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REVIEW

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Diagnostic strategy in cancer patients with acute respiratory failure

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Abstract *Objective:* Nearly 15% of cancer patients experience acute respiratory failure (ARF) requiring admission to the intensive care unit, where their mortality is about 50%. This review focuses on ARF in cancer patients. The most recent literature is reviewed, and emphasis is placed on current controversies, most notably the risk/benefit ratio of fiberoptic bronchoscopy and BAL in patients with severe hypoxemia. *Background:* Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is the cornerstone of the causal diagnosis. However, the low diagnostic yield of about 50%, related to the widespread use of broad-spectrum antimicrobial therapy in cancer patients, has generated interest in high-resolution computed tomography (HRCT) and primary surgical lung biopsy. In patients with hypoxemia, bronchoscopy and BAL may trigger a need for invasive mechanical ventilation, thus considerably decreasing the chances of survival. *Discussion:* The place for recently developed, effective, noninvasive diagnostic tools (tests on sputum, blood, urine, and nasopharyngeal aspirates) needs to be determined. The prognosis is not markedly influenced by cancer characteristics; it is determined chiefly by the cause of ARF, need for mechanical ventilation, and presence of other organ failures. Although noninvasive ventilation reduces the need for endotracheal intubation and diminishes mortality rate, its prolonged use in patients with severe disease may preclude optimal diagnostic and therapeutic management. The appropriateness of switching to endotracheal mechanical ventilation in patients who fail noninvasive ventilation warrants evaluation. *Conclusion:* This review discusses risks and benefits from invasive and non invasive diagnostic and therapeutic strategies in critically ill cancer patients with acute respiratory failure. Avenues for research are also suggested in order to improve survival in these very high risk patients.

Keywords Pneumonia · Neutropenia · Bone marrow transplantation · Bronchoalveolar lavage · Mechanical ventilation

Introduction

Acute respiratory failure (ARF) is defined clinically as tachypnea, recruitment of accessory respiratory muscles or respiratory muscle exhaustion, arterial oxygen saturation lower than 90% on room air, pulmonary infiltrates, and a need for high-concentration face-mask oxygen or for invasive or noninvasive mechanical ventilation (MV). In patients receiving anticancer treatment ARF is both common and life threatening. A number of diagnostic and therapeutic challenges remain, and despite standardization efforts the optimal management is still debated [1, 2, 3]. According to the definitions used, ARF occurs in nearly 5% of patients with solid tumors and up to 50% of those with hematological malignancies [4, 5, 6, 7]. Recipients of allogenic bone marrow transplantation carry

the higher risk of respiratory events [8, 9]. In contrast, this risk is lower in recipients of autologous stem cell transplantation [6, 7]. These rates are rising in parallel with the lengthening survival times achieved by cancer patients [10] and with the use of increasingly intensive curative regimens [11, 12] associated with higher levels of immunosuppression and toxicity [13, 14, 15, 16]. In addition, ARF occurs in nearly 30% of patients with neutropenia or bone marrow transplantation (BMT) [3, 17, 18, 19, 20]. ARF in cancer patients exacts a huge toll: among cancer patients admitted to the ICU for ARF, more than half die before ICU discharge, chiefly as a result of limited benefits from MV, which still carries a nearly 75% mortality rate in this population [21, 22, 23]. Similarly, in a cohort of unselected medical-surgical ICU patients treated with MV cancer patients were one of the subgroups with the highest mortality rates [24]. Finally, although fiberoptic bronchoscopy with bronchoalveolar lavage (FB-BAL) remains the cornerstone of the diagnostic strategy for cancer patients with ARF [25], this investigation carries a number of risks [2, 3, 26, 27], and its diagnostic and therapeutic yield is only about 50% [2, 3, 18, 28, 29]. The extraordinary expansion of new noninvasive diagnostic tools (e.g., thin-section HRCT [30], serum, and urine antigen assays, immunofluorescence tests, and polymerase chain reaction, PCR) mandates a reappraisal of the role of semi-invasive investigations such as FB-BAL. Similarly, work is needed to define the current place for lung biopsy performed transbronchially, transcutaneously, with computed tomography guidance during video-assisted thoracoscopy or by thoracotomy.

This detailed review of recently published studies of ARF in adult cancer patients complements previous reviews [25, 31, 32] by adding new data, while narrowing the focus to patients managed in the ICU and possibly receiving MV. The review centers on the diagnostic strategy and the prognostic impact of establishing a specific diagnosis using bronchoscopy and BAL or noninvasive diagnostic tools. Thus the various causes of ARF in cancer patients are not described in detail. After discussing the diagnostic strategy in adult cancer patients with ARF requiring ICU admission, we will review the available diagnostic tools and their yields then the factors that help to predict the outcome. The data reported in this review are not relevant to ARF in patients with other causes of immunosuppression such as immunosuppressive therapy for systemic vasculitis or connective tissue disease, solid organ transplantation, or HIV infection. Importantly, factors specific to cancer patients influence the management of ARF: they include a distinctive pattern of lung diseases, a specific profile of immunosuppression, and low yields of FB-BAL. Furthermore, because this review is confined to ICU patients, it does not discuss lung toxicity from radiation therapy or delayed lung complications of BMT. We will conclude the review with suggestions for future research.

