Intensive Care Med (2014) 40:1168–1170
DOI 10.1007/s00134-014-3394-5

EDITORIAL

Pieter O. Depuydt
Marcio Soares

Cancer patients with ARDS: survival gains and unanswered questions

Received: 30 June 2014
Accepted: 1 July 2014
Published online: 15 July 2014

P. O. Depuydt
Department of Intensive Care Medicine, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium

M. Soares
Post-Graduation Program, Instituto Nacional de Câncer, Rio de Janeiro, Brazil

M. Soares (✉)
Department of Clinical Research, D'Or Institute for Research and Education, Rua Diniz Cordeiro, 30-Botafogo, Rio de Janeiro, RJ 22281-100, Brazil
e-mail: marciosoaresms@gmail.com
Tel.: +55 21 3883 6000

Acute respiratory distress syndrome (ARDS) is a devastating diffuse pulmonary inflammation, triggered by a wide array of direct and indirect pulmonary insults, but frequently leading down the common path of acute respiratory failure (ARF) requiring mechanical ventilation (MV), multiorgan dysfunction, and death despite advanced organ support. While no single therapy with curative potential for ARDS has been identified yet, a multimodality approach, including restrictive ventilator settings to limit additional iatrogenic lung injury, careful patient positioning, and judicious use of muscle relaxants, has however led to gradual but marked improvements in survival over the last two decades [1]. Nevertheless, when short-term death is averted, ARDS very often leaves the patient in a debilitated state from which functional recovery is protracted and often incomplete and long-term post-hospital mortality is disproportionally high [2–4]. Of note, severe comorbidities are prevalent in ARDS patients and further contribute to worsen long-term morbidity and mortality in these patients [4].

Remarkably, in an article published recently in *Intensive Care Medicine*, Azoulay and colleagues provide a relevant contribution to this field by evaluating a large cohort of patients with malignancies and ARDS admitted to 14 referral cancer centers in France and Belgium over a 22-year period [5]. It is well known that patients with solid and hematological malignancies are vulnerable to respiratory complications caused by the underlying malignancy, toxic effects of chemotherapy and, chiefly, infections. Again, over the two last decades we have witnessed that short- and medium-term survival in cancer patients, once ARF occurs, has evolved from dismal to encouraging rates, comparable to (or even surpassing) those of patients with ARF and other major comorbidities. Consequently, the current paper does not come as a total surprise, yet it adds weight to this observation by its large scope in terms of time frame and numbers of patients, its thorough analysis, and by applying the up-to-date Berlin ARDS definitions. As such, it may set a milestone along the winding path of treating critically ill oncological and hematological patients.

There is more to learn from this paper, however. First, it shows that the initial enthusiasm to apply noninvasive ventilation (NIV) as a preferable way to provide mechanical ventilatory support while avoiding the complications of endotracheal intubation in these fragile patients has matured. The sharp rise in NIV use, from 14 to 32 % since the turn of the century, has come to a plateau phase. Moreover, overall NIV failure rates exceeded 70 %, particularly in more severely ill patients. In previous studies in cancer patients, ARDS was associated with NIV failure [6–8]. Therefore, the present study provides additional evidence that NIV should not be

Table 1 Unanswered questions and avenues for research in patients with malignancies and ARDS

How to improve and assist physicians regarding ICU referral and triage criteria for patients with malignancies and ARDS?
What are the efficacy and safety of NIV use in patients with mild to moderate ARDS?
Should preemptive therapy against invasive fungal infections be offered to high-risk patients?
Multidimensional long-term physical, psychological, and cognitive sequelae along with HRQOL in ARDS survivors should be better described and understood
Impact of residual organ dysfunctions and compromise in performance status on the offering (or continuity) of the most appropriate anticancer treatment deserves to be better evaluated
Understanding of the prior two items is essential to assist in the design of rehabilitation programs able to improve the outcomes and HRQOL in ARDS survivors
Post-hospital social and psychological burden in family members and informal caregivers of ARDS survivors should also be assessed

ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *NIV* noninvasive ventilation, *HRQOL* health-related quality of life

standard first-line support for the oncological/hematological patient with ARDS. In our opinion, until new data from randomized trials become available, NIV can be used cautiously as a supportive tool in some patients with incipient or less severe ARDS, but should be avoided in the moderate and severe Berlin definition categories of ARDS. Second, ARDS is not a single disease, but rather a heterogeneous condition, and reversal or clearance of its trigger is as important as quality of organ support. Such considerations are illustrated again by the divergence in ARDS survival according to its underlying cause. This justifies a thorough diagnostic workup, especially focused on finding a potential infectious etiology. In the study by Azoulay et al. invasive fungal infections, namely pulmonary aspergillosis and *Pneumocystis jirovecii* pneumonia, accounted for one-third of ARDS cases. Along this line, the effect of preemptive therapy against invasive fungal infections deserves to be evaluated in high-risk patients. Thirdly, severity of illness, as measured by the sequential organ failure assessment (SOFA) at ICU admission, has decreased over time. This could mean that reluctance to call for ICU assistance in case of respiratory deterioration has diminished and that patients are admitted to the ICU in an earlier, still more reversible, phase of their critical illness. This earlier referral policy could have acted as a lever to increase the gains in survival, although evidence to prove this concept remains weak [9].

However, while we may have reached a benchmark to measure future progress, much about ARDS in oncological/hematological patients remains unknown. The full impact of ARDS extends beyond the fact of whether or not patients leave the hospital alive. Within the last few years, several studies have shown that long-term morbidity induced by ARDS is substantial, as patients may suffer from persistent physical constraints and weakness to new-onset neurocognitive disorders, such as depression and long-lasting cognitive impairment [2, 3, 10, 11]. Among the major comorbidities, malignant disease has a major physical and psychological burden in itself [12]. Survivors of ARDS thus may face ARDS-induced deterioration of quality of life superimposed upon that of the underlying malignancy. In addition, poor performance status or persisting organ functional deficits post ARDS may postpone or thwart subsequent aggressive antineoplastic therapy, and thus may prematurely end a therapeutic path which was started with initially curative intentions [13]. Finally, ICU admission, especially involving prolonged mechanical ventilation, is a particularly distressing event not only for the patient but also for the caregivers, who may experience a period of emotional roller coaster ride, owing to uncertainty about short-term survival, being followed by a prolonged period of caregiving [14]. As such, carefully judging the survival benefits of prolonged respiratory support in the light of the oncological or hematological prospects of the patient in the longer run, balanced against the burden imposed on patients and relatives, remains an important exercise in the care of these patients. These should certainly be targets to be addressed in future research (Table 1). Meanwhile, close collaboration and careful communication between intensivist and referring oncologist/hematologist, each adding their own expertise, are paramount to provide the best care for patients and families.

Acknowledgments Dr. Soares is supported in part by research grants from the National Council for Scientific and Technological Development (CNPq) and Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Brazil.

Conflicts of interest None

References

1. Tonelli AR, Zein J, Adams J, Ioannidis JP (2014) Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 published randomized trials and 29 meta-analyses. Intensive Care Med 40:769–787
2. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM, Canadian Critical Care Trials Group (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293–1304
3. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, Wozniak AW, Colantuoni E, Ely EW, Rice TW, Hopkins RO, NIH NHLBI ARDS Network (2013) Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am J Respir Crit Care Med 188:567–576
4. Wang CY, Calfee CS, Paul DW, Janz DR, May AK, Zhuo H, Bernard GR, Matthay MA, Ware LB, Kangelaris KN (2014) One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. Intensive Care Med 40:388–396
5. Azoulay E, Lemiale V, Mokart D, Pène F, Kouatchet A, Perez P, Vincent F, Mayaux J, Benoit D, Bruneel F, Meert AP, Nyunga M, Rabbat A, Darmon M (2014) Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med. doi: 10.1007/s00134-014-3354-0
6. Adda M, Coquet I, Darmon M, Thiery G, Schlemmer B, Azoulay E (2008) Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. Crit Care Med 36:2766–2772
7. Depuydt PO, Benoit DD, Roosens CD, Offner FC, Noens LA, Decruyenaere JM (2010) The impact of the initial ventilatory strategy on survival in hematological patients with acute hypoxemic respiratory failure. J Crit Care 25:30–36
8. Azevedo LC, Caruso P, Silva UV, Torelly AP, Silva E, Rezende E, Netto JJ, Piras C, Lobo SM, Knibel MF, Teles JM, Lima RA, Ferreira BS, Friedman G, Rea-Neto A, Dal-Pizzol F, Bozza FA, Salluh JI, Soares M (2014) Outcomes for patients with cancer admitted to the ICU requiring ventilatory support: results from a prospective multicenter study. Chest. doi: 10.1378/chest.13-1870
9. Song JU, Suh GY, Park HY, Lim SY, Han SG, Kang YR, Kwon OJ, Woo S, Jeon K (2012) Early intervention on the outcomes in critically ill cancer patients admitted to intensive care units. Intensive Care Med 38:1505–1513
10. Chiumello D, Taccone P, Berto V, Marino A, Migliara G, Lazzerini M, Gattinoni L (2012) Long-term outcomes in survivors of acute respiratory distress syndrome ventilated in supine or prone position. Intensive Care Med 38:221–229
11. Guérin C, Girbes AR (2014) Improved ICU outcomes in ARDS patients: implication on long-term outcomes. Intensive Care Med 40:448–450
12. Azoulay E, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J, Vincent F, Nyunga M, Bruneel F, Laisne LM, Rabbat A, Lebert C, Perez P, Chaize M, Renault A, Meert AP, Benoit D, Hamidfar R, Jourdain M, Darmon M, Schlemmer B, Chevret S, Lemiale V (2013) Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium–a groupe de recherché respiratoire en réanimation onco-hématologique study. J Clin Oncol 31:2810–2818
13. Soares M, Toffart AC, Timsit JF, Burghi G, Irrazábal C, Pattison N, Tobar E, Almeida BF, Silva UV, Azevedo LC, Rabbat A, Lamer C, Parrot A, Souza-Dantas VC, Wallet F, Blot F, Bourdin G, Piras C, Delemazure J, Durand M, Tejera D, Salluh JI, Azoulay E, for the Lung Cancer in Critical Care (LUCCA) Study Investigators (2014) Intensive Care in Patients with Lung Cancer: A Multinational Study. Ann Oncol. doi: 10.1093/annonc/mdu234
14. Cameron JI, Herridge MS, Tansey CM, McAndrews MP, Cheung AM (2006) Well-being in informal caregivers of survivors of acute respiratory distress syndrome. Crit Care Med 34:81–86

Intensive Care Med (2014) 40:1106–1114
DOI 10.1007/s00134-014-3354-0

ORIGINAL

Acute respiratory distress syndrome in patients with malignancies

Elie Azoulay
Virginie Lemiale
Djamel Mokart
Frédéric Pène
Achille Kouatchet
Pierre Perez
François Vincent
Julien Mayaux
Dominique Benoit
Fabrice Bruneel
Anne-Pascale Meert
Martine Nyunga
Antoine Rabbat
Michael Darmon

Received: 7 March 2014
Accepted: 23 May 2014
Published online: 5 June 2014

Take home message: Pulmonary and extrapulmonary infections were responsible for 90 % of ARDS cases in patients with solid or hematological malignancies. One-third of the underlying infections were due to opportunistic pathogens. Survival improved significantly over time. Noninvasive ventilation was attempted in 30 % of patients but failed in 70 %, and failure was associated with increased mortality. The particularly high mortality among patients with invasive fungal infections indicates a pressing need for specific studies on early antifungal therapy in high-risk patients.

On behalf of the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (Grrr-OH).

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-014-3354-0) contains supplementary material, which is available to authorized users.

E. Azoulay · V. Lemiale
Intensive Care Unit of the Saint-Louis University Hospital, Paris, France

D. Mokart
Intensive Care Unit of Institut Paoli Calmette, Marseille, France

F. Pène · A. Rabbat
Intensive Care Unit of Cochin University Hospital, Paris, France

A. Kouatchet
Intensive Care Unit of Angers University Hospital, Angers, France

P. Perez
Intensive Care Unit of Nancy University Hospital, Nancy, France

F. Vincent
Intensive Care Unit of Bobigny University Hospital, Bobigny, France

J. Mayaux
Intensive Care Unit of Pitié-Salpêtrière University Hospital, Paris, France

D. Benoit
Intensive Care Unit of Ghent University Hospital, Ghent, Belgium

F. Bruneel
Intensive Care Unit of Versailles Hospital, Versailles, France

A.-P. Meert
Intensive Care Unit of Brussels University Hospital, Brussels, Belgium

M. Nyunga
Intensive Care Unit of Roubaix Hospital, Roubaix, France

M. Darmon
Intensive Care Unit of Saint-Etienne Teaching Hospital, Saint-Étienne, France

E. Azoulay (✉)
Sorbonne Paris-Cité, Medical School, AP-HP, Hôpital Saint-Louis, Medical ICU, Paris-Diderot University, 1 avenue Claude Vellefaux, 75010 Paris, France
e-mail: elieazoulay.icm@sls.aphp.fr; elie.azoulay@sls.aphp.fr
Tel.: +33 142 499 421

Abstract *Purpose:* Little attention has been given to ARDS in cancer patients, despite their high risk for pulmonary complications. We sought to describe outcomes in cancer patients with ARDS meeting the Berlin definition. *Methods:* Data from a cohort of patients admitted to 14 ICUs between 1990 and 2011 were used for a multivariable analysis of risk factors for hospital mortality. *Results:* Of 1,004 included patients (86 % with hematological malignancies and 14 % with solid tumors), 444 (44.2 %) had neutropenia. Admission SOFA score was 12 (10–13). Etiological categories were primary infection-related ARDS ($n = 662$, 65.9 %; 385 bacterial infections, 213 invasive aspergillosis, 64 *Pneumocystis* pneumonia); extrapulmonary septic shock-related ARDS ($n = 225$, 22.4 %; 33 % candidemia); noninfectious ARDS ($n = 76$, 7.6 %); and undetermined cause ($n = 41$, 4.1 %). Of 387 (38.6 %) patients given

noninvasive ventilation (NIV), 276 (71 %) subsequently required endotracheal ventilation. Hospital mortality was 64 % overall. According to the Berlin definition, 252 (25.1 %) patients had mild, 426 (42.4 %) moderate and 326 (32.5 %) severe ARDS; mortality was 59, 63 and 68.5 %, respectively ($p = 0.06$). Mortality dropped from 89 % in 1990–1995 to 52 % in 2006–2011 ($p < 0.0001$). Solid tumors, primary ARDS, and later admission period were associated with lower mortality. Risk factors for higher mortality were allogeneic bone-marrow transplantation, modified SOFA, NIV failure, severe ARDS, and invasive fungal infection. *Conclusions:* In cancer patients, 90 % of ARDS cases are infection-related, including one-third due to invasive fungal infections. Mortality has decreased over time. NIV failure is associated with increased mortality. The high mortality associated with invasive fungal infections warrants specific studies of early treatment strategies.

