Acute Respiratory Failure in Patients with Hematologic Malignancies

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KEYWORDS

• High-resolution computed tomography • Immunocompromised • Noninvasive tests • Bronchoalveolar lavage

KEY POINTS

- Acute respiratory failure in patients with hematologic malignancies is frequent and associated with high mortality.
- Early recognition of acute respiratory failure in this population is necessary for improving outcomes.
- The diagnostic strategy for critically ill patients with hematologic malignancies differs from that in patients not admitted to the intensive care unit because of a different risk/benefit ratio of bronchoscopy and bronchoalveolar lavage (BAL) in deeply hypoxemic patients.
- Noninvasive diagnostic tests have a high diagnostic yield, whereas fiberoptic bronchoscopy with BAL adds limited diagnostic information.

INTRODUCTION

In immunosuppressed patients with cancer, the development of acute respiratory failure (ARF) is a common event. Overall, 15% of patients with hematologic malignancies present with a pulmonary event during the course of the disease and up to half the patients with prolonged neutropenia (ie, induction of acute leukemia or recipients of allogeneic hematopoietic stem cell transplants) have a pulmonary complication.[1] ARF is the leading cause of admission to the intensive care unit (ICU) for patients treated for hematologic malignancies, followed by shock and neurologic failure.[2–4] Etiologies of ARF are numerous and include pulmonary infections, complications of chemotherapy or of new anticancer drugs, or specific pulmonary involvement by the malignancy. In 20% of the cases, more than 1 cause is identified.

In critically ill hematology patients, survival after ICU management has greatly improved over the last 2 decades, thanks to a better selection of the patients eligible for intensive care and improvements in cancer treatments and in ICU management.[5–9] However, the need for intubation and invasive mechanical ventilation remains, and is associated with a 60% in-hospital mortality because it may reflect the subset of the sickest patients who also have several associated organ dysfunctions, including shock or renal, brain, or liver dysfunction.[2] Great hopes were prompted by the use of noninvasive mechanical ventilation (NIV) in this population,[5,10] but subsequent studies

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showed controversial results.[11–13] Recently, NIV was shown not to be superior to standard oxygen therapy in a multicenter prospective randomized study,[14] and NIV may be associated with an increased risk of intubation and death.[15]

Survival after ICU management is also linked to the early recognition of ARF and early transfer to the ICU.[3,16,17] Studies have shown that ARF from an undetermined cause was associated with higher mortality.[18,19] However, in this population, causes of ARF can be multifactorial and making an appropriate diagnosis may be very difficult. In an autopsy series of hematopoietic stem cell transplant recipients, only 28% of diagnoses were made before death.[20] Rapid and appropriate treatment of all possible causes of ARF is the key to improved outcome.

This article focuses on the clinical approach and diagnostic strategies for ARF in patients with nonpulmonary malignancy, specifically those with hematologic malignancies.

CLINICAL APPROACH

The first step is to recognize early signs of ARF in the hematology ward so early transfer to the ICU may be considered. Early recognition of ARF in this population is the key for improving outcomes.[16,17].

Some investigators described early criteria to diagnose early acute lung injury (EALI) before the onset of ARF and acute lung injury and in order to start a specific treatment as early as possible.[21] The EALI score is based on oxygen requirement (1 point for an oxygen requirement >2–6 L/min or 2 points for >6 L/min), respiratory rate (1 point for a respiratory rate $\geq$30 breaths/min), and immune suppression (1 point for baseline immune suppression). A score greater than or equal to 2 identified patients who progressed to acute lung injury requiring positive pressure noninvasive ventilation with 89% sensitivity and 75% specificity. This score could be easily used by clinicians for patients in hematology wards. More complex scores have been described but are difficult to use in practice.[22]

The second step is to make a rapid and accurate diagnosis of the underlying cause. However, the clinical lung examination is not specific and additional pulmonary signs should be carefully screened. Therefore, a systematic and rationalized approach is necessary to narrow the differential diagnosis.

