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ORIGINAL

Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis

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Abstract *Background:* Invasive pulmonary aspergillosis (IPA) is a life-threatening infection documented in up to 15% of hematology patients who require intensive care for acute respiratory failure. We report outcomes in hematology patients given mechanical ventilation (MV) with IPA. *Methods:* Retrospective study of all hematology patients given MV with IPA between January 1998 and March 2011 at a single center. Predictors of 6-month survival or mortality were identified using multivariable analysis. *Results:* We studied 67 patients including 49 (73%) with neutropenia, 23 (34%) with long-term steroid therapy, and 14 (21%) with allogeneic bone marrow transplantation. Incidence of IPA in the ICU decreased between 1998 and 2011, and mortality in patients receiving mechanical ventilation did not change. IPA was confirmed in 6 patients by autopsy and was probable in 61 patients based on host factors, clinical and radiographic features, and either *Aspergillus* isolation (50 patients) or *Aspergillus* antigen detection alone (11 patients). Concomitant bacterial infections were documented in 24 (36%) patients. ICU and 6-month mortality rates were 67 and 82%, respectively. Mortality was stable throughout the study period. Concomitant bacterial infection was independently associated with higher mortality [HR, 2.1 (1.2–3.8)]. Mortality was lower in patients given voriconazole [OR, 0.5 (0.3–0.9)]. *Conclusion:* Hospital mortality remains high in hematology patients requiring MV with IPA, particularly when concommittant infection occurred. The use of voriconazole improved survival.

Keywords Aspergillosis · ICU · Mechanical ventilation · Outcome

Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening complication of hematological malignancies [1–3]. In recent studies, 1-year mortality in patients with IPA was about 60% [4]. Risk factors for IPA among patients with hematological malignancies include prolonged neutropenia and bone marrow transplantation (BMT) [3, 5]. Another risk factor is long-term steroid therapy, which is associated with quantitative and qualitative functional impairments of macrophages, monocytes, neutrophils, and lymphocytes [5].

Until recently, the incidence of IPA was difficult to assess because no unequivocal diagnostic criteria were available. In 2008, the EORTC issued criteria for proven, probable, and possible IPA [6]. The diagnosis is based on clinical and radiographic findings, antigenemia, cultures, and/or histology. In recent clinical trials in hematology patients, the incidence of IPA ranged from 0.5 to 2.3% per year [4, 7, 32], with striking differences according to the underlying malignancy, presence of graft-versus-host disease in allogeneic BMT recipients, and use of prophylactic versus preemptive antifungal therapy [8–13].

In hematology patients, acute respiratory failure is the leading reason for admission to the intensive care unit (ICU) [1, 14]. Two recent cohort studies [14–18] found that possible or probable IPA was present in 12 and 13% of patients with documented causes of acute respiratory failure, respectively, and that IPA was associated with higher mortality, most notably when mechanical ventilation (MV) was needed [2, 7].

Over the last decade, advances in noninvasive diagnostic strategies for patients with acute respiratory failure have been translated into higher diagnostic yields and improved patient outcomes [1, 16–18]. Moreover, the standardization of IPA criteria has improved the recognition of IPA cases and allowed the development of practical management guidelines [19–21]. These changes may have affected the management and prognosis in hematology patients with IPA.

The objective of this study was to assess the outcomes of hematology patients requiring invasive MV or noninvasive MV (NIV) with IPA between 1998 and 2011.

Patients and methods

This retrospective study included all patients with IPA admitted to the medical ICU of the Saint-Louis Hospital, Paris, between 1998 and March 2011. The hospital is a 650-bed university hospital with 330 hematology beds. The 12-bed closed ICU admits 600–800 patients per year, among whom about one-third are hematology patients. During the study period, the number of cancer patients admitted to the ICU remained stable, and mortality in patients receiving mechanical ventilation did not change. Diagnostic methods were the same until 2009, when bronchoscopy and BAL were done only in cases with inconclusive noninvasive diagnostic strategies [16].

Inclusion criteria were age over 18 years, hematological malignancy, and diagnosis of IPA made in the ICU or days before ICU admission. IPA was defined according to the 2008 EORTC criteria [22]. We included only proven and probable IPA.