Keywords Neutropenia · Bronchoscopy · Pneumonia · Invasive aspergillosis · Candidemia · *Pneumocystis*

Introduction

Pulmonary involvement is frequent and severe in patients with solid or hematological malignancies [1]. Acute respiratory failure occurs in up to half the patients treated for malignancies [2] and carries a variable risk of death depending on the cause, need for mechanical ventilation, concomitant organ dysfunctions, presence of graft-versus-host disease, and goals of care [3–9].

Acute respiratory distress syndrome (ARDS) in patients with malignancies exhibits several specific features, particularly in patients with neutropenia [10]. Although circulating and resident alveolar neutrophils have been considered pivotal in the pathophysiology of ARDS [11], patients with neutropenia are at high risk for ARDS [12], and alveolar macrophages play a prominent role in the response to acute lung injury [13, 14]. In patients with or without neutropenia, ARDS may be related to infectious or non-infectious causes. Causes of primary ARDS, i.e., ARDS due to a direct lung insult, include bacterial or opportunistic infections such as invasive pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia, other fungal infections, and severe viral infections [2]. Secondary ARDS is related to a systemic process such as severe sepsis or septic shock from extrapulmonary bacterial or fungal infections [15]. Non-infectious lung insults such as drug-related toxicity [16] and infiltration by malignant cells [17] may produce a clinical picture similar to ARDS, although diffuse alveolar damage is generally absent [18].

Despite the considerable improvements in outcomes achieved in recent years [19, 20], patients with malignancies and ARDS are frequently excluded from observational studies and interventional trials [21]. ARDS is more often fatal in patients with malignancies than in other patients [22, 23]. However, few studies have specifically investigated the risk factors for death among patients with malignancies and ARDS. In a single-center study of 68 patients with ARDS and hematological malignancies, multiorgan failure was an independent risk factor for death [24]. A retrospective assessment of patients in ARDS network trials showed a significantly higher risk of death in the 116 patients with cancer than in the 2,399 other patients [23]. However, outcome data are lacking from large multicenter cohort studies focusing specifically on ARDS patients with malignancies managed in high-volume centers where intensivists and oncologists/hematologists work closely together to ensure optimal management.

Our primary objective was to obtain recent data on ARDS outcomes in patients with malignancies. We used the new operational Berlin definition to define ARDS [25, 26]. Our secondary objectives were to assess how the Berlin definition of ARDS operates in this specific population, to look for associations between ARDS causes and hospital mortality, and to describe trends in outcomes over time. To meet these objectives, we conducted a large multicenter cohort study of patients managed in specialized centers.

Patients and methods

The appropriate ethics committees approved this study (CPP Pitié Salpétrière, SPLF ethics committee, and CE-ERB Bichat). We retrospectively analyzed data from six previously published prospective and retrospective outcome studies of patients with malignancies who required intensive care unit (ICU) admission [1, 4, 9, 10, 19, 27, 28]. Patients were included in these studies between 1990 and 2011 in 14 university or university-affiliated centers in France and Belgium belonging to a research network on critical respiratory diseases in patients with malignancies (*Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie*, GRRR-OH). Of the six studies, only one [10] focused specifically on patients with ARDS and malignancies, and all patients in this study had neutropenia. In each center, a senior intensivist and a senior oncologist/hematologist were available around the clock and made ICU-admission decisions together.

In the datasets of these six studies, we identified patients with malignancies who met the Berlin definition of ARDS within 3 days after ICU admission: [25, 26] (1) new or worsening respiratory symptoms over the last 7 days; (2) bilateral opacities on chest radiographs; (3) absence of suspected hydrostatic/cardiogenic pulmonary edema; and (4) $PaO_2/FiO_2 \leq 300$. ARDS severity was categorized according to the Berlin definition as mild (200 mmHg $< PaO_2/FiO_2 \leq 300$ mmHg); moderate (100 mm Hg $< PaO_2/FiO_2 \leq 200$ mmHg), or severe ($PaO_2/FiO_2 \leq 100$ mmHg) [25, 26]. All PaO_2/FiO_2 were assessed with a PEEP level ≥ 5.

The data reported in the tables and figures were collected from the patient charts or study databases. The sequential organ failure assessment (SOFA) score was computed at ICU admission to estimate the risk of death based on organ dysfunctions. To assess the influence of ARDS on mortality, we computed a modified SOFA score (mSOFA) obtained by excluding the respiratory component.

We defined neutropenia as a neutrophil count $<500/mm^3$ at ARDS onset. The underlying malignancy was categorized as either in partial or complete remission or as progressive, newly diagnosed, or unknown status.

Diagnostic tests used to identify the cause of ARDS included noninvasive or invasive (i.e., bronchoscopy and bronchoalveolar lavage) investigations, as deemed appropriate by the intensivist in charge [1]. Bronchial or pulmonary biopsies were not performed routinely given the acute illness severity and bleeding risk in many patients. The cause was identified by consensus among intensivists, oncologists/hematologists, and consultants, according to recent definitions [1]. Invasive fungal infections (IFIs) met the most recent EORTC-MSG definitions [29]. Sepsis definitions and management were as published previously [28, 30]. The study patients received NIV or endotracheal mechanical ventilation (MV) according to their respiratory status and acute illness severity.

Statistical analysis

Results are reported as medians (interquartile range, IQR) or numbers (%). Categorical variables were compared using the Chi square test or Fisher's exact test, as appropriate and continuous variables using the nonparametric Wilcoxon test or Mann–Whitney test. Kaplan–Meier survival curves were plotted. We chose the log-rank test to compare the three ARDS-severity categories. We performed conditional backward logistic regression analyses to identify variables that significantly influenced hospital mortality. Variables yielding $p < 0.20$ in bivariate analyses were entered into the model, as well as variables deemed clinically relevant. Variables yielding $p \leq 0.10$ were maintained in the final model. For the multivariable analysis, missing data were handled using multiple imputation with chained equations [31]. For each variable, we computed the odds ratio (OR) for death with the 95 % confidence interval (95 % CI). Collinearity and interactions were tested. The Hosmer–Lemeshow test was used to check goodness-of-fit of the logistic regression.

We looked for changes in hospital mortality according to period of ICU admission, in four categories: 1990–1996; 1996–2000; 2001–2006; and 2006–2011.

All tests were two-sided and p values <0.05 were considered significant. Statistical tests were done using the SPSS 13 software package (IBM, Armonk, NY, USA).

Results

Over the 22-year study period, 1,004 patients with malignancies met the Berlin definition of ARDS. They accounted for 16.5 % of all ICU patients with malignancies and for 35 % of ICU patients with malignancies and acute respiratory failure (Fig. 1). Of the 1,004 study patients, 85.4 % had hematological malignancies including 115 allogeneic bone-marrow or hematopoietic-stem-cell transplants (BMT/HSCT) and 14.6 % solid tumors (Tables 1, 2). Acute leukemia and non-Hodgkin lymphoma were the most common hematological malignancies, whereas lung and breast cancers were the most common solid tumors. Over the study period, the

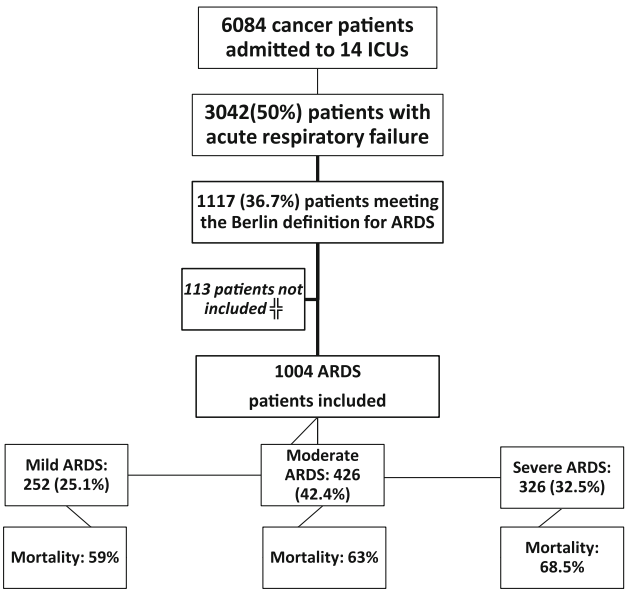

Fig. 1 Patient flow chart and distribution among in three ARDS severity categories in the Berlin definition. ╬ reasons for non-inclusion were as follows: 55 patients did not receive noninvasive or endotracheal mechanical ventilation and vital status at hospital discharge was unknown in 58 patients

Table 1 Patient characteristics at admission to the intensive care unit

Median (IQR) or *n* (%)	Study population (*n* = 1,004)	Survivors (*n* = 364)	Non-survivors (*n* = 640)	*p* value
Male gender	642 (63.9 %)	240 (65.9 %)	402 (62.8 %)	0.32
Age (years)	58 (48–67)	57 (47–67)	58 (48–67)	0.33
Underlying malignancy				
Acute leukemia	298 (29.7 %)	96 (26.4 %)	202 (31.6 %)	0.08
Non-Hodgkin's lymphoma	318 (31.7 %)	115 (31.6 %)	203 (31.7 %)	0.97
Myeloma	113 (11.3 %)	34 (9.3 %)	79 (12.3 %)	<0.0001
Solid tumor	147 (14.6 %)	60 (16.5 %)	87 (13.6 %)	0.21
Miscellaneous	95 (9.5 %)	46 (12.6 %)	48 (7.7 %)	0.01
Allogeneic BMT/HSTC[a]	115 (11.5 %)	36 (9.9 %)	79 (12.3 %)	0.23
Neutropenia	444 (44.2 %)	148 (40.7 %)	296 (46.3 %)	0.08
Stage				
Progressive	458 (45.6 %)	171 (47.0 %)	287 (44.8 %)	0.0003
Partial/complete remission	237 (23.6 %)	100 (27.4 %)	137 (21.4 %)	
Newly diagnosed	72 (7.2 %)	33 (9.1 %)	39 (6.1 %)	
Unknown	237 (23.6 %)	60 (16.5 %)	177 (27.7 %)	

[a] Bone-marrow transplantation/hematopoietic-stem-cell transplantation

Table 2 ARDS causes, severity and treatment, and hospital mortality

Median (IQR) or *n* (%)	Study population (*n* = 1,004)	Survivors (*n* = 364)	Non-survivors (*n* = 640)	*p* value
SOFA score (31) on day-1	12 [10–13]	10 [8–12]	13 [10–13]	<0.0001
mSOFA score on day-1	9 [6–11]	7 [5–10]	9 [7–11]	<0.0001
Emergency surgery	64 (6.4 %)	34 (9.3 %)	30 (4.7 %)	0.004
Sepsis	745 (74.2 %)	275 (75.5 %)	470 (73.4 %)	0.46
Cause of ARDS				
Pulmonary infection[a]	662 (65.9 %)	281 (77.2 %)	381 (59.5 %)	<0.0001
Secondary ARDS[a]	225 (22.4 %)	55 (15.1 %)	170 (26.6 %)	<0.0001
Fungal infection[b]	293 (30.7 %)	83 (23.2 %)	210 (35.1 %)	0.0001
Pneumocystis	64 (6.4 %)	30 (8.2 %)	34 (5.3 %)	0.07
No definite diagnosis[c]	41 (5.7 %)	12 (4.5 %)	29 (6.4 %)	0.29
Berlin categories				
Mild (P/F >200)	252 (25.1 %)	103 (28.3 %)	149 (23.3 %)	
Moderate (P/F 100–200)	426 (42.4 %)	158 (43.4 %)	268 (41.8 %)	0.06
Severe (P/F < 100)	326 (32.5 %)	103 (28.3 %)	223 (34.8 %)	
Organ Support				
NIV	387 (38.6 %)	174 (47.8 %)	213 (33.3 %)	<0.0001
NIV failure	276 (27.5 %)	103 (28.3 %)	173 (27.0 %)	0.67
Endotracheal MV	893 (88.9 %)	293 (80.5 %)	600 (93.8 %)	<0.0001
Vasopressors	731 (72.8 %)	241 (66.2 %)	490 (76.6 %)	0.0004
Renal replacement therapy	306 (30.5 %)	99 (27.2 %)	207 (32.3 %)	0.09

SOFA sequential organ failure assessment score, which can range from 0 to 24, *mSOFA* modified sequential organ failure assessment score, which does not take respiratory characteristics into account and can range from 0 to 20

[a] Data available for 756 patients

[b] Data available for 955 patients

[c] Data available for 717 patients

proportions of patients with acute leukemia and lymphoma increased (23 %/23 % in 1990–1995 vs 37 %/42 % in 2006–2011, respectively; $p < 0.0001$) and the proportion with myeloma decreased (28 % in 1990–1995 vs 5 % in 2006–2011, $p < 0.0001$). Proportions of patients with solid tumors and of BMT/HSCT recipients remained unchanged over time. Day-1 SOFA score was 12 (10–13) overall and decreased significantly over time (13 [11–13] in 1990–1995, 12 [10–13] in 1996–2000, 12 [10–13] in 2001–2005, and 11 [8–14] in 2006–2011; $p = 0.002$). At ICU admission, 444 (42.1 %) patients had neutropenia and 237 (23.6 %) were in partial or complete remission from their malignancy. ICU admission occurred after emergent surgery in 64 (6.4 %) patients.

Severe infection was documented clinically or microbiologically in 887 (88.3 %) patients. Vasopressors were needed in 73 % of patients and renal replacement therapy in 30.5 % (Table 2). The proportion of patients requiring dialysis increased over the four study periods (24, 25, 25 and 38 %, respectively; $p = 0.001$), whereas the proportion requiring vasopressors remained unchanged.

IFIs accounted for more than one-third of primary and secondary ARDS cases. Primary ARDS related to infection was found in 662 (65.9 %) patients, including 385 (58 %) with clinically or microbiologically documented bacterial infection and 277 (42 %) with IFI [213 with invasive pulmonary aspergillosis (17 certain, 119 probable, 77 possible) and 64 patients with certain *P. jirovecii* pneumonia]. Secondary ARDS occurred in 225 (22.4 %) patients with septic shock, including 80 (36 %) with candidemia. Noninfectious conditions were the primary cause of ARDS in 76 (7.6 %) patients. The cause of ARDS was undetermined in 41 (4.1 %) patients.

Factors independently associated with IFI were acute leukemia (OR, 1.78; 95 % CI, 1.22–2.60), lymphoma (OR, 2.01; 95 % CI, 1.37–2.95), first-line endotracheal MV (OR, 3.17; 95 % CI, 1.77–5.69), and endotracheal MV after NIV failure (OR, 2.11; 95 % CI, 1.14–3.91). Neutropenia and allogeneic BMT/HSCT were not independently associated with IFI.

Hospital mortality was 64 % overall and dropped significantly over time (from 89 % in 1990–1995 to 52 % in 2006–2011, $p < 0.0001$, Fig. 2). According to the Berlin definition, 252 (25.1 %) patients had mild, 426 (42.4 %) moderate, and 326 (32.5 %) severe ARDS (Fig. 1). Hospital mortality was 59, 63, and 68.5 % in these three groups, respectively ($p = 0.06$, Fig. 3). Mortality also dropped significantly in recipients of allogeneic stem cells transplantation (Fig. S1) or according to the type of underlying malignancy (Fig. S2).

NIV was used initially in 387 (38.6 %) patients. Among them, 276 (71 %) subsequently required endotracheal MV and 111 (29 %) did not. NIV use varied across the four study periods (14, 32, 33, and 26 %, respectively; $p = 0.0002$). The proportions of patients given NIV were similar across the three Berlin severity categories 85/252 (33.7 %) patients with mild ARDS, 173/426 (40.6 %) with moderate ARDS, and 129/326 (39.6 %) with severe ARDS ($p = 0.18$). However, NIV failed more often in the moderate and severe categories: endotracheal MV was subsequently required in 54/85

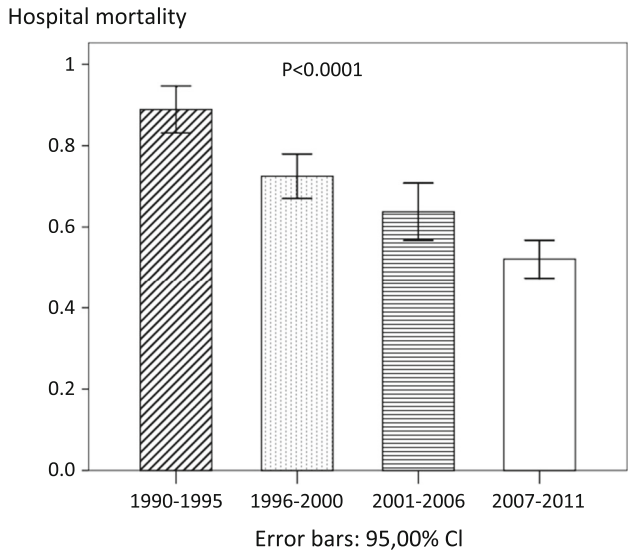

Fig. 2 Hospital mortality according to period of admission to the intensive care unit

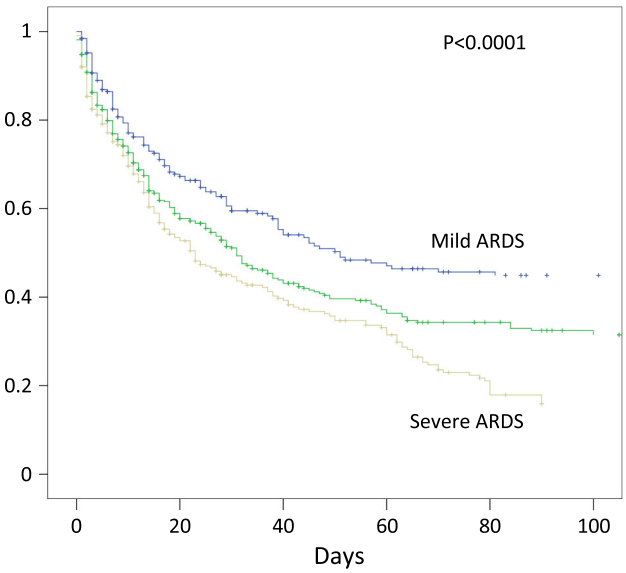

Fig. 3 Cumulative survival according to ARDS severity category in the Berlin definition. The *blue line* indicates mild ARDS, *red line* moderate ARDS and *gray line* severe ARDS. The three groups were compared using the log-rank test ($p < 0.0001$)

Table 3 Factors independently associated with hospital mortality

	OR	95 % CI	*p* value
Solid tumor	0.51	(0.34–0.77)	0.002
Need for emergency surgery	0.61	(0.35–1.05)	0.07
Allogeneic BMT/HSCT	1.71	(1.07–2.71)	0.04
mSOFA (per point)	1.11	(1.06–1.16)	<0.001
Cause of respiratory involvement			
No definite diagnosis	1	(Reference)	–
Primary ARDS	0.41	(0.20–0.88)	0.02
Secondary ARDS	0.90	(0.41–2.01)	0.80
Invasive fungal infection	1.72	(1.25–2.37)	0.001
Ventilation			
NIV	1	(Reference)	–
NIV failure	2.93	(1.80–4.79)	<0.001
Endotracheal MV	3.24	(2.02–5.24)	<0.001
ARDS severity			
Mild	1	(Reference)	–
Moderate	1.25	(0.88–1.78)	0.22
Severe	1.61	(1.10–2.36)	0.01

Hosmer–Lemeshow = 0.36; C-stat = 0.87

OR odds ratio, 95 % *CI* 95 % confidence interval, *BMT/HSCT* bone-marrow transplantation/hematopoietic-stem-cell transplantation, *mSOFA* modified sequential organ failure assessment, which does not take respiratory characteristics into account and can range from 0 to 20, *ARDS* acute respiratory distress syndrome, *NIV* noninvasive ventilation, *MV* mechanical ventilation

(63.5 %) patients with mild ARDS, 120/173 (69.4 %) with moderate ARDS and 102/129 (79.1 %) with severe ARDS ($p = 0.04$).

By multivariate analysis (Table 3), two factors were independently associated with lower hospital mortality, namely, solid tumor (versus hematological malignancy) and primary ARDS (versus undetermined ARDS etiology). Factors independently associated with higher mortality were allogeneic BMT/HSCT, worse admission mSOFA score, IFI, and NIV failure. Among the three Berlin severity categories, only severe ARDS was associated with increased mortality, whereas mortality was not significantly different between the mild and moderate categories. When period of ICU admission was entered into the multivariable model, a significant decrease in hospital mortality over time was found. With 1990–1995 as the reference, the ORs were 0.39 (95 % CI, 0.20–0.76) for 1996–2000, 0.26 (95 % CI, 0.13–0.51) for 2001–2005, and 0.16 (95 % CI, 0.09–0.30) for 2006–2011 and did not modified the final model (i.e., independent predictors of mortality).

As regard to the potential confusion bias induced by inclusion of patients with solid tumors, a sensitivity analysis was performed after exclusion of these patients (Table S2). The model was not significantly modified.

Discussion

In our large multicenter study of 1,004 patients with solid or hematological malignancies and ARDS meeting the new operational Berlin definition, about 90 % of ARDS cases were due to infections. Opportunistic organisms accounted for over one-third of all ARDS cases, with invasive aspergillosis and *Pneumocystis* pneumonia in primary ARDS and candidemia in secondary ARDS. Importantly, mortality decreased significantly over time, to 52 % during the most recent period, despite adjustment for patients' or ARDS severity, cause of the respiratory involvement or allogeneic stem cell transplantation. We found lower mortality rates in patients with solid tumors or primary ARDS and higher mortality rates in patients with allogeneic BMT/HSCT or IFIs. NIV was used initially in one-third of the patients but usually failed, with the highest failure rates occurring in the most severe ARDS category. NIV failure was associated with higher mortality.

Data on ARDS in patients with malignancies are scarce. Of two recent single-center studies in small numbers of patient, one identified multiorgan failure and the other greater acute illness severity and older age as risk factors for mortality [23, 24]; in one of these studies, NIV use was associated with lower mortality [24]. Other small studies focused on specific clinical situations such as neutropenia, neutropenia recovery, or drug-related pulmonary toxicity [10, 14, 16]. None of these studies used the Berlin definition of ARDS. In earlier studies of ARDS, SOFA scores and the need for vasopressors or renal replacement therapy were higher in patients with than without malignancies [25, 32, 33], in keeping with our data. The decreased mortality over time is also consistent with previously published studies of critically ill patients with malignancies [19]. Of note, although patient's characteristics differed across study periods (Table S1), decreased mortality over time remains significant after adjustment for patients' or ARDS severity, cause of the respiratory involvement or allogeneic stem cell transplantation. However, the 40 % decrease seen in our study is particularly large and suggests a role for optimal patient triage to ICU admission and ARDS management in ICUs that are highly experienced in managing patients with ARDS and malignancies, such as those to which our patients were admitted. Then, we believe that decreased mortality may only partially explained by the use of protective ventilation. More specifically, changes in the invasive or noninvasive diagnostic strategy for ICU patients with acute respiratory failure have increased the proportion of patients in whom the cause of ARDS is identified [1]. Primary ARDS was associated with lower mortality, indicating a need for further work on optimizing the diagnosis and treatment of secondary ARDS [17, 34, 35]. Allogeneic BMT/HSCT recipients, in particular, still have very high mortality rates if they require endotracheal MV [36].

Our study identifies two targets for improvement. The higher mortality after NIV failure is in keeping with studies of patients who had acute respiratory failure with [37] or without [38] malignancies. In one of these earlier studies, the risk of NIV failure was highest with ARDS [39]. Mortality rates of up to 90 % have been reported in patients with acute respiratory failure, immunosuppression, and endotracheal MV [40]. Overall, NIV has clearly decreased the risk of death by obviating the need for endotracheal MV in some patients. In keeping with our results, the initial enthusiasm to apply NIV was followed by a tempering that may be related to adverse events of failed NIV. Moreover, in recent years, mortality rates decreased significantly in patients managed with endotracheal MV [5, 19] and concern has been voiced that first-line NIV might be deleterious in patients with malignancies and acute respiratory failure, [41] particularly when criteria for ARDS are met [39]. Studies designed to clarify the potential benefits of early NIV in patients with malignancies and hypoxemic acute respiratory failure are warranted [41]. Our data and an earlier study [39] suggest that NIV may be best avoided in patients with malignancies and severe ARDS and should be considered only with caution in those with mild or moderate ARDS.

In our study, IFIs caused more than one-third of the ARDS cases. The main IFIs were invasive pulmonary aspergillosis and *P. jirovecii* pneumonia in primary ARDS and candidemia in secondary ARDS. IFI was independently associated with hospital mortality. Empirical antifungal therapy is the standard of care for neutropenic patients with hematological malignancies who remain febrile despite broad-spectrum antibacterial treatment [29]. In high-risk patients, primary prophylaxis is effective in preventing invasive aspergillosis and decreasing the rate of deaths related to fungal infections [42]. In a randomized trial in neutropenic patients with persistent fever despite broad-spectrum antibiotics [43], compared to empirical antifungal treatment, preemptive antifungal treatment increased the incidence of IFIs, without increasing mortality, and there was some evidence that empirical treatment decreased mortality among patients receiving induction chemotherapy [43]. However, in patients with ARDS, the frequency of invasive aspergillosis is highest during induction chemotherapy for acute leukemia or lymphoma. The role for empirical anti-aspergillosis therapy in these patients should be evaluated without delay.

Our study has several limitations. First, the participating ICUs had a high annual volume of patients with malignancies. As a volume-outcome relationship is likely in these patients, the improved outcomes over time found in our study may not apply to all ICUs. For instance, undermined ARDS etiologies occurred in only 4.1 % of the patients as most of the patients who were intubated underwent extensive diagnostic tests in highly skilled centers. However, critically ill patients with malignancies are routinely managed in specialized ICUs working closely with oncologists and hematologists. Second, the retrospective design and long study period raises the possibility of changes in diagnostic strategies and standard treatments. The improved outcomes over time are probably ascribable to advances in both the treatment of malignancies and intensive care [19]. Third, we did not collect data on tidal volumes, plateau pressures, ventilatory strategies, or rescue therapy (prone positioning, extracorporeal membrane oxygenation) and we were therefore unable to determine the extent to which improvements in these areas may have contributed to the improved survival over time [32, 44]. Until recently [32, 45], prone positioning was controversial, and extracorporeal membrane oxygenation was used in only eight of our patients. Fifth, the data used for our study were extracted from our research group database and obtained in studies that were not specifically designed to investigate ARDS [1, 9, 10, 19, 27, 46]. However, given the dearth of data on ARDS in patients with malignancies, we believe our strategy was a useful means of obtaining a sufficiently large cohort to provide convincing outcome information. Our study shows that mortality remains high in this population but has dropped significantly. Consequently, patients with malignancies should no longer be excluded from observational or interventional studies of ARDS. Last, we identified IFI as an independent predictor of death. However, advances in antifungal therapy have improved the outcomes of patients with invasive aspergillosis [6, 47], or candidemia, a fact that may have decreased the mortality in this patient group during our most recent study period.

In summary, pulmonary or extrapulmonary infections caused up to 90 % of ARDS cases in patients with malignancies. IFIs accounted for one-third of these infections. Mortality has decreased significantly over time. NIV failure occurred in 70 % of the cases and was associated with death, most notably among patients with severe ARDS, in whom initial NIV is probably unwise. Among the three ARDS categories defined in the Berlin definition, only severe ARDS was associated with increased mortality. The high mortality in patients with IFIs indicates a pressing need for specific studies of early antifungal therapy in high-risk patients.

Acknowledgments French Ministry of Health.

Conflicts of interest Elie Azoulay is in the board of Gilead and has received research grant from MSD and Pfizer.

References

1. Azoulay E, Mokart D, Lambert J, Lemiale V, Rabbat A, Kouatchet A, Vincent F, Gruson D, Bruneel F, Epinette-Branche G, Lafabrie A, Hamidfar-Roy R, Cracco C, Renard B, Tonnelier JM, Blot F, Chevret S, Schlemmer B (2010) Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 182:1038–1046
2. Maschmeyer G, Beinert T, Buchheidt D, Cornely OA, Einsele H, Heinz W, Heussel CP, Kahl C, Kiehl M, Lorenz J, Hof H, Mattiuzzi G (2009) Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: guidelines of the infectious diseases working party of the German society of haematology and oncology. Eur J Cancer 45:2462–2472
3. Azevedo LC, Caruso P, Silva UV, Torelly AP, Silva E, Rezende E, Netto JJ, Piras C, Lobo SM, Knibel MF, Teles JM, Lima RA, Ferreira BS, Friedman G, Rea-Neto A, Dal-Pizzol F, Bozza FA, Salluh JI, Soares M (2014) Outcomes for patients with cancer admitted to the ICU requiring ventilatory support: results from a prospective multicenter study. Chest

4. Azoulay E, Thiery G, Chevret S, Moreau D, Darmon M, Bergeron A, Yang K, Meignin V, Ciroldi M, Le Gall JR, Tazi A, Schlemmer B (2004) The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 83:360–370
5. Azoulay E, Kouatchet A, Jaber S, Lambert J, Meziani F, Schmidt M, Schnell D, Mortaza S, Conseil M, Tchenio X, Herbecq P, Andrivet P, Guerot E, Lafabrie A, Perbet S, Camous L, Janssen-Langenstein R, Collet F, Messika J, Legriel S, Fabre X, Guisset O, Touati S, Kilani S, Alves M, Mercat A, Similowski T, Papazian L, Meert AP, Chevret S, Schlemmer B, Brochard L, Demoule A (2013) Noninvasive mechanical ventilation in patients having declined tracheal intubation. Intensive Care Med 39:292–301
6. Burghi G, Lemiale V, Seguin A, Lambert J, Lacroix C, Canet E, Moreau AS, Ribaud P, Schnell D, Mariotte E, Schlemmer B, Azoulay E (2011) Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis. Intensive Care Med 37:1605–1612
7. Groeger JS, Lemeshow S, Price K, Nierman DM, White P Jr, Klar J, Granovsky S, Horak D, Kish SK (1998) Multicenter outcome study of cancer patients admitted to the intensive care unit: a probability of mortality model. J Clin Oncol 16:761–770
8. Groeger JS, White P Jr, Nierman DM, Glassman J, Shi W, Horak D, Price K (1999) Outcome for cancer patients requiring mechanical ventilation. J Clin Oncol 17:991–997
9. Azoulay E, Alberti C, Bornstain C, Leleu G, Moreau D, Recher C, Chevret S, Le Gall JR, Brochard L, Schlemmer B (2001) Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. Crit Care Med 29:519–525
10. Mokart D, van Craenenbroeck T, Lambert J, Textoris J, Brun JP, Sannini A, Chow-Chine L, Hamouda S, Fouche L, Ettori F, Faucher M, Blache JL (2012) Prognosis of acute respiratory distress syndrome in neutropenic cancer patients. Eur Respir J 40:169–176
11. Tate RM, Repine JE (1983) Neutrophils and the adult respiratory distress syndrome. Am Rev Respir Dis 128:552–559
12. Ognibene FP, Martin SE, Parker MM, Schlesinger T, Roach P, Burch C, Shelhamer JH, Parrillo JE (1986) Adult respiratory distress syndrome in patients with severe neutropenia. N Engl J Med 315:547–551
13. Mokart D, Guery BP, Bouabdallah R, Martin C, Blache JL, Arnoulet C, Mege JL (2003) Deactivation of alveolar macrophages in septic neutropenic ARDS. Chest 124:644–652
14. Azoulay E, Darmon M, Delclaux C, Fieux F, Bornstain C, Moreau D, Attalah H, Le Gall JR, Schlemmer B (2002) Deterioration of previous acute lung injury during neutropenia recovery. Crit Care Med 30:781–786
15. Villar J, Perez-Mendez L, Blanco J, Anon JM, Blanch L, Belda J, Santos-Bouza A, Fernandez RL, Kacmarek RM (2013) A universal definition of ARDS: the PaO2/FiO2 ratio under a standard ventilatory setting—a prospective, multicenter validation study. Intensive Care Med 39:583–592
16. Azoulay E, Attalah H, Harf A, Schlemmer B, Delclaux C (2001) Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. Chest 120:1695–1701
17. Azoulay E, Fieux F, Moreau D, Thiery G, Rousselot P, Parrot A, Le Gall JR, Dombret H, Schlemmer B (2003) Acute monocytic leukemia presenting as acute respiratory failure. Am J Respir Crit Care Med 167:1329–1333
18. Sharma S, Nadrous HF, Peters SG, Tefferi A, Litzow MR, Aubry MC, Afessa B (2005) Pulmonary complications in adult blood and marrow transplant recipients: autopsy findings. Chest 128:1385–1392
19. Azoulay E, Mokart D, Pene F, Lambert J, Kouatchet A, Mayaux J, Vincent F, Nyunga M, Bruneel F, Laisne LM, Rabbat A, Lebert C, Perez P, Chaize M, Renault A, Meert AP, Benoit D, Hamidfar R, Jourdain M, Darmon M, Schlemmer B, Chevret S, Lemiale V (2013) Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol 31:2810–2818
20. Mokart D, Lambert J, Schnell D, Fouche L, Rabbat A, Kouatchet A, Lemiale V, Vincent F, Lengline E, Bruneel F, Pene F, Chevret S, Azoulay E (2013) Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. Leuk Lymphoma 54:1724–1729
21. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND (2009) Has mortality from acute respiratory distress syndrome decreased over time?: a systematic review. Am J Respir Crit Care Med 179:220–227
22. Schmidt M, Zogheib E, Roze H, Repesse X, Lebreton G, Luyt CE, Trouillet JL, Brechot N, Nieszkowska A, Dupont H, Ouattara A, Leprince P, Chastre J, Combes A (2013) The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 39:1704–1713
23. Soubani AO, Shehada E, Chen W, Smith D (2014) The outcome of cancer patients with acute respiratory distress syndrome. J Crit Care 29:183 e7–183 e12
24. Turkoglu M, Erdem GU, Suyani E, Sancar ME, Yalcin MM, Aygencel G, Aki Z, Sucak G (2013) Acute respiratory distress syndrome in patients with hematological malignancies. Hematology 18:123–130
25. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, Rhodes A, Slutsky AS, Vincent JL, Rubenfeld GD, Thompson BT, Ranieri VM (2012) The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 38:1573–1582
26. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307:2526–2533
27. Pene F, Percheron S, Lemiale V, Viallon V, Claessens YE, Marque S, Charpentier J, Angus DC, Cariou A, Chiche JD, Mira JP (2008) Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med 36:690–696
28. Legrand M, Max A, Peigne V, Mariotte E, Canet E, Debrumetz A, Lemiale V, Seguin A, Darmon M, Schlemmer B, Azoulay E (2012) Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 40:43–49

29. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Munoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE (2008) Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. Clin Infect Dis 46:1813–1821
30. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
31. Vesin A, Azoulay E, Ruckly S, Vignoud L, Rusinova K, Benoit D, Soares M, Azeivedo-Maia P, Abroug F, Benbenishty J, Timsit JF (2013) Reporting and handling missing values in clinical studies in intensive care units. Intensive Care Med 39:1396–1404
32. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L (2013) Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368:2159–2168
33. Hernu R, Wallet F, Thiolliere F, Martin O, Richard JC, Schmitt Z, Wallon G, Delannoy B, Rimmele T, Demaret C, Magnin C, Vallin H, Lepape A, Baboi L, Argaud L, Piriou V, Allaouchiche B, Aubrun F, Bastien O, Lehot JJ, Ayzac L, Guerin C (2013) An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. Intensive Care Med 39:2161–2170
34. Azoulay E, Canet E, Raffoux E, Lengline E, Lemiale V, Vincent F, de Labarthe A, Seguin A, Boissel N, Dombret H, Schlemmer B (2012) Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. Eur Respir J 39:648–653
35. Moreau AS, Lengline E, Seguin A, Lemiale V, Canet E, Raffoux E, Schlemmer B, Azoulay E (2014) Respiratory events at the earliest phase of acute myeloid leukemia. Leuk Lymphoma
36. Pene F, Aubron C, Azoulay E, Blot F, Thiery G, Raynard B, Schlemmer B, Nitenberg G, Buzyn A, Arnaud P, Socie G, Mira JP (2006) Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. J Clin Oncol 24:643–649
37. Depuydt PO, Benoit DD, Vandewoude KH, Decruyenaere JM, Colardyn FA (2004) Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. Chest 126:1299–1306
38. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, Guerin C, Schortgen F, Lefort Y, Antonelli M, Lepage E, Lemaire F, Brochard L (2000) Treatment of acute hypoxemic non hypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA 284:2352–2360
39. Adda M, Coquet I, Darmon M, Thiery G, Schlemmer B, Azoulay E (2008) Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. Crit Care Med 36:2766–2772
40. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 344:481–487
41. Azoulay E, Lemiale V (2012) Non-invasive mechanical ventilation in hematology patients with hypoxemic acute respiratory failure: a false belief? Bone Marrow Transplant 47:469–472
42. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S (2007) Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 356:335–347
43. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, Dhedin N, Isnard F, Ades L, Kuhnowski F, Foulet F, Kuentz M, Maison P, Bretagne S, Schwarzinger M (2009) Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 48:1042–1051
44. Chiumello D, Taccone P, Berto V, Marino A, Migliara G, Lazzerini M, Gattinoni L (2012) Long-term outcomes in survivors of acute respiratory distress syndrome ventilated in supine or prone position. Intensive Care Med 38:221–229
45. Gattinoni L, Pesenti A, Carlesso E (2013) Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure: impact and clinical fallout through the following 20 years. Intensive Care Med 39:1909–1915
46. Peigne V, Rusinova K, Karlin L, Darmon M, Fermand JP, Schlemmer B, Azoulay E (2009) Continued survival gains in recent years among critically ill myeloma patients. Intensive Care Med 35:512–518
47. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415

Diagnostic Strategy for Hematology and Oncology Patients with Acute Respiratory Failure

Randomized Controlled Trial

Élie Azoulay[1], Djamel Mokart[2], Jérôme Lambert[3], Virginie Lemiale[4], Antoine Rabbat[5], Achille Kouatchet[6], François Vincent[7], Didier Gruson[8], Fabrice Bruneel[9], Géraldine Epinette-Branche[1], Ariane Lafabrie[1], Rebecca Hamidfar-Roy[10], Christophe Cracco[11], Benoît Renard[12], Jean-Marie Tonnelier[13], François Blot[14], Sylvie Chevret[3], and Benoît Schlemmer[1]

[1]Medical Intensive Care Unit and [3]Biostatistics Department, Saint-Louis Teaching Hospital, Paris, France; [2]Paoli Calmette Institute, Marseille; [4]Cochin Teaching Hospital, Paris; [5]Hotel Dieu Teaching Hospital, Paris; [6]Angers Teaching Hospital, Angers; [7]Avicenne Teaching Hospital, Bobigny; [8]Pellegrin Teaching Hospital, Bordeaux; [9]Mignot Hospital, Le Chesmay; [10]Michallon Teaching Hospital, Grenoble; [11]Salpêtrière Teaching Hospital, Paris; [12]Regional Hospital Center, La Roche sur Yon; [13]Brest Teaching Hospital, Brest; and [14]Gustave Roussy Institute, Villejuif, France

***Rationale*: Respiratory events are common in hematology and oncology patients and manifest as hypoxemic acute respiratory failure (ARF) in up to half the cases. Identifying the cause of ARF is crucial. Fiberoptic bronchoscopy with bronchoalveolar lavage (FO-BAL) is an invasive test that may cause respiratory deterioration. Recent noninvasive diagnostic tests may have modified the risk/benefit ratio of FO-BAL.**

***Objectives*: To determine whether FO-BAL in cancer patients with ARF increased the need for intubation and whether noninvasive testing alone was not inferior to noninvasive testing plus FO-BAL.**

***Methods*: We performed a multicenter randomized controlled trial with sample size calculations for both end points. Patients with cancer and ARF of unknown cause who were not receiving ventilatory support at intensive care unit admission were randomized to early FO-BAL plus noninvasive tests (n = 113) or noninvasive tests only (n = 106). The primary end point was the number of patients needing intubation and mechanical ventilation. The major secondary end point was the number of patients with no identified cause of ARF.**

***Measurements and Main Results*: The need for mechanical ventilation was not significantly greater in the FO-BAL group than in the noninvasive group (35.4 vs. 38.7%; $P = 0.62$). The proportion of patients with no diagnosis was not smaller in the noninvasive group (21.7 vs. 20.4%; difference, −1.3% [−10.4 to 7.7]).**

***Conclusions*: FO-BAL performed in the intensive care unit did not significantly increase intubation requirements in critically ill cancer patients with ARF. Noninvasive testing alone was not inferior to noninvasive testing plus FO-BAL for identifying the cause of ARF.**

Clinical trial registered with www.clinicaltrials.gov (NCT00248443).

Keywords: neutropenia; bone marrow transplantation; polymerase chain reaction; nasopharyngeal aspirates; *Pneumocystis jiroveci* pneumonia

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Acute respiratory failure is the leading reason for intensive care unit admission in hematology and oncology patients and still carries a high mortality rate. Bronchoalveolar lavage is the cornerstone of the etiologic diagnosis. However, this procedure may be unsafe in patients who are hypoxemic. Recently developed noninvasive tests are now performed, a practice that may have affected the risk/benefit ratio of bronchoalveolar lavage.

What This Study Adds to the Field

In hematology and oncology patients with hypoxemic acute respiratory failure, fiberoptic bronchoscopy and bronchoalveolar lavage is safe when performed early after intensive care unit admission. However, this procedure added diagnostic information to that obtained by noninvasive tests in only 18% of patients and had little therapeutic impact. Noninvasive tests identified the cause of acute respiratory failure more frequently and more quickly than did bronchoalveolar lavage.

The number of patients treated for malignancies is increasing steadily (1–3). To achieve the highest possible cure rates, aggressive treatments have been introduced, including high-dose chemotherapy, stem-cell transplantation (4), and targeted therapies (5–8). As a result, overall and disease-free survival rates have improved substantially (9) at the price of life-threatening toxic and infectious complications, which chiefly target the lung. In patients with cancer, acute respiratory failure (ARF), the leading reason for intensive care unit (ICU) admission, still carries a 50% overall mortality rate (10, 11). Mortality rates are even higher when intubation is needed or the cause of ARF escapes identification (10, 12–14).

Cancer patients with ARF must receive immediate empirical therapy and supportive care in the ICU (15). The cause of ARF must be identified. The risk of death is higher when the cause of ARF remains unknown (10, 12–14). Fiberoptic bronchoscopy and bronchoalveolar lavage (FO-BAL) is now the cornerstone of the etiologic diagnosis. However, FO-BAL has been reported to induce hypoxia or cardiovascular alterations (16–19), most notably in patients with severe hypoxemia (20, 21), and ventilatory support may be required after the procedure (22–24). Furthermore, early FO-BAL provides the diagnosis in fewer than 50% of patients (13). Recently developed noninvasive tests on sputum (25), induced sputum (26), nasopharyngeal aspirates (27), serum (28, 29), and urine are now performed routinely (30). The risk/benefit ratio of FO-BAL may be less favorable now than before the introduction of these tests.

(*Received in original form January 6, 2010; accepted in final form June 25, 2010*)

Supported by a grant from the Assistance-Publique Hôpitaux de Paris (AOM 04,139) and the French Society for Intensive Care Medicine. Funded primarily by the French Ministry of Health.

This study was presented at the American Thoracic Society conference in San Diego (2009).

Correspondence and requests for reprints should be addressed to Élie Azoulay, M.D. Ph.D., AP-HP, Hôpital Saint-Louis, Medical ICU, 1 Avenue Claude Vellefaux, 75010 Paris, France. E-mail: elie.azoulay@sls.aphp.fr

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 182. pp 1038–1046, 2010
Originally Published in Press as DOI: 10.1164/rccm.201001-0018OC on June 25, 2010
Internet address: www.atsjournals.org

TABLE 1. PATIENT CHARACTERISTICS AT RANDOMIZATION

Characteristics	Routine Day 1 FO-BAL (*n = 113*)	± Day 3 FO-BAL (*n = 106*)
Age	62 (49–69)	61 (50–71)
Male sex	79 (69.9)	74 (69.8)
Underlying malignancy		
Acute leukemia	37 (32.7)	33 (31.1)
Non-Hodgkin lymphoma	21 (18.6)	24 (22.6)
Multiple myeloma	16 (14.2)	9 (8.5)
Hodgkin disease	3 (2.7)	5 (4.7)
Myelodysplastic syndrome	6 (5.3)	4 (3.8)
Chronic myeloid leukemia	1 (0.9)	2 (1.9)
Chronic lymphoid leukemia	5 (4.4)	10 (9.4)
Miscellaneous hematologic malignancies	3 (2.7)	6 (5.7)
Solid tumors*	21 (18.6)	13 (12.3)
Time (days) between diagnosis of the malignancy and ICU admission	185 (35–1,296)	254 (50–1,027)
Complete or partial remission of the malignancy	40 (36.7)	43 (41.8)
Hematopoietic stem cell transplantation		
Allogeneic	13 (11.5)	11 (10.4)
Autologous	16 (14.2)	14 (13.2)
Comorbidities		
Cardiovascular	43 (38.1)	41 (38.7)
Chronic respiratory insufficiency	21 (18.8)	13 (12.3)
Chronic renal insufficiency	6 (5.3)	6 (5.7)
Diabetes	15 (13.3)	8 (7.6)
At least one comorbidity	61 (54)	54 (50.9)
Time (days) from hospital to ICU admission	2 (0–14)	2 (1–12)
Time (days) between respiratory symptom onset and ICU admission	2 (0–5)	2 (1–6)
Pa_{O_2} (mm Hg) on room air at ICU admission	55 (48–64)	59 (50–64)
Pa_{CO_2} (mm Hg) at ICU admission	35 (32–42)	34 (29–39)
pH at ICU admission	7.43 (7.38–7.47)	7.45 (7.40–7.49)
Oxygen flow required, L/min	6 (4–15)	9 (5–15)
Number of quadrants involved on chest radiograph	2 (1–4)	3 (2–4)
Logistic Organ Dysfunction score	5 (2–6)	5 (2–7)
Clinical presentation		
Body temperature, °C	39 (38.2–39.5)	39 (38.3–39.6)
Cough	73 (64.6)	66 (62.9)
Chest pain	18 (16.7)	20 (19.5)
Purulent sputum	21 (18.6)	23 (21.9)
Diffuse crackles at lung auscultation	81 (71.7)	77 (72.6)
Skin rash	24 (21.2)	20 (18.9)
Gastrointestinal symptoms	24 (21.4)	19 (18.1)
Associated organ dysfunction at admission		
Hypotension	28 (25)	27 (25.5)
Acute kidney injury†	34 (30.1)	33 (31.1)
Confusion	21 (18.8)	15 (14.1)
Neutropenia at ICU admission	36 (33)	32 (31.4)
Time (days) from admission to randomization	0 (0–1)	0 (0–1)
Antibacterial agents at admission	88 (76.1)	86 (83)

Definition of abbreviations: FO-BAL = fiberoptic bronchoscopy with bronchoalveolar lavage; ICU = intensive care unit; Pa_{O_2} = partial pressure of oxygen in arterial blood; Pa_{CO_2} = partial pressure of carbon dioxide in arterial blood.

Values are presented as median (25th–75th percentiles)

* Solid tumors were lung cancers (n = 16); breast cancers (n = 6); gastrointestinal cancers (n = 4); and miscellaneous cancers (n = 8).

† Acute kidney injury was defined as an abrupt and sustained increase (×1.5) in the baseline creatinine level.

Neutropenia was a decrease in peripheral blood neutrophils to less than 500 cells per mm^3.

We conducted a multicenter randomized controlled trial to compare management strategies with and without FO-BAL in hypoxemic patients with ARF and hematologic or solid malignancies. Noninvasive tests were performed in all patients. The primary end point was the intubation rate. Diagnostic yield was the major secondary end point. Part of the study results have been previously reported in abstract form (31).

METHODS

Patients

We studied 219 critically ill cancer patients with ARF in 16 ICUs in France, who were randomly allocated to management with FO-BAL on Day 1 (invasive strategy) or no FO-BAL (noninvasive strategy). Noninvasive tests were performed in all patients. A computer-generated random allocation sequence was prepared by the statistician. Randomization was stratified by center and used permuted blocks of size six. Group assignment was done by calling a central telephone system to ensure allocation concealment. Blinding was not feasible, because FO-BAL was performed on Day 1 in one of the groups.

Consecutive patients with cancer requiring ICU admission for ARF were eligible. ARF was defined as oxygen saturation less than 90% or Pa_{O_2} less than 60 mm Hg on room air combined with severe dyspnea at rest with inability to speak in sentences or respiratory rate greater than 30 breaths per minute or clinical signs of respiratory distress.

Patients with contraindications to FO-BAL (coma, shock, or Sa_{O_2} <90% while breathing oxygen through a Venturi mask) were not included. We did not include patients with cardiogenic pulmonary edema, ARF due to known causes, endotracheal mechanical ventilation, treatment-limitation decisions, pregnancy or lactation, or previous enrollment in this or another interventional trial. The appropriate ethics committee approved the study in March 2005. We obtained written informed consent from all patients.

TABLE 2. CAUSES OF ACUTE RESPIRATORY FAILURE IN THE TWO DIAGNOSTIC-STRATEGY GROUPS

Cause	Routine Day 1 FO-BAL, N = 113 (%)	N (%) Diagnosed by BAL	± Day 3 FO-BAL, N = 106 (%)	N (%) diagnosed by BAL
Bacterial pneumonia	47 (41.6)		39 (36.8)	
Microbiologically documented	32 (68)	17 (36.2)	27 (70)	4 (10.2)
Clinically documented	15 (32)	—	12 (30)	—
Viral pneumonia	7 (6.2)	6 (86)	19 (17.9)	10 (55.5)
Invasive yeast and mold infections	14 (12.4)	7 (50)	9 (8.5)	3 (33.3)
Including invasive pulmonary aspergillosis only	10 (8.8)	6 (60)	8 (7.5)	3 (37)
Pneumocystis pneumonia*	9 (8)	9 (100)	10 (9.4)	1 (10)
Pulmonary infiltration by the malignancy	10 (8.8)	3 (30)	6 (5.7)	0
Cardiogenic pulmonary edema	7 (6.2)	0	3 (2.8)	0
Respiratory failure during neutropenia recovery	2 (1.8)	0	1 (0.9)	0
Pulmonary toxoplasmosis	1 (0.9)	1 (100)	1 (0.9)	0
Pulmonary tuberculosis	0		1 (0.9)	0
Cryptogenic organizing pneumonia	1 (0.9)	0	1 (0.9)	0
Idiopathic alveolar hemorrhage	1 (0.9)	1 (100)	0	
Miscellaneous†	2 (1.8)	0	3 (2.8)	0
Total number of identified causes	101		93	
Patients with two identified causes	7 (6.2)		8 (7.5)	
Patients with three identified causes	2 (1.8)		1 (0.9)	
No identified cause	23 (20.3)		23 (21.7)	

Definition of abbreviation: FO-BAL = fiberoptic bronchoscopy with bronchoalveolar lavage. Definition of cardiac dysfunction is detailed in the online supplement.

* Although polymerase chain reaction testing was positive in all cases of *Pneumocystis* pneumonia, retrieval of the pathogen in induced sputum or BAL fluid was required for the diagnosis.

† The five diagnoses were drug-related pulmonary toxicity (n = 2); alveolar proteinosis (n = 1); nontumoral eosinophilic pneumonia (n = 1); and capillary leak syndrome (n = 1).

Data in Tables 1–4 were collected prospectively. We recorded the time from ICU admission to diagnosis of the cause of ARF. Comorbidities were assessed using the Charlson-Deyo score (32). The Logistic Organ Dysfunction score was determined to assess the severity of organ dysfunctions (33). Patients were monitored daily for clinically or microbiologically documented infection and organ dysfunction. The durations of endotracheal and noninvasive mechanical ventilation and the lengths of the ICU and hospital stays were recorded.

To standardize sample collection and processing, we developed a manual that was accepted by all participating laboratories before study initiation. It was included in the case-record form and faxed to each center after each patient was randomized.

In both groups, 10 sets of noninvasive tests were performed on ICU admission (Table 4). In the invasive-strategy group, the ICU physician or attending pulmonologist performed FO-BAL, as described elsewhere (12, 34, 35), in the affected lung region identified clinically or by chest radiography or computed tomography. Details on sample collection are provided in the online supplement. BAL fluid was sent to several laboratories for testing. In the noninvasive-strategy group, FO-BAL was performed after Day 3 if the cause of ARF remained unknown. As detailed in the online supplement, positive noninvasive tests were not necessarily considered diagnostic. Instead, the results were interpreted according to published data. Thus, a positive polymerase chain reaction test for *Pneumocystis jiroveci* was not sufficient to diagnose *Pneumocystis* pneumonia (31), and presence of *Aspergillus* spp. in BAL fluid or sputum was taken to indicate invasive aspergillosis only in patients with compatible clinical and computed tomography findings or positive antigenemia (36). All diagnoses of invasive fungal infections were made according to the criteria of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (36). *Candida* spp. in BAL fluid or sputum was taken to indicate colonization but not infection (37). Positive cytomegalovirus polymerase chain reaction test or antigenemia was not sufficient for the diagnosis of cytomegalovirus pneumonia (38).

Etiologic diagnoses of ARF were established by the investigators according to preestablished definitions that were validated by each participating ICU in a previous prospective noninterventional study by

TABLE 3. OUTCOMES AND ICU MANAGEMENT IN THE TWO DIAGNOSTIC-STRATEGY GROUPS

	Routine Day 1 FO-BAL (*n = 113*)	Noninvasive Group (*n = 106*)	
Primary end point			*P* Value
Need for endotracheal mechanical ventilation, pts	40	41	0.68
Estimated rate (95% CI)	35.4% (26.6–45)	38.7% (29.4–48.7)	OR = 0.87 (0.50–1.50) Adjusted OR* = 1.11 (0.58–2.11); *P* = 0.76
Major secondary end point			
Number of patients with no identified diagnosis	23	23	Between-group risk difference (90% CI),%
Estimated rate (95% CI)	20.4% (13.4–29)	21.7% (14.3–30.8)	−1.3 (−10.4 to 7.7)
Other secondary end points			*P* value
Day 28 deaths	33	35	
Estimated rate (95% CI)	29.2% (21–38.5)	33% (24.2–42.8)	0.56
Median number of antibiotic-free days (Q1–Q3)	2 (0–2)	2 (0–3)	0.78
ICU-acquired infections	9	13	
Estimated rate (95% CI)	8% (3.7–14.6)	12.2% (6.7–20.1)	0.37
Acquisition of multiresistant bacteria	6	10	
Estimated rate (95% CI)	25.3% (2–11.2)	9.4% (4.6–16.7)	0.30

Definition of abbreviations: CI = confidence interval; FO-BAL = fiberoptic bronchoscopy with bronchoalveolar lavage; ICU = intensive care unit; OR = odds ratio; Q1–Q3 = interquartile range (25th–75th percentile).

* Estimated odds ratio adjusted on site effects and on predictors of mechanical ventilation (gastrointestinal symptoms, oxygen flow required at ICU admission, number of quadrants involved on chest radiograph, and Logistic Organ Dysfunction score at ICU admission).

TABLE 4. INFECTIONS DIAGNOSED BY NONINVASIVE TESTS

Test/Infections	Actually Performed*	Positive Test	Diagnostic Test†
1. Imaging studies		Not sufficient for diagnosing pulmonary infections	
Chest radiograph	219		
High-resolution computed tomography	191		
2. Echocardiography	191	For diagnosing cardiogenic ulmonary edema only	
3. Sputum examination for			
Bacteria	194	39	34
Candida spp.	193	8	0
Other fungi	193	8	6
Tuberculosis	193	1	1
4. Induced sputum (*P. jiroveci*)	148	10	10
5. Nasopharyngeal aspirates	190	18	16
6. Blood cultures	219	27	25
7. Polymerase chain reaction test for			
Herpes viridae	184	9	3
Cytomegalovirus	219	10	3
8. Circulating *Aspergillus* galactomanan	219	11	11
9. Serologic tests for			
Chlamydiae pneumoniae	203	1	1
Mycoplasma pneumoniae	203	2	2
Legionella pneumophila	203	3	3
10. Urine antigen for			
Legionella pneumophila	214	1	1
Streptococcus pneumoniae	214	5	5

* Reasons for not performing noninvasive tests were early endotracheal mechanical ventilation or identification of a diagnosis within hours after randomization. In addition, sputum could not be obtained from 6 patients and induced sputum was not collected in 22 patients.