In a cancer patient with ARF, look for evidence supporting the most likely diagnoses in order to initiate appropriate empirical therapy and to guide causal investigations

A detailed and systematic appraisal of the clinical history is the first step toward identifying the cause of ARF in a cancer patient. According to our clinical experience, the degree of immunosuppression and the spectrum of possible causes depend to a considerable extent on the profile of comorbidities (e.g., cardiovascular risk factors, smoking history, chronic lung disease, chronic liver disease, and corticosteroid therapy), type of malignancy, anticancer treatments used, neutrophil count, and prophylactic treatments actually taken by the patient. A thorough physical examination provides key information on the respiratory manifestations (bronchial, interstitial, alveolar, vascular, or pleural symptoms), the severity of the ARF, and the time elapsed since respiratory symptom onset [25, 33]. Furthermore, extrathoracic manifestations such as skin lesions [34], lymph node enlargement, joint symptoms, or head-and-neck abnormalities may rapidly provide the causal diagnosis [35]. This first step in the diagnostic strategy often reduces the number of possible causes to two or three [25]. It should be borne in mind that cancer patients can experience venous thromboembolism (regardless of their platelet count) or acquire infectious diseases while traveling. Table 1 presents the main causes of ARF in hematology and oncology patients. Once congestive heart failure is ruled out, causes are often classified into infectious and noninfectious conditions. This approach is of limited usefulness in cancer patients because it seems to assume that all the infectious and noninfectious causes can occur in every cancer patient. This is not the case. For instance, an autopsy study by Agusti et al. [36] clearly established that alveolar hemorrhage (AH) is specific to BMT recipients, and a subsequent study confirmed this finding [31]. Similarly, Patterson et al. [37] have shown that invasive pulmonary aspergillosis should be considered routinely when immunodeficiency is present but is significantly more common with intensive treatment regimens and prolonged neutropenia, i.e., in patients undergoing induction therapy for acute leukemia and in BMT recipients. In addition, in 2002 the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer proposed classifying fungal infections (confirmed, probable, possible) in cancer patients and BMT recipients based on host and microbiological factors combined with clinical findings [38].

Six factors have been suggested for selecting causal hypotheses in cancer patients with ARF and can be conveniently listed using the mnemonic DIRECT: *d*elay since malignancy onset or BMT, pattern of *i*mmune deficiency, *r*adiographic appearance, clinical *e*xperience and knowledge of the literature, *c*linical picture, and findings by HRC*T*. The DIRECT approach provides valuable

Table 1 Causes of acute respiratory failure in cancer patients included in published studies

Infections
Bacterial infections
Common pyogenic bacteria
Streptococcus pneumoniae
Staphylococcus aureus
Haemophilus influenzae
Pseudomonas aeruginosa and Enterobacteriaceae
Intracellular bacteria
Legionella pneumophilia
Chlamydia and Mycoplasma pneumoniae
Other bacteria
Actinomyces israeli
Nocardia spp.
Pneumocystis jirovecii
Invasive fungal Infections
Molds
Aspergillosis
Emerging mycotic infections: trichosporosis, fusariosis, zygomycetes
Yeasts
Lung involvement during candidemia
Endemic fungal infections
Histoplasmosis, coccidioidomycosise, blastomycosis
Viral infections (primary infections or reactivations)
Seasonal respiratory viruses
Influenzae, parainfluenzae, rhinovirus
Respiratory syncytial virus
Herpes virus
Cytomegalovirus, herpes virus, zoster virus and HHV6
Other viruses: adenovirus
Mycobacterial infections
Tuberculosis and atypical mycobacteria
Noninfectious causes
Cardiogenic pulmonary edema
Capillary leak syndrome
Lung infiltration
Drug-induced toxicity
Alveolar hemorrhage
Transfusion-related acute lung injury
Radiation-induced lung damage
Alveolar proteinosis
Diffuse alveolar damage
Bronchiolitis
Cryptogenic organized pneumonia
Second malignancy

The DIRECT approach: a guide to select initial antimicrobial treatments and appropriate investigations

Delay since malignancy onset or BMT
Patterns of **I**mmune deficiency
Radiographic appearance
Clinical **E**xperience and knowledge of the literature
Clinical picture
Findings by the high resolution computed **T**omodensitometry (HRCT)

guidance for selecting empirical antimicrobial drugs, other treatments, and diagnostic investigations. Under no circumstances can DIRECT be used to establish the causal diagnosis: invasive or noninvasive investigations must be performed to obtain a definitive diagnosis, as this improves patient survival [4, 22, 39, 40]. Patients with no definite diagnosis despite investigation have higher mortality. However, subjecting cancer patients to invasive MV in order to perform bronchoscopy or surgical lung biopsy can also lead to increased mortality. Therefore whenever the DIRECT approach is implemented, the comparison between invasive investigations to obtain a definitive diagnosis at any cost vs. empirical or noninvasive approach when the complications associated with the investigation are high awaits future studies.

The first factor is the delay from the diagnosis of the malignancy to the onset of ARF. As shown in Fig. 1, whereas AH, fluid overload, or infection (opportunistic or nonopportunistic) can occur at any time, malignancy-related lung infiltration (carcinomatosis, leukostasis, or lung infiltration by leukemia or lymphoma cells) develops either before anticancer treatment is started or during relapses [25]. Similarly, pulmonary complications due to treatment toxicity occur during or after the consolidation phase [41, 42, 43, 44]. Overall, cardiac pulmonary edema occurs in about 10% of patients with acute respiratory failure [4, 45], and pulmonary infiltration by the malignancy occurs mainly in patients with acute leukemia and lymphoma [46, 47]. Diffuse alveolar hemorrhage occurs more frequently in recipients of stem cell or bone marrow transplantation [31, 36]. In addition, infectious involvement of the lungs is the leading cause of ARF in cancer patients [4], with a constant risk for bacterial pneumonia all over the course of the disease, and risk of opportunistic infections in patients with high-dose steroids, specific chemotherapy regimen, or stem cell transplantation [26, 48, 49].

