# Invasive Aspergillosis in Critically Ill Patients without Malignancy

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**Using criteria designed for invasive aspergillosis (IA) in patients with cancer, we aimed to determine the impact of IA in patients without malignancy in a medical intensive care unit (ICU). In this retrospective study, 127 patients out of 1,850 admissions (6.9%) hospitalized between 2000 and 2003 had microbiological or histopathologic evidence of *Aspergillus* during their ICU stay. There were 89 cases (70%) without hematologic malignancy. These patients were classified as proven IA (n = 30), probable IA (n = 37), possible IA (n = 2), or colonization (n = 20). In these patients, mean SAPS II score was 52 with a predicted mortality of 48%. The observed mortality was 80% (n = 71). Mortality of the proven and the probable IA was 97 and 87%, respectively. Postmortem examination was done in 46 out of 71 patients, and 27 autopsies (59%) showed hyphael invasion with *Aspergillus*. *Aspergillus* infections occurred in five critically ill patients with proven IA who did not have any predisposing factors according to the currently available definitions. Three of these patients had Child C liver cirrhosis. IA is an emerging and devastating infectious disease in patients in the ICU without malignancy. In those patients, host criteria for probable fungal infections should probably be adapted.**

**Keywords:** aspergillosis; critically ