Diagnostic Strategy for Hematology and Oncology Patients with Acute Respiratory Failure

Randomized Controlled Trial

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***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.

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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).

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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

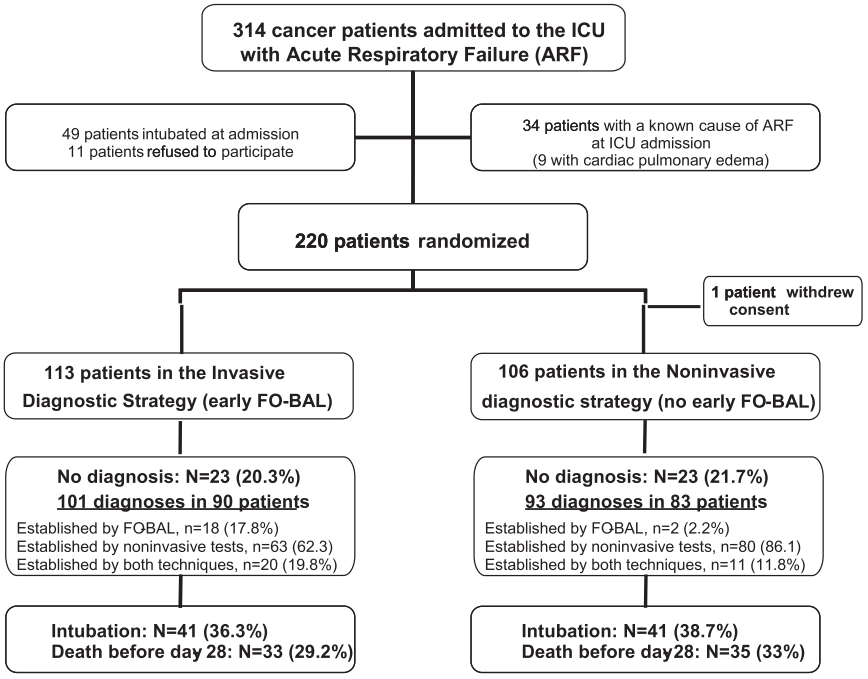

Figure 1. Patient flow chart. ARF = acute respiratory failure; FO-BAL = fiberoptic bronchoscopy with bronchoalveolar lavage; ICU = intensive care unit; invasive strategy = group managed with routine FO-BAL within 1 day of ICU admission; noninvasive strategy = group managed without FO-BAL unless the cause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

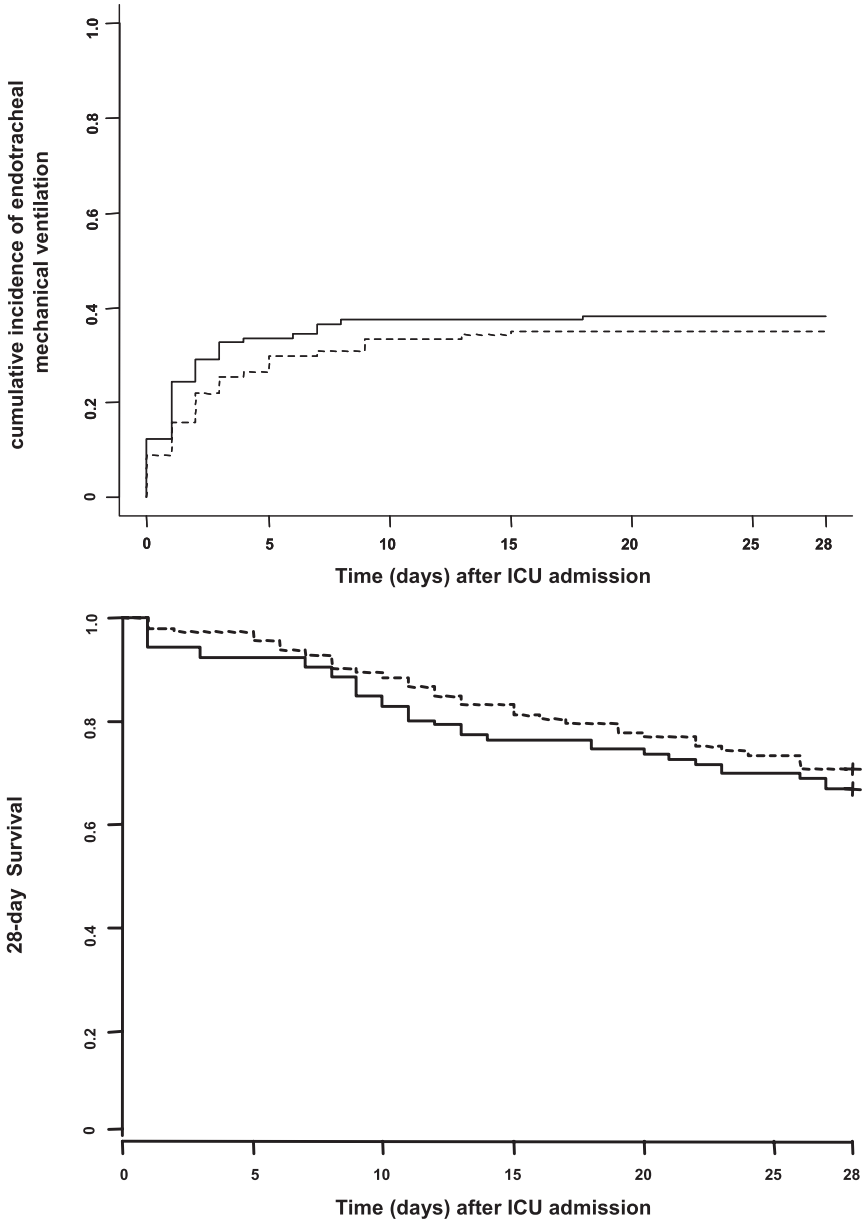

Figure 2. Need for endotracheal mechanical ventilation and 28-day mortality in the two groups. The solid line represents patients in the noninvasive-strategy group and the dotted line patients in the invasive-strategy group. ICU = intensive care unit.

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.

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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.