MAJOR ARTICLE

Imaging Findings in Acute Invasive Pulmonary Aspergillosis: Clinical Significance of the Halo Sign

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(See the editorial commentary by Vandewoude and Vogelaers on pages 380–1)

Background. Computed tomography (CT) of the chest may be used to identify the halo sign, a macronodule surrounded by a perimeter of ground-glass opacity, which is an early sign of invasive pulmonary aspergillosis (IPA). This study analyzed chest CT findings at presentation from a large series of patients with IPA, to assess the prevalence of these imaging findings and to evaluate the clinical utility of the halo sign for early identification of this potentially life-threatening infection.

Methods. Baseline chest CT imaging findings from 235 patients with IPA who participated in a previously published study were systematically analyzed. To evaluate the clinical utility of the halo sign for the early identification and treatment of IPA, we compared response to treatment and survival after 12 weeks of treatment in 143 patients who presented with a halo sign and in 79 patients with other imaging findings.

Results. At presentation, most patients (94%) had $\geq$1 macronodules, and many (61%) also had halo signs. Other imaging findings at presentation, including consolidations (30%), infarct-shaped nodules (27%), cavitary lesions (20%), and air-crescent signs (10%), were less common. Patients presenting with a halo sign had significantly better responses to treatment (52% vs. 29%; $P < .001$) and greater survival to 84 days (71% vs. 53%; $P < .01$) than did patients who presented with other imaging findings.

Conclusions. Most patients presented with a halo sign and/or a macronodule in this large imaging study of IPA. Initiation of antifungal treatment on the basis of the identification of a halo sign by chest CT is associated with a significantly better response to treatment and improved survival.

Severely immunocompromised patients, particularly those with hematopoietic stem cell transplants (HSCTs) or hematological malignancies, are at high risk for invasive fungal infection [1, 2]. Invasive pulmonary aspergillosis (IPA) is increasing in incidence in this population [3] and is associated with unacceptably high morbidity and mortality [4–6], especially when diagnosis and treatment are delayed [3, 7, 8]. Despite recent advances in antifungal treatment, clinical outcomes are still generally considered to be inadequate [5, 8–10], with the best reported response rates in the range of 50%–60% [9, 11, 12].

Response to treatment and survival can, potentially, be improved if specific antifungal treatment for IPA is initiated at an early stage of infection. However, an early diagnosis of IPA based on histopathological or mycological evidence can be difficult to establish [9, 13–15]. Sputum cultures are neither sensitive nor specific: positive sputum culture results do not always correlate with invasive disease, and negative sputum culture results are common in patients with proven IPA [16–18]. Coagulation abnormalities and coexisting thrombocytopenia may preclude invasive procedures for tissue har-

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vesting [19]. Moreover, examination and culture of tissue samples can be inconclusive because of sampling error or previous exposure to antifungals [20]. Investigative efforts have focused on molecular and serological diagnostic techniques, and, although these techniques show promise, they have varying degrees of sensitivity [21]. Galactomannan detection has been incorporated into the diagnostic criteria for invasive aspergillosis; however, because of variable sensitivity [22, 23] and false positivity, which have been reported in patients receiving piperacillin-tazobactam or other antibiotics [24–28], this serological marker on its own has not been widely accepted as supporting a definitive diagnosis of infection. Measurement of (1,3)-β-D glucan in blood may be a useful preliminary screening tool for invasive aspergillosis, although this antigen is present in many pathogenic fungi. Extensive efforts have been made to detect the DNA of *Aspergillus* species, but a lack of technical standardization and a relatively poor understanding of DNA release and kinetics continue to hamper the broad applicability of this technique [21].

Invasive aspergillosis in severely immunocompromised patients typically involves the lung [11], and chest computed tomography (CT) may detect lung involvement at an early stage of infection [29, 30]. In particular, the halo sign—that is, a macronodule ($\geqslant$1 cm in diameter) surrounded by a perimeter of ground-glass opacity—is regarded to be an early indicator of IPA [31–33] and has been incorporated into the inclusion criteria of clinical studies [9, 11, 34, 35]. Systematic CT screening for the halo sign in high-risk patients has been recommended, because the initiation of antifungal treatment on the basis of this finding may lead to better outcomes [36, 37]. Previous studies of the halo sign as an early indicator of IPA, however, have been limited to individual investigations of relatively small size [34, 38]. Consequently, it has been difficult to reach a consensus on the utility of the halo sign as an early indicator of IPA [39].

