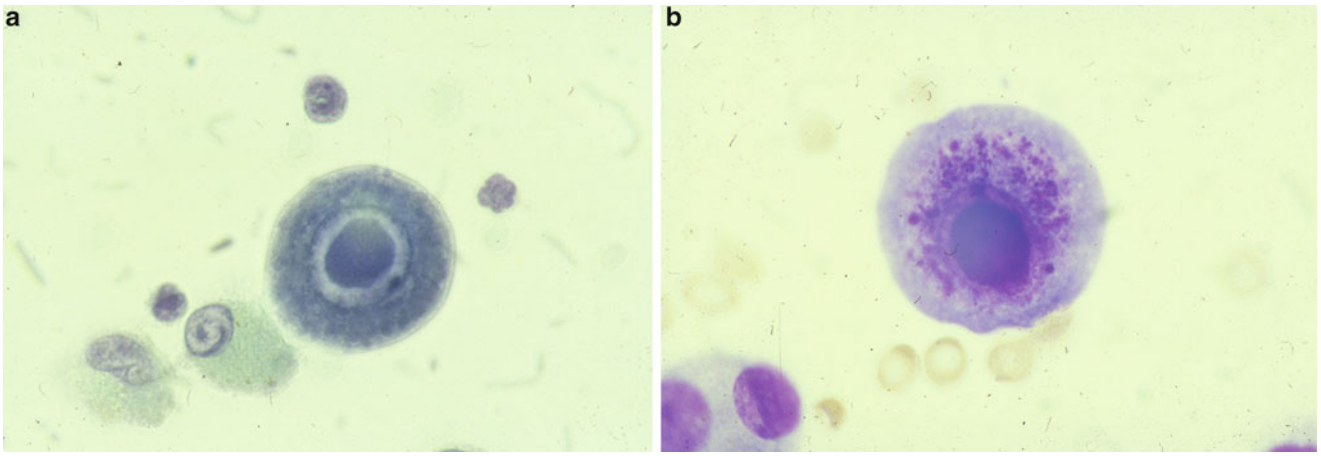

FIGURE 16-6. Bronchoalveolar cytocentrifuged smears in CMV pneumonia. (**a**) Papanicolaou staining: The slide shows the cytomegaly of an infected alveolar macrophage and, additionally, typical haloed "owl-eyed" basophilic intranuclear inclusions (Papanicolaou staining). (**b**) May-Grunwald-Giemsa staining: Intracytoplasmic inclusions, which are pathognomonic of CMV infection.

Neither clinical presentation nor imaging are specific of infectious or noninfectious forms [97].

Secondary alveolar proteinosis (**AP**) is rare, occurring mostly during prolonged neutropenia. It is the result of a complex process probably combining pneumocyte II stimulation and quantitative and functional defects of the alveolar macrophages. This results in an impaired clearance of pulmonary surfactant and the accumulation of a lipoproteinaceous periodic acid-Schiff (PAS)-positive material in the alveolar space (see Figure 16-8) [98, 99]. It usually mimics an insidious pulmonary edema. The diagnosis may be suspected on the sticky aspect of the BAL fluid and then by difficulties to count the cells. The usual stainings do not identify AP. The cytologist must be aware of this possibility and examine the alveolar material on PAS or Black Sudan staining. Secondary AP rarely complicates with severe respiratory failure [99]. When it occurred during neutropenia, it usually improves at neutrophil recovery. However, as for AH, some cases are associated with infections.

Pulmonary veno-occlusive disease is a very rare event after HSCT. It mainly manifests by pulmonary arterial hypertension, but with a normal pulmonary artery occlusion pressure. The diagnosis is extremely difficult. By analogy with liver veno-occlusive disease, it is hypothesized that it is due to chemotherapy and/or radiation toxicity on the small vessels [100, 101].

The engraftment syndrome may be observed during neutrophil recovery, at a median onset of 16 days after transplant, and usually associates ≥2 of the following criteria: fever, skin rash, weight gain due to capillary leakage, and respiratory failure without other identified cause [102]. It is hypothesized that degranulation of upcoming neutrophils could induce lung injury. Engraftment syndrome is associated with a large dose of mononuclear cells infused, the use of G-CSF or GM-CSF, early neutrophil recovery, non-myeloablative conditioning, the use of amphotericin B therapy, and autologous rather than allogeneic transplant [102–105]. An incidence up to 48 % has been reported in children after allogeneic myeloablative transplant, one fourth of them suffering from pulmonary symptoms. As severe patients may require steroids [104, 105], it is important to quickly rule out an infection.

