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Etiology, diagnosis, and management of pneumonia in immunosuppressed patients

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ABSTRACT

Patients with a compromised immune system suffer a wide variety of insults. Pulmonary complications remain a major cause of both morbidity and mortality in immunocompromised patients. When such individuals present with radiographic infiltrates, the clinician faces a diagnostic challenge. The differential diagnosis in this setting is broad and includes both infectious and non-infectious conditions. Evaluation of the immunocompromised host with diffuse pulmonary infiltrates can be difficult, frustrating, and time-consuming. This common and serious problem results in significant morbidity and mortality, approaching 90%. Infections are the most common causes of both acute and chronic lung diseases leading to respiratory failure. Non-invasive diagnostic methods for evaluation are often of little value, and an invasive procedure (such as bronchoalveolar lavage, transbronchial biopsy or even open lung biopsy) is therefore performed to obtain a microbiologic and histologic diagnosis. Bronchoscopy allows certain identification of some aetiologies, and often allows the exclusion of infectious agents. Early use of computed tomography scanning is able to demonstrate lesions missed by conventional chest X-ray. However, even when a specific diagnosis is made, it might not impact patient's overall survival and outcomes.

Keywords: Immunosuppressed host; opportunistic infections; pneumonia; acute respiratory failure.

INTRODUCTION

Patients with a compromised immune system suffer a wide range of lung diseases. In this subpopulation, pulmonary complications remain a major cause of both morbidity and

mortality. When an immunocompromised host presents with radiographic infiltrates, the clinician faces a broad differential diagnosis which includes infectious and non-infectious processes. Furthermore, the radiographic findings can be, in many cases, nonspecific and some of the most common aetiologies may have overlapping clinical and imaging features.

Over the last two decades, scientific evidence has brought to the table different important questions. Firstly, an aggressive diagnostic approach to identify the underlying cause of the disease is necessary, as diagnostic delay increases the risk of mortality. Secondly, the evaluation of these infiltrates usually requires a bronchoscopy. This technique allows an adequate and certain identification of many aetiologies, and usually aids in excluding infectious agents even if the procedure is otherwise unrevealing. Thirdly, the early use of computed tomography (CT) scanning commonly demonstrates lesions that are missed by simple chest radiography. Despite these improvements in the diagnostic tools, initial therapeutic interventions include the use of broad-spectrum antibiotics and other anti-infectives (antiviral and antifungal treatments) in order to ensure that patients are receiving the appropriate therapy [1]. With the microbiological results of these invasive techniques, the treatments are then adjusted. Frustratingly, the outcomes in immunocompromised patients with radiographic lung infiltrates are still poor. Many original and review articles have focused on the management of this condition. The present review attempts to provide a comprehensive and systematic picture of the current knowledge and an integrated approach to these challenging patients.

DIFFERENTIAL DIAGNOSIS

Immunocompromised patients show a wide variety of lung insults. Infections are the most common cause of both acute and chronic lung diseases in these patients, but many other non-infectious conditions affecting the lungs must be considered. The clinical presentation of these non-infectious conditions often

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Spectrum of lung lesions in the immunosuppressed host