Therefore, in the present study, we reviewed chest CT findings from a large series of patients with IPA included in the Global Comparative Aspergillosis Study [11], the largest study of invasive aspergillosis ever conducted, and correlated imaging findings at presentation with global response to treatment and survival at 12 weeks after the start of treatment. These analyses were used to evaluate the utility of chest CT imaging findings, including the halo sign, as early indicators of IPA.

PATIENTS AND METHODS

Clinical database. The clinical data for this analysis were generated by the Data Review Committee (DRC) of the Global Comparative Aspergillosis Study (National Library of Medicine clinical trials registry NCT00003031 and NCT00001646) [11]. The global DRC comprised 8 clinicians and 4 radiologists. Using a standardized protocol based on predefined criteria, the DRC was responsible for confirming a diagnosis of probable or definite invasive aspergillosis for each patient entered into the study.

The definitions of invasive aspergillosis used in this study were similar to the criteria of the European Organisation for Research and Treatment of Cancer/Mycoses Study Group [39]. However, in this study, the finding of a halo sign (or air crescent sign) in a patient with allogeneic HSCT or hematological malignancy and recent neutropenia was sufficient to support a diagnosis of probable IPA, with or without mycological or histopathological confirmation.

The DRC also assessed the global response to treatment at 12 weeks after study entry: satisfactory response to treatment was defined as a complete or partial global response, which incorporated clinical, mycological, and radiological responses [11]. All radiological and efficacy assessments by the DRC were performed blinded to the study drug.

Image database. The image database used for this analysis included the baseline CT from 235 patients enrolled in the Global Comparative Aspergillosis Study who had a DRC-confirmed diagnosis of definite or probable IPA and who had at least 1 lesion on baseline chest CT. In patients with lesions other than halo signs and air crescent signs, the diagnosis of IPA was based on mycological and/or histopathological confirmation.

Acquisition methodology for the CT studies varied according to local equipment and clinical imaging protocols at the 95 referral sites. Images were translated from a variety of formats into an internal, proprietary format for electronic display. Film-based CT images were digitized at 175 μm/pixel and 12 bits/pixel with a laser light source (Lumisys). Individual frames from multiformat film were digitally excised and cropped, and any demographic identifiers were removed. Fewer than 5% of images were available as primary raw digital images directly from the scanners.

The image data were displayed through a computer-assisted masked reading program (CAMR; Bio-Imaging Technologies). The digitized images were viewed on electronic displays in a darkened room on as many as 8 extended graphics array (XGA) 21-inch diagonal cathode ray tube monitors (ViewSonics). Each image set was analyzed by 1 of 4 DRC radiologists, and their findings were entered on paper database forms or directly into an electronic record, according to a defined protocol sequence. The imaging from each case was reviewed by the DRC radiologist after the subject completed participation in the study.

To ensure uniformity of assessments, the baseline imaging for a subset of 20% of patients in this study was initially evaluated in a pilot evaluation by >1 radiologist. The images from 81 patients (the majority of which included halo signs) were analyzed by >1 DRC radiologist; the average inter-radiologist agreement was 72%, which is consistent with published data

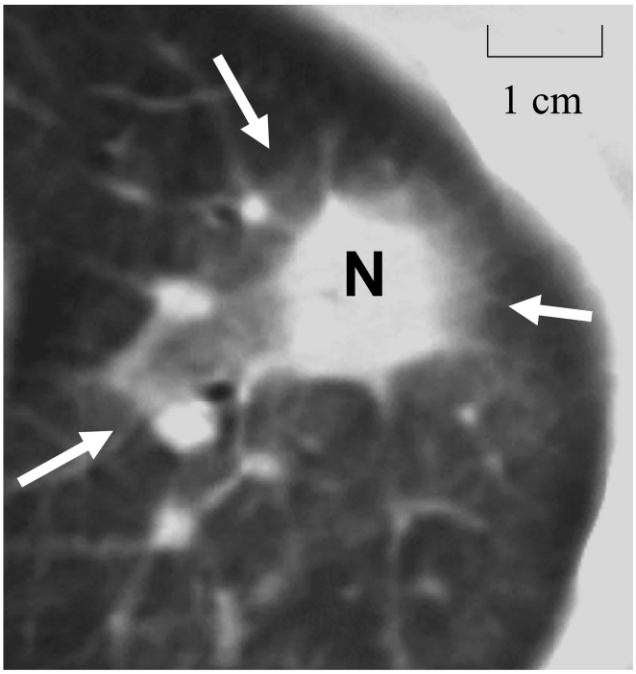

Figure 1. Computed tomographic section through the lung, demonstrating a halo sign in a patient with hematological malignancy. The sign consists of 2 parts: a solid nodular core (N), through which no pulmonary parenchyma is visible, and a ground-glass perimeter of intermediate density *(arrows),* through which pulmonary parenchyma is still visible. Note that the nodule is >1 cm in diameter and that the area of ground-glass opacity surrounds more than three-quarters of the nodule.

[40]. Differences in interpretation were resolved by discussion and/or by the senior radiologist.

Radiological definitions and interpretation categories. The DRC radiologists used a standard glossary of CT imaging definitions to categorize pulmonary lesions [41]. A "nodule" was defined as an ovoid soft-tissue opacity that completely obscured the background of underlying bronchovasculature. Subcategories of nodules included the macronodule (i.e., a large nodule ⩾1 cm in diameter) and the cluster of small nodules (<1 cm in diameter). An "infarct-shaped nodule" was defined as a nodule that abutted a pleural surface and conformed to the hump shape of a small pulmonary infarct [42].

"Ground-glass opacity" was defined as hazy increased attenuation of lung, intermediate between air and liquid, through which the background of underlying bronchovasculature was still visible. The "halo sign" (figure 1) was defined as a macronodule surrounded by a perimeter of ground-glass opacity [31–33]. DRC guidelines required that the perimeter of ground-glass opacity surround >75% of the available non–pleural-opposed edge of a macronodule. This surrounding ground-glass opacity was differentiated from unsharp margination attributable to edge irregularity or partial volume effect as a result of motion or excessive CT section thickness.

The "air crescent sign" was defined as a crescentic pocket of gas occupying a separation interface between a lung sequestrum attributable to necrosis and a rim of viable lung [31, 43]. The air crescent sign was distinguished from nonspecific thick-walled and thin-walled cavities not containing a sequestrum.

A "consolidation" was defined as an abnormal opacification of the peripheral air spaces, such that the underlying bronchovasculature was totally obscured [41]. A consolidation generally maintained the shape of preexisting aerated lung anatomy and was sometimes accompanied by air bronchograms [41]. Consolidations were subclassified as being infarct shaped if they were a segment or larger in size, wedge shaped, and pleural based, and if they roughly conformed to the shape of the underlying anatomy [31, 32].

Small-airway findings included any of the following: centrilobular opacity (i.e., a discrete nodular opacity <1 cm in diameter in the core of a secondary lobule), tree-in-bud opacity (an opacified segment of small branching bronchioles), and peribronchial opacity consistent with bronchopneumonia. Other airway findings included bronchiectasis and bronchial wall thickening [41].

Data analysis. Comparative data were analyzed by χ^2 test to assess the significance of differences in proportions. The probability of type 1 error was set at .05 for the purpose of hypothesis testing. The SAS procedure LIFETEST was used to produce the Kaplan-Meier curves, and the SAS procedure PHREG was used to compute the hazard ratios and the corresponding 95% CIs [44]. The significance of the difference in survival was assessed by the log-rank test.

RESULTS

The study population comprised 235 patients with DRC-confirmed probable or definite IPA and at least 1 lesion on baseline chest CT. This group included 156 male patients and 79 female patients, ranging in age from 12 to 79 years (mean, 49.5 years). The majority of patients (203; 86%) had hematological immunosuppressive conditions, including leukemia (116 patients), allogeneic HSCT (57 patients), or other hematological conditions (30 patients). Relatively few patients (32; 14%) had nonhematological immunosuppressive conditions, including high-dose corticosteroid treatment (12 patients), HIV infection (11 patients), heart transplant (6 patients), renal transplant (2 patients), and solid tumor (1 patient).

Most patients (222; 94%) presented with at least 1 macronodule on chest CT (table 1); 176 (79%) presented with multiple macronodules (mean, 3.4; range, 1–14), and 133 (60%) had bilateral (multiple) macronodules. Macronodules were distributed approximately in proportion to expected regional lung size: 57% in the right lung, 43% in the left lung, 36% in the

Table 1. Imaging findings in patients with invasive pulmonary aspergillosis.