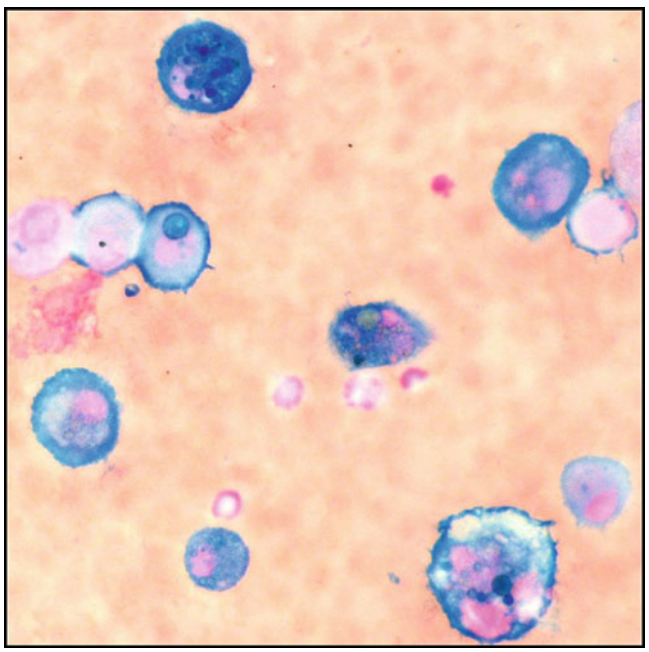

FIGURE 16-7. Alveolar hemorrhage: Bronchoalveolar lavage cytocentrifuged slide stained by Perls' Prussian blue method. The hemosiderin-laden macrophages (siderophages) characteristic of alveolar hemorrhage are identified by their blue cytoplasm (Courtesy of Dr. Jeanne Tran Van Hieu, Pathology department, Henri Mondor University Hospital, Créteil, France).

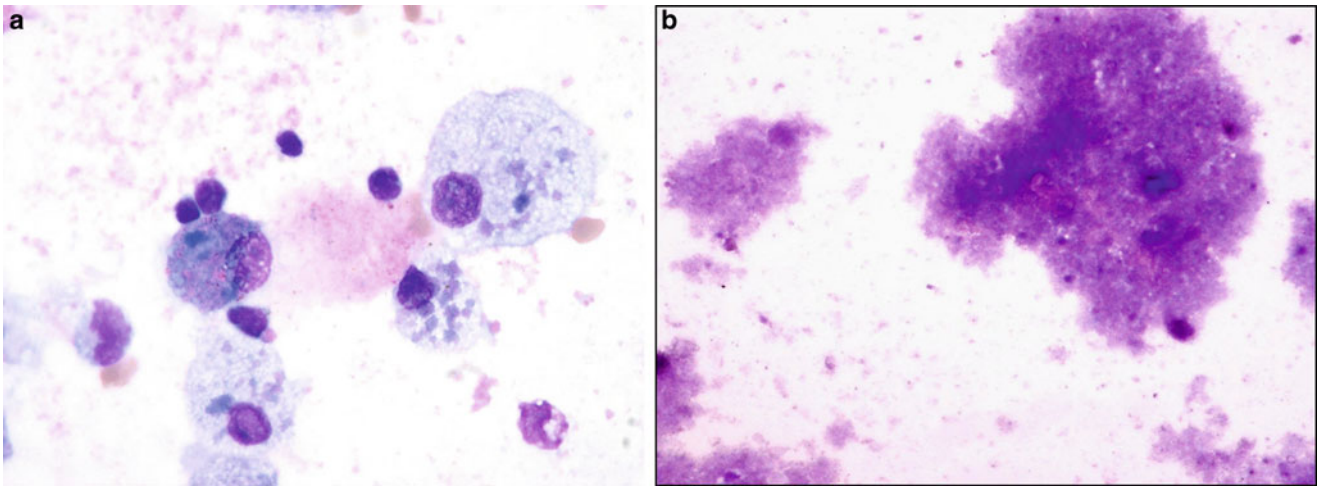

FIGURE 16-8. Secondary alveolar proteinosis: Bronchoalveolar lavage, May-Grünwald-Giemsa (MGG) staining. The presence of eosinophilic pale floccular material between alveolar macrophages and inflammatory cells on MGG-stained slides is highly suggestive of lipoproteinous material (**a**). This can be confirmed using the periodic acid-Schiff (PAS) method that showed positive staining (**b**) (Courtesy of Dr. Jeanne Tran Van Hieu, Pathology department, Henri Mondor University Hospital, Créteil, France).