The authors previously described a clinical approach described by the mnemonic, DIRECT[1] (**Box 1**), to assist clinicians in determining ARF cause and guide initial treatment and complementary investigations.[23] It is based on the analysis of the delay since the onset of malignancy or hematopoietic stem cell transplant, or the delay since initial effective antibiotic therapy or chemoprophylaxis; the pattern of immune deficiency; the radiographic appearance; the experience and knowledge of the literature; the clinical picture (ie, septic shock, skin rash, or associated extrapulmonary symptoms); and patterns observed on the computed tomography (CT) scan.

Box 1
DIRECT criteria for identifying the most likely causes of acute respiratory failure in patients with cancer

Delay since malignancy onset or HSCT

Immune deficiency pattern

Radiographic appearance

Experience and knowledge of the literature

Clinical picture

HRC**T** findings

Abbreviations: HRCT, high-resolution computed tomography; HSCT, hematopoietic stem cell transplantation.

Also, given advances in patient management and the many new anticancer and antiinflammatory drugs, managing patients in perfect synchrony with hematologists is an obvious requirement. Some of the adverse events of these recently developed agents are still to be described. For example, idelalisib is now described to be responsible for acute pneumonitis[24] and anti–tumor necrosis factor drugs have been associated with an increased risk of nocardiosis.[25]

DIAGNOSTIC STRATEGIES

After a careful clinical examination, patients can be classified based on the clinical pulmonary pattern (focal consolidation vs diffuse crackles, cardiac insufficiency vs noncardiac pulmonary involvement, pleural effusions, extrathoracic findings). A careful approach to additional diagnostic studies must be guided by the clinical findings and the DIRECT screening.

Transthoracic Echocardiography

This test should be obtained in order to rule out cardiogenic pulmonary edema.[26] Performing echocardiography also allows examination of the lungs and pleura, which is helpful when it is not feasible for the patient to undergo lung high-resolution computed tomography (HRCT).[26,27] Note that, because of vascular toxicity from chemotherapy and diastolic cardiac insufficiency, only a

complete assessment by a cardiologist or a trained intensivist can rule out cardiac pulmonary edema. Moreover, biomarkers well validated in the emergency department to distinguish between cardiac and noncardiac ARF have a high negative predictive value (NPV) but a low diagnostic yield. The authors discourage their use in this setting.

High-resolution Computed Tomography

In febrile neutropenic patients, the diagnostic value of conventional chest radiographs is very low. In contrast, in neutropenic patients with fever and a normal chest radiograph, lung HRCT identifies 60% to 100% of abnormalities.[28,29] In patients with allogeneic stem cell transplant, lung HRCT had a significantly higher sensitivity (89%) and NPV (80%) than chest radiograph (68% and 47%, respectively).[29,30] However, given a NPV of 80%, a lung HRCT considered as normal is not sufficient to rule out an infection in this population of patients.

Lung HRCT can also differentiate fungal from nonfungal lung infiltrates.[31,32] Specific radiographic patterns have been part of the European Organization for Research and Treatment of Cancer (EORTC) definitions of pulmonary aspergillosis since 2002.[33] Nodular or cavitary lesions are suggestive of invasive fungal infection (IFI), whereas consolidations are suggestive of bacterial infections and ground-glass opacities of viral pneumonia or *Pneumocystis jiroveci* pneumonia. However, CT patterns are not pathognomonic of any given cause and should be interpreted according to the clinical context and in comparison with previous HRCTs when available.

Microbiological Analysis

Noninvasive tests, which include culture-based and non–culture-based tests (**Table 1**), should be performed routinely. In a previous study, the authors showed that noninvasive tests could yield a diagnosis in 55% of cases.[34]

Culture-based tests

These tests include blood cultures, assisted or induced sputum analysis, and nasopharyngeal aspirates or swabs. These tests require 48 to 72 hours of culture, but have a low diagnostic yield because the patients often are heavily pretreated by antiinfective agents.

Direct sputum examination may allow detection of fungus in patients with airway invasive infections in nonneutropenic patients. Blood cultures remain the best investigation for the diagnosis of candidemia, but may take 48 to 96 hours to grow, which can lead a delayed start of an appropriate treatment and increased mortality.[35] Analysis of high-quality induced sputa by routine staining is able to identify *Pneumocystis* in most patients.