Imaging finding	No. (%) of patients ($N = 235$)
Macronodule (≥1 cm in diameter)[a]	222 (94.5)
Halo sign[b]	143 (60.9)
Consolidation[c]	71 (30.2)
Macronodule, infarct shaped	63 (26.8)
Cavitary lesion[d]	48 (20.4)
Air bronchograms	37 (15.7)
Clusters of small nodules (<1 cm in diameter)	25 (10.6)
Pleural effusion	25 (10.6)
Air crescent sign	24 (10.2)
Nonspecific ground-glass opacification	21 (8.9)
Consolidation, infarct shaped	18 (7.7)
Small-airway lesions[e]	16 (6.8)
Atelectasis	7 (3.0)
Hilar/mediastinal lesion	4 (1.7)
Pericardial effusion	2 (0.9)

NOTE. Patients may have >1 type of lesion.

[a] Includes macronodules with or without halo sign and infarct-shaped macronodules.

[b] A macronodule with a perimeter of ground-glass opacity.

[c] Includes infarct-shaped consolidations.

upper zones, 32% in the mid zones, and 31% in the lower zones.

Many patients (143; 61%) had at least 1 halo sign, and a large proportion of these patients (59; 41%) had >1 (mean, 1.8; range, 1–6). Although most patients who presented with halo signs had hematological conditions, 8 patients with halo signs had nonhematological conditions: 1 was HIV positive, 4 received high-dose steroids, 2 were heart transplant recipients, and 1 was a renal transplant recipient.

A minority of patients (63; 27%) had nodules that were categorized as infarct shaped. Few patients (48; 20%) in this series presented with cavitary lesions, and fewer (24; 10%) presented with air crescent signs. Consolidations were identified in a minority of patients (71; 30%), and few patients (18; 7.7%) had infarct-shaped consolidations. Clusters of small nodules were uncommon (25 patients; 11%), as were other lesion types, including small-airway lesions and pleural effusions (table 1).

To assess global response to treatment and survival at 12 weeks and the clinical impact of the halo sign, we focused on the 222 patients who presented with at least 1 macronodule: 143 of these patients presented with halo signs, and 79 presented with macronodules without halo signs. The 13 patients excluded from this analysis presented with nonspecific radiological findings, including consolidations (9 patients), other opacities (3 patients), and pleural lesions (1 patient).

In the group of patients with halo signs, the satisfactory global response rate at 12 weeks was 52% (75 of 143 patients), compared with 29% (23 of 79 patients) in the group with macronodules without halo signs ($P < .001$). Survival to 12 weeks was also significantly greater (71% vs. 53%; $P < .01$) among patients with halo signs at presentation (figure 2).

Individual 2-by-2 χ^2 comparisons demonstrated that the halo sign was associated with improved outcomes in patients with hematological conditions, nonhematological conditions, baseline neutropenia, or no baseline neutropenia, as well as in allogeneic HSCT recipients (table 2). The highest rate of satisfactory global response at 12 weeks was 62% (48 of 77 patients), for patients with a halo sign at presentation who were initially treated with voriconazole. The lowest rate of satisfactory global response was 16% (6 of 38 patients), for patients with macronodules without halo signs who were initially treated with conventional amphotericin B (figure 3).

DISCUSSION

Confirming the diagnosis of invasive fungal infection in severely immunocompromised patients remains one of the great challenges in infectious disease medicine. It has been reported that IPA may be identified by chest CT at an early stage of disease, and the initiation of specific antifungal treatment on the basis of CT findings may lead to better outcomes. Until now, however, data supporting this hypothesis have been inconclusive. The Global Comparative Aspergillosis Study [11] created an imaging database of unprecedented size and scope that provided a unique opportunity to systematically analyze the presenting CT findings from >200 patients with IPA. The results of this analysis clearly demonstrate that chest CT is an essential tool in managing such patients.

The vast majority of these patients with IPA presented with at least 1 macronodule on chest CT. This suggests that, in high-risk patients, the absence of a macronodule argues against a diagnosis of IPA. More than half of our patients presented with halo signs. All other findings at presentation, including infarct-shaped nodules, consolidations, and infarct-shaped consolidations, were much less common. Small-airway findings consistent with airway invasive aspergillosis [45] were uncommon in our study group. Cavitary lesions, including the air crescent sign, were observed at presentation in only a minority of patients in this series; these lesions are considered to be characteristic of later-stage disease.

Published reports have identified the halo sign as an early indicator of IPA, specifically in immunocompromised patients with hematological conditions [7, 9, 31–36]. On the basis of these reports, the halo sign on chest CT in selected patient populations was incorporated into the entry criteria for the Global Comparative Aspergillosis Study. As a result, we were not surprised that a relatively large proportion of patients (61%) in this study had at least 1 halo sign at study entry.