The length of time since allogeneic BMT (or stem cell transplantation) also provides causal orientation. Fig. 2 shows the main infectious and noninfectious causes of ARF in allogeneic BMT recipients according to the time since transplantation, whether neutropenia is present, and whether graft-versus-host reaction is present. Before neutropenia recovery bacterial infection is the leading cause of pulmonary infection. After neutropenia recovery during graft vs. host disease and corresponding immunosuppressive treatments, cytomegalovirus (CMV) pneumonia, and invasive aspergillosis are likely to occur. However, using current preventive strategies and routine detection of CMV antigenemia or real-time PCR, genuine cases of CMV pneumonia are rare [50, 51, 52]. The second factor is the pattern of immune deficiency typical of the underlying malignancy and of the treatments used. For instance, acute hypoxemic ARF in a patient on fludarabine for a chronic lymphoproliferative disease should be considered to denote *Pneumocystis jirovecii* pneumonia until proven otherwise [53]. Similarly, antipneumococcal

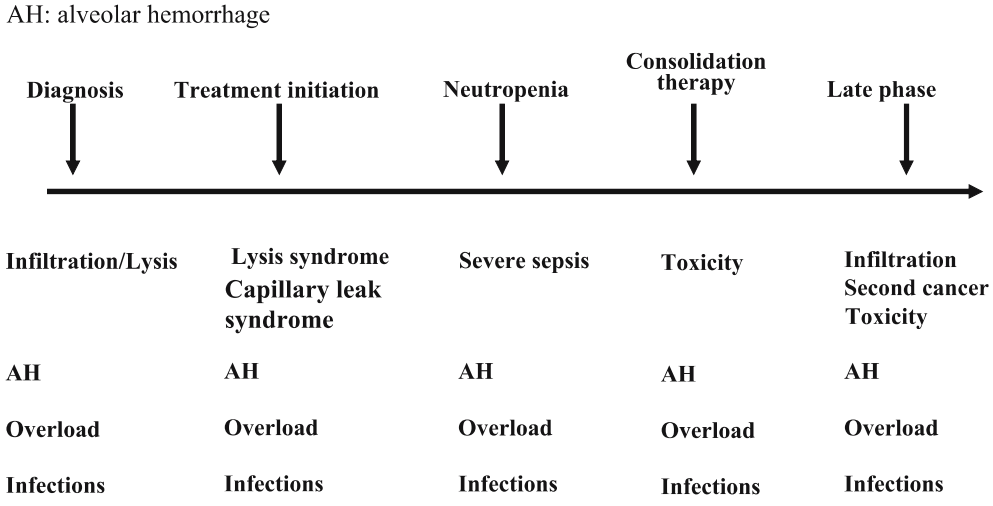

Fig. 1 Causes of acute respiratory failure according to time since the diagnosis of malignancy. *AH* Alveolar hemorrhage

antibiotics must be given immediately to a patient with myeloma or splenectomy presenting with severe acute focal pneumonia and shock. Table 2 lists the infections associated with each pattern of immune deficiency.

The third factor is the set of findings on chest radiography. Similar to physical findings, radiographic abnormalities lack causal specificity [54, 55]. Even good-quality radiograms including a lateral view are inadequately sensitive for determining the cause of ARF [55, 56] This low sensitivity has led to the suggestion that chest radiography is unhelpful in patients with febrile neutropenia [57]; HRCT has shown evidence of infection in over 50% of neutropenic patients with normal chest radiographic findings [54, 58].

The fourth factor is clinical experience combined with knowledge of clinical, autopsy, and experimental studies in the medical literature. As mentioned above, the likelihood of AH or invasive aspergillosis varies according to the underlying condition [36, 37]. Pulmonary *Legionella* infection is common in early-stage hairy cell leukemia [59], lung infiltration with blast cells and pulmonary lysis syndrome in monoblastic leukemia [47], and respiratory symptom exacerbation in patients recovering from neutropenia [60, 61].

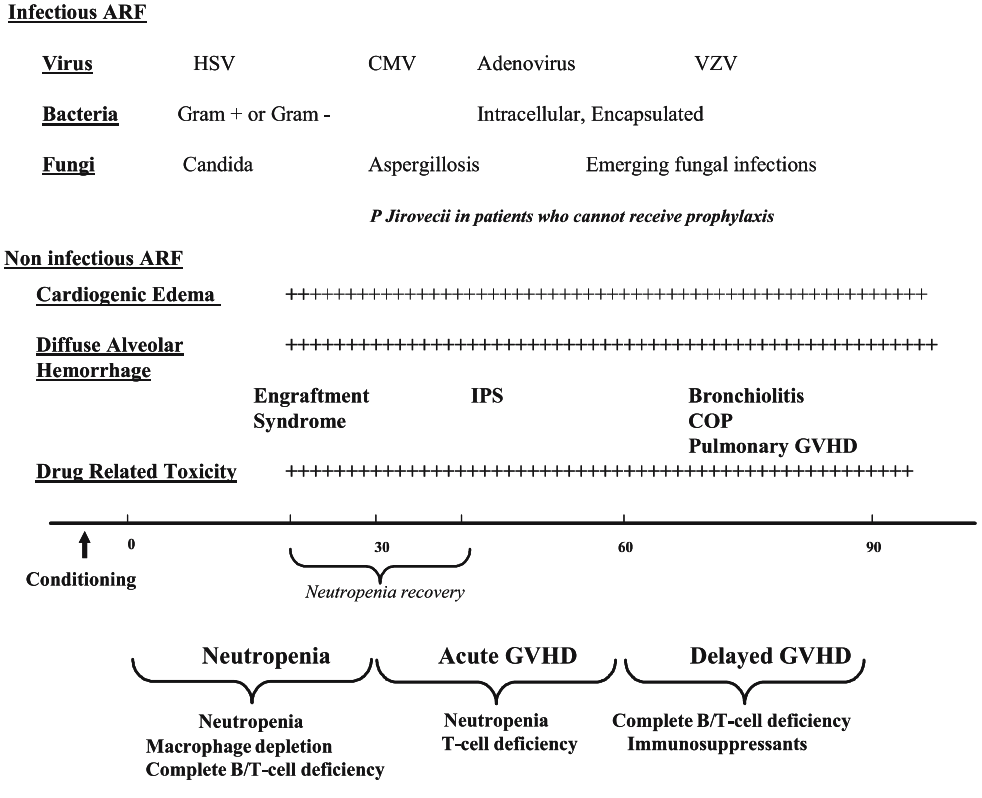

Fig. 2 Causes of acute respiratory failure according to the time since allogenic bone marrow transplantation. *HSV* Herpes simplex virus; *VZV* varicella zoster virus; *GVHD*: graft versus host disease; *IPS* idiopathic pulmonary syndrome; *COP* cryptogenic organized pneumonia

Table 2 Nature of immune deficiencies and infections according to the diagnosis

Diagnosis	Deficiencies	Main infections
Acute myeloid leukemia	Phagocytosis Cell-mediated immunity	Bacteria Yeasts
Acute lymphocytic leukemia	Phagocytosis Cell-mediated immunity	Bacteria Yeasts, herpes viruses, *P. jirovecii*
Lymphomas	Cell-mediated immunity	*P. jirovecii* , yeasts, bacteria, encapsulated bacteria
Myelomas	Immunoglobulins	Encapsulated bacteria
Chronic lymphocytic leukemia	Phagocytosis Cell-mediated immunity	Encapsulated bacteria Intracellular organisms
Chronic myeloid leukemia	Phagocytosis	Bacteria
Solid cancer	Compression, obstruction, ulceration	Bacteria
Bone marrow transplantation	Phagocytosis Cell-mediated immunity Immunoglobulins	Bacteria Encapsulated bacteria Yeasts, *P. jirovecii*
Associated condition	Asplenia in general associated with defect in immunoglobulins, altered phagocytosis and cell-mediated immunity	Encapsulated bacteria

The fifth factor is careful evaluation of the clinical picture. However, a study carried out at our institution found that abnormalities upon auscultation were often limited and failed to provide the causal diagnosis in patients with ARF [4]. Extrathoracic abnormalities are uncommon but provide valuable guidance and should be looked for carefully. They may include skin lesions, joint abnormalities, gastrointestinal symptoms, neurological symptoms, and enlarged peripheral lymph nodes. Interestingly, the time from respiratory symptom onset to ICU admission can provide useful orientation [25]. However, the clinical differences between cancer patients and HIV-infected patients should be borne in mind. For instance, *P. jirovecii* pneumonia runs a subacute course in HIV-infected patients, who usually have a 2- or 3-week history of symptoms at diagnosis, whereas the clinical presentation in cancer patients may mimic a bacterial infection, with an acute course and the development of life-threatening manifestations within a few hours [62]. Epidemiological data, clinical findings (time with respiratory symptoms and whether fever is present), and chest radiography findings can be used to differentiate five clinical patterns of reference (Table 3). Each pattern is associated with a number of possible diagnoses, empirical treatments, and required investigations.

The sixth factor consists in thin-section HRCT findings (with sections at 1-mm intervals and, if needed, sections during expiration). HRCT is more sensitive than chest radiography [57] even in nonneutropenic patients [55]. Heussel et al. [55] evaluated the performance of HRCT in cancer patients with lung infiltrates: overall sensitivity and negative predictive value were about 90%, but specificity and positive predictive value were low. In a few cases HRCT shows lesions specific of a cause (e.g., halo image during the neutropenic phase and crescent-shaped lucency during neutropenia recovery in patients with pulmonary aspergillosis, and images suggesting alveolar proteinosis or carcinomatosis). Nevertheless, the sensitivity of these images is low [63]. When reading HRCT scans, attention should be given to detecting individual abnormalities such as focal or diffuse ground-glass images; nodules in a peribronchial and perivascular, centrilobular, or subpleural distribution; alveolar consolidation; visible interlobular septae; pleural effusions; and cavities. The pattern of individual abnormalities may then suggest a specific cause, although specificity is low [55, 56]. Thus HRCT provides diagnostic orientation rather than a definitive diagnosis in cancer patients with ARF. HRCT helps to select the nature and site of endoscopic sample collection (distal protected specimens, BAL, or transbronchial biopsies) [54]. However, experience acquired at our ICU indicates that HRCT fails to decrease the need for FB-BAL or for noninvasive diagnostic investigations. Outside the ICU, however, HRCT is strongly advocated by several European groups as a safe tool for establishing the causal diagnosis of ARF in cancer patients [40, 64].

Diagnostic strategy for acute respiratory failure in cancer patients

In cancer patients with ARF the goal of the above diagnostic strategy is to provide guidance for the immediate empirical treatment, most notably antimicrobial therapy and life-supporting interventions. However, investigations must be obtained very rapidly to confirm or refute the initial diagnoses. There is convincing evidence that early identification of the cause of ARF (with or without FB-BAL) improves the prognosis [4, 18, 29, 65]. The diagnostic strategy in cancer patients with ARF is fairly well standardized. Ruling out acute cardiogenic pulmonary edema is the first step and might avoid useless procedures in about 10% of patients [4, 45].

Table 3 Causal diagnosis of acute respiratory failure using clinical data available at the bedside (pace of progression, temperature and radiographic findings) (*FB-BAL* fiberoptic bronchoscopy with bronchoalveolar lavage, *CT* computed tomography, *fast* < 2 days, *moderate to fast* 2–7 days, *slow* > 7 days) (from [25])

Features	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5
Pace of progression	Slow	Fast	Fast	Moderate to fast	Moderate to fast
Fever	<38°C	Yes	Yes	Yes	Yes
Radiographic findings	Diffuse infiltrate	Diffuse infiltration	Focal or diffuse alveolar	Nodules ± cavitation	Focal alveolar
Suspected diagnoses	Congestive heart failure, drug-related pulmonary toxicity, malignant infiltration	Opportunistic (*P. jirovecii*, CMV, tubercle bacillus), drug-related pulmonary toxicity, malignant infiltration	Bacteria, sepsis, acute respiratory distress syndrome	Yeasts, legionellosis, tubercle bacillus, venous thromboembolism	Mycobacteria, nocardia, Rhodococcus, BOOP/tumor
First-line investigations	Echocardiography, FB-BAL, lung biopsy	FB-BAL	Blood culture, sputum culture, distal protected specimen, treat immediately	CT, CT-guided biopsy, bronchoscopy + transbronchial biopsy, open-lung biopsy	Repeat bronchoscopy, biopsy

Cardiogenic pulmonary edema should be considered routinely, regardless of the presentation, as it is associated with a specific diagnostic strategy and with a far better prognosis than other causes [4]. A three-step approach can be used to rule out acute cardiogenic pulmonary edema (a) evaluation of patient-related factors (e.g., history of congestive heart failure, cardiovascular risk factors, and exposure to cardiotoxic chemotherapy agents such as anthracyclines); (b) examination for physical and radiographic findings suggesting congestive heart failure (gallop rhythm, lower limb edema, heart shadow enlargement, and electrocardiographic abnormalities); and (c) routine echocardiography in cancer patients with ARF. Myocardial scanning with radiolabeled technetium is more sensitive than echocardiography for detecting congestive heart failure, most notably diastolic heart failure [66], but is difficult to perform in ICU patients with ARF. The B-type natriuretic peptide level in serum may be useful for differentiating cardiogenic ARF from other causes of ARF [67, 68] but has not been validated in cancer patients.

The second step consists in looking for evidence of a lung infection. Noninfectious causes of ARF in cancer patients are usually diagnosed after exclusion of infections. However, infectious and noninfectious causes may occur in combination [48, 59, 69, 70, 71]. On the other hand, a number of conditions such as drug-induced pneumonia or "idiopathic" pneumonia (in allogeneic BMT recipients) induce ARF in the absence of pathogens (*P. jirovecii*, CMV, tubercle bacillus, and other intracellular organisms) [41, 72].

In cancer patients with pulmonary disorders that do not require ICU admission for severe respiratory or systemic symptoms FB-BAL remains the cornerstone of the diagnosis of ARF [25]. After elimination of acute cardiogenic pulmonary edema BAL establishes the diagnosis in half the patients. In ICU patients, however, the benefits of obtaining a diagnosis should be weighed against the risks associated with FB-BAL [25, 27, 73, 74]. The main risk is respiratory status deterioration requiring MV, a dreaded event that carries a nearly 75% mortality rate (Table 4). The adverse event rate associated with BAL is less than 1% overall but is higher in ICU patients [27, 75], although possibly decreased by the use of noninvasive positive pressure ventilation or continuous positive airway pressure [76, 77]. In severely hypoxemic cancer patients 5% to 15% of FBs are associated with adverse events, which consist chiefly in hemoptysis and respiratory status deterioration [26], most notably in BMT recipients [1, 2, 3]. Several studies have reported the incidence of complications after FB in cancer patients to be between 11% and 40% [20, 78, 79, 80]. More specifically, MV initiation after FB has been reported not only in bone marrow recipients [1, 2, 3] but also in many critically ill cancer patients [81, 82]. The low diagnostic and therapeutic yield of FB-BAL in cancer patients (Table 5) and BMT recipients (Table 6) has generated interest in other tools for identifying the cause of ARF. Von

Table 4 Mortality associated with mechanical ventilation in hematology and oncology patients (excluding recipients of bone marrow or stem cell transplantation) in studies carried out between 1999 and 2005 (*MV* mechanical ventilation, *NIV* noninvasive mechanical ventilation)