Data in Tables 1 and 2 were extracted from the medical charts. Neutropenia was defined as a leukocyte count $<1{,}000/mm^3$ or a neutrophil count $<500/mm^3$. The circulating galactomannan antigen test was considered positive when antigenemia was >0.5 ng/ml [23]. High-resolution thoracic computed tomography (CT) was performed in the radiology department when the patient's clinical status allowed transportation, as determined by the intensivist in charge. CT signs of IPA were nodular and excavated nodular lesions with or without pleural involvement and the halo sign [24–26]. We recorded whether IPA was confined to the lungs or diffuse, that is, associated with intracranial and/or sinus involvement [27]. Clinical characteristics, organ dysfunction, mechanical ventilation (MV or NIV), co-infections, and mortality at the ICU or hospital discharge were available for all patients. Criteria for invasive or noninvasive mechanical ventilation were based on clinical findings, and were started according to physicians who cared for the patient.

Circulating *Aspergillus* galactomannan (GM) was detected using a sandwich immunocapture ELISA (Platelia Aspergillus; Bio-Rad, Marnes-la-Coquette, France) [23, 28]. The assay was performed as recommended by the manufacturer. Results were expressed as an index of positivity. A positive GM test was defined as indices ≥ 0.5 on two consecutive samples including retesting of the first positive sample. Sequential sera were tested in parallel on the same ELISA plate.

Statistical analysis

All data are presented as frequencies (percentage) for qualitative variables and medians (25th–75th percentiles) for quantitative variables. The outcome variable of interest was length of survival. A Cox proportional hazards regression model was used to identify independent prognostic variables among the baseline characteristics of patients at ICU admission. All variables associated with survival at a 20% threshold by Cox model in univariate analysis were included, and a *P*-value-based backward selection was performed. The Kaplan-Meier method was used to construct survival curves comparing patients with and without voriconazole. All tests were two-sided, and statistical analyses were performed using R 2.12.2 (R foundation, Vienna, Austria).

Results

Between 1998 and March 2011, 67 patients with hematological malignancies were admitted to the ICU for acute respiratory failure related to IPA. Figure 1 (panel a) shows that the annual incidence of IPA decreased significantly from six cases per year in 1998 to three cases per year in 2010 (Fig. 1a) ($P < 0.02$). As shown in Table 1, 14 (21%) patients were allogeneic BMT recipients [time since

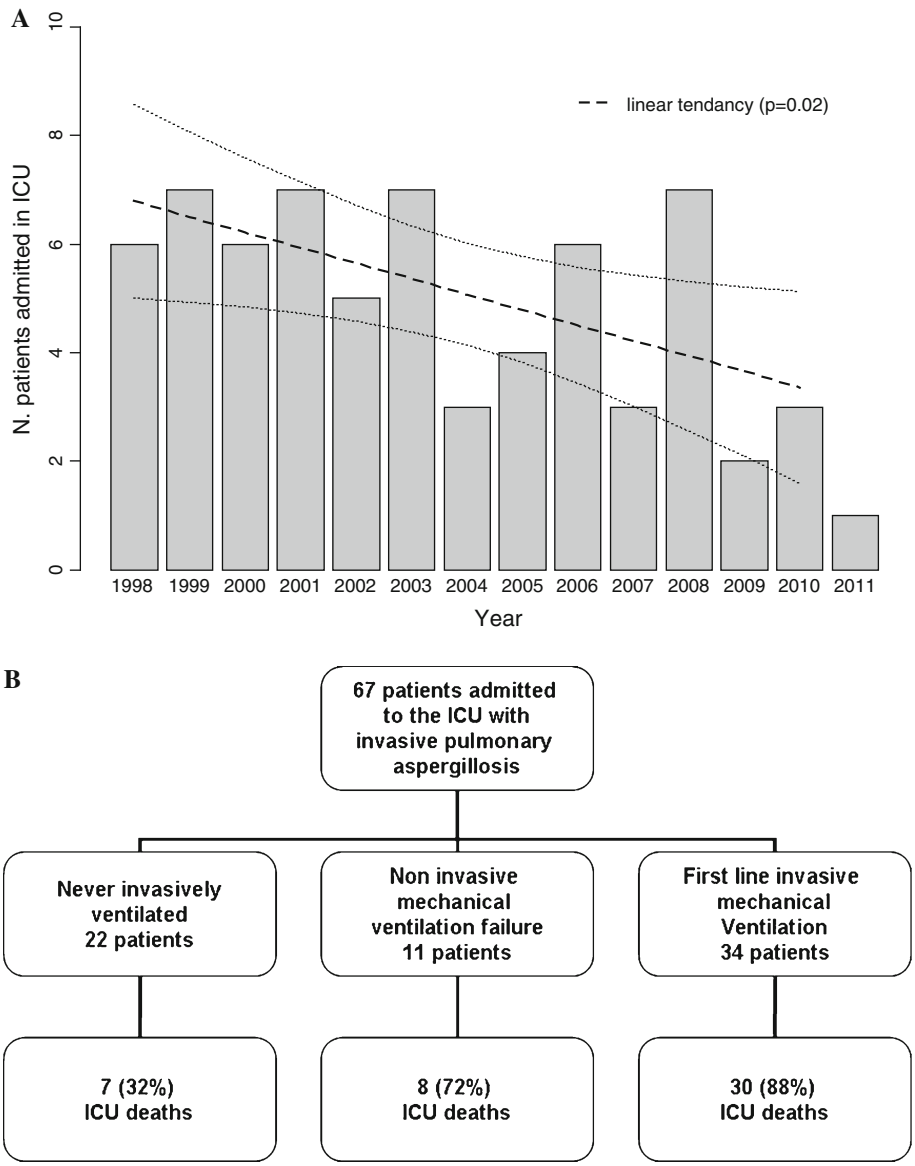

Fig. 1 **a** Annual incidence of invasive pulmonary aspergillosis (IPA) in critically ill patients with hematological malignancies. The number of patients admitted to the intensive care unit for IPA decreased significantly after 2003. **b** Patient flow chart according to ventilation group. NIV, noninvasive mechanical ventilation; eMV, endotracheal mechanical ventilation

transplantation was 100 (62–201) days], 49 (73%) had IPA complicating prolonged neutropenia, and 23 (34%) had received long-term steroid therapy for their hematological malignancy. Time between first symptoms and diagnosis of IPA, which did not vary for patients diagnosed with IPA before ($n = 28$) or after ($n = 39$) ICU admission, was 7 (4–15.5) days and 7 (4–16) days, respectively. Also, time between IPA diagnosis and ICU admission was −7 (−3.25; −11.75) days and 4 (2–9.25) days, in patients diagnosed with IPA before or during ICU stay, respectively.

The most common malignancies were acute leukemia and non-Hodgkin's lymphoma. Respiratory symptoms at IPA diagnosis had been present for 6 (3–15) days and consisted of tachypnea (91%), fever (90%), cough (40%), chest pain (18%), and hemoptysis (12%). Chest radiographs visualized diffuse alveolar infiltrates in 32 (48%) patients, nodules or focale infiltrate in 10 (28%), and pleural effusions in 13 (20%). Chest CT was performed in 41 (61%) patients. Alveolar consolidations were the only CT scan abnormalities in nine (22%) patients. The *Aspergillus* infection involved the sinuses in 8/21 patients and the brain in 7/27 patients when CT scans were done.

In five (7.4%) patients, the diagnosis was proven IPA, based on biopsy findings. The remaining 62 (92.5%) patients had probable IPA, based on positive tests on bronchoalveolar lavage fluid ($n = 23$) or on sputum or tracheal aspirates ($n = 31$). *Aspergillus fumigatus* was the most common species ($n = 27$, 45.8%). The circulating GM test was positive at some point in 44 (75.6%) patients. In addition to IPA, 24 (36%) patients had a

