MAJOR ARTICLE

Application of the 2008 Definitions for Invasive Fungal Diseases to the Trial Comparing Voriconazole Versus Amphotericin B for Therapy of Invasive Aspergillosis: A Collaborative Study of the Mycoses Study Group (MSG 05) and the European Organization for Research and Treatment of Cancer Infectious Diseases Group

Raoul Herbrecht,[1] Thomas F. Patterson,[2] Monica A. Slavin,[3] Oscar Marchetti,[4] Johan Maertens,[5] Elizabeth M. Johnson,[6] Haran T. Schlamm,[7] J. Peter Donnelly,[8] and Peter G. Pappas[9]

[1]Department of Oncology and Hematology, Hôpital de Hautepierre and Université de Strasbourg, France; [2]University of Texas Health Science Center and South Texas Veterans Health Care System, San Antonio; [3]Peter MacCallum Cancer Center and University of Melbourne, Australia; [4]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital (CHUV), Switzerland; [5]Universitaire Ziekenhuizen Leuven, Campus Gasthuisberg, KU Leuven, Belgium; [6]Public Health England Mycology Reference Laboratory and National Collection of Pathogenic Fungi, Bristol, United Kingdom; [7]Pfizer Global Research and Development, New York, New York; [8]Radboud University Medical Center, Nijmegen, The Netherlands; and [9]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham

Background. Strict definition of invasive aspergillosis (IA) cases is required to allow precise conclusions about the efficacy of antifungal therapy. The Global Comparative Aspergillus Study (GCAS) compared voriconazole to amphotericin B (AmB) deoxycholate for the primary therapy of IA. Because predefined definitions used for this trial were substantially different from the consensus definitions proposed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group in 2008, we recategorized the 379 episodes of the GCAS according to the later definitions.

Methods. The objectives were to assess the impact of the current definitions on the classification of the episodes and to provide comparative efficacy for probable/proven and possible IA in patients treated with either voriconazole or AmB. In addition to original data, we integrated the results of baseline galactomannan serum levels obtained from 249 (65.7%) frozen samples. The original response assessment was accepted unchanged.

Results. Recategorization allowed 59 proven, 178 probable, and 106 possible IA cases to be identified. A higher favorable 12-week response rate was obtained with voriconazole (54.7%) than with AmB (29.9%) ($P < .0001$). Survival was higher for voriconazole for mycologically documented (probable/proven) IA (70.2%) than with AmB (54.9%) ($P = .010$). Higher response rates were obtained in possible IA treated with voriconazole vs AmB with the same magnitude of difference (26.2%; 95% confidence interval [CI], 7.2%–45.3%) as in mycologically documented episodes (24.3%; 95% CI, 11.9%–36.7%), suggesting that possible cases are true IA.

Conclusions. Recategorization resulted in a better identification of the episodes and confirmed the higher efficacy of voriconazole over AmB deoxycholate in mycologically documented IA.

Keywords. voriconazole; amphotericin B; neutropenia; allogeneic hematopoietic stem cell transplantation; preemptive therapy.

Received 27 June 2014; accepted 10 November 2014; electronically published 19 November 2014.

Correspondence: Raoul Herbrecht, MD, Department of Oncology and Hematology, Hôpital de Hautepierre, Université de Strasbourg, 67098 Strasbourg, France (raoul.herbrecht@chru-strasbourg.fr).

Clinical Infectious Diseases® 2015;60(5):713–20

DOI: 10.1093/cid/ciu911

Invasive aspergillosis (IA) is an opportunistic fungal infection occurring primarily in patients with prolonged neutropenia and in those receiving high-dose chemotherapy or immunosuppressants. Although significant advances have been made in the diagnosis of this disease, it remains difficult to obtain a mycological confirmation of infection [1].

The first international consensus definitions of invasive fungal diseases were published by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) in 2002 [2], which defined 3 levels of certainty of IA proven, probable, or possible disease. The definitions were subsequently revised in 2008 to restrict the definitions of possible invasive diseases to the more likely cases based on more specific pulmonary abnormalities [3].

Neither of the 2 major clinical trials conducted in IA during the last decade—the Global Comparative Aspergillus Study (GCAS), which compared voriconazole to amphotericin B (AmB) followed by other licensed antifungal therapy, and a comparison of liposomal AmB 3 mg/kg daily to 10 mg/kg daily—was able to apply these definitions strictly [4, 5]. Hence, patients with host factors and nodular lung lesions surrounded by a halo sign in the absence of mycological confirmation were classified as probable IA. According to current revised EORTC/MSG definitions, these cases cannot be considered as probable IA disease as there is no mycological support, but can only be deemed possible cases. Such possible cases represented a significant proportion of the total number of cases in these studies, so this may have had an impact on their conclusions. As these form the basis of the current guidelines for treating IA, we recategorized all the cases of aspergillosis enrolled into the GCAS and applied the 2008 EORTC/MSG definitions for invasive fungal diseases.

PATIENTS AND METHODS

Objectives

The primary objective was to assess the impact of the revised EORTC/MSG definitions on the classification of IA compared to those that were originally used in the GCAS. Secondary objectives were to provide comparative efficacy data in mycologically documented (probable or proven) and possible IA in patients treated with either voriconazole or AmB.

Patients

The GCAS was a prospective, randomized, multicenter trial conducted between July 1997 and October 2000 comparing voriconazole (6 mg/kg intravenously twice daily on day 1 followed by 4 mg/kg intravenously twice daily for ≥7 days, followed by 200 mg twice daily orally), with AmB deoxycholate (1.0–1.5 mg/kg intravenously once daily) as first-line therapy in patients with IA followed by other licensed antifungal therapy [4]. The protocol had been approved by the institutional review boards, and written informed consent had been obtained from all patients or their legal guardians.

Original Procedure and Recategorization

Originally, a data review committee of 4 teams of 2 clinicians and 1 radiologist blinded to study drug assignment confirmed the diagnosis of probable or definite IA for each patient and rejected from modified intent-to-treat (mITT) population those cases that did not meet the predefined criteria [4]. These criteria differed in several points from those subsequently defined by the EORTC/MSG in 2002 and revised in 2008 (Table 1) [2, 3]. Five physicians (R. H., T. F. P., O. M., M. A. S., J. M.), belonging to either the MSG or the EORTC Infectious Diseases Group, recategorized all the episodes according to the 2008 revised criteria.

Data available included demographics, underlying condition and predisposing factors, clinical and detailed radiological signs, and mycological data. In addition, we included the results of galactomannan serum levels that had been determined by a central laboratory from frozen samples after the original analysis had been done. Overall, 249 patients had a serum

Table 1. Major Differences Between Original Classification in the Global Comparative Aspergillosis Study and Recategorization According to 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group Criteria

Criteria	Original Classification in GCAS	Recategorization According to 2008 Criteria
Host factors + nodule with a halo or an air crescent sign, no positive mycology[a]	Probable invasive aspergillosis[a]	Possible invasive aspergillosis
Host factors + nodule (without halo) or dense well-circumscribed lesion(s), no positive mycology[a]	Uncertain (not eligible)	Possible invasive aspergillosis
Positive microscopy or culture in bronchoalveolar lavage fluid in neutropenic patients or allogeneic HSCT[b]	Definite invasive aspergillosis	Probable invasive aspergillosis
Positive *Aspergillus* galactomannan in serum[c]	Results not available at time of primary analysis	Results available and used for the recategorization

Abbreviations: GCAS, Global Comparative Aspergillosis Study; HSCT, hematopoietic stem cell transplant.

[a] In the absence of other documented etiology.

[b] With presence of appropriate radiological signs.

[c] Positive *Aspergillus* galactomannan in bronchoalveolar lavage fluid is also accepted as mycological criteria in 2008 criteria, but no sample has been tested in patients included in this study.

galactomannan collected at baseline. The experts were blinded to the treatment groups, to the response and survival, and to adverse events. All discrepancies by >1 expert were reviewed in a second turn to reach a consensus.