Table 1
Noninvasive diagnostic tests used in evaluating acute respiratory failure

Radiography	
Chest radiography	
Thin-section HRCT	
Echocardiography or pleural ultrasonography	
Microbiology	
Bacteria	Blood culture Sputum analysis culture Serology: *Chlamydia*, *Mycoplasma*, *Legionella* Urine tests: *Pneumococcus* and *Legionella* antigens
Virus	Serum: herpes consensus PCR test Cytomegalovirus PCR Nasopharyngeal aspiration with multiplex PCR test
Fungi	Sputum analysis (*Aspergillus*) Circulating *Aspergillus* antigen galactomannan Serum beta1,3-D-glucan Sputum (induced): tests for *P jiroveci* (Grocott-Gomori silver staining and immunofluorescence), PCR for *P jiroveci*
Biological markers	
BNP or proBNP C-reactive protein Procalcitonin	

Abbreviations: BNP, brain natriuretic peptide; PCR, polymerase chain reaction.

Virus detection

Viruses are easily detected with polymerase chain reaction (PCR) analysis of various noninvasive (nasopharyngeal aspirates or swabs) or invasive (bronchoalveolar lavage [BAL]) samples. Multiplex molecular assays can be performed on respiratory samples and are more sensitive in detecting viruses than immunofluorescence in immunocompromised patients.[36] They provide a specific diagnosis in half the patients in whom other investigations yielded no diagnoses. Specific serum PCR should systematically include cytomegalovirus PCR.

Fungal markers

Galactomannan Galactomannan (GM) is a component of the *Aspergillus* cell membrane. GM level is a robust marker and is part of the revised EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) criteria for aspergillosis.[34] It can be sampled in serum and pulmonary fluids.

BAL fluid analysis is more sensitive when guided by HRCT, particularly regarding GM detection, which is more sensitive and specific than GM detection in serum to diagnose invasive pulmonary aspergillosis.[37–39] GM level was also correlated to the outcome.[40] The authors consider BAL galactomannan not properly assessed in our ICU hematologic populations, and therefore we are reluctant to recommend its usage.

β-(1,3)-D-Glucan Serum β-(1,3)-D-glucan is an early marker for IFI, with a sensitivity of 78% depending on the clinical context and the type of fungal infection (68% aspergillosis, 85% candidemia, and 100% *Pneumocystis*) and a specificity of 70%. It has a very good NPV (80%–100%) and a good positive predictive value (PPV) for pneumocystis pneumonia when levels are higher than 500 pg/mL.[41] It was included in EORTC/MSG criteria for aspergillosis in 2008.[42] However, the benefit of this test is controversial because of low specificity and high cost.[43] Furthermore, it was recently tested in unselected immunocompromised hematology patients admitted to the ICU, but showed only moderate diagnostic performance, with a low specificity and sensitivity.[44] The NPV was high (94%), making it potentially useful in ruling out IFI and possibly in antifungal deescalation.

Fungal polymerase chain reaction

Aspergillus polymerase chain reaction Aspergillus PCR is a recent method used to diagnose invasive pulmonary aspergillosis. It is not yet included in EORTC/MSG criteria but may be a useful marker with an NPV ranging from 92% to 99% and a 98% specificity.[45,46] PPV is only 75%, and sensitivity 66%, making it impossible to be used alone. When combined with GM, sensitivity increases to 88%.

***Pneumocystis* polymerase chain reaction** *P jiroveci* pneumonia is based on the identification on a respiratory sample of cysts using various stains (toluidine blue O, Grocott-Gomori silver stain, or Giemsa stains) or indirect immunofluorescence.[35] However, because of the specific pathophysiology of *P jiroveci* pneumonia in hematology patients, the sensitivity of classic staining and immunofluorescence in patients without human immunodeficiency virus (HIV) is lower than in HIV-related *P jiroveci* pneumonia. *Pneumocystis* PCR in respiratory samples is a very sensitive method, but issues are raised about the threshold between colonization and infection.[35,47] However, a negative PCR rules out a pneumocystis pneumonia.