Idiopathic (noninfectious) interstitial pneumonia is a complication reported in most allogeneic HSCT studies, with a high mortality rate. This diagnosis implies to have ruled out at least the main infections classically presenting as diffuse interstitial pneumonia, especially viral pneumonia and PjP, cardiac dysfunction, and fluid overload [106]. In myeloablative transplant, it has been associated with leukemia or myelodysplastic syndrome, severe acute and chronic GVHD, high-dose total body irradiation, and older age. In allogeneic HSCT, its incidence has been reduced from 8.4 % after myeloablative to 2.2 % after non-myeloablative conditioning [107]. A recent study showed that among 69 HSCT recipients who had developed an idiopathic pulmonary syndrome between 1992 and 2006 in Seattle, a retrospective microbiological screening of BAL material for 3 bacteria, 25 viruses searched with NAT, and galactomannan identified that 56.5 % of the patients had one pathogen (mainly HHV-6, rhinovirus, CMV, and aspergillus), and this finding was associated with an increased mortality at day 100 [76]. This confirms that the rate of "idiopathic" pneumonia is highly depending on how far infection is searched.

Bronchiolitis obliterans (BO or obliterative bronchiolitis) is an important factor contributing to death usually from 6 months after HSCT. Reported only after allogeneic HSCT, the condition has been related to older age, unrelated donor, total body irradiation, decreases in serum immunoglobulin G, and chronic GVHD, with a frequency of 3–10 % in patients with chronic GVHD who survive 120 days [108]. It seems to be prevented by T-cell depletion of the graft [109]. BO usually occurs insidiously, with cough, dyspnea, and wheezing, but may complicate with fever and mimic bronchopulmonary infection. Its hallmark is airway obstruction. The lung CT scan shows hyperinflated bronchiectasis, with a mosaic pattern. BAL and other endoscopic samples are of limited value as they just aim to rule out infection. As no noncontributory BAL can definitely rule out infection, it is preferable to perform two consecutive BALs at 1–2 weeks interval to increase the chance to not miss any pathogen. It is often associated with sinusitis and complicated by infections, especially those caused by *Haemophilus influenzae*, *S. pneumoniae*, *Aspergillus* species, and respiratory viruses. Despite immunosuppressors, the prognosis is poor.

Alveolar or nodular infiltrates may be seen in the setting of allogeneic HSCT as a result of **bronchiolitis obliterans organizing pneumonia** (BOOP)—also called cryptogenic organizing pneumonia [108, 110]. BOOP is much less common than BO and is also considered a manifestation of GVHD but has also been reported after autologous HSCT. It occurs earlier than BO, usually in the first 3 months following transplant. The CT scan shows nodular opacities and patchy consolidations. Pulmonary function tests show a restrictive defect. A histologic diagnosis is strongly recommended because BOOP may mimic infection, but can be reversible with corticosteroid therapy.

Malignant lung lesions may be seen after HSCT, either due to a primary or secondary cancer, localized relapse of the hematologic malignancy (see Figure 16-9), or EBV lymphoproliferative diseases (see Chap. X).

16.5 Principles of Management

Management of pneumonia after HSCT requires a high degree of suspicion and the early use of diagnostic procedures. The increasing availability of indirect markers of infection tends to decrease the early use of BAL. However, BAL remains the easier and safer procedure to identify both infectious and noninfectious causes of pneumonia. More invasive diagnostic

procedures such as transbronchial or lung biopsy need to be selected in situations in which BAL is noncontributory while weighing the risk of increased morbidity.

16.5.1 Clinical Approach to Pneumonia

A systematic approach to pneumonia in any HSCT recipient should include consideration of the following: history, clinical presentation, and imaging.

16.5.1.1 History

Knowledge of a patient's exposure, travel, environmental risks, and previous documented infection, the hospital epidemiology, and the pretransplant donor and recipient serologies particularly with regard to CMV and toxoplasmosis are essential. A history of recurrent MDR bacterial infection may require special consideration in choosing antibiotics [21]. Evaluation of the patient's compliance to anti-infective prophylaxis, especially to TMP-SMX, may be essential in evaluating the risk of PjP [51]. Whether the patient is neutropenic, lymphopenic, or hypogammaglobulinemic at presentation may be important to list the main infectious hypotheses.