Table 1 Patient characteristics and risk factors associated with mortality

Patient characteristics ($n = 67$)	N (%) or median (IQR)
Male n (%)	44 (66)
Age	47 [39.5–57]
Underlying disease	
Acute myeloid leukemia	19 (28)
Acute lymphoid leukemia	7 (10)
Non-Hodgkin's lymphoma	18 (28)
Hodgkin's disease	1 (1.5)
Chronic lymphocytic leukemia	5 (7.5)
Multiple myeloma	6 (9)
Chronic myeloid leukemia	2 (3)
Other diseases*	9 (13)
Underlying risk factor	
Neutropenia	49 (73)
Allogeneic BMT	14 (21)
Long-term steroids	23 (34)
Respiratory symptoms at presentation	
Fever	60 (90)
Dyspnea	53 (59)
Chest pain	12 (18)
Tachypnea	61 (91)
Cough	27 (40)
Hemoptysis	8 (12)
Extrapulmonary signs	
Shock	42 (63)
Acute kidney injury	21 (31)
Coma	17 (25)
Thrombopenia	7 (10)
Liver failure	6 (9)
Concomitant infection	24 (36)
Chest X-ray ($n = 65$)	
Normal	4 (6.2)
Focal infiltrate	31 (48)
Diffuse infiltrate	30 (46)
Pleural effusion	13 (20)
CT scan ($n = 41$)	
Alveolar condensation	9 (21.9)
Centrolobular nodules	13 (31.7)
Halo sign	15 (36.5)
Excavated lesion	9 (21.9)
Pleural effusion	6 (14.6)
Sinusitis	8/21 (38)
Cerebral aspergillosis	7/27 (26)
Treatment by voriconazole	36 (54)
Length of ICU stay (days)	10 [4–18]
Median survival time	15 [IC 95%: 11–27]
ICU mortality (J30 mortality)	45 (67)
6 months mortality	55 (82)

IQR interquartile range, *BMT* bone marrow transplantation, *CT* computed tomography of the chest, *ICU* intensive care unit

* Myelodysplasia, paroxysmal noctural hemoglobinuria, medullar aplasia

bacterial or opportunistic infection (19 patients had gram-negative infection, 2 patients with gram-positive infection, 1 patient with fungus and 2 patients had concomitant *Pneumocystis jiroveci* infection).

As reported in Fig. 1, panel b, 34 (50.7%) patients received first-line endotracheal MV and 33 (49.2%) first-line NIV; of these 33 patients, 11 subsequently required endotracheal MV. In addition, 42 (61%) patients presented with shock, 21 (31%) with acute kidney injury, and 17 (25%) with coma.

Six (8.9%) patients were receiving prophylactic antifungal therapy. In all patients but one, the day of diagnosis was the day of initiation of antifungal treatment. One patient died before any antifungal agent could be administered. Twelve (17.9%) patients received more than one antifungal agent; among them ten patients had combination including voriconazole. In 20 (29.8%) patients, the first-line antifungal agent failed and was therefore replaced by another drug.

MV duration was 9 (5–13.5) days, and ICU stay length was 10 (4–18) days. Overall ICU mortality was 67% (45 deaths) and did not vary across the study period. As reported in Fig. 1b, mortality was higher in patients who received endotracheal MV than in patients who had never been intubated. Table 2 reports the results of the univariate analysis of risk factors associated with mortality. In multivariate analysis, two independent prognostic factors were identified: treatment by voriconazole [HR = 0.5 (0.3–0.9), $P = 0.03$] and concomitant infection [HR = 2.1 (1.2–3.8), $P = 0.01$] (Fig. 2).

Discussion

Few data are available on survival of patients who require MV to treat IPA, complicating a hematological malignancy. We report outcomes in 67 such patients managed between 1998 and 2011. ICU mortality rate was 67% overall, 88% among patients who received first-line endotracheal MV, 72% in those who required endotracheal MV after failed NIV, and 37% in those who responded to NIV. A factor independently associated with survival was use of voriconazole, whereas the major factor associated with mortality was concomitant infection.

Several studies conducted outside the ICU setting have assessed the risk factors for IPA and the outcomes of IPA complicating hematological malignancies [2, 3, 7, 29]. Among hematology patients admitted to the ICU with acute respiratory failure, up to 15% had IPA [1, 16]. None of the available studies assessed specific outcomes in patients requiring ventilatory support.

In our study, risk factors for IPA were long-term steroid therapy, prolonged neutropenia, and allogeneic BMT [3, 5]. In hematology wards, the incidence of invasive aspergillosis has remained stable over time, despite greater use of prophylactic and preemptive antifungal therapy. The cumulative incidence has ranged from 0.5 to 2.3% per year depending on BMT type [4, 7, 32, 33]. The incidence of IPA may be decreasing in patients receiving MV, probably as a result of changes in triage policies [30, 35]. The smaller number of allogeneic BMT recipients in our population compared to those in non-ICU