Definition of Aspergillosis Cases for Recategorization

All enrolled patients into GCAS were recategorized according to the revised EORTC/MSG definitions [3]. In summary, proven IA was defined by a positive microscopy, culture, or histopathology from a usually sterile fluid or tissue; probable IA was defined by host factors, presence of typical clinical and/or radiological signs, and positive microscopy, culture from sputum, or bronchoalveolar lavage (BAL) fluid or by single or multiple positive galactomannan test in serum with a cutoff index of ≥0.5 (Platelia Aspergillus, Bio-Rad); possible infection was defined by presence of host factors and of typical radiological signs but without any mycological support. BAL fluid was not tested for galactomannan. Episodes were classified according to the data available at baseline before starting therapy. Cases that did not meet the criteria for proven, probable, or possible IA were classified as either not aspergillosis when an alternative etiology had been established or uncertain if there was no explanation.

Original categorization included 3 categories: definite, probable, and uncertain or not aspergillosis. Recategorization included 4 categories: proven, probable, possible, and uncertain or not aspergillosis.

Response Assessment

The original response assessment was accepted unchanged: favorable responses were defined by partial (≥50% decrease in size of the lesion and clinical improvement) or complete responses, and unfavorable responses were defined by stable disease, treatment failure, or indeterminate responses [4]. Post hoc efficacy analysis was performed in all patients with IA and also separately on possible cases (equivalent to preemptive therapy) and on the mycologically documented (probable and proven) cases (equivalent to targeted therapy).

The original assessment of response at the end of randomized therapy and survival at 12 weeks in all 379 patients enrolled in the trial was accepted unchanged. The 12-week response was assessed in 27 cases from the uncertain or not aspergillosis group that had not been included in the original analysis as they had been upgraded to eligible cases after recategorization. Eighteen of these patients died before week 12 and were classified as failing treatment, and 9 were alive. For these 9 cases, the last available efficacy assessment was extended to week 12: 8 were treatment failures, indeterminate, or stable and were all classified as unfavorable response at week 12 (3 in voriconazole group and 5 in AmB group), 1 was a partial response, and was accepted as a favorable response at 12 weeks (AmB group).

Statistics

All eligible cases were assessed for response at end of randomized therapy and at week 12 and for the secondary outcome of 12-week survival. Treatment groups were compared by the differences in their baseline characteristics and in response rates by using, where appropriate, 2-sided unpaired *t* test, Fisher exact test, or χ^2 test and, when appropriate, the corresponding 2-sided 95% confidence interval (CI). Survival curves were compared by the log-rank test. *P* values < .05 were considered significant.

RESULTS

Agreement Between the Experts

There was concordance in the recategorization in 312 of the 379 (82.3%) cases. A single expert disagreement occurred in 52 (13.7%) cases. These cases were reviewed by the coordinator for consistency, and a decision in favor of the majority was made. In 15 (4.0%) cases, a disagreement by 2 members led to a second round of review and a discussion to obtain a final agreement. Initial classification remained unchanged in 181 (47.8%) cases. A change in category was made in 198 (52.2%) cases.

Recategorization of the Cases

Of the 379 patients, 102 patients had been originally excluded from the mITT analysis because they did not meet the protocol-specified criteria for a diagnosis of definite or probable IA (Figure 1). The most common cause for exclusion was absence of a halo sign around a nodular lesion. Of these 102 cases, 42 cases now met the 2008 EORTC/MSG criteria for possible IA (because of a nodule without halo or a focal dense lesion at computed tomography [CT]), 28 now met the criteria for probable IA (positive galactomannan in serum or positive microscopy or culture in a respiratory sample and a nodule without halo or a focal dense lesion at CT), 3 were upgraded to proven IA (2 patients receiving steroids and 1 nonneutropenic patient with myeloma and a positive culture from a cerebral abscess, lung biopsy, and vitrectomy), and 29 remained classified as uncertain or not aspergillosis (Figure 1).

Of the 169 probable IA cases in the original study, 101 remained probable (host criteria, typical imaging, and mycological confirmation by positive culture from a relevant site in 39 patients; microscopy or histopathology from a relevant site without positive culture in 29 patients; and positive serum galactomannan only in 33 patients), 64 were downgraded from probable to possible IA (host criteria, nodule with a halo or air-crescent sign, and no mycological confirmation), and 4 were downgraded to uncertain (insufficient host factors in 2 patients, positive culture from a wound swab without histopathology demonstrating tissue invasion in 1 patient, and insufficient radiological signs in 1 patient) (Figure 1).