16.5.1.2 Clinical Presentation

Symptoms and signs of pneumonia may or may not be typical of a known infectious cause. However, none is very specific. As in all immunosuppressed patients, few findings may be present, so any symptoms must be carefully and quickly evaluated, because of the consideration that any infection can rapidly progress. Fever, cough, or sputum production may be absent. Hypoxemia may be the sole finding, and even if the X-ray is normal, in case a chest CT scan cannot be obtained quickly, a bronchoscopic evaluation should be considered. The presence of any such symptom may, however, reflect a noninfectious etiology. Acute thoracic pain, with or without hemoptysis, may indicate embolic disease but may also denote *Aspergillus* infection. Pneumothorax may reveal—or complicate—PjP, mycobacterial or *Aspergillus* infection, or fibrosis. The rapid onset of pneumonia is mainly consistent with bacterial pneumonia, PjP, pulmonary edema or hemorrhage, or thromboembolism, but this may also occur with viral infections in immunosuppressed patients. A subacute onset more suggests IFD, although it may present abruptly.

16.5.1.3 Imaging

Posttransplantation pneumonia may be focal, multifocal, diffuse and interstitial, alveolar, or mixed. Every effort must be made to quickly obtain chest X-rays of optimal quality and/or a high-resolution chest CT scan when easily available. X-rays in supine position are rarely helpful. Additionally, most X-ray patterns are nonspecific and many patients have mixed types of infiltrates. When an X-ray appears negative or shows only minimal changes, there is good evidence that a chest CT may reveal abnormalities. CT scan has the best negative predictive value to rule out pneumonia and will show lung images 5 days before chest X-ray [111]. CT may additionally provide localization of the lesions, guiding invasive procedures, and inform on their proximity to pulmonary vessels. This information is also important to evaluate the

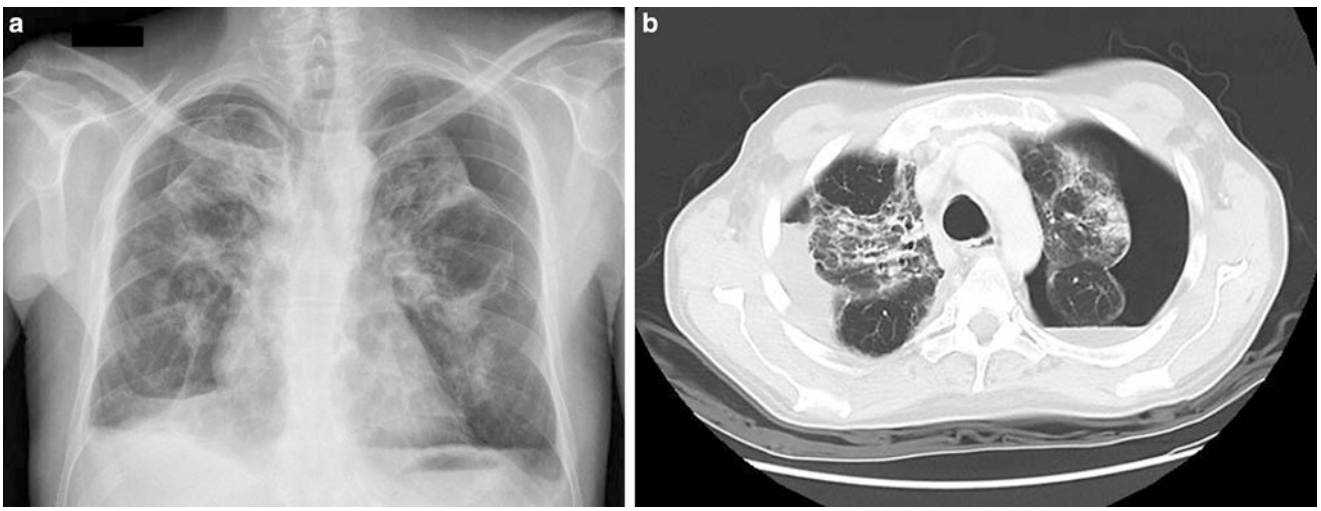

FIGURE 16-9. This 37-year-old patient received an allogeneic HSCT from his HLA-identical sister for refractory Hodgkin disease 20 months ago. He developed chronic respiratory failure due to concomitant causes: Hodgkin pulmonary relapse documented at 18 months and pulmonary fibrosis likely favored by previous mediastinum irradiation. (**a**) The chest X-ray shows bilateral partial pneumothorax, more important on the left side, bilateral pleural effusions, and multiple condensations. (**b**) The CT scan confirms the multiple retractile lesions of the lungs with bronchial dilatations and pleural thickening. It also confirms the left pneumothorax.