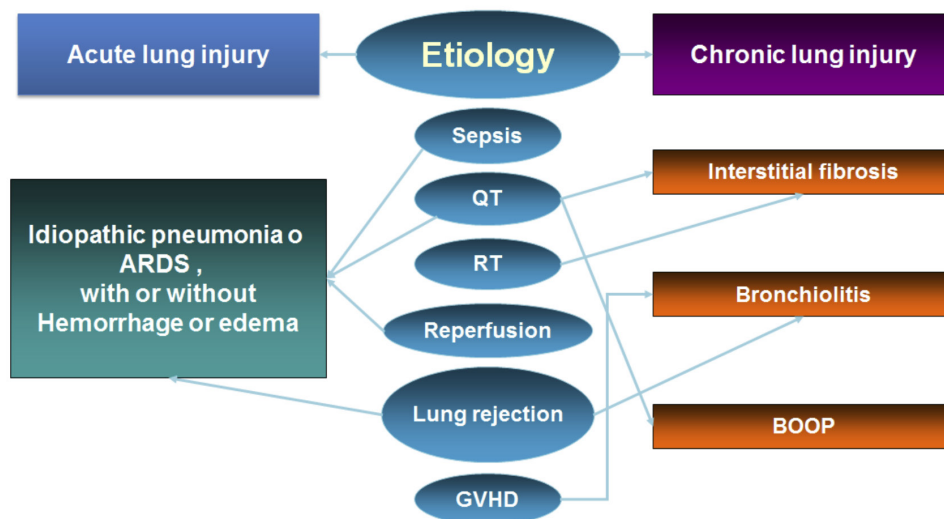


Figure 1 | Spectrum of lung lesions in the immunosuppressed host

ARDS: Adult Respiratory Distress Syndrome; BOOP: bronchiolitis obliterans with organizing pneumonia; GVHD: Graft versus host disease; QT: Chemotherapy; RT: Radiotherapy; . Modified and adapted from reference 2

mimics an infectious presentation, thus causing diagnostic dilemmas. The spectrum of non-infectious lung injuries in the immunosuppressed host includes interstitial oedema, interstitial fibrosis, diffuse idiopathic pneumonia, acute respiratory distress syndrome, and obliterative bronchiolitis [2]. Occasionally, alveolar haemorrhage may be present as a secondary complication. Other conditions such as sepsis, irradiation, graft rejection, reperfusion injury, graft-versus-host disease (GVHD), and chemotherapeutic agents and other drug reactions such as biological treatments are also included in the differential diagnosis (Figure 1). These conditions most often present as diffuse pulmonary infiltrates on chest radiograph. Thus, establishing a specific diagnosis and determining the specific aetiology is usually problematic. From a pragmatic standpoint, excluding infectious causes is the principal aim of the diagnostic work algorithm. The expansion of modern microbiological diagnostic techniques based on the detection of genetic products of microorganisms, or their proteins and metabolites, has managed to improve the diagnostic accuracy when facing immunosuppressed patients with pulmonary infiltrates.

The evaluation of the immunocompromised host with diffuse pulmonary infiltrates can be difficult, frustrating, and time-consuming. This common but serious problem results in significant morbidity and mortality, approaching 90% of patients between both. It is estimated that the lungs are involved in at least 75% of immunocompromised patients with any complication. At autopsy, over 90% of these patients present histological pulmonary affectation. However, in 15% of cases even

the pathologist cannot make a definitive diagnosis, which result in non-specific diagnoses such as "diffuse alveolar damage", or "interstitial pneumonitis and fibrosis". Several series of trans-bronchial lung biopsies, bronchoalveolar lavage (BAL), and even open lung biopsies resulted in similar failure rates (15-30%) in reaching a definitive diagnosis. Yet even when a specific diagnosis is made, it may not necessarily improve the outcome and survival. The mortality rate varies between 15 and 90%, depending on the underlying disease, the severity of lung involvement, and the degree of impairment of the host immunity.

Interstitial and alveolar parenchymal lung changes are two of the most common and serious complications in this group of patients. The morbidity rate reaches 50% and up to 90% if endotracheal intubation and mechanical ventilation are necessary. Opportunistic and bacterial infections are common causes of pulmonary infiltrates, and must be distinguished from other conditions such as drug reactions, volume overload, pulmonary haemorrhage, and malignant diseases. An accurate and prompt diagnosis of potentially treatable causes can be lifesaving. Non-invasive diagnostic methods for evaluation are often of poor value, and invasive procedures (such as BAL, transbronchial biopsy or even open lung biopsy) are therefore performed to obtain a histological diagnosis [3]. Nevertheless, narrowing the diagnostic alternatives should minimize the need for risky, costly, and possibly unnecessary diagnostic and therapeutic interventions. The differential diagnosis of pulmonary infiltrates in the immunocompromised host is summarized and shown in Table 1.

Table 1 Differential diagnosis of pulmonary infiltrates in the immunocompromised host

INFECTIOUS	NON-INFECTIOUS
Viral CMV, RSV, Influenza, PIV, ADV, SARS-COV-2, HSV, VZV, HHV6	Alveolar haemorrhage
Fungal Molds (<i>Aspergillus</i> , breakthrough IFI such as <i>Fusarium</i> , <i>Mucor</i> , <i>Scedosporium</i> , <i>Lomentospora</i>) Yeasts (<i>Pneumocystis jirovecii</i> , <i>Cryptococcus</i> and emerging yeasts) Dimorphic fungi (endemic mycoses)	ARDS Acute GVHD Heart failure Pulmonary / fat embolism Hyperleukocyte syndromes
Bacterial GNB, GPB, <i>Nocardia</i> , mycobacteria	Lymphoma Aspiration
Protozoa and parasites <i>Toxoplasma</i> , <i>Strongyloides</i> , <i>Paragonimus</i> , geohelminths	BOOP Idiopathic pneumonia or chemotherapy drug toxicity Other causes