[d] Includes cavitary lesions with or without air crescent signs.
[e] Includes peribronchial and centrilobular opacities.

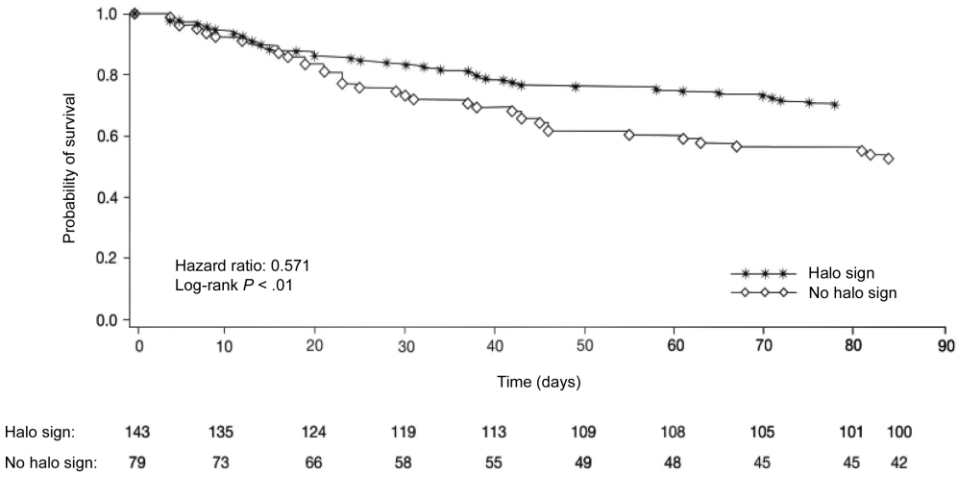

Figure 2. Time to death for patients with ($n = 143$) and patients without ($n = 79$) a halo sign at presentation. The no. of patients still alive at each time point is given below the graph.

These imaging-based diagnoses were also supported by mycological and/or histopathological confirmation in one-third of patients, further supporting the known association between the halo sign and IPA.

The halo sign has been pathophysiologically characterized as a discrete nodule of angioinvasive aspergillosis with infarction and coagulative necrosis surrounded by alveolar hemorrhage. IPA is considered to be the most common cause of angioinvasive fungal infection in severely immunocompromised patients [30, 46]. Although this imaging finding is not pathognomonic for IPA because it may have other infectious etiologies, such as *Pseudomonas aeruginosa* and Zygomycetes species [30, 33, 47], IPA is by far the most common cause of the halo sign in the population at high risk for fungal infection.

In a small series, the halo sign was present in 25% of patients with pulmonary zygomycosis [48], and, in a multivariate analysis, the finding of >10 nodules or a pleural effusion were independent predictors of pulmonary zygomycosis. It is interesting to note that only 4 patients with IPA in our series presented with >10 nodules, and only 10% (25 of 235 patients) presented with pleural effusions. We enrolled into our study 1 patient with a halo sign at presentation who subsequently had zygomycosis confirmed and was prematurely discontinued from the study. Additionally, when the DRC reviewed this patient's imaging results, the presence of a halo sign was not confirmed. This patient was not included in the present analysis.

Because of technical difficulties, we were unable to incorporate serum galactomannan results from this series of patients with IPA into our analysis. However, in a prospective trial of HSCT recipients, Weisser et al. [49] prospectively compared serial galactomannan results and pathological changes on CT scan. They found that positive galactomannan results did not precede imaging findings by CT scan, and they recommended the initiation of *Aspergillus*-active antifungal treatment on the basis of CT imaging as opposed to positive galactomannan results. Quantitative PCR may also support the diagnosis of invasive aspergillosis at an early stage [50].

A recent retrospective analysis of chest CT data identified another imaging finding, the hypodense sign, which is thought to be caused by vascular obstruction with secondary lung infarction and sequestration. This sign was observed in one-third of 43 immunocompromised patients with IPA [51]. Notably, this imaging finding was generally detected after the finding of a halo sign, thus limiting its utility for early diagnosis of IPA.

Neutrophil dysfunction, a frequent consequence of hematological malignancy and allogeneic HSCT, is the most common host defense defect associated with invasive aspergillosis [52, 53]. In contrast, impaired cell-mediated immunity, commonly associated with patients with HIV/AIDS, organ transplant recipients, and patients receiving steroids or other immunosup-

Table 2. Rate of satisfactory treatment response by underlying condition and presence or absence of halo sign.