Table 2 Univariate analysis of risk factors associated with mortality

Patient characteristics ($n = 67$)	Hazard ratio [95% confidence interval]	P
Male *n* (%)	1.01 [0.57–1.77]	0.98
Age	1 [0.98-1.02]	0.68
Underlying disease		
Acute leukemia (myeloid or lymphoid)	1	0.30
Lymphoma (Hodgkin's or non-Hodgkin's)	0.61 [0.33–1.13]	
Other disease	0.66 [0.30–1.42]	
Underlying risk factor		
Neutropenia	1.04 [0.60–1.91]	0.90
Allogeneic BMT	1 [0.52–1.94]	0.99
Long-term steroids	1.21 [0.69–2.11]	0.50
Respiratory symptoms at presentation		
Fever	0.48 [0.22–1.09]	0.11
Dyspnea	1.42 [0.72–2.82]	0.30
Chest pain	0.78 [0.37–1.66]	0.51
Tachypnea	1.35 [0.54–3.40]	0.51
Cough	0.79 [0.46–1.36]	0.40
Hemoptysis	0.74 [0.32–1.74]	0.47
Extrapulmonary signs		
Shock	1.39 [0.78–2.45]	0.25
Acute kidney injury	1.50 [0.86–2.60]	0.16
Coma	1.09 [0.60–1.97]	0.77
Thrombopenia	1.0 [0.43–2.33]	0.99
Liver failure	1.41 [0.60–3.28]	0.45
Concomitant infection	1.76 [1.02–3.04]	0.05
Chest X-ray ($n = 65$)		
Normal	1.31 [0.46–3.77]	0.15
Focal infiltrate	0.61[0.35–1.08]	
Diffuse infiltrate	1	
Pleural effusion	0.86 [0.43–1.71]	0.65
Treatment by voriconazole	0.66[0.39–1.12]	0.12

studies can be ascribed to the low ICU admission rates for MV of patients with active graft-versus-host disease, a condition associated with dismal survival rates [30–32, 34]. However, in our patients admitted to the ICU for acute respiratory failure, MV may have been started before the diagnosis of proven or probable IPA was established.

All our patients met 2008 EORTC criteria for proven or probable IPA [22, 36]. One-third of the patients were unable to undergo CT of the chest because they had severe acute lung injury or acute respiratory distress syndrome precluding transportation to the radiology department. Alveolar consolidations without any of the patterns considered specific of IPA (nodules, halo sign, and air crescent) were noted in 21.9% of the patients who had chest CT performed, in keeping with earlier data [24–26]. The circulating GM assay is particularly helpful in patients without specific CT patterns [16, 17, 23, 37].

Voriconazole therapy was independently associated with lower mortality in our study. Voriconazole is recognized as a valuable resource for the treatment of IPA [19]. We confirmed that voriconazole improves survival even in the sickest patients with IPA requiring MV.

Concomitant bacterial infection was associated with increased mortality in our patient population. Immunocompromised patients who require ICU admission and MV are known to be at very high risk for bacterial infections [1].

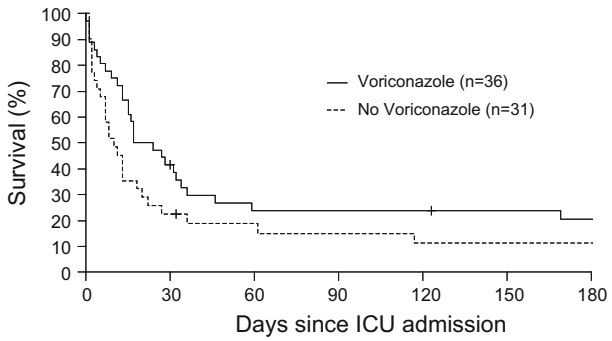

Fig. 2 Effect of voriconazole use on survival in patients with invasive pulmonary aspergillosis. The *solid line* indicates survival in patients treated with voriconazole and the *dashed line* the patients given other antifungal agents without voriconazole, $P = 0.12$

Our study has several limitations. We used a retrospective design, and we identified only 67 patients over a 13-year period. Obviously, during this period, significant changes may have occurred in triage policies, diagnosis methods, prevention strategies, treatments, as well as outcomes. However, even though the incidence decreased