ADV: adenovirus; ARDS: Adult Respiratory Distress Syndrome; BOOP: bronchiolitis obliterans with organizing pneumonia; CMV: cytomegalovirus; GNB: gram-negative bacteria; GPB: gram-positive bacteria; GVHD: Graft versus host disease; HHV6: human herpes virus-6; HSV: herpes simplex virus; IFI: invasive fungal infection; PIV: parainfluenza virus; RSV: respiratory syncytial virus; VZV: varicella-zoster virus.

OPPORTUNISTIC LUNG INFECTIONS

Opportunistic infections are a major cause of morbidity and mortality in severely immunocompromised patients, such as those under chemotherapy or biological therapies, those with haematological malignancy, aplastic anaemia or advanced and untreated HIV infection, or recipients of solid organ or stem cell transplantation. The type and degree of the immune defect dictates the profile of potential opportunistic pathogens; T-cell-mediated defects increase the risk of viral (cytomegalovirus [CMV], respiratory viruses) and *Pneumocystis jirovecii* (PJ) infections, whereas neutrophil defects are associated with bacterial pneumonia and invasive aspergillosis. However, patients often have combined immune defects, and a wide range of other opportunistic infections can cause pneumonia [4-6]. Importantly, conventional non-opportunistic pathogens are frequently found in immunocompromised hosts and should not be overlooked. The radiological pattern of disease (best assessed by CT scan) and the onset speed help identify the likely pathogen(s); this can then be supported by targeted investigation including the early use of bronchoscopy in selected patients. Rapid and expert clinical assessment can identify the most likely pathogens, allowing timely appropriate therapy.

Opportunistic infections occur when the loss of adequate innate or adaptive immune responses allows a normally low-virulent organism to cause infection. The type and degree of the immune defect dictate the profile of potential opportunistic pathogens. For example, prolonged high-dose glucocorticoids (>20 mg/day for >21 days) and calcineurin inhibitors predispose to *Pneumocystis jirovecii* pneumonia (PJP); biological agents prescribed for immuno-mediated diseases are associated with specific immune defects that increase the

risk of opportunistic lung infections (such as those of tumour necrosis factor- α [TNF α] inhibitors and risk of mycobacterial disease, endemic fungi and *Legionella pneumophila*; or anti-CD20 drugs and mycobacterial disease, CMV pneumonitis and PJP). Common infections in otherwise healthy individuals should not be forgotten as they can cause infection in immunocompromised hosts. Opportunistic lung infections are a major cause of morbidity and mortality in patients who are immunocompromised by non-treated HIV infection, haematological malignancies, aplastic anaemia or chemotherapy treatment, as well as those recipients of solid organ or stem cell transplants. Opportunistic infections can also hinder the treatment with new biological therapies for inflammatory or immune-mediated conditions. Expert clinical assessment, early diagnosis, and aggressive treatment are required for a positive outcome. CT is more sensitive than thorax radiography in order to define the predominant pattern(s) of lung involvement. When combined with knowledge of the patient's immune status (loss of T-cell- or antibody-mediated immunity, or defects in neutrophil-mediated immunity), it often identifies the most likely pathogens.

Several recent review articles provide a concise overview and focus of the most common opportunistic lung infections in immunosuppressed patients [7-10].

IMAGING TECHNIQUES IN THE DIAGNOSIS OF PULMONARY ALTERATIONS IN IMMUNOCOMPROMISED PATIENTS

CT thorax scans are preferred over chest X-rays to define the radiological pattern of disease in immunocompromised hosts. Chest CT and the microbiological analysis of biologic

specimens are the first line diagnostic tools in immunosuppressed hosts. Sometimes, invasive methods are also mandatory. Image interpretation requires a complete assessment of the often-complex clinical context. Some key clinical and radiological aspects make it possible to orient the diagnosis correctly and to understand the current role of CT in the therapeutic strategy. Performing chest CTs in immunosuppressed patients pursues two objectives: early detection of lesions requiring urgent treatment not visible in the chest X-rays, and better characterization of findings to outline diagnostic and therapeutic possibilities. Reconstructions with slice thickness <1.5 mm of high-resolution computed tomography (HRCT) are required since many of the pulmonary complications present with interstitial patterns.

Therefore, chest HRCT plays a fundamental role. It must be urgently performed if there are clinical signs of severity in the first 24h, or in the absence of a response to antibiotics therapy in 72-96h, when invasive fungal infections (IFI) must be considered to initiate early antifungal treatment, a determinant prognostic factor. In patients clinically classified as being in high risk of IFI, antifungal drugs must be empirically administered. However, in lower risk subgroups, therapeutic delay can be acceptable in cases of very likely clinical manifestations or early positive specific infection biomarkers, which reduces the high costs and toxicity of these drugs. Serum galactomannan antigen test and beta-D- glucan detection are the fungal biomarkers usually used, and the chest HRCT is early performed early. However, galactomannan, a component of the *Aspergillus* cell membrane, is falling into disuse as a fungal biomarker due to its diminished sensitivity associated to antifungal prophylaxis strategy. In patients under antifungal prophylaxis, the galactomannan antigen test is more profitable when performed in BAL. The performance of a HRCT scan becomes even more important as an urgent diagnostic test that allows early antifungal therapy when IFI-compatible lesions are visualized. In addition, it can suggest other possible aetiologies and guide the acquisition of BAL through bronchoscopy, thus speeding up the diagnosis of germs not covered by the initial empirical therapy. In other respiratory manifestations HRCT is also necessary to identify and characterize non-infectious complications, relapse, and secondary neoplasms that can go unnoticed in radiographic tests or show similar patterns.

When studying the HRCT of an immunocompromised patient, a complete knowledge of the clinical context and the underlying condition, treatment, and complications is crucial. Treatment-induced non-infectious pulmonary complications (aggressive chemotherapy and, in certain cases, solid organ or hematopoietic precursors transplantation [SOT or HPT]) are also frequent and determine prognosis. Pulmonary tumour disease includes infiltration due to haematological or metastatic solid neoplasms, primary pulmonary neoplasm, and post-transplantation lymphoma. Chemotherapeutic drugs do not only depress immune function, but some of them are responsible for pulmonary toxicity. It can be suspected by the radiologic pattern and its temporal relation with the treatment. Other therapeutic agents can cause respiratory failure, often

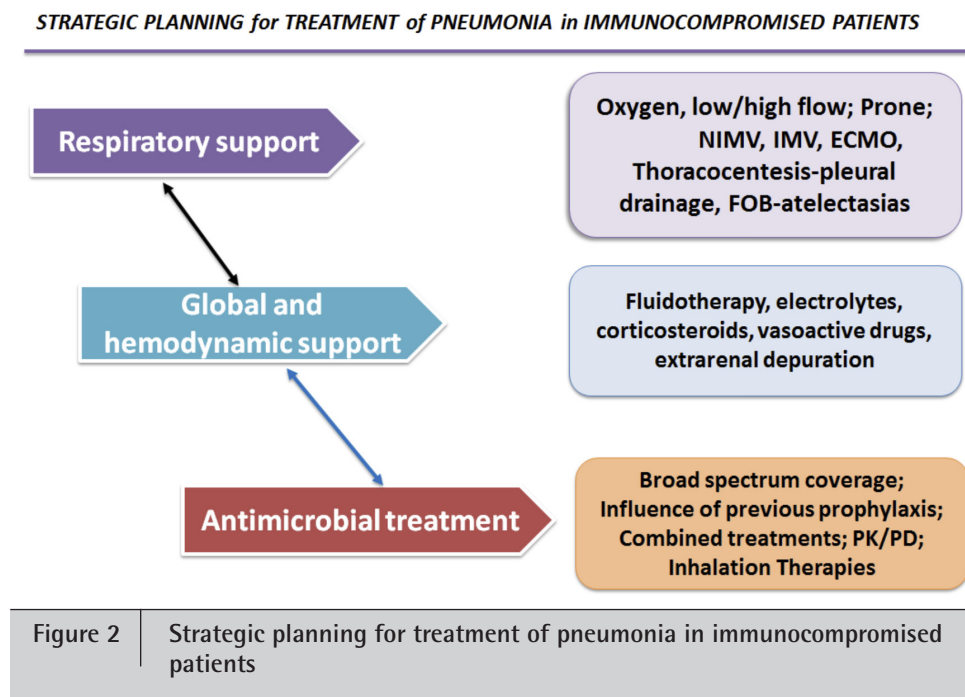
presenting with a radiologic expression similar to alveolar damage, oedema, or haemorrhage.

In a didactic and summarized way, the main key pulmonary radiological findings that can be found in the differential diagnosis of infectious and non-infectious causes of pulmonary infiltrates are the following [11]:

- Nodes and masses (infections, pulmonary infiltration due to hematologic neoplasms, secondary neoplasms)
- Cavitations (fungal, mycobacterial, and bacterial infections, lymphoma, histiocytosis, etc.)
- Areas of attenuation in ground glass, consolidations, or opacities (infections, disease non-infectious complications, non-infectious complications secondary to treatment)
- Budding tree images (these images represent bronchioles filled with mucous, liquid or pus. They usually correspond to an infectious bronchiolitis that can be due to many different microorganisms)
- Bronchial wall thickening (it can be due to unspecific respiratory infection, smoking, *bronchiolitis obliterans*, lymphoid infiltration, or other bronchial conditions)
- Peri-lymphatic interstitial thickening
- Obstructive bronchial lesions
- Air entrapment areas
- Pulmonary fibrosis (it can be secondary to distress, toxicity of chemotherapy, infection, or radiotherapy, or correspond to an unclassifiable interstitial pneumonia or to a graft-versus-host disease (GVHD)-related pleuro-parenchymatous fibroelastosis)
- Bronchial dilations (they can be seen in a transitory way in the sinus of infectious consolidations and in organizing pneumonia; irreversible dilations [bronchiectasis] in areas of air entrapment are a characteristic finding of *bronchiolitis obliterans* unlike those observed in areas of fibrosis due to traction)
- Interstitial pulmonary emphysema -air leak syndrome- (it is a typical complication of advanced post-HPT *bronchiolitis obliterans* and a marker of poor prognosis)
- Spontaneous pneumothorax
- Pulmonary cysts (small cysts in the upper fields can correspond to pneumatoceles due to infection by PJ; bilateral cysts, isolated or associated with nodes and lymphadenopathies should make us think of the possibility of a pulmonary disease due light chains deposit disease in patients with multiple myeloma or macroglobulinemia and obstructive functional pattern)

Regarding the follow-up of pulmonary lesions, periodical repetition of HCRT scan is recommended in patients with fever and documented infection until resolution of the findings:

In cases of good clinical response, it is possible to wait for several weeks and even for 1 or 2 months (the estimated resolution time of the findings). During the first week of treatment, worsening of IFI lesions is not usually related to a poorer



FOB: fiberoptic bronchoscopy; IMV: invasive mechanical ventilation; NIMV: Noninvasive mechanical ventilation; PK/PD: pharmacokinetics/pharmacodynamics.

evolution (paradoxical response). Moreover, in all infections, immune-reconstitution syndrome (IRS) must be conveniently recognized so as not to be taken as an absence of response. IRS is expressed as an inflammatory exacerbation secondary to neutrophil recovery or to the withdrawal of immunosuppressant therapy which, in turn, translates into clinical worsening and lesion growth.

Suspecting a lack of response (due to clinical and/or radiographic findings worsening), it is important to repeat the diagnostic tests to rule out initially unidentified mixed infections or other underlying or *de novo* processes that involve serious pulmonary complications (such as *bronchiolitis obliterans*, GVHD, idiopathic pneumonia syndrome, or interstitial lung disease) [12].

In immunosuppressed patients, thorax HRCT scanning aids in the differential diagnosis of infectious and non-infectious pulmonary complications by integrating image findings and clinical data. Furthermore, it needs to be promptly performed in cases of acute clinical symptoms and suspicion of IFI. It will allow the assessment of treatment response, detection of malignancy, and optimization of BAL or lung biopsy sampling [13].