† The following positive tests were not considered diagnostic: blood cultures positive for coagulase-negative *Staphylococcus*, n = 2; sputum positive for coagulase-negative *Staphylococcus*, n = 2; sputum positive for *Stenotrophomonas maltophilia*, n = 1; sputum positive for *Pseudomonas aeruginosa*, n = 1; sputum positive for fungi, n = 10 (8 *Candida* spp., 1 *Aspergillus*, and 1 *Rhizopus* sp.); influenza viruses considered confined to the upper respiratory tract with other pathogens responsible for the pulmonary infiltrates, n = 2; and viral reactivation with positive serum polymerase chain reaction for herpes virus (n = 6) or cytomegalovirus (n = 7) but no evidence of herpes or cytomegalovirus pneumonia.

the same research group (12). Because blinding of the investigators to group assignment was not feasible, the diagnoses were reviewed centrally by an independent committee (*see* ACKNOWLEDGMENT) whose members were blinded to group assignment.

In both groups, empirical antibiotic therapy, ventilatory assistance (high-flow oxygen, noninvasive or endotracheal mechanical ventilation), and other life-supporting treatments were used according to published guidelines (12, 13). In all 16 centers, standardized criteria were used to decide when noninvasive or endotracheal mechanical ventilation was appropriate. FO-BAL was performed routinely when intubation was required.

When designing this study, we recognized that two questions were of major clinical interest: safety and efficacy of FO-BAL. Thus, one question was whether FO-BAL induced respiratory deterioration requiring intubation. The other question was whether a diagnostic strategy that did not include FO-BAL was at least as effective in terms of diagnostic yield as a strategy with FO-BAL. Given evidence in the literature that FO-BAL was associated with respiratory deterioration (12, 22–24), we chose the intubation rate as our primary end point. However, we performed a second sample-size calculation to evaluate whether the noninvasive strategy was not inferior in terms of diagnostic yield, which was our major secondary end point. The required sample size was larger for the primary end point than for the major secondary end point. Other secondary end points were 28-day mortality, ICU-acquired infections, number of antibiotic-free days, and infection by multiresistant bacteria.

Statistical Analysis

Assuming a baseline intubation rate of 70% in cancer patients with ARF (12–14, 39, 40), we needed 208 patients to have 85% power for detecting a 20% absolute intubation-rate decrease with a two-sided chi-square test and α set at 0.05.

We also computed the sample size needed to demonstrate noninferiority of the noninvasive strategy for identifying the cause of ARF, which was our major secondary end point. With α set at 0.05, 206 patients were needed to have 85% power for excluding an at least 15% between-group difference. In previous studies, 20% of patients had no diagnosis (41). We decided to include 220 patients overall.

The statistical analysis was planned before study initiation. No interim analyses were done, but serious adverse events were continuously recorded and analyzed then immediately communicated to the French health authorities. Group comparisons were performed on an intention-to-treat basis. Data are reported as numbers (percentages) or medians (interquartile ranges: 25th–75th percentiles). Continuous variables were compared using the Wilcoxon rank sum test and proportions using the Fisher exact test. Exact 95% confidence intervals (CI) were calculated for proportions. For the primary end point (need for intubation), an adjusted odds ratio was calculated using a logistic mixed model with center as a random effect and a set of predictors of intubation as fixed effects. Prognostic analyses based on logistic regression were performed after multiple imputation for missing data. For exploratory purposes, similar analyses were performed in the subset of patients not intubated on Day 1.

When estimating the cumulative intubation rate (primary criterion), the competing risks of death and ICU discharge before intubation were taken into account. Noninferiority of the noninvasive strategy (major secondary criterion) was established if the upper limit of the 90% CI around the estimate of the percentage-points difference was less than 15%. Overall survival was estimated using the Kaplan-Meier method, then compared using the log-rank test. All analyses were performed on SAS software, version 8.2 (SAS Institute, Cary, NC) and R version 2.8.1. (http://www.R-project.org).

The funding sources had no role in the design, conduct, or data analysis of the present study or in the decision to submit the manuscript for publication.

RESULTS

Among the 314 patients with cancer admitted for ARF to the 16 participating ICUs between September 2005 and November 2007, 220 were randomized (Figure 1). One patient withdrew informed consent on Day 1, leaving 219 patients, 113 in the

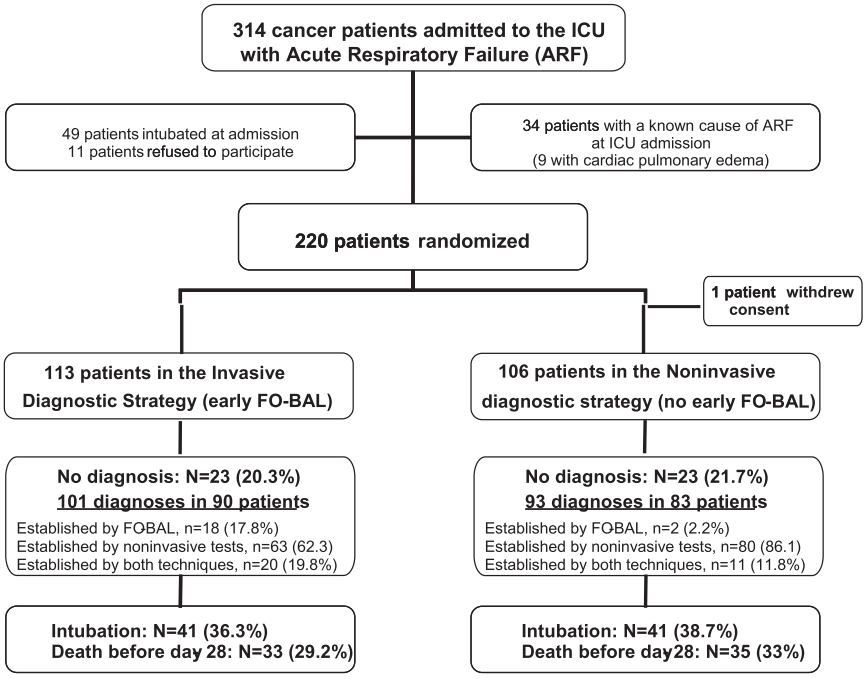

Figure 1. Patient flow chart. ARF = acute respiratory failure; FO-BAL = fiberoptic bronchoscopy with bronchoalveolar lavage; ICU = intensive care unit; invasive strategy = group managed with routine FO-BAL within 1 day of ICU admission; noninvasive strategy = group managed without FO-BAL unless the cause of acute respiratory failure remained unknown on Day 3.

invasive-strategy group and 106 in the noninvasive-strategy group. Table 1 reports the main patient characteristics at ICU admission, which were balanced between the groups. All patients had a fever and severe hypoxemia requiring oxygen therapy. The two groups were balanced in terms of ARF severity. At admission, 174 (79.5%) patients were receiving one or more antibacterial agents, combined with an antifungal agent in 65 (29.7%) patients and an antiviral agent in 36 (16.4%) patients. No statistically significant between-group differences were found regarding the antibiotic classes used (*see* the online supplement). Among the 219 patients, 186 (85%) had recently received cancer chemotherapy; time from chemotherapy to ICU admission was 16 (7–54) days; and 68 (31%) patients had neutropenia at ICU admission.

Table 2 reports the etiologic diagnoses and the percentage of diagnoses provided by noninvasive tests. Bacterial infection was the leading etiology, followed by infections by viruses, yeasts and molds, or *Pneumocystis*. In the invasive-strategy group, FO-BAL was diagnostic in 35 (34%) of the 104 patients who had FO-BAL (reasons for not performing FO-BAL are reported in the online supplement), including 16 whose diagnosis was also established by noninvasive tests, leaving 19 diagnoses in 18 patients whose diagnosis was established only by FO-BAL. The 19 diagnoses were as follows: bacterial pneumonia, n = 8; *Pneumocystis* pneumonia, n = 4; viral pneumonia, n = 2; pulmonary infiltration by the malignancy, n = 2; invasive pulmonary aspergillosis, n = 1; pulmonary toxoplasmosis, n = 1; and idiopathic alveolar hemorrhage, n = 1.

The complete set of noninvasive tests was performed in 93 (88%) noninvasive-strategy patients and 96 (85%) invasive-strategy patients (reasons for not performing noninvasive tests are reported in the online supplement). Noninvasive tests (Tables 3 and 4) supplied the diagnosis in 134 (70.9%) of 189 patients. In the noninvasive-strategy group, 38 (36%) patients underwent FO-BAL either at intubation or after Day 3, which provided a diagnosis not found by noninvasive tests in two patients.

As shown in Table E2 of the online supplement, 86 patients had a diagnosis of bacterial pneumonia; 59 (68.6%) were microbiologically documented and 27 (31.4%) were clinically documented. Table 4 shows that 34 diagnoses were made by sputa examinations, 25 by blood cultures, 6 by serologic tests, and 6 by urine antigens. Nine patients had both positive sputum and blood cultures. Three patients had positive blood culture and urine antigen yielding streptococcus pneumonia. One patient had positive sputum and urine antigen identifying pneumococcal disease. In addition, 21 BAL identified causative bacteria, including 4 patients from the noninvasive group who were intubated at Day 1 and had bronchoscopy and BAL.

In the invasive-strategy group, FO-BAL results influenced treatment decisions in 34 (32.7%) of 104 patients, including 11 in whom a treatment was introduced, 10 in whom a treatment was stopped, and 13 in whom narrower-spectrum antimicrobial agents were given. A larger proportion of patients had treatment changes related to FO-BAL among the 35 patients whose FO-BAL was diagnostic than among the other 69 patients (47 vs. 12%; $P < 0.001$). Noninvasive tests influenced treatment decisions in 41 (44%) of the 93 noninvasive-strategy patients who had the complete set of noninvasive tests.

When the diagnosis was identified by both FO-BAL and noninvasive tests, time from ICU admission to diagnosis was 65 (21–87) hours by FO-BAL and 47 (16–72) hours by noninvasive tests ($P = 0.002$). The diagnosis was made by noninvasive tests first in 49% of cases, FO-BAL first in 15%, and both simultaneously in 36% ($P = 0.037$). Time to diagnosis for bacterial pneumonia, non-*Aspergillus* and *Pneumocystis* fungal pneumonia, and viral infections was shorter in the noninvasive-strategy group than in the invasive-strategy group (1 [0–2] vs. 2 [0.5–4] days; 1 [1–1.5] vs. 2.5 [2–3]; and 2 [1–3] vs. 4.5 [3–6] days, respectively). The diagnosis of *Pneumocystis* pneumonia took longer in the noninvasive-strategy group (3 [−7] days vs. 1 [0–1] day).

Among the 106 patients who were not intubated at the time of FO-BAL, 39 (36.8%) received noninvasive ventilation during the procedure (*see* Table E1). In the invasive-strategy group, of the 95 patients who were not intubated at the time of FO-BAL, 24 (25.3%) experienced substantial respiratory deterioration induced by FO-BAL. Noninvasive ventilation was required in 13 of these patients and intubation in 11. All patients in the noninvasive-strategy group who underwent FO-BAL because they had no etiologic diagnosis by Day 3 required intubation after the procedure.

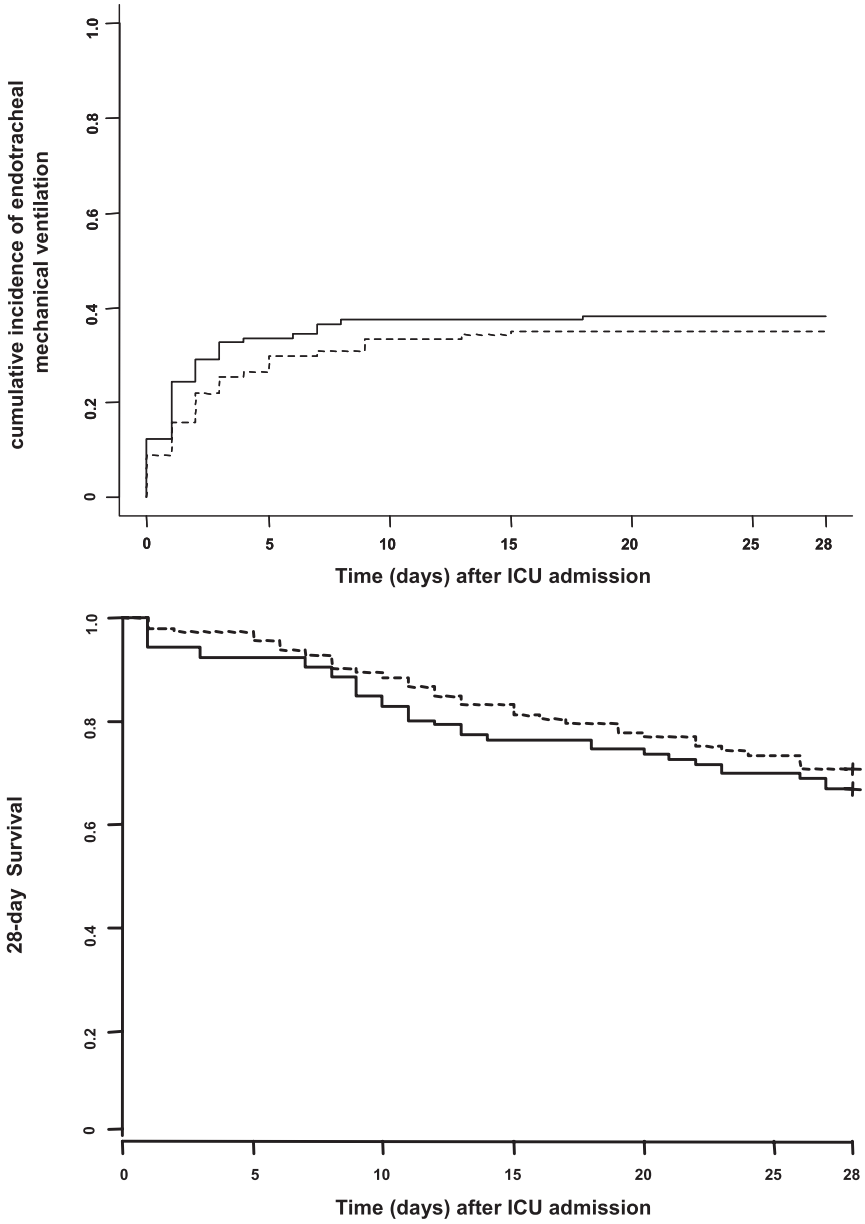

Figure 2. Need for endotracheal mechanical ventilation and 28-day mortality in the two groups. The solid line represents patients in the noninvasive-strategy group and the dotted line patients in the invasive-strategy group. ICU = intensive care unit.

There was no statistically significant difference in the primary end point (i.e., need for intubation) between the two groups (Table 3, Figure 2). When only patients not intubated on Day 1 were considered, no statistically significant difference in intubation rates was found between the groups. No statistically significant differences in outcomes occurred across the 16 participating ICUs.

The noninvasive strategy was not inferior to the invasive strategy: 23 patients in each group had no diagnosis (20.4 vs. 21.7%, absolute difference −1.3%; 90% CI, −10.4% to 7.7%). There were no significant differences in baseline characteristics between the group of patients with at least one diagnosis and the group of patients with no identified diagnosis. Failure to establish the diagnosis was not significantly more common in the patients on empirical antimicrobial therapy at the time of the diagnostic evaluation, compared with the other patients.

No differences were found for any of the other secondary end points (Table 3). In the invasive-strategy group, no statistically significant difference in the intubation or Day 28 mortality rate was found among the 34 patients in whom FOBAL influenced treatment decisions and the other patients.

Duration of endotracheal mechanical ventilation was 8 (4–17) days; ICU length of stay was 8 (4–14) days; and hospital stay length was 20 (11–32) days. None of these durations showed statistically significant differences between the two groups.

Time from hospital to ICU admission was more than 2 days in 106 (48%) patients. The number of patients admitted within 2 days of hospital admission was equally distributed in the two randomized groups (48 vs. 49%; $P = 0.89$). Diagnostic yield from BAL or noninvasive tests, and the distribution of each single diagnosis, was similar in patients admitted to the ICU before or after 2 days from hospital admission. Similarly, the number of patients with documented resistant bacteria was not different. However, there were more undetermined diagnoses in patients admitted before than after 2 days of hospital admission (27 vs. 15%; $P = 0.04$). Nevertheless, need for mechanical ventilation and Day 28 mortality were not significantly different between these two groups (*see* Table E3).

DISCUSSION

This study produced two major findings. First, in cancer patients with hypoxemic ARF, FO-BAL performed in the ICU was safe, with no increase in the need for endotracheal mechanical ventilation. Second, the noninvasive strategy was not inferior to the invasive strategy in terms of diagnostic yield and, overall, noninvasive diagnostic tests had a higher diagnostic yield than FO-BAL. Also, we found no statistically significant difference in 28-day mortality between the two study groups, and the time to diagnosis was shorter for the noninvasive approach, except when the diagnosis was *Pneumocystis* pneumonia.

Our finding that routine FO-BAL did not increase the need for intubation contradicts previous studies in ICU patients (12, 42) or hematology-ward patients (22–24). Factors that may have improved the tolerance of FO-BAL in our patients include performance of all FO-BAL procedures in the ICU under close monitoring. Moreover, approximately 37% of the FO-BAL procedures were assisted with noninvasive mechanical ventilation, which probably significantly influenced both the incidence of respiratory deterioration after bronchoscopy and the diagnostic yield of FO-BAL (12, 43, 44). All 11 (10%) noninvasive-strategy patients who had FO-BAL on Day 3 required intubation, in keeping with earlier studies showing worse outcomes in patients with no diagnosis (10, 12–14). However, whether FO-BAL contributed to the need for intubation in this subgroup is unclear.

The diagnostic yield was not lower without routine FO-BAL. In earlier studies, FO-BAL provided the diagnosis in only half the cases at best and prompted treatment changes in only one-third of cases (13, 42). The first comparison of FO-BAL and noninvasive tests showed similar yields (41). In another study, combining BAL and sputum analysis increased the diagnostic yield (45). In a noninterventional cohort study (12), noninvasive tests were positive in 66.7% of patients, adding substantially to FO-BAL (12), but selection bias could not be ruled out. The randomized controlled study reported here provides convincing evidence that the noninvasive strategy is safe and effective, even in patients with polymicrobial infections (46). FO-BAL added no diagnostic information in 82% of patients.

In the invasive-strategy group, FO-BAL was performed within 24 hours after ICU admission, provided the diagnosis in 34% of patients, and was the only diagnostic test in 18% of patients. Given the absence of statistically significant respiratory deterioration after FO-BAL performed in the ICU, FO-BAL should be considered within the first 24 hours after ICU admission (47). The 11 patients in the noninvasive-strategy group who had no identified diagnosis on Day 3 and in whom FO-BAL was performed required intubation, and 6 of them died in the ICU. Studies are needed to evaluate specifically the diagnostic yield of late FO-BAL and the contribution of pulmonary biopsy in patients with negative noninvasive tests.

Our study has several limitations. First, our results may not apply to hypoxemic patients in hospital wards, in whom poor tolerance of FO-BAL has been reported (13, 22–24, 42). Second, the high diagnostic yield of noninvasive tests might be ascribable to diagnoses being based on inadequate data. However, predefined definitions were met for each diagnosis and validated by independent experts. Lung biopsies in patients with no identified diagnosis and autopsies in patients who died would probably have provided valuable information. Nevertheless, we designed our study to be as relevant to clinical practice as possible, and in clinical practice lung biopsy and autopsy are rarely performed. Third, the low diagnostic yield of FO-BAL in our study (34%) may have masked inferiority of the noninvasive strategy. However, in a previous literature review, the yield of FO-BAL was less than 50% in patients who usually had the procedure outside the ICU. In our study, 80% of patients were receiving antimicrobials at the time of FO-BAL, which probably decreased the diagnostic yield and therapeutic impact of FO-BAL. However, this high rate of antimicrobial treatment reflects clinical reality. Moreover, the rate of treatment changes based on test results cannot be interpreted, because the study protocol did not mandate such changes. Fourth, 19 (41.3%) of the 46 patients with undetermined diagnoses died, including 13 patients who died in the ICU. Lung biopsy was not performed in any of these patients. They required intubation shortly after ICU admission, died after only 3 (2–7) days in the ICU, and had severe hypoxemia, so that surgical biopsy carried unacceptable risks. The five patients who underwent lung biopsy were patients with lymphoma who remained stable over time, although dependent on oxygen. In all five patients, the biopsy showed pulmonary infiltration by the malignancy, and all these patients survived. Fifth, the fact that all our patients presented with hypoxemia and organ failures may limit the applicability of our results. Also, most excluded patients were intubated at admission. Therefore, the trial results do not apply to patients intubated at admission. Sixth, the fact that time to etiologic diagnosis (except *Pneumocystis carinii* pneumonia) was shorter for the noninvasive group may be a consequence that all institutions did not have full-time invasive testing. Finally, our results in cancer patients may not apply to patients with other causes of immunodeficiency.

Conclusions

In hematology and oncology patients with early hypoxemic ARF, FO-BAL is safe when performed in the ICU. Noninvasive diagnostic tests provide the diagnosis in most of these patients. Because 18% of patient diagnoses are made only by FOB-BAL, this procedure should be added to noninvasive tests if feasible early after ICU admission.

Author Disclosure: E.A. received $1,001–$5,000 from Pfizer in advisory board fees; $1,001–$5,000 from Pfizer, $1,001–$5,000 from Gilead in lecture fees; and $10,001–$50,000 from Pfizer France in industry-sponsored grants. D.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. V.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.E-B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.H-R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J-M.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank Professor Laurent Brochard, Créteil, France, for helping to design the study. They also thank the independent experts who reviewed and validated the etiologic diagnoses: Professor Bernard Maitre, Créteil, France; Professor Gilles Hilbert, Bordeaux, France; and Professor

Vincent Levy, Bobigny, France. The authors are indebted to A. Wolfe for helping to prepare the manuscript. No potential conflict of interest relevant to this article was reported.

References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, *et al.* Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9:730–756.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
3. Kinsey T, Jemal A, Liff J, Ward E, Thun M. Secular trends in mortality from common cancers in the United States by educational attainment, 1993–2001. *J Natl Cancer Inst* 2008;100:1003–1012.
4. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, Fassas A, Zangari M, Hollmig K, Pineda-Roman M, *et al.* Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006;354:1021–1030.
5. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, *et al.* Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994–1004.
6. Thomas MB, Abbruzzese JL. Opportunities for targeted therapies in hepatocellular carcinoma. *J Clin Oncol* 2005;23:8093–8108.
7. Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R, Cortes J, O'Brien S, Nicaise C, Bleickardt E, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006;354:2531–2541.
8. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, *et al.* CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;7:379–391.
9. Brenner H, Gondos A, Arndt V. Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. *J Clin Oncol* 2007;25:3274–3280.
10. Azoulay E, Thiery G, Chevret S, Moreau D, Darmon M, Bergeron A, Yang K, Meignin V, Ciroldi M, Le Gall JR, *et al.* The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine (Baltimore)* 2004;83:360–370.
11. Chaoui D, Legrand O, Roche N, Cornet M, Lefebvre A, Peffault de Latour R, Sanhes L, Huchon G, Marie JP, Rabbat A. Incidence and prognostic value of respiratory events in acute leukemia. *Leukemia* 2004;18:670–675.
12. Azoulay E, Mokart D, Rabbat A, Pene F, Kouatchet A, Bruneel F, Vincent F, Hamidfar R, Moreau D, Mohammedi I, *et al.* Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. *Crit Care Med* 2008;36:100–107.
13. Azoulay E, Schlemmer B. Diagnostic strategy in cancer patients with acute respiratory failure. *Intensive Care Med* 2006;32:808–822.
14. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481–487.
15. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. *Crit Care Med* 2007;35:808–814.
16. Gibson PG, Breit SN, Bryant DH. Hypoxia during bronchoalveolar lavage. *Aust N Z J Med* 1990;20:39–43.
17. Hertz MI, Woodward ME, Gross CR, Swart M, Marcy TW, Bitterman PB. Safety of bronchoalveolar lavage in the critically ill, mechanically ventilated patient. *Crit Care Med* 1991;19:1526–1532.
18. Davies L, Mister R, Spence DP, Calverley PM, Earis JE, Pearson MG. Cardiovascular consequences of fibreoptic bronchoscopy. *Eur Respir J* 1997;10:695–698.
19. Bauer TT, Torres A, Ewig S, Hernandez C, Sanchez-Nieto JM, Xaubet A, Agusti C, Rodriguez-Roisin R. Effects of bronchoalveolar lavage volume on arterial oxygenation in mechanically ventilated patients with pneumonia. *Intensive Care Med* 2001;27:384–393.
20. Verra F, Hmouda H, Rauss A, Lebargy F, Cordonnier C, Bignon J, Lemaire F, Brochard L. Bronchoalveolar lavage in immunocompromised patients. Clinical and functional consequences. *Chest* 1992;101:1215–1220.
21. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001;56:i1–i21.
22. Dunagan DP, Baker AM, Hurd DD, Haponik EF. Bronchoscopic evaluation of pulmonary infiltrates following bone marrow transplantation. *Chest* 1997;111:135–141.
23. White P, Bonacum JT, Miller CB. Utility of fiberoptic bronchoscopy in bone marrow transplant patients. *Bone Marrow Transplant* 1997;20:681–687.
24. Murray PV, O'Brien ME, Padhani AR, Powles R, Cunningham D, Jeanes A, Ashley S. Use of first line bronchoalveolar lavage in the immunosuppressed oncology patient. *Bone Marrow Transplant* 2001;27:967–971.
25. Danes C, Gonzalez-Martin J, Pumarola T, Rano A, Benito N, Torres A, Moreno A, Rovira M, Puig de la Bellacasa J. Pulmonary infiltrates in immunosuppressed patients: analysis of a diagnostic protocol. *J Clin Microbiol* 2002;40:2134–2140.
26. Kovacs JA, Gill VJ, Meshnick S, Masur H. New insights into transmission, diagnosis, and drug treatment of *Pneumocystis carinii* pneumonia. *JAMA* 2001;286:2450–2460.
27. Martino R, Ramila E, Rabella N, Munoz JM, Peyret M, Portos JM, Laborda R, Sierra J. Respiratory virus infections in adults with hematologic malignancies: a prospective study. *Clin Infect Dis* 2003;36:1–8.
28. Schvoerer E, Henriot S, Zachary P, Freitag R, Fuchs A, Fritsch S, Risch S, Meyer N, Caillard S, Lioure B, *et al.* Monitoring low cytomegalovirus viremia in transplanted patients by a real-time PCR on plasma. *J Med Virol* 2005;76:76–81.
29. Maertens J, Van Eldere J, Verhaegen J, Verbeken E, Verschakelen J, Boogaerts M. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. *J Infect Dis* 2002;186:1297–1306.
30. Roson B, Fernandez-Sabe N, Carratala J, Verdaguer R, Dorca J, Manresa F, Gudiol F. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. *Clin Infect Dis* 2004;38:222–226.
31. Azoulay E, Mokart D, Lemiale V, Rabbat A, Kouatchet A, Vincent F, Gruson D, Bruneel F, Hamidfar R, Cracco C, *et al.* Diagnostic strategies in cancer patients with acute respiratory failure: a multicentre randomized controlled trial. *Am J Respir Crit Care Med* 2009;179:A1560.
32. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–619.
33. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D. The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *JAMA* 1996;276:802–810.
34. Azoulay E, Parrot A, Flahault A, Cesari D, Lecomte I, Roux P, Saidi F, Fartoukh M, Bernaudin JF, Cadranel J, *et al.* AIDS-related *Pneumocystis carinii* pneumonia in the era of adjunctive steroids: implication of BAL neutrophilia. *Am J Respir Crit Care Med* 1999;160:493–499.
35. Azoulay E, Fieux F, Moreau D, Thiery G, Rousselot P, Parrot A, Le Gall JR, Dombret H, Schlemmer B. Acute monocytic leukemia presenting as acute respiratory failure. *Am J Respir Crit Care Med* 2003;167:1329–1333.
36. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, Denning DW, Donnelly JP, Edwards JE, Erjavec Z, *et al.* Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002;34:7–14.
37. Azoulay E, Mayaud C. Candida pneumopathy: fact or fiction? *Rev Pneumol Clin* 1999;55:349–351.
38. Gentile G, Donati PP, Capobianchi A, Rolli M, Iori AP, Martino P. Evaluation of a score system for the severity and outcome of cytomegalovirus interstitial pneumonia in allogeneic bone marrow recipients. *J Infect* 1997;35:117–123.
39. Kress JP, Christenson J, Pohlman AS, Linkin DR, Hall JB. Outcomes of critically ill cancer patients in a university hospital setting. *Am J Respir Crit Care Med* 1999;160:1957–1961.
40. Gruson D, Hilbert G, Valentino R, Vargas F, Chene G, Bebear C, Allery A, Pigneux A, Gbikpi-Benissan G, Cardinaud JP. Utility of fiberoptic bronchoscopy in neutropenic patients admitted to the intensive care unit with pulmonary infiltrates. *Crit Care Med* 2000;28:2224–2230.
41. Rano A, Agusti C, Jimenez P, Angrill J, Benito N, Danes C, Gonzalez J, Rovira M, Pumarola T, Moreno A, *et al.* Pulmonary infiltrates in

non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures. *Thorax* 2001;56:379–387.
42. Rabbat A, Chaoui D, Lefebvre A, Roche N, Legrand O, Lorut C, Rio B, Marie JP, Huchon G. Is BAL useful in patients with acute myeloid leukemia admitted in ICU for severe respiratory complications? *Leukemia* 2008;22:1361–1367.
43. Antonelli M, Conti G, Riccioni L, Meduri GU. Noninvasive positive-pressure ventilation via face mask during bronchoscopy with BAL in high-risk hypoxemic patients. *Chest* 1996;110:724–728.
44. Maitre B, Jaber S, Maggiore SM, Bergot E, Richard JC, Bakthiari H, Housset B, Boussignac G, Brochard L. Continuous positive airway pressure during fiberoptic bronchoscopy in hypoxemic patients. A randomized double-blind study using a new device. *Am J Respir Crit Care Med* 2000;162:1063–1067.
45. Peikert T, Rana S, Edell ES. Safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. *Mayo Clin Proc* 2005;80:1414–1420.
46. Rolston KV, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. *Clin Infect Dis* 2007;45:228–233.
47. Walsh FW, Rolfe MW, Rumbak MJ. The initial pulmonary evaluation of the immunocompromised patient. *Chest Surg Clin N Am* 1999;9:19–38.