risk of hemoptysis in aspergillosis. CT may also detect small pleural effusions. Some CT findings may suggest the presence of particular infections. For example, the halo sign—a macronodule (≥1 cm in diameter) surrounded by a perimeter of ground-glass opacity—is very evocative of early aspergillosis during neutropenia [112], but may also be seen in other infections (e.g., legionella, mycobacterial infection, mucormycosis, or viral infections). Similarly, the reversed halo sign or "atoll sign"—a focal ground-glass attenuation surrounded by a ring of consolidation—has been shown to be often due to mucormycosis in hematology patients, but may also be observed in other infections, including aspergillosis [113]. Ground-glass opacities are very nonspecific and consistent with any infectious and many noninfectious processes such as pulmonary edema or hemorrhage. However, even with more characteristic lesions—such as the air crescent sign which is rare after HSCT but very evocative of mold infection—a CT scan does not replace the need for identification of the pathogen for diagnosis. Magnetic resonance imaging (MRI) usually does not provide more information than CT, except in the detection of lung abscesses [114]. The usefulness of PET scan is limited for diagnosis of acute pneumonia but may be better in nodular, subacute lesions [115], to identify extrapulmonary lesions or to follow the treatment efficacy [116–118]. Any workup using imaging should be completed rapidly, and it should lead quickly to a diagnostic procedure or, in most cases, to an empiric approach considering the most likely hypotheses.

16.5.2 Diagnostic Investigation

Blood cultures should be performed routinely, but they are of limited value in diagnosing pneumonia except for when the pathogen has a high propensity for the blood, such as *Streptococcus pneumoniae*, or in neutropenia. Special culture media are required when *Nocardia* or atypical mycobacteria are suspected. The blood should also be quickly sampled for CMV antigenemia or quantitative real-time PCR (qPCR) in patients at risk. The microbial documentation of any other site of infection, such as skin biopsy of cerebrospinal fluid, may be useful.

Blood biomarkers for the diagnosis of IFD include the detection of galactomannan by an enzyme-linked immunosorbent assay and of (1-3) β(beta)-D-glucan by a colorimetric assay. (1-3) β(beta)-D-glucan is a panfungal marker, while galactomannan is mainly associated with aspergillosis, although it may be positive in other mold infections, e.g., fusariosis. A meta-analysis of 27 studies showed that the galactomannan test has a sensitivity of 0.71 and a specificity of 0.89 for proven invasive aspergillosis [119]. The assay seems to be more useful for the prospective screening of neutropenic patients rather than for diagnosing pneumonia and also more useful in neutropenic than in non-neutropenic patients [120, 121]. The cutoff of positivity usually recommended is an index ≥0.5 in plasma or serum [121]. In an autopsy-based study, the sensitivity and specificity of the serum (1-3) β(beta)-D-glucan test for the detection of IFD were 95.1 % and 85.7 %, respectively [122]. Serum (1-3) β(beta)-D-glucan test is also very useful in the indirect diagnosis of PjP [63, 123]. Fungal NAT have also been widely investigated in HSCT recipient [124], but no consensus on their use in clinical practice currently exists. At this time, no noninvasive test that can replace the specificity of direct pulmonary investigation exists.

Although *sputum* may be analyzed to yield organisms colonizing the oropharynx, the clinical relevance of the results is not evidence based in the setting of HSCT. A positive culture may be valuable when agents that do not normally inhabit the oropharynx are isolated, especially *Legionella*, mycobacteria, and some fungi, or to document MDR colonization which may guide an empirical antibacterial treatment. In HSCT recipients with pneumonia, a positive sputum culture may be highly suspicious for pulmonary aspergillosis. Similarly, the presence of *M. tuberculosis* in the sputum may be considered the cause of the pneumonia when clinical and radiologic signs support this etiology. This assertion is to be considered with more caution for nontuberculous mycobacteria [125].