MANAGEMENT OF THE SEVERELY IMMUNOCOMPROMISED CRITICALLY ILL PATIENT

A large group of severely ill immunocompromised patients become critically ill patients. The proportion of critical

patients with a deficient immune system has recently risen up to a third of all intensive care unit (ICU) admissions. Immunocompromised patients include patients receiving long-term (> 3 months) or high-dose (> 0.5 mg/kg/day) steroids or other immunosuppressant drugs, SOT recipients, patients with solid tumours requiring chemotherapy in the last 5 years, or with haematological malignancies independently of its diagnosis and therapeutic strategies, as well as patients with primary immune deficiencies (PID). In the last two decades, ICU admissions of patients with HIV/AIDS infection and severe infectious pulmonary lesions have largely decreased due to the extension of effective and early antiretroviral treatment. Other factors contributing to this trend include the increased aggressiveness and duration of cancer treatments, greater use of organ and hematopoietic cell transplantation, and introduction of steroid sparing agents for the treatment of autoimmune and autoinflammatory diseases. Thus, a large number of patients are now expected to live for many years with immune deficiencies that put them at risk for severe infections.

Severe respiratory infections are the leading reason for ICU admission in immunocompromised patients [14], who are at risk for hypoxemic acute respiratory failure (ARF) and sepsis. Life-supporting interventions must be implemented simultaneously to investigations directed to identify the cause of the pulmonary involvement (Figure 2). In these patients, lack of definite aetiological diagnosis is related to increased mortality rates. Moreover, specific pathogen identification is crucial for antimicrobial stewardship. However, the aetiological diagnosis can be extremely challenging, as the effects of the infection

Table 2	The DIRECT approach to acute respiratory failure in immunocompromised patients*
	D. Delay: time since respiratory symptoms onset; since antibiotic, antiviral or antifungal prophylaxis or treatment; since transplantation; since the diagnosis of malignancy or inflammatory disease
	I. Immune deficiency: knowledge on the nature of immune defects and ongoing antibiotic, antiviral or antifungal prophylaxis will help avoiding missing opportunistic infections
	R. Radiographic appearance: A chest radiograph will not only report the extent and patterns of pulmonary infiltrates (consolidation, air bronchogram, nodules, cavitations, tree in bud, interstitial pattern...), but also the presence and importance of pleural effusion, mediastinal mass, cardiomegaly, pericarditis, etc
	E. Experience: clinical experience of the ICU team and specialist consultants with this type of patients (treatment-related toxicity, viral reactivation, atypical form of diseases, cardiac involvement, graft versus host disease, obliterans bronchiolitis, etc.)
	C. Clinical picture: the presence of shock is likely to be associated with bacterial infection, but may be seen in hemophagocytic lymphohistiocytosis, toxoplasmosis, disseminated miliary tuberculosis, adenoviral infections, HHV6 reactivations or severe SARS-CoV-2 infection. Similarly, absence of fever or presence of tumoral syndrome (liver, spleen, and lymph nodes) will be considered as a possible orientation
	CT scan provides a better description of the radiographic patterns and guides the diagnostic strategy towards non-invasive or invasive diagnostic tests

* Adapted and modified from reference 8

combine with those of the underlying disease and treatments to create extraordinarily complex clinical pictures.

In addition, some patients have more than one concurrent infection, and others have non-infectious causes of ARF that mimic infection. Furthermore, fiberoptic bronchoscopy and bronchoalveolar lavage (FOB/BAL) are commonly used for diagnosis [15], but may cause further respiratory deterioration in patients with hypoxemia. The development of non-invasive diagnostic tests with high sensitivity and specificity (e.g., on blood, plasma, sputum, urine, or nasal swabs) has obviated the need for FOB/BAL in some patients. The utility of these non-invasive tests is being evaluated, and will hopefully provide clinicians with additional tools in the diagnosis of these complex patients.

ARF in an immunocompromised patient may be due to infection by more than one viral, bacterial, fungal, or parasitic agent. In addition, non-infectious factors may contribute to cause ARF and should be routinely sought. These factors, which are simply enumerated but not discussed in this review, include radiation, drug-related pulmonary toxicity, diffuse alveolar haemorrhage, pulmonary oedema, and lung lesions due to the underlying disease (e.g., leukemic infiltrates, engraftment syndrome, GVHD, lymphangitic carcinomatosis, and pulmonary vasculitis, among others). Existing guidelines for managing lung disease in critically ill immunocompromised patients emphasize the importance of obtaining valid diagnostic samples [16]. However, antimicrobial therapy is often started immediately, before samples are collected. As a result, causative pathogens are only identified in approximately half the patients with bacterial pneumonia. A detailed analysis of the clinical, laboratory, and imaging findings can provide a valuable diagnostic orientation in these cases. Nevertheless, the frequency of bacterial pneumonia is probably underestimated, as many cases are atypical and, therefore, escape recognition. Apart from infectious agents, non-infectious pulmonary abnormalities may be mistakenly diagnosed as clinically

documented infections. Pulmonary side-effects from cytotoxic drugs, radiotherapy or pulmonary involvement by the underlying malignancy should be included into differential diagnosis and eventually be clarified by invasive diagnostic procedures.