over time, no changes in outcomes could be observed. Moreover, to our knowledge there are few studies of patients receiving MV for proven or probable IPA. Second, we were not able to obtain an autopsy for all the patients who died. Routine autopsy would be expected to increase the proportion of proven cases, as autopsy studies have shown that IPA is the most often missed infectious diagnosis in patients with malignancies [38]. Third, mortality was considerably higher in our population than in recent randomized trials [19, 20]. This difference can be ascribed in part to the use of MV in half of our patients, since MV is the strongest determinant of mortality in hematology patients with acute respiratory failure [1]. NIV was associated with lower mortality rates in recent studies, whereas failure of NIV requiring endotracheal MV was associated with higher mortality than patients receiving first-line MV [39]. Another contributor to the high mortality rate in our study was the large proportion of patients with multiple organ failures at ICU admission. Fourth, our patients were included over a 13-year period, during which time outcomes improved and triage policies evolved in critically ill cancer patients [17, 36]. Moreover, voriconazole was not available in France during the earlier part of our study (before 2002) [19]. However, mortality remained stable over time, and the beneficial effect of voriconazole therapy was ascribable to the drug itself and not to a time effect, but we could not find an effect of voriconazole during the 2002–2011 period (data not shown).

Fourth, because of the retrospective design of the study, we could not be sure that the radiological figure was related to IPA and no other bacterial infections according to the amount of concomitant infection. Nevertheless, bacterial infection and diffuse lesions on chest X-ray were associated with mortality in univariate analysis.

In summary, mortality is high in patients treated for hematological malignancies who require MV with IPA-related acute respiratory failure. Concomitant bacterial infection is associated with higher mortality rates, whereas the use of voriconazole is associated with lower mortality rates. This study suggests that a trial of ICU management should be offered to critically ill hematology patients with IPA, but outcome should be frequently assessed in this setting to avoid futility according to the increased mortality associated with concomittant bacterial infection.

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References

1. 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
2. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, Pfaller M, Chang C, Webster K, Marr K (2009) Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 48:265–273
3. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Ame S, Fohrer C, Lioure B, Bilger K, Lutun P, Marcellin L, Launoy A, Freys G, Bergerat JP, Herbrecht R (2008) Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis 47:1176–1184
4. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, Ito J, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, Hadley S, Herwaldt LA, Kauffman CA, Knapp K, Lyon GM, Morrison VA, Papanicolaou G, Patterson TF, Perl TM, Schuster MG, Walker R, Wannemuehler KA, Wingard JR, Chiller TM, Pappas PG (2010) Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 50:1091–1100
5. Baddley JW (2010) Clinical risk factors for invasive aspergillosis. Med Mycol 49(supp1):S7–S12
6. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, Denning DW, Donnelly JP, Edwards JE, Erjavec Z, Fiere D, Lortholary O, Maertens J, Meis JF, Patterson TF, Ritter J, Selleslag D, Shah PM, Stevens DA, Walsh TJ (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 34:7–14
7. Marr KA, Carter R, Boeckh M (2002) Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 100:4358–4366
8. Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, Pigneux A, Cornely OA, Ullmann AJ, Bofarull RM, de la Camara R, Weisser M, Liakopoulou E, Abecasis M, Heussel CP, Pineau M, Ljungman P, Einsele H (2010) Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Haematologica 95:1762–1768

9. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359
10. Illmer T, Babatz J, Pursche S, Stolzel F, Schuler U, Schaich M, Ehninger G (2011) Posaconazole prophylaxis during induction therapy of patients with acute lymphoblastic leukaemia. Mycoses 54:e143–e147
11. Leventakos K, Lewis RE, Kontoyiannis DP (2010) Fungal infections in leukemia patients: how do we prevent and treat them? Clin Infect Dis 50:405–415
12. 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
13. Vehreschild JJ, Bohme A, Buchheidt D, Arenz D, Harnischmacher U, Heussel CP, Ullmann AJ, Mousset S, Hummel M, Frommolt P, Wassmer G, Drzisga I, Cornely OA (2007) A double-blind trial on prophylactic voriconazole (VRC) or placebo during induction chemotherapy for acute myelogenous leukaemia (AML). J Infect 55:445–449
14. Azoulay E, Schlemmer B (2006) Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 32:808–822
15. Azoulay E, de Miranda S, Bele N, Schlemmer B (2008) Diagnostic strategy for acute respiratory failure in patients with haematological malignancy. Rev Mal Respir 25:433–449
16. 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
17. 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
18. 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
19. 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
20. Herbrecht R, Maertens J, Baila L, Aoun M, Heinz W, Martino R, Schwartz S, Ullmann AJ, Meert L, Paesmans M, Marchetti O, Akan H, Ameye L, Shivaprakash M, Viscoli C (2010) Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. Bone Marrow Transplant 45:1227–1233
21. Hiemenz JW, Raad II, Maertens JA, Hachem RY, Saah AJ, Sable CA, Chodakewitz JA, Severino ME, Saddier P, Berman RS, Ryan DM, Dinubile MJ, Patterson TF, Denning DW, Walsh TJ (2010) Efficacy of caspofungin as salvage therapy for invasive aspergillosis compared to standard therapy in a historical cohort. Eur J Clin Microbiol Infect Dis 29:1387–1394
22. 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 K, Munoz P, Odds FC, Perfect J, Restrepo A, Ruhnke M, Segal BH, Sobel J, 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 Disease Mycoses Study Groups (EORTC/MSG) Consensus Group. CID 46:1813
23. Herbrecht R, Letscher-Bru V, Oprea C, Lioure B, Waller J, Campos F, Villard O, Liu KL, Natarajan-Ame S, Lutz P, Dufour P, Bergerat JP, Candolfi E (2002) Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol 20:1898–1906
24. Caillot D, Latrabe V, Thiebaut A, Herbrecht R, De Botton S, Pigneux A, Monchecourt F, Mahi L, Alfandari S, Couaillier JF (2010) Computer tomography in pulmonary invasive aspergillosis in hematological patients with neutropenia: an useful tool for diagnosis and assessment of outcome in clinical trials. Eur J Radiol 74:e172–e175
25. Kawel N, Schorer GM, Desbiolles L, Seifert B, Marincek B, Boehm T (2011) Discrimination between invasive pulmonary aspergillosis and pulmonary lymphoma using CT. Eur J Radiol 77:417–425
26. Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, Wingard JR, Herbrecht R, Ribaud P, Patterson TF, Troke PF, Denning DW, Bennett JE, de Pauw BE, Rubin RH (2007) Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 44:373–379
27. van de Beek D, Patel R, Campeau NG, Badley A, Parisi JE, Rabinstein AA, Manno EM, Wijdicks EF (2008) Insidious sinusitis leading to catastrophic cerebral aspergillosis in transplant recipients. Neurology 70:2411–2413
28. Bergeron A, Belle A, Sulahian A, Lacroix C, Chevret S, Raffoux E, Arnulf B, Socie G, Ribaud P, Tazi A (2010) Contribution of galactomannan antigen detection in BAL to the diagnosis of invasive pulmonary aspergillosis in patients with hematologic malignancies. Chest 137:410–415
29. Wingard JR, Ribaud P, Schlamm HT, Herbrecht R (2008) Changes in causes of death over time after treatment for invasive aspergillosis. Cancer 112:2309–2312
30. Thiery G, Azoulay E, Darmon M, Ciroldi M, De Miranda S, Levy V, Fieux F, Moreau D, Le Gall JR, Schlemmer B (2005) Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol 23:4406–4413
31. 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

32. Morgan J, Wannemuehler KA, Marr KA, Hadley S, Kontoyiannis DP, Walsh TJ, Fridkin SK, Pappas PG, Warnock DW (2005) Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program. Med Mycol 43(Suppl 1): S49–S58
33. Ribaud P, Chastang C, Latge JP, Baffroy-Lafitte L, Parquet N, Devergie A, Esperou H, Selimi F, Rocha V, Esperou H, Selimi F, Rocha V, Derouin F, Socie G, Gluckman E (1999) Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. Clin Infect Dis 28:322–330
34. Gallien S, Fournier S, Porcher R, Bottero J, Ribaud P, Sulahian A, Socie G, Molina JM (2008) Therapeutic outcome and prognostic factors of invasive aspergillosis in an infectious disease department: a review of 34 cases. Infection 36:533–538
35. Escher M, Perneger TV, Chevrolet JC (2004) National questionnaire survey on what influences doctors' decisions about admission to intensive care. BMJ 329:425
36. Nucci M, Nouer SA, Grazziutti M, Kumar NS, Barlogie B, Anaissie E (2010) Probable invasive Aspergillosis without prespecified radiologic findings: proposal for inclusion of a new category of Aspergillosis and implications for studying novel therapies. Clin Infect Dis 51:1273–1280
37. Maertens J, Buve K, Theunissen K, Meersseman W, Verbeken E, Verhoef G, Van Eldere J, Lagrou K (2009) Galactomannan serves as a surrogate endpoint for outcome of pulmonary invasive aspergillosis in neutropenic hematology patients. Cancer 115:355–362
38. 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
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