Procalcitonin

Procalcitonin (PCT) level may be useful to exclude bacterial sepsis when less than usual thresholds. However, in immunocompromised patients, association of PCT with mortality is controversial.[48] Moreover, interventional studies are necessary to confirm its utility in reducing antibiotic consumption and multidrug-resistant bacteria in patients with cancer.[49] However, based on current evidence, the value of PCT is mostly based on its high NPV. Otherwise, high PCT concentrations have been observed in nonbacterial and even noninfectious diseases.

Does Bronchoalveolar Lavage Need to be Performed?

Fiberoptic bronchoscopy with BAL (FO-BAL) is a cornerstone for investigating lung infiltrates in immunosuppressed patients, allowing direct visualization of the bronchial tree and sampling of pulmonary secretions and distal alveoli via lavage. However, its diagnostic yield varies across published studies.[10,34,50–52] Moreover, FO-BAL has been described as responsible for respiratory deterioration in immunosuppressed patients with ARF.[19,34,51] More recently, FO-BAL was proved to be safe when performed early after admission to the ICU in patients with spontaneous breathing and receiving NIV.[53] High-flow oxygen can also be applied in this setting. However, many studies show a low diagnostic yield of this procedure[34,50,51] and, in a randomized study, BAL added diagnostic information to noninvasive tests in only 18% of patients and was less helpful when performed later in the course of respiratory failure.[53] Given this evidence, the authors recommend avoiding

FO-BAL in specific settings, such as pulmonary infiltration from malignancies, *P jiroveci* pneumonia, and drug-related pulmonary toxicity, as well as for the diagnosis of new clinical scenarios or new pulmonary toxicities.[53]

Lung Biopsy

Lung biopsy can be considered when no diagnosis is obtained after all the previous explorations, or when a minimally invasive CT-guided biopsy can easily be performed by a trained radiologist in the setting of ensured hemostasis on stable patients. Only few data are available, because the procedure is not commonly performed in this population of immunosuppressed patients in poor condition. Three modalities exist: transbronchial, CT scan–guided, and surgical biopsies.

Transbronchial lung biopsies

Transbronchial lung biopsy (TBLB) along with BAL obtain a higher diagnostic yield than BAL alone in immunocompromised patients, and seems to be a safe procedure.[54,55] A recent study tested cryotransbronchial biopsies in very selected patients with good results, few complications, and a change in therapy in 80% of the cases.[56] However, studies to assess the risk/benefit ratio in these patients, who are frequently thrombocytopenic or with hemostasis disorders, are warranted.

Computed tomography scan–guided lung biopsies[57,58]

This technique has a high diagnostic yield, with a sensitivity of 94%, specificity of 100%, and NPV of 73%. It is less sensitive for infectious or inflammatory process than malignancy, with 60% specific diagnoses and 20% to 30% of infectious diagnoses,[58,59] and induced a change of therapy in 80% of the cases when a specific diagnosis was made. Major complications include pneumothorax (21%), requiring drainage in 2.0% of cases.[60]

Surgical biopsies[61]

Video-assisted thoracoscopic biopsies in trained hands and safe conditions have a high diagnostic yield, but have not yet been properly evaluated in hematology patients with ARF of undetermined cause. Open lung biopsy can lead to a diagnosis in 60% of cases.[61] In a series of hematopoietic stem cell transplant recipients, an infectious cause was found in one-third of the cases (mainly cytomegalovirus) and a specific cause in two-thirds of the cases.[62] It induced change of therapy in two-thirds of the cases.

In patients with acute respiratory distress syndrome receiving mechanical ventilation, open lung biopsies at bedside were reported to be safe (26% of immediate complications: pneumothorax, minimal bleeding) and resulted in major changes in management in 89% of the patients, with a decision to limit care in 12 of 17 patients who died.[63]

SUMMARY

Significant advances have been made in the management and diagnosis of ARF in immunocompromised patients. However, the cause of ARF remains undiagnosed in many individuals, leading to increased mortality. Improvements are still needed to better characterize the role of fungal PCR, new biomarkers, and the appropriate timing and circumstance for pulmonary biopsies. Particular attention should be given to new anticancer drugs and their potential pulmonary toxicities that are yet to be described and documented.

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