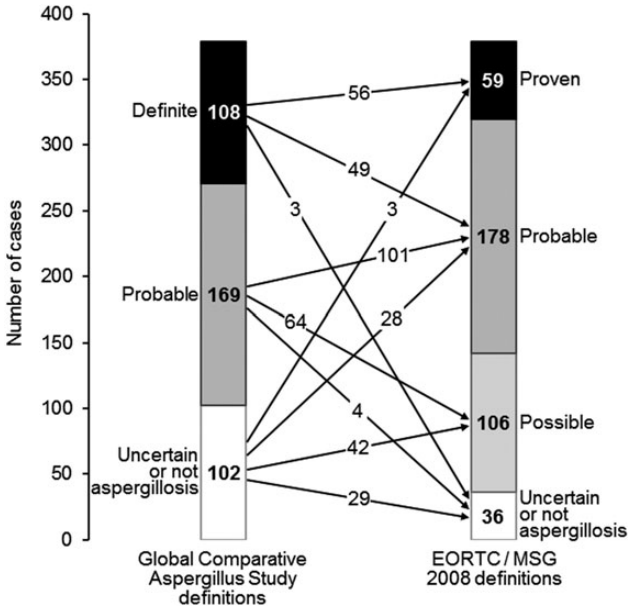

Figure 1. Recategorization of the 379 cases. Left bar: original classification of the cases in the original Global Comparative Aspergillus Study (GCAS). Right bar: distribution of the cases after recategorization. The numbers in the figure show how cases originally classified in the GCAS [4] would be now be defined according to European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions [3].

Table 2. Main Characteristics of the 343 Patients With a Possible, Probable, or Proven Invasive Aspergillosis After Recategorization

Characteristics	Voriconazole (n = 179)	Amphotericin B (n = 164)	*P* Value
Age, y, median (range)	42 (13–79)	52.5 (12–75)	.20
Sex, male, No. (%)	117 (65.4)	101 (61.6)	.50
Underlying condition, No. (%)			.69
Allogeneic HSCT	41 (22.9%)	34 (20.7)	
Autologous HSCT	11 (6.1)	8 (4.9)	
Acute myeloblastic leukemia	64 (35.8)	63 (38.4)	
Acute lymphoblastic leukemia	15 (8.4)	12 (7.3)	
Other hematologic malignancy	21 (11.7)	25 (15.2)	
Solid organ cancer	2 (1.1)	0	
Solid organ transplant	11 (6.1)	6 (3.7)	
Other nonmalignant disease[a]	14 (7.8)	16 (9.8)	
Neutrophils <500/μL	90 (50.3)	81 (49.4)	.91

Abbreviation: HSCT, hematopoietic stem cell transplant.

[a] Mostly high-dose steroid-treated or human immunodeficiency virus–positive patients.

Of the 108 cases originally classified as definite IA, 56 remained proven (positive culture from a tissue biopsy or a sterile fluid in 7 patients, positive histology or microscopy from a tissue or a sterile fluid in 49 patients), 49 were downgraded to probable IA (positive culture from BAL fluid or bronchial aspirate or brushing in 48 patients, positive sinus aspirate in 1 patient), and 3 were downgraded to uncertain (positive culture in BAL fluid but nonconsistent or lack of radiological data) (Figure 1).

The new recategorization identified 59 proven, 178 probable, and 106 possible IA cases and 36 uncertain or not aspergillosis.

Characteristics of the Patients With IA

The distribution of demographic characteristics and of underlying conditions did not differ between voriconazole-treated and AmB-treated patients with possible, probable, or proven IA (Table 2). Half of the patients were neutropenic at baseline.

Response at End of Randomized Therapy

Overall, 343 cases of possible, probable, and proven IA were identified (179 in voriconazole arm and 164 in AmB arm) after recategorization. Favorable response at end of randomized therapy was higher for patients treated with voriconazole than in those given AmB (97/179 [54.2%] vs 34/164 [20.7%], respectively, $P < .0001$; difference in treatment group: 33.5% [95% CI of the difference: 23.2%–43.8%]; Table 3). Subgroup analysis according to levels of certainty showed a higher favorable end of randomized treatment response for those cases of possible IA, and of mycologically documented (probable or proven) IA treated with voriconazole (Table 3).

Response at Week 12

A higher favorable response at week 12 was seen for those treated with voriconazole than for those given AmB (98/179 [54.7%] vs 49/164 [29.9%], respectively, $P < .0001$; difference in treatment group: 24.9% [95% CI of the difference: 14.4%–35.4%]; Table 3).

Subgroup analysis showed a higher favorable 12-week response rate for patients given voriconazole for possible and for mycologically documented (probable or proven) IA (Table 3).

Survival

A larger proportion of patients with possible, probable, or proven IA survived to week 12 in the voriconazole group compared with those randomized to AmB (73.7% vs 59.1%, $P = .0028$; hazard ratio [HR], 0.57 [95% CI, .39–.82]; Figure 2).

Subgroup analysis showed a numerically higher survival for patients with a possible IA who had been treated with voriconazole (81.8%) compared with those given AmB (68.6%); however, the difference did not reach statistical significance ($P = .11$; HR, 0.53 [95% CI, .25–1.15]). Survival was higher for patients given voriconazole for a mycological documented (probable or proven) IA than for those treated with AmB (70.2% vs 54.9%,

Table 3. Response Rate at End of Randomized Therapy and at Week 12 According to Treatment Group and Level of Certainty

	Possible Invasive Aspergillosis		Probable and Proven Invasive Aspergillosis		All Episodes of Invasive Aspergillosis	
Response	VOR (n = 55)	AmB (n = 51)	VOR (n = 124)	AmB (n = 113)	VOR (n = 179)	AmB (n = 164)
Response at end of randomized therapy						
Favorable response[a], No. (%)	34 (61.8)	12 (23.5)	63 (50.8)	22 (19.5)	97 (54.2)	34 (20.7)
Unfavorable response[b], No. (%)	21 (38.2)	39 (76.5)	61 (49.2)	91 (80.5)	82 (45.8)	130 (79.3)
Difference in response rate, % (95% CI)	38.3 (19.4–57.2)		31.3 (19.1–43.6)		33.5 (23.2–43.8)	
P value	<.0001		<.0001		<.0001	
Response at week 12						
Favorable response[a], No. (%)	36 (65.5)	20 (39.2)	62 (50.0)	29 (25.7)	98 (54.7)	49 (29.9)
Unfavorable response[b], No. (%)	19 (34.5)	31 (60.8)	62 (50.0)	84 (74.3)	81 (45.3)	115 (70.1)
Difference in response rate, % (95% CI)	26.2 (7.2–45.3)		24.3 (11.9–36.7)		24.9 (14.4–35.4)	
P value	.011		.0002		<.0001	

Abbreviations: AmB, amphotericin B; CI, confidence interval; VOR, voriconazole.

[a] Complete or partial response.

[b] Stable disease, progression, or indeterminate.

respectively, $P = .010$; HR, 0.58 [95% CI, .38–.88]). Separation of probable and proven cases showed persistence of a significant difference in favor of voriconazole in probable IA but not in proven IA (Table 4). Twelve-week survival was higher for the 41 allogeneic hematopoietic stem cell transplant recipients treated with voriconazole than for the 34 who had been given AmB (68.3% vs 35.3%, respectively, $P = .0017$; HR, 0.35 [95% CI, .17–.66]).

Irrespective of the treatment arm, univariate analysis showed improved 12-week survival for possible IA compared with probable and proven IA (75.5% vs 62.9%, respectively, $P = .021$; HR, 0.60 [95% CI, .43–.93]). There was no difference in 12-week survival between probable and proven IA (62.9% vs 62.7%, respectively, $P = .91$; HR, 0.97 [95% CI, .60–1.57]) nor between patients who were neutropenic at baseline and those who were not (67.3% vs 66.3%, respectively, $P = .97$; HR, 0.99 [95% CI, .69–1.44]).

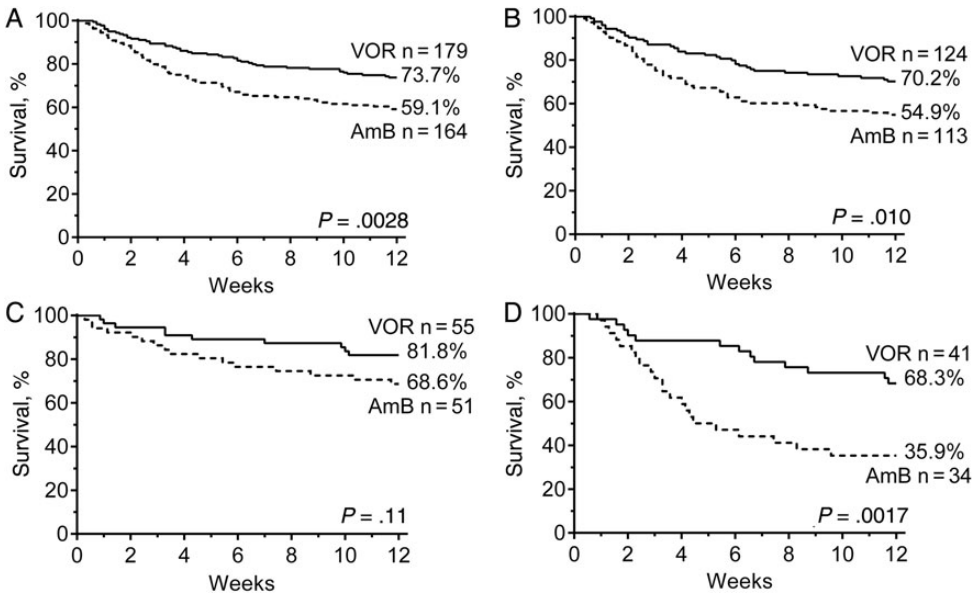

Figure 2. Twelve-week survival curves according to treatment arm in all possible, probable, and proven invasive aspergillosis (IA) (*A*); probable and proven IA (*B*); possible IA (*C*); and possible, probable, and proven IA in allogeneic hematopoietic stem cell transplant recipients (*D*). Abbreviations: AmB, amphotericin B; VOR, voriconazole.

Table 4. Comparison of 12-Week Favorable Response and Survival Rates in the Original Global Comparative Aspergillus Study and After Recategorization According to Level of Certainty of Aspergillosis

	Possible Invasive Aspergillosis		Probable Invasive Aspergillosis		Proven (Definite) Invasive Aspergillosis		All Episodes of Invasive Aspergillosis	
Response	Original	Recategorization	Original	Recategorization	Original	Recategorization	Original	Recategorization
Response at week 12								
Voriconazole								
Favorable response, No./total (%)	NA	36/55 (65.5)	46/77 (59.7)	49/89 (55.1)	30/67 (44.8)	13/35 (37.1)	76/144 (52.8)	98/179 (54.7)
Amphotericin B								
Favorable response, No./total (%)	NA	20/51 (39.2)	34/92 (37.0)	23/89 (25.8)	8/41 (19.5)	6/24 (25.0)	42/133 (31.6)	49/164 (29.9)
Survival at week 12								
Voriconazole								
Survived (%)	NA	81.8	75.3	73.0	67.2	62.9	70.8	73.7
Amphotericin B								
Survived (%)	NA	68.6	62.0	52.8	48.8	62.5	57.9	59.1

Abbreviation: NA, not applicable.

Twelve-week survival was lower for allogeneic hematopoietic stem cell transplant recipients than for other patients (53.3% vs 70.5%, respectively, $P = .007$; HR, 1.72 [95% CI, 1.19–2.97]).

Impact of Recategorization on Efficacy Results

Response and survival rates at week 12 are similar in results after recategorization in all episodes as well as in subgroups of probable and of proven IA compared with the original GCAS results (Table 4). As groups are not independent, no formal statistical comparison was performed.

DISCUSSION

Most recent clinical trials investigating efficacy and safety of antifungal agents in IA have applied the updated EORTC/MSG definition criteria to establish the level of certainty of the diagnosis of IA, and to minimize intra- and interstudy variability in the patient population. Two of the largest trials of the treatment of IA to date, the GCAS and the comparative liposomal AmB study, were conducted before these revised criteria had been elaborated and therefore there are significant differences in the definition of IA cases between recent and older trials [4–8]. IA remains difficult to diagnose early, as no diagnostic test has a high sensitivity at early stage of disease [1]. Many IA cases are suspected only because of typical risk factors and suggestive clinical and radiological features but cannot be confirmed with either direct mycological tests (microscopy, culture, or histopathology) or indirect tests such as *Aspergillus* galactomannan.

Not surprisingly, the recategorization of cases from the GCAS using the 2008 EORTC/MSG criteria identified almost 50% fewer patients with proven IA. This is appropriate, as most of the cases that were downgraded had been categorized as proven based on a positive culture or microscopy from BAL fluid despite the fact that the lower respiratory tract can be colonized by *Aspergillus* even among patients with underlying hematological disorders. Up to one-quarter of cancer patients and hematopoietic stem transplant recipients have a significant concomitant respiratory condition (eg, bronchiolitis, chronic obstructive pulmonary disease), and it has been suggested that this could predispose to colonization by *Aspergillus* [9]. The absence of another etiology likely increases the probability of IA in these patients, but positive BAL fluid is not accepted as a surrogate marker of tissue invasion. Classification of such episodes as a probable IA is thus appropriate.

In our series, probable IA was also defined more stringently. EORTC/MSG definitions require mycological evidence to classify a case as probable IA. The original GCAS trial, as well as the comparative liposomal AmB trial, accepted as probable aspergillosis cases defined by a nodule surrounded by a halo sign in patients at high risk of fungal disease even in the absence of mycological documentation [4, 5]. In the GCAS, 97 of 277 (35.0%) cases in the mITT population were inadequately classified as probable based on the revised criteria, whereas in the comparative liposomal AmB trial as many as 59% of the cases were not mycologically documented. The integration of galactomannan results obtained in 65.7% of the patients significantly increased the rate of mycological documentation. Lack of galactomannan results in one-third of the patients and long storage of the serum before galactomannan testing are limitations in this study. Storage may be associated with a major decrease in galactomannan index and therefore our recategorization may still underestimate the true rate of probable cases [10].

As expected, we and others have shown that possible IA has a much better outcome than probable or proven IA [5, 6].

Therefore, a very high proportion of possible cases in any given study may result in an overly optimistic estimation of the efficacy of treatment. In our analysis, 12-week survival in probable and proven IA (70.2%) was similar to that observed in the original analysis (70.8%) in the voriconazole-treated patients. By contrast, similar recategorization of cases in the comparative liposomal AmB trial showed a 12-week survival of only 58% in the subset of patients with true probable or proven IA (3 mg/kg arm) vs 71% for the whole population [5, 6].

It remains unclear whether possible cases truly represent IA in patients at risk. A negative serum galactomannan test may not be sufficient to exclude the diagnosis as the sensitivity of the test can be <70% even in neutropenic patients [11]. Moreover, the detection of galactomannan may be impaired in patients receiving prior antimold therapy, patients having positive anti-*Aspergillus* antibodies, and very likely among those with limited disease [12, 13]. The difference in response rates and in survival between patients treated with voriconazole and those given AmB is of the same magnitude for possible IA as for probable and proven IA. This difference in response and survival rates between voriconazole-treated patients and AmB-treated patients is not explained by earlier discontinuation of therapy for toxicity in the AmB arm [4, 14, 15]. Therefore, the significant benefit of voriconazole over AmB treatment among patients with possible IA strongly supports the notion that many of these patients did, indeed, actually have IA and therefore required antifungal therapy, likely representing true cases (albeit early disease). This likely explains the better response than was seen for those with proven and probable IA.

Integration of baseline serum galactomannan results and application of the 2008 EORTC/MSG criteria resulted in more reliable identification of patients with probable or proven IA, and identification of a significant subgroup of patients with well-defined possible IA missing from the earlier analysis. The efficacy results did not change despite this reclassification confirming the superiority of voriconazole over AmB. These results also strongly support the contention that possible IA as defined by the 2008 EORTC/MSG criteria represents an early phase of the invasive process in many of these highly immunosuppressed patients. The improved survival also supports the view that therapy be given preemptively for IA among high-risk patients.

Notes

Acknowledgments. The Global Comparative Aspergillosis Study and this recategorization study were sponsored by Pfizer Inc.

Potential conflicts of interest. R. H. has served as a consultant and a member of advisory boards or on speakers' bureaus for Pfizer, Gilead, Merck Sharp & Dohme (MSD), Schering-Plough, and Astellas; and has received a research grant from Pfizer. T. F. P. has received research grants from Astellas and Merck; and has been a consultant or scientific advisory board member for Astellas, Merck, Scynexis, Toyoma, and Viamet. M. A. S. has been a member of advisory boards for and received research funding from Pfizer, MSD, Schering-Plough, and Gilead Sciences. O. M. has served as a scientific consultant for Essex Schering-Plough, Gilead, Merck, Novartis, and Pfizer; has received unrestricted research grants from Associates of Cape Cod, bioMérieux, Bio-Rad, Essex Schering-Plough, Gilead, Merck, Novartis, Pfizer, Roche Diagnostics, Fungal Infection Network of Switzerland Foundation, Leenaards Foundation, FAMMID Foundation, and the European Community's Seventh Framework program (FP7-2007-2013) under grant agreement HEALTH-F2-2010-26033-ALLFUN; and has served as a speaker on behalf of Essex Schering-Plough, Gilead, Merck, Pfizer, and Roche Diagnostics. J. M. has served as a consultant to Schering-Plough, Gilead Sciences, MSD, Pfizer Inc, Bio-Rad, Fujisawa Healthcare, Inc, Astellas, Nextar, Zeneus (Cephalon), Viropharma, and Boehringer-Ingelheim; has received research funding from Bio-Rad, MSD, and Pfizer Inc; and has been on the speaker's bureau for Schering-Plough, Gilead Sciences, MSD, Pfizer Inc, Bio-Rad, Fujisawa Healthcare, Inc, Astellas, and Zeneus (Cephalon). E. M. J. has served as a member of advisory boards or of speakers' bureaus for Pfizer, Gilead, MSD, Schering-Plough, and Astellas. H. T. S. is a former employee of Pfizer, and owns stock in the company. J. P. D. has served as a consultant for Astellas, Gilead, Merck/MSD, and Pfizer; as a grant investigator for Astellas, Gilead, Merck/MSD, and Pfizer; as an investigator for Astellas and Pfizer; as a research contractor for Gilead; as a scientific advisor for Astellas, Gilead, Pfizer; and on the speakers' bureaus of Gilead, Merck/MSD, and Pfizer. P. G. P. has received research support from Astellas, Merck, Gilead, Scynexis, and T2 Biosystems; and has served as an ad hoc scientific advisor for Astellas, Merck, Gilead, Scynexis, T2 Biosystems, and Viamet.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Segal BH. Aspergillosis. N Engl J Med **2009**; 360:1870–84.
2. Ascioglu S, Rex JH, de Pauw B, 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.
3. De Pauw B, Walsh TJ, Donnelly JP, et al. 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 **2008**; 46: 1813–21.
4. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med **2002**; 347:408–15.
5. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis **2007**; 44:1289–97.
6. Cornely OA, Maertens J, Bresnik M, et al. Efficacy outcomes in a randomised trial of liposomal amphotericin B based on revised EORTC/MSG 2008 definitions of invasive mould disease. Mycoses **2011**; 54: e449–55.
7. Herbrecht R, Maertens J, Baila L, et al. 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 **2010**; 45:1227–33.
8. Viscoli C, Herbrecht R, Akan H, et al. An EORTC phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. J Antimicrob Chemother **2009**; 64:1274–81.
9. Nivoix Y, Velten M, Letscher-Bru V, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis **2008**; 47:1176–84.

10. Johnson GL, Sarker SJ, Hill K, et al. Significant decline in galactomannan signal during storage of clinical serum samples. Int J Mol Sci **2013**; 14:12970–7.
11. Marchetti O, Lamoth F, Mikulska M, Viscoli C, Verweij P, Bretagne S. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant **2012**; 47:846–54.
12. Herbrecht R, Letscher-Bru V, Oprea C, et al. *Aspergillus* galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol **2002**; 20:1898–906.
13. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis **2004**; 190:641–9.
14. Patterson TF, Boucher HW, Herbrecht R, et al. Strategy of following voriconazole versus amphotericin B therapy with other licensed antifungal therapy for primary treatment of invasive aspergillosis: impact of other therapies on outcome. Clin Infect Dis **2005**; 41:1448–52.
15. Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. Cancer **2008**; 112:2309–12.