The basic rules described in certain reference publications [8] provide a helpful guidance for determining the cause of pulmonary infiltrates and selecting appropriate diagnostic strategies. In immunocompromised patients with ARF, the first step in the aetiological evaluation is an accurate clinical assessment. The authors of this review advocate the use of the mnemonic DIRECT (Table 2) based on the following data: days since respiratory symptoms onset, type of immunodeficiency, radiographic pattern, experience of the assessing clinician, clinical findings, and high-resolution computed tomography (HRCT) findings. Most of these variables are easily evaluated at the bedside, and their analysis usually restricts the number of possible aetiologies to two or three. Additional invasive and non-invasive investigations should be performed as needed. The diagnostic strategy should be tailored to the pretest probability of the disease being sought. Importantly, the indications of FOB/BAL are changing to avoid exposing patients to unnecessary potential adverse events. When FOB/BAL is considered as mandatory, it should be performed under optimal monitoring and high-flow oxygen therapy should be used to correct hypoxemia. The risk for intubation should be assessed carefully as it is associated with higher mortality. The introduction of non-invasive tests, notably those based on next-generation sequencing (NGS), transcriptomics, and proteomics, may reduce the need for FOB/BAL.

Pre-emptive treatment with mold-active systemic anti-fungal agents improves clinical outcomes, while other microorganisms are preferably treated only when microbiologically documented. High-dose trimethoprim/sulfamethoxazole is the first-choice agent for the treatment of PJP. CMV pneumonia is treated primarily with ganciclovir or foscarnet in most pa-

tients, assessing the possibility of specific intravenous immunoglobulins in α -HTP receptors [17]. In a considerable number of patients, clinical outcomes may be favourable despite ARF. Hence, intensive care should be unrestrictedly provided in patients whose prognosis is not desperate due to other reasons.

SUMMARY AND CONCLUSIONS

The management of immunocompromised patients with diffuse pulmonary infiltrates remains a common and recurrently difficult problem with a wide range of diagnostic possibilities. Non-invasive diagnostic procedures are of low utility, and the drugs available for empiric therapy have sometimes severe toxic effects. Although guidelines for management have been developed, they may be predicated on data from a single institution or depend on diagnostic procedures and laboratory facilities not necessarily available to physicians in all locations.

The increase in survival in patients with cancer and immune-mediated inflammatory diseases is paralleled by an increase in the frequency of critically ill immunosuppressed patients with severe infections. Severe bacterial pneumonias, followed by viral, fungal, and more rarely, parasitic infections are the leading cause for acute hypoxemic respiratory failure in these patients. When ICU admission is needed, mortality rates are high. Knowledge of the underlying immune deficiency and a complete clinico-radiological evaluation can guide the diagnostic strategy by targeting the most likely infectious agents and deciding on invasive versus non-invasive approaches. Increasingly sophisticated non-invasive diagnostic tools entailing lower morbidity than invasive techniques and are now available or under evaluation (e.g., real-time PCR, next-generation sequencing, and transcriptomics). These tools might allow an earlier diagnosis and thus improve survival in immunocompromised patients with severe pulmonary infections.

Controversy still exists regarding whether making a definitive diagnosis in these patients has an impact on the overall outcome. An individualized approach must take into consideration local resources, patient's age and prognosis, type of immunosuppression, family and patient's opinions regarding the use of invasive measures and heroic support, and previous patterns of infection in the institution. Invasive procedures should only be performed if a specific therapeutic management is expected to change based upon results.

CONFLICT OF INTERESTS

The authors declare no conflict of interest in relation to this article.

MS has given lectures and participated in advisory boards under the auspices of various companies (Angelini, Gilead, MSD, Pfizer, Shionogi) in the last year.

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