	Satisfactory response rate, no. with satisfactory response/total (%)		
Population	Halo sign	No halo sign	*P*
Whole study population	75/143 (52.4)	23/79 (29.1)	<.001
Patients with hematological conditions	70/135 (51.9)	18/60 (30.0)	<.005
Patients with nonhematological conditions	5/8 (62.5)	5/19 (26.3)	NS
Neutropenic patients	42/90 (46.7)	4/17 (23.5)	.08
Nonneutropenic patients	33/53 (62.3)	19/62 (30.7)	<.01
Allogeneic HSCT recipients	7/20 (35.0)	7/35 (20.0)	NS

NOTE. HSCT, hematopoietic stem cell transplant; NS, not significant.

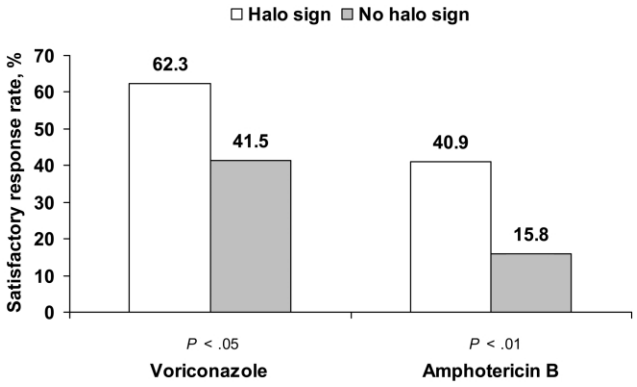

Figure 3. Rate of satisfactory treatment response, by treatment arm and presence or absence of halo sign at presentation.

pressive therapies, is only sporadically associated with IPA. Not surprisingly, only a small proportion (13.6%) of the patients with IPA in this series had nonhematological underlying conditions; however, a halo sign at presentation was still identified in 8 (25%) of these patients.

The finding of a halo sign at baseline was strongly associated with improved responses to treatment and better survival. Regardless of treatment randomization or baseline condition, there was a difference of >20% in response between patients with a halo sign and patients without a halo sign. These observations have been supported by a recently published study that also reported improved outcomes in a series of patients with IPA who presented with a halo sign [54]. In our study, response rates were highest among patients with a halo sign at presentation who were treated initially with voriconazole; the lowest response rates were seen among patients without a halo sign at presentation who were treated initially with amphotericin B.

To investigate other potential explanations for the improved outcomes in these patients, we compared baseline clinical characteristics of patients presenting with and patients presenting without halo signs. Using individual 2-by-2 χ^2 comparisons, we found that the presence of a halo sign at baseline was associated with more favorable outcomes, regardless of neutropenic status or underlying condition.

Our analysis of the imaging data collected in the Global Comparative Aspergillosis Study supports the utility of chest CT for the early detection of IPA in severely immunocompromised patients. Early initiation of effective antifungal treatment for IPA, based on the finding of a halo sign, is associated with significantly improved response to treatment and with improved survival.

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Potential conflicts of interest. R.E.G has received honoraria from Pfizer and Schering-Plough. H.T.S. and P.F.T. are employees of Pfizer. O.L. has served on the speakers' bureaus of Pfizer, Merck, and Astellas. J.R.W. has served as a consultant/advisor for Pfizer, Merck, Schering-Plough, and Nektar; has received honoraria from Pfizer and Merck; and has received research funding from Pfizer. R.H. has served as a consultant/advisor for Pfizer, Merck, Gilead, and Schering-Plough and has received research funding from Pfizer. P.R. has received honoraria from Pfizer, Merck, and Schering-Plough. T.F.P. has served as a consultant/advisor for Pfizer, Schering-Plough, Astellas, Merck, Affinium, Basilea, Diversa, Eisai, J Uriach, MediciNova, Microbia, Nektar, Rib-X, and Human Genome Sciences; has been on the speakers' bureaus of Pfizer, Schering-Plough, Astellas, and Merck; and has received research funding from Schering-Plough, Astellas, Merck, Enzon, and Pfizer. D.W.D. has received research funding from Pfizer. B.E.dP. has received honoraria from Pfizer and Merck. R.H.R. has served as a consultant/advisor for, and has received honoraria from, Pfizer and Merck. H.T.S. is a shareholder in Pfizer, and J.E.B. is a shareholder in Merck. J-W.O., P.S., and C.D.: no conflicts.

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