From the Authors:

We appreciate the comments of Dr. Chang and colleagues for their interest in our article (1).

Extensively drug-resistant tuberculosis (XDR-TB) has been reported as the most serious negative prognostic factor in patients with multidrug-resistant tuberculosis (MDR-TB); the fluoroquinolones and injectable anti-TB drugs have been increasingly accepted as the most important drugs for successful MDR-TB treatment. With emphasizing the important role of these drugs, XDR-TB is currently defined as MDR-TB with bacillary resistance to both any fluoroquinolone and at least one of three second-line injectable drugs (SLIDs). However, streptomycin (SM) is also an injectable anti-TB drug, but is not included in the XDR-TB–defining drugs. If we assume that the use of both fluoroquinolone and injectable anti-TB drugs (including SM) can result in the most favorable outcome in MDR-TB, it would be natural that SLID-resistant pre–XDR-TB with SM susceptibility is the most favorable outcome group among pre–XDR-TB as in our study (1); it is the only group that can use both fluoroquinolone and injectable drugs.

However, these observations bring up a new question about the XDR-TB definition, whether SM resistance should be included or not, as Dr. Chang commented. If SM resistance is included in the XDR-TB definition, there would be two possibilities: the first, MDR-TB with bacillary resistance to any fluoroquinolone, at least one SLID, and SM; and the second, MDR-TB with bacillary resistance to any fluoroquinolone and one of four injectable drugs (three SLIDs and SM). When the XDR-TB was redefined as the first definition, treatment success rate and mean survival time of SM-resistant XDR-TB (by the first definition) were not different from SM-susceptible XDR-TB in our study: 25.9% versus 31.2% (P = 0.627) and 63.1 months versus 59.1 months (P = 0.955), respectively. According to the second definition, patients with more favorable outcome, such as SM-resistant/ofloxacin-resistant patients with pre–XDR-TB would be redefined as XDR-TB (1, 2). Collectively, the mean survival time was not different among the current XDR-TB definition (61.7 mo), XDR-TB by the first definition (63.2 mo), and XDR-TB by the second definition (67.1 mo). Based on these findings, modification of the current XDR-TB definition to either the first or the second definition would not be more beneficial in defining the patients with MDR-TB with the worst prognosis. However, considering the inconsistent results regarding the impact of SM resistance on the XDR-TB outcome in another study (3), further studies are needed to explore the best XDR-TB definition.

Author Disclosure: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Doh Hyung Kim, M.D., Ph.D.
Dankook University Hospital
Cheonan, South Korea

Tae Sun Shim, M.D., Ph.D.
Asan Medical Center
Seoul, South Korea

References

1. Kim DH, Kim HJ, Park SK, Kong SJ, Kim YS, Kim TH, Kim EK, Lee KM, Lee SS, Park JS, *et al.* Treatment outcomes and survival based on drug resistance patterns in multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010;182:113–119.
2. Chan ED, Strand MJ, Iseman MD. Multidrug-resistant tuberculosis (TB) resistant to fluoroquinolones and streptomycin but susceptible to second-line injection therapy has a better prognosis than extensively drug-resistant TB. *Clin Infect Dis* 2009;48:e50–e52.
3. Hwang SS, Kim HR, Kim HJ, Kim MJ, Lee SM, Yoo CG, Kim YW, Han SK, Shim YS, Yim JJ. Impact of resistance to first-line and injectable drugs on treatment outcomes in MDR-TB. *Eur Respir J* 2009;33: 581–585.

Diagnostic Strategy for Hematology and Oncology Patients with Acute Respiratory Failure

To the Editor:

In their article, Azoulay and colleagues report no difference in diagnostic yields or the need for intubation between noninvasive and bronchoscopic methods of diagnosing acute respiratory failure in hematology and oncology patients (1).

In this analysis, the authors report no statistically significant differences between antimicrobial classes in the two groups at ICU admission; however, number of days of antimicrobial therapy prior to randomization is not reported. Longer duration of antimicrobial therapy prior to bronchoalveolar lavage or noninvasive tests for microorganisms reduces the yield of these analyses (2–4). Failure to adjust for this duration may confound the results.

The authors describe how diagnostic results affected initiation, discontinuation, or narrowing of antimicrobial therapy in the invasive arm. A parallel description of how results affected management in the noninvasive arm would be extremely valuable to physicians incorporating this study into clinical decision-making.

Author Disclosure: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Amit Gohil, M.B.Ch.B.
Nayer Khazeni, M.D., M.S.
Stanford University
Stanford, California

References

1. Azoulay E, Mokar D, Lambert J, Lemiale V, Rabbat A, Kouatchet A, Vincent F, Gruson D, Bruneel F, Epinette-Branche G, *et al.* Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial *Am J Respir Crit Care Med* (In press)
2. Kuehnhardt D, Hannemann M, Schmidt B, Heider U, Possinger K, Eucker J. Therapeutic implication of BAL in patients with neutropenia. *Ann Hematol* 2009;88:1249–1256.
3. Shannon V, Andersson B, Lei X, Champlin Rand Kontoyiannis D. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2010;45:647–655.
4. Bandyopadhyay T, Gerardi DA, Metersky ML. A comparison of induced and expectorated sputum for the microbiological diagnosis of community acquired pneumonia. *Respiration* 2000;67:173–176.

From the Authors:

We read carefully the letter from Drs. Gohil and Khazeni in response to our article (1). Duration of antimicrobial therapy prior to ICU admission was not statistically different between the two study groups: 4 (1–11) and 5 (1–12) days, in the invasive and noninvasive groups, respectively (P = 0.39). In addition, prevalence of neutropenia, a condition in which empiric antibiotics are the rule, was not different in the two study groups (32% versus 30%, P = 0.88). When adjusted on both duration of antimicrobial therapy and neutropenia, no marked difference in odds ratio (OR) estimates could be found (need for intubation: OR, 0.86 [0.50–1.50]; P = 0.60; undetermined diagnosis: OR, 0.93 [0.48–1.79]; P = 0.81).

Otherwise, in our protocol, the question of how diagnostic strategy could affect antimicrobial therapy was only assessed in patients from the invasive group. Nevertheless, we computed and compared the number of antibiotics received at ICU admission and at Day 3 in both study groups.

In the noninvasive arm, patients received a median of 2 (1–3) antibiotics at ICU admission and 3 (2–4) at Day 3. In the invasive arm, they received 2 (1–3) antibiotics at ICU admission and 3 (2–4) at Day 3.

Finally, we have tabulated below the number (%) of patients with any antibiotherapy modification (i.e., initiation or discontinuation) between ICU admission and Day 3 (Table 1). No significant difference was observed between the two study groups.

Author Disclosure: E.A. has received advisory board fees from Gilead France and Pfizer France (each $1,001–$5,000); he has received lecture fees from Pfizer ($1,001–$5,000); and he has received industry-sponsored grants from Gilead and Pfizer ($10,001–$50,000). J.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

ELIE AZOULAY, M.D., PH.D.
Hôpital Saint-Louis
Paris, France

JÉRÔME LAMBERT, M.D.
Hôpital Saint Louis
Paris, France
and
Université Paris 7
Paris, France

DJAMEL MOKART, M.D.
Institut Paoli-Calmettes
Marseille, France

Reference

1. Azoulay E, Mokart D, Lambert J, Lemiale V, Rabbat A, Kouatchet A, Vincent F, Gruson D, Bruneel F, Epinette-Branche G, *et al.* Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182:1038–1046.

TABLE 1. PATIENTS WITH ANTIBIOTHERAPY MODIFICATION BETWEEN ICU ADMISSION AND DAY 3

	Noninvasive Diagnostic Strategy	Invasive Diagnostic Strategy
Overall	92 (87%)	97 (84%)
Antibiotic class		
Piperacilline or ticarcilline	4 (4%)	6 (5%)
Piperacillin/tazobactam	14 (13%)	26 (23%)
Third-generation cephalosporins		
not active against *Pseudomonas*	8 (8%)	8 (7%)
active against *Pseudomonas*	10 (9%)	13 (12%)
Imipenem	14 (13%)	15 (13%)
Aminoglycosides	26 (25%)	25 (22%)
Glycopeptides	23 (22%)	17 (15%)
Macrolides	20 (19%)	27 (24%)
Fluoroquinolones	23 (22%)	24 (21%)
Co-trimoxazole	28 (26%)	23 (20%)
Antiviral therapy	14 (13%)	20 (18%)
Antifungal agents	15 (14%)	24 (21%)

Activated Protein C Nebulization in Severe Late Acute Respiratory Distress Syndrome

To the Editor:

We report the use of nebulized activated protein C (aPC) in a 60-year-old postoperative patient with severe late acute respiratory distress syndrome (ARDS) secondary to pneumonia and septic shock. The patient had persistent severe gas exchange impairment and respiratory mechanics for 15 days despite protective ventilation (tidal volume $\leq$ 8 ml/Kg and plateau pressure $\leq$ 30 cm H_2O). Methylprednisolone was started on Day 9 after intubation, without response. After obtaining informed consent from the family, 2.5 mg of aPC was nebulized for 30 minutes every 3 hours. A significant improvement in respiratory function was observed 3 days later despite a new episode of septic shock and hyperthermia secondary to bacteriemia and wound abscess, which required surgical drainage. Nebulized aPC was tapered to 2.5 mg/6 hours on Day 6 and stopped on Day 7, when Pa_{O_2}/Fi_{O_2} was greater than or equal to 250. Eight days after starting aPC nebulization, the weaning process was initiated, and the patient weaned from mechanical ventilation 15 days after the first dose of aPC without evidence of hemorrhage.

The pathogenesis of ARDS is characterized by an early exudative inflammatory state and a late fibroproliferative phase (1). However, evidence of fibroproliferation has been observed as early as 24 hours after ARDS diagnosis (2). Therapy should aim at enhancing alveolar repair while inhibiting excessive fibroblast proliferation (3). The activation of the coagulation pathways can amplify the inflammatory response, and the use of anticoagulants to prevent lung injury has been proposed (4). aPC is a natural anticoagulant with antiinflammatory and antiapoptotic effects (5). Experimental studies have shown that early inhaled aPC is beneficial in lung injury (6). A hemorrhage is a main concern during aPC infusion. In ARDS, local administration by means of nebulization acts directly on the affected tissue, and permits the use of a lower dose, decreasing secondary effects and cost. The daily dose in this case (20 mg) represents roughly half the dose that the patient (80 kg) would require intravenously. A 30-minute nebulization and a 3-hour interval between doses were chosen to have aPC present in lung tissue for most of the time, mimicking the intravenous infusion. After tapering the drug, Pa_{O_2}/Fi_{O_2} continued to improve, so we stopped the treatment, without untoward effect.

Our case does not demonstrate a cause-effect link between aPC inhalation and lung function improvement, but suggests that this therapy is feasible and apparently did not cause harm.

Author Disclosure: D.P. has received lecture fees from Eli Lilly ($1,001–$5,000). M.d.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

DAVID PESTAÑA, M.D., PH.D.
MIGUEL DE BLAS, M.D.
CARMEN SOMOZA, M.D.
CONCEPCIÓN ROYO, M.D.
Hospital Universitario La Paz
Madrid, Spain

References

1. Deal EN, Hollands JM, Schramm GE, Micek ST. Role of corticosteroids in the management of acute respiratory distress syndrome. *Clin Ther* 2008;30:787–799.
2. Marshall RP, Bellingan G, Webb S, Puddicombe A, Goldsack N, McAnulty RJ, Laurent GJ. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *Am J Respir Crit Care Med* 2000;162:1783–1788.
3. Raghavendran K, Pryhuber GS, Chess PR, Davidson BA, Knight PR, Notter RH. Pharmacotherapy of acute lung injury and acute respiratory distress syndrome. *Curr Med Chem* 2008;15:1911–1924.
4. Idell S. Anticoagulants for acute respiratory distress syndrome: can they work? *Am J Respir Crit Care Med* 2001;164:517–520.
5. Joyce DE, Gelbert L, Ciaccia A, DeHoff B, Grinnell BW. Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis. *J Biol Chem* 2001;276:11199–11203.
6. Nick JA, Coldren CD, Gevaci MW, Poch KR, Fouty BW, O'Brien J, Gruber M, Zarini S, Murphy RC, Kuhn K, *et al.* Recombinant human activated protein C reduces human endotoxin-induced pulmonary inflammation via inhibition of neutophil chemotaxis. *Blood* 2004;104:3878–3885.