Reference	*n*	Hospital mortality
Kress et al. [23]	MV 153	67%
Azoulay et al. [104]	MV 46, NIV 9	78%
Hilbert et al. [29]	NIV 64	25%
Staudinger et al. [110]	MV 180	77%
Hilbert et al. [22]	MV 14, NIV 8	MV 93%, NIV 50%
Azoulay et al. [21]	MV 189, NIV 48	70.8%
Kassawneh et al. [116]	MV 78	75%
Darmon et al. [114]	MV 49, NIV 42	71.4%
Massion et al. [120]	MV 48	75%
Kroschinsky et al. [138]	MV 54	74%
Vallot et al. [139]	MV 168	83%
Meert et al. [113]	NIV 40	57.5%
Benoit et al. [105]	MV 87	67.8%
Larché et al. [108]	MV 68, NIV 12	79.4
Azoulay et al. [4]	MV 114, NIV 79	75%
Depuydt et al. [140]	MV 166, NIV 27	71%
Soares et al. [141]	MV 444, NIV 19	64%
Total	MV 1804, NIV 348	MV 75%, NIV 50%

Table 5 Diagnostic yield of bronchoalveolar lavage in hematology patients (*HM* hematological malignancy)

Reference	*n*	Diagnosis	Diagnostic impact	Therapeutic impact
Stover et al. [96]	97	HM	66	–
Martin et al. [142]	100	HM	30	–
Xaubet et al. [143]	96	HM	49	31
Campbell et al. [144]	22	HM	55	–
Pisani et al. [145]	150	HM	39	–
Maschmeyer et al. [146]	46	Neutropenia	30	–
Cordonnier et al. [100]	56	Neutropenia	53	24
Cazzadori et al. [147]	142	HM	36	–
Von Eiff et al. [40]	90	HM	66	65
White et al. [3]	68	HM	31	24
Ewig et al. [28]	49	HM	31	16
Gruson et al. [18]	41	Neutropenia	63	28
Hilbert et al. [22]	24/46	HM	62	71
Murray et al. [2]	27	HM	33	28
Azoulay et al. [4]	203	HM	49.5	45.1
Pagano et al. [148]	127	HM	53	14
Jain et al. [82]	104	HM	56	–
Hohenadel et al. [81]	95	HM	30	–
Total	1537		46.2	34.6

Table 6 Diagnostic yield of bronchoalveolar lavage in bone marrow transplant recipients (*auto* autologous bone marrow transplantation, *allo* allogeneic bone marrow transplantation)

Author	*n*	Type of patients	Diagnostic impact	Therapeutic impact	Complications
Springmeyer et al. [20]	22	Auto-allo	58	–	13
Cordonnier et al. [17]	52	Allo	50	–	0
Cordonnier et al. [9]	69	Allo	66	–	–
Milburn et al. [19]	40	Allo	80	76	0
Springmeyer [78]	15	Auto-allo	89	–	40
Heurlin et al. [149]	18	Auto-allo	61	–	–
Weiss et al. [80]	47	Auto-allo	47	–	12
Campbell et al. [79]	27	–	74	63	11
AbuFarsakh et al. [150]	77	Auto-allo	42	–	–
White et al. [93]	68	Auto-allo	31	24	15 (7% MV)
Dunagan et al. [1] [a]	71	Auto-allo	38	42	27 (4% MV)
Glazer et al. [151]	79	Auto-allo	67	62	–
Gruson et al. [39]	38	Auto-allo	42	–	–
Gruson et al. [18]	52	Auto-allo	38	28	17
Huaringa et al. [127]	89	Auto-allo	42	–	–
Total	764	Auto-allo	55	49	0 to 40%

[a] 32% mechanical ventilation

Eiff and coworkers [40] advocated first-line use of CT, reserving FB-BAL for patients who fail empirical treatment based on CT results and those who have diffuse interstitial disease [83]. FB-BAL and lung biopsy are at the same level in this diagnostic strategy. Other groups have used lung biopsy in patients failing empirical treatment based on physical and radiographic findings without using FB-BAL [16, 84]. Interestingly, thin-section CT used before FB-BAL has been shown to increase diagnostic yield when samples are taken from sites with ground-glass images or consolidation [30].

In our experience with ICU patients, lung biopsy has lost much of its usefulness [4], probably because an increasing number of diagnoses is provided by noninvasive investigations such as serum antigen assays, immunofluorescence, and PCR. The same experience has been reported recently by others [85]. Good yields have been reported with transbronchial biopsy in patients with diffuse lung disease due to infections (*P. jirovecii* or CMV) or other conditions (malignant lung infiltration or cryptogenic organizing pneumonia) [82, 86]. In our experience, their contribution is modest. Fine-needle lung biopsy has not been evaluated in patients with ARF or MV but has been found beneficial in patients with hematological malignancies and focal lung lesions [87]. Finally, despite recent advances in lung biopsy during video-assisted thoracoscopy [88], the feasibility of this method in severely hypoxemic ICU patients remains in doubt.

Our group is evaluating the diagnostic impact of the noninvasive investigations (without FB-BAL) listed in Table 7. These investigations are used in combination with thoracentesis and in-depth evaluation of extrathoracic lesions if present. They have been evaluated individually in earlier studies [45, 51, 52, 89]. However, the performance of these tests used in combination has not been determined. In addition, these noninvasive tools are as sensitive as FB-BAL but do not carry a risk of respiratory status deterioration. FB-BAL remains the investigation of reference before lung biopsy in specific infections (e.g., *P. jirovecii* pneumonia) and in noninfectious disorders. However, the widespread use of prophylactic treatments [90] in high-risk patients is reducing the rate of these conditions. Our study of noninvasive tools will comprise an early reappraisal of the clinical situation after 72 h to determine whether FB-BAL is in order, as Rano et al. [45] found a threefold mortality increase in patients who had no causal diagnosis after 5 days with ARF.

Finally, a careful strategy is required also for the diagnosis of noninfectious ARF, which may account for one-half the cases of acute respiratory failure. Many of these patients require a substantial change in their anticancer treatment, such as high-dose corticosteroid therapy, additional chemotherapy to control malignant lung infiltration, and discontinuation of a presumably toxic chemotherapeutic agent despite the major risk of decreasing the chances for recovery. Two situations deserve special attention: AH and respiratory status deterioration during recovery from neutropenia. In both cases a careful causal evaluation is in order The diagnostic criteria of AH comprises the evidence of widespread alveolar injury with hypoxemia and BAL showing progressively bloodier return from three separate subsegmental bronchi or the presence of 20% or more hemosiderin-laden macrophages or the presence of blood in at least 30% of the alveolar surfaces of lung tissue [31]. In patients with AH, only when extensive tests for infection confirm negative can idiopathic diffuse AH related to BMT [31, 91] or chemotherapy-induced AH [42, 72, 92, 93] be considered. Similarly, in patients recovering from bone marrow failure, lung infections (most notably aspergillosis) and noninfectious lung diseases are particularly severe, probably because inflammatory processes are exacerbated by neutropenia recovery [60] and, in some patients, by granulocyte colony-stimulating factor therapy used to hasten bone marrow recovery [41, 94, 95]. Neutropenia recovery is not associated with respiratory symptoms in patients with no previous history of lung disease, a fact that emphasizes the need for extensive causal investigations when lung disease develops during neutropenia recovery.

In our experience with ICU patients, most of the noninfectious lung disorders fall into one of the following three categories. (a) Acute or subacute nonspecific lung infiltration with severe hypoxemia at the inaugural phase of malignant lymphoma [96] or acute leukemia [47, 97]. CT of the chest, when feasible, can support a suspected

Table 7 Noninvasive diagnostic investigations for cancer patients with acute respiratory failure

Radiography
Chest radiography
Thin-section high-resolution computed tomography
Echocardiography or pleural ultrasonography
Sputum
Bacteria
Tubercle bacillus
Fungi (aspergillus)
Tests for *Pneumocystis jirovecii* (MGG staining and immunofluorescence)
PCR for *Pneumocystis jirovecii*
Blood cultures
Serum tests
Serology: Chlamydia, Mycoplasma, Legionella
Herpes consensus PCR test
Circulating aspergillus antigen
Circulating cytomegalovirus antigen
Nasopharyngeal aspiration
Tests for viruses (PCR and immunofluorescence)
Urine tests
Cytology, bacteriology
Legionella antigen
Biological markers
Brain natriuretic peptide (BNP) or ProBNP
C reactive protein
Fibrin
Procalcitonin

diagnosis of specific infiltration corresponding to malignant cell adhesion to the pulmonary vasculature with endothelial injury and subsequent alveolar damage [98]. In this situation we do not perform BAL; instead, we rapidly initiate chemotherapy and broad-spectrum antibiotics active against common community-acquired organisms and intracellular organisms. Valuable information can be obtained from noninvasive investigations (urinary *Legionella antigens*, sputum tests, and others). When empirical antibiotic therapy combined with chemotherapy is not promptly effective, FB-BAL is indispensable. (b) Progressive, subacute, insidious lung infiltration in a patient with the evidence of malignancy recurrence. Radiographic findings are similar to those in the previous situation. CT shows peribronchial and perivascular lung nodules consistent with specific lesions (Hodgkin disease, non-Hodgkin malignant lymphoma, or solid tumor) [98], abnormalities strongly suggestive of carcinomatosis [99], changes suggesting alveolar proteinosis related to recurrence of a myeloproliferative disease [100], or findings that are nonspecific but similar to those present at the diagnosis of the malignancy. Lung involvement with the malignancy is highly likely and can be confirmed by the bone marrow smear or a biopsy of a lymph node or other accessible lesions (e.g., skin nodule, hepatic nodule, or head and neck lesion). In this situation transbronchial biopsy is extremely useful given its good sensitivity [82, 86]. (c) Respiratory failure, usually acute, in a patient receiving consolidation therapy for lymphoma or leukemia (usually lymphoblastic) in remission. A fever and severe hypoxemia are present; radiographs show diffuse interstitial infiltrates characterized chiefly by a diffuse ground-glass appearance. There are no extrathoracic abnormalities. In these patients receiving several cancer chemotherapy agents and corticosteroids, an opportunistic infection (*P. jirovecii* pneumonia, CMV, tuberculosis, and viral infection) must be ruled out convincingly before a diagnosis of drug related pulmonary toxicity (e.g., induced by methotrexate) can be considered [42]. The degree of compliance with prophylactic antimicrobials (sulfamethoxazole and trimethoprim) is a key consideration. Careful history-taking and a thorough physical examination should be performed, with special attention to a more fugacious respiratory episode during the last few chemotherapy courses. FB-BAL is essential to rule out (albeit not with complete certainty) an opportunistic infection and to look for evidence of drug related pulmonary toxicity (eosinophilic or lymphocytic alveolitis) [101, 102]. Here, noninvasive diagnostic tools are useful only when they indicate an infection consistent with all the components of the clinical picture, and when antimicrobial therapy ensures full resolution of all clinical and radiographic abnormalities. Transbronchial biopsy performed during FB-BAL [82, 86] or CT-guided lung biopsies can provide useful information [87].

In our opinion, indications for lung biopsy fall into this category of disorders: if lung biopsy still has a role to play, this is its remaining indication. Similarly, new diagnostic tests such as *P. jirovecii* PCR [50, 103] are extremely useful in this situation.

Outcome in cancer patients with acute respiratory failure

Recent studies of outcomes in cancer patients admitted to the ICU have highlighted five important facts. First, mortality rates have decreased over the years [21, 23, 104, 105, 106, 107, 108, 109, 110] as a result of strict patient selection for ICU admission in compliance with recommendations [111, 112], of advances in hematology and oncology [10] and of the introduction of noninvasive MV in ICU patients [21, 22, 113].

Second, classical prognostic factors have lost much of their values. For example, adverse effects on prognosis of neutropenia is controversial [21, 105, 114], autologous BMT is associated with better outcome than allogenic BMT [115, 116], in part because of improvements in the management of hematology patients [117, 118] and in part because of methodological advances in the field of outcome studies [23, 114].

Third, most studies find that short-term survival is independent of the characteristics of the malignancy (diagnosis, stage at diagnosis, whether the patient is in partial or complete remission) [23, 104, 106, 110, 119, 120]. This important fact is ascribable, in our opinion, to improved selection of patients for ICU admission. Among cancer patients requiring ICU admission slightly fewer than one-half are admitted [112], with the main selection criteria being previous state of health, comorbidities and whether life-prolonging treatment is available [21, 104].

Fourth, physiological scores are unhelpful for predicting the outcome in cancer patients admitted to the ICU [107, 109, 115, 121, 122, 123]. The nature and number of organ failures, in contrast, are directly correlated with the risk of death [106, 108, 119]. In addition, changes in the number of organ failures over the first few ICU days are tightly correlated with survival [4, 108, 124]. Endotracheal MV is the life-supporting treatment most closely associated with mortality (Table 4). In addition, even today death usually follows MV in patients with allogeneic BMT, particularly those receiving immunosuppressive therapy for active severe graft-versus-host disease [115, 125, 126, 127, 128, 129]. The use of noninvasive mechanical ventilation (NIMV) has been associated with increased survival [115, 125, 126, 127, 128, 129]. However, we have recently reported possible adverse effects from prolonged NIMV and the grim prognosis associated with failure to NIMV [115, 125, 126, 127, 128, 129]. We recommend a trial of NIMV in cancer patients with acute respiratory failure. However, clinicians must

be aware that prolonging NIMV for more than 3 days might result in a delayed intubation and optimal alveolar recruitment and in a dismal survival rate.

Fifth, in cancer patients admitted to the ICU for ARF, outcomes vary widely according to the cause of the ARF. For instance, the survival rate is high in patients with cardiogenic pulmonary edema but is far lower in patients with invasive pulmonary aspergillosis [4]. Nevertheless, these findings should be interpreted in the light of recent advances in the diagnosis [52, 130] and treatment of pulmonary aspergillosis [131, 132]. Thus, as discussed above, the mortality rate is higher when diagnostic investigations fail to establish the diagnosis [4, 32, 45].

Avenues for research

Several areas could be explored to improve our knowledge of ARF in cancer patients. First, studies evaluating the prognostic impact of identifying the cause of ARF in cancer patients admitted to various types of ICUs would be useful. The results would probably confirm the low yield of FB-BAL, further supporting the need for a reappraisal of the risk/benefit ratio of this investigation in hypoxemic patients at high risk for endotracheal intubation (ETI). Another advantage would be collection of additional confirmation that the mortality rate is higher when investigations fail to identify the cause of the ARF. These considerations are also available for the use of HRCT, transbronchial biopsy, and open lung biopsy.

An interventional study comparing a noninvasive diagnostic strategy (Table 7) to a strategy including BAL would supply valuable information on the role for BAL. Using ETI for MV as the primary evaluation criterion would allow for an evaluation of the impact of BAL on the need for ETI. In addition, this study might establish that BAL is not superior over noninvasive testing for identifying the cause of ARF. For example, over the recent years, detection of viruses in nasopharyngeal exudates (using immunofluorescence or PCR) has become the gold standard technique to diagnose viral pulmonary infection and PCR remains the only practical tool for detecting some viruses [133, 134, 135].

Outcomes in cancer patients who fail noninvasive MV in the ICU warrant study. The mortality rate in these patients is nearly 100% when ETI is required after more than 3 days of noninvasive MV [4]. Death at this stage may be due to failure of optimal treatment with progression to diffuse alveolar damage or fibrosis. However, an alternative hypothesis is suboptimal treatment, with noninvasive MV failing to ensure optimal continuous alveolar recruitment or precluding a number of invasive or noninvasive diagnostic investigations. A study involving routine postmortem lung biopsy might determine the main cause of death in this situation. Results showing a high rate of undiagnosed infection (e.g., tuberculosis or *P. jirovecii*) or treatment toxicity [136] would challenge the appropriateness of the initial treatment strategy. However, two recent autopsy studies in BMT recipients have reported controversial results [49, 137].

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