Nasopharyngeal aspirates or washings are useful to detect respiratory viruses in patients with URT infection [81, 84]. However, the correlation with the cause of the concomitant pneumonia is only presumptive as coinfections are frequent [84].

The standard for diagnosing pulmonary infection after HSCT is *bronchoscopic sampling with BAL* [126] (Table 16-1). Lavage is safe, minimally invasive, and reproducible. Its overall diagnostic yield is comparable to the one of lung biopsy, but with more infectious diagnostic and much less complications [126].

The clinician who consults with a pulmonary specialist for BAL should consider platelet transfusions if the patient is thrombocytopenic and should alert the microbiology laboratories to ensure that all potential organisms are sought. Oxygen saturation or arterial pressure should be assessed before the procedure. Fever, transient hypoxemia, and worsening of chest X-rays may be expected in as many as one half of patients during the few hours following the procedure [127]. When the patient is hypoxemic (paO2 < 70 mmHg spontaneously or with O2 supplementation) or tachypneic before BAL, he usually benefits from noninvasive ventilation immediately after the procedure. The overall diagnostic yield of BAL in infectious pneumonia occurring in hematologic patients varies between 27 and 55 % [2, 95, 128–131] depending on many parameters such as the following:

- The localization of the pulmonary lesions: whether they are accessible by BAL or not.

Table 16-1. Investigations on bronchoscopic samples in HSCT recipients

	Laboratory investigations	
Sample	Essential	Optional
Protected bacteriologic sample (brush or catheter)	Gram stain	Search for bacteria in neutrophils
	Quantitative cultures	
Aspiration	*Legionella*: immunofluorescence (IF), culture on BCYE medium or more selective media	India ink
	Mycobacteria and *Nocardia*: AFB stain, culture	
	Fungi: wet mount, culture	
Lavage fluid	Cytologic examination of lavage fluid on smear and after cytocentrifugation: direct examination, differential count, viral inclusions, pathogens	
	Stains	Stains
	–May-Grünwald-Giemsa	–Gomori methenamine silver (or alternative stain for *P. jirovecii*)
		–Papanicolaou
		–Periodic acid-Schiff
		–Perls' Prussian blue (hemosiderin-laden macrophages)
	Microbiologic processing	
	–Gram stain, bacterial culture	–Quantitative culture of BAL fluid
	–Legionella: culture on BCYE medium or more specific media	–PCR for *Legionella pneumophila*
	–Mycobacteria	–PCR for *Chlamydia pneumoniae*
	–Fungi: wet mount stain, culture	–PCR for *Mycoplasma pneumonia*
	–*P. jirovecii*: IF and/or qPCR	–PCR for *Mycobacterium tuberculosis*
		–Galactomannan antigen
	Virus	
	–All possible viruses, particularly the herpes family, adenovirus, and respiratory viruses: IF	–PCR for HSV, VZV, CMV, EBV, HHV-6
		–PCR for respiratory viruses and adenovirus
	Other	–Toxoplasmosis: IF, PCR
Transbronchial biopsy[a]	Histology	

[a]Transbronchial biopsy is essential for noninfectious processes and less contributive than BAL for infectious pneumonia. However, it is usually not proposed in the initial investigation of pneumonia, due to its possible complications (pneumothorax, bleeding).

BCYE buffered charcoal yeast extract, *AFB* acid-fast bacillus, *IF* immunofluorescence, *PCR* polymerase chain reaction.

- Whether the patient is neutropenic. The yield of the procedure is usually lower in neutropenic than in non-neutropenic patients [131].
- The type of the causal infection: for example, the diagnostic yield of BAL with conventional mycological techniques—without galactomannan tested in the BAL fluid—for aspergillus pneumonia is usually lower than 50 %, while it is higher than 90 % in PjP or CMV pneumonia, for which one rarely needs a lung biopsy [67].
- The laboratory exams performed on fibroscopic samples. The laboratory protocol should be established in advance in a multidisciplinary approach according to the expected, infectious and noninfectious, causes of pneumonia, eventually adapted to seasons for respiratory viruses.
- The criteria used to define specific entities. For example, it is generally believed that the presence of candida in a BAL fluid or bronchial aspiration does not necessary mean a candida pneumonia, while the presence of aspergillus in an HSCT recipient does [132]. However, for some causes of pneumonia, there are until now no consensus definition. The increasing availability of NAT for many pathogens should not replace, in many instances, more classical techniques, until the need for classical techniques is shown to be no longer useful in diagnosing a given infection.
- The delay elapsed between presentation and BAL and the number and duration of previous antibiotics before performing BAL [133]. The diagnostic yield of BAL has been shown to be better when it is performed early after the onset of pulmonary symptoms. In a series of 297 HSCT patients who underwent a BAL, the diagnostic yield of the procedure was 56.8 % in patients since less than 24 h versus 32.8 % in the others [131]. In another study, the diagnostic yield was 73 % in patients who underwent BAL within 4 days of presentation and 31 % thereafter [2]. This may be due to the effect of previous anti-infectives on the probability to identify a pathogen, but also to the fact that lung inflammatory lesions may persist some time after the

infection is controlled, so that delayed BAL may be performed in patients with a favorable outcome but still imaging and clinical signs. Therefore, it is recommended to do a BAL as soon as possible.
– Finally, although pneumonia is less frequent after autologous than after allogeneic HSCT, the diagnostic yield of BAL has been reported to be lower in pneumonia occurring after autologous rather than after allogeneic HSCT [133].

However, despite these variabilities, BAL, when well tolerated and correctly processed at the laboratory, represents the best diagnostic strategy for a minimum of complications. It should also be noticed that cytologic examination of BAL fluid will also document alveolar hemorrhage [96] or alveolar proteinosis [99].

A routine BAL protocol for HSCT recipients should include at least total and differential cell counts on cytocentrifuge preparations using May-Grünwald-Giemsa stains, as well as cytologic examination on cell pellets obtained by centrifugation and cytocentrifugation that are stained with the May-Grünwald-Giemsa stains and the Papanicolaou stain for viruses and the Gomori-Grocott method for *P. jirovecii* and fungi (Table 16-1). Other stains are necessary to identify alveolar proteinosis (PAS) [99], mycobacteria (Zielh), and siderophages (Perls' Prussian blue) [96].

A sample of fluid should be sent for bacteriologic and fungal cultures and viral tests. Galactomannan detection may be done in BAL fluid, especially in neutropenic patients with aspergillosis [128, 134], but with a higher cutoff (≥1) than in serum [121]. Aspiration and BAL fluids should be examined for *Legionella pneumophila* by cultures and eventually NAT and for *Nocardia* and mycobacteria. Due to the better sensitivity of qPCR over conventional stainings and IF assays [54, 55, 59], some laboratories already use qPCR exclusively. The viruses of interest in HSCT patients are the viruses of the herpes family, adenoviruses, and respiratory viruses (i.e., respiratory syncytial virus, influenza, and parainfluenza, rhinoviruses, metapneumoviruses, coronaviruses, enteroviruses, and bocavirus) which should be determined particularly in the setting of known exposures and during seasonal outbreaks [79].

A *protected bacteriologic sample* (*PBS*), done by a protected brush specimen or a plugged telescoping catheter, should be processed by quantitative culture techniques. Although determined from mechanically ventilated patients, the minimal threshold bacterial concentration required to usually consider the isolated pathogen as the cause of the pneumonia is 10^3 colony-forming units (CFUs)/mL for PBS and 10^4 to 10^5 CFUs/mL in the BAL fluid [135, 136].

Due to the increased risk it provides for bleeding and pneumothorax, *transbronchial biopsy* is not routine in acute pneumonia occurring in patients with HSCT and should not be proposed with the first bronchoscopy and BAL [137, 138]. Also, it does not add significant informations to concomitant BAL in most cases [133, 138, 139].

In cases in which noncontributory bronchoscopy, one should consider performing a second BAL and/or a transbronchial biopsy or better, a transthoracic needle aspiration when the lesion(s) is nodular and subpleural [126]. After HSCT, focal lesions that develop or persist despite antibiotics are mostly of fungal origin [140]. Successful fine needle aspiration, guided by either ultrasound or CT, has been reported, with a complication rate around 15 %, and is useful for documenting IFD when other procedures failed [140, 141]. The final decision between lung biopsy through open or video-assisted thoracoscopy or empirical treatment to cover the most likely organisms should be made by the transplant physician and the lung specialist after weighing the risks of surgery, empirical treatment, and failure to reach a diagnosis and the etiologies most likely at that time after transplantation. Lung biopsy is more helpful when the clinical course is prolonged and the pattern is nodular or cavitary.

16.5.3 Starting Treatment and Reevaluation of Efficacy

Because any pneumonia that occurs after HSCT may be life threatening, empirical antibiotics against the likely organisms must be started immediately. The best approach is to conduct bronchoscopic investigation with BAL as soon as possible; this should not, however, delay the initiation of treatment, especially when acute (likely bacterial) pneumonia is present or with patients who are neutropenic. Consideration should be given to the likelihood of fungus in patients with prolonged neutropenia and in those with GVHD on steroid therapy. Some empirical treatments may render subsequent testing negative, especially that for bacteria and viruses, yet they may be warranted. Some empirical treatments will not affect the chance of isolating the pathogen for at least several days after the empirical treatment is begun (e.g., TMP-SMX for *P. jirovecii*, antifungal agents for aspergillosis).

Daily clinical reevaluation should be performed, especially when no diagnosis is initially established and the patient does not improve. The use of noninvasive markers, when initially positive, is mostly useful to assess the treatment efficacy:

– Patients with initial positive blood cultures should be sampled for blood culture controls daily until negative.
– It has been shown in aspergillus infection with an initial positive serum or plasma galactomannan test that the quantitative evolution of the test correlates with the prognosis as soon as from the first week of therapy [142, 143].

Serial follow-up X-rays or, preferably, lung CT scans should be repeated according to the type and severity of the pneumonia. However, some infections, although favorably evolving, may be associated with a long persistence of image abnormalities, which may take several months to decrease or disappear. In the absence of new lesions, it should not be per

se a reason to reinvestigate the patient if the clinical outcome is favorable. In aspergillosis, it has been shown that a transient increase of the volume of the fungal lesions on CT scan may occur at the time of neutropenia recovery without any significance of treatment failure [112].

New investigations should be rapidly undertaken when the pneumonia does not respond to empirical treatment. Even when the cause of the pneumonia has been established, the occurrence of new infiltrates should be regarded as suspicious for treatment failure or new infections, as the association or succession of several causes of pneumonia is not uncommon in this setting. When a BAL has been initially done on accessible lesions, a second one should not be considered before most of the results of the laboratory be back, except if the BAL has been performed in poor conditions or in case of new lesions. Usually, a delay of 1 week before a first noncontributory BAL and a second BAL is minimal. If the initial lesion is peripheral and nodular and the BAL was noncontributive, a transthoracic fine needle biopsy should be considered. If the lesion is subacute or chronic and there is no response to targeted or empirical treatment, surgical biopsy may be contemplated for chronic nodular lesions.

16.6 Place of Intensive Care and Ventilatory Support

Pneumonia is the cause of the ICU transfer in roughly one third of the cases both in allogeneic [144] and autologous [145] HSCT recipients. Although the prognosis of HSCT patients transferred in the ICU has slightly increased over time [146], the decision of transfer remains difficult in terms of the emotional burden for the patient, family, and caregivers. The use of predictive scores—such as the sepsis-related organ failure assessment (SOFA) [147]—assessed at ICU transfer in HSCT recipients is debated [148]. Patients with acute respiratory failure benefit from ICU support and can be investigated by BAL, knowing that BAL does not increase the need for mechanical ventilation [149]. The prognosis of ICU support is usually better in autologous rather than in allogeneic HSCT recipients, and those with severe acute GVHD and under corticosteroids usually do not clearly benefit from ICU support [146]. Guidelines should be adapted to new data, but, in general, the clinician should consider the individual's chance of survival and of return to an acceptable life before transferring the patient to an ICU. The patient and the family should be provided with reasonable estimations of prognosis before transfer; in addition, the likelihood of continuing life support should be considered regularly during the course of treatment. Patients who respond to noninvasive mechanical ventilation have a better prognosis than those who required mechanical ventilation [150].

16.7 Summary

Pneumonia is a principal determinant of posttransplantation survival. Because of the predictable timing of some infections after most types of transplantations, some prophylactic regimens have been instituted with far-reaching benefits. However, any change in the transplant procedure, conditioning, or immunosuppressive regimen may affect the incidence and cause of infectious pneumonia. Additionally, new pathogens are emerging, and familiar pathogens are becoming more resistant. A high level of suspicion when pneumonia occurs in a transplant recipient and vigilance in diagnosing and treating will continue to be required to prevent an increase in mortality from pneumonia. The development of indirect diagnostic procedures is essential in the evaluation of pneumonia, but their clinical pertinence must be established in large prospective studies, and, until now, they do not replace direct investigation of the lung, mainly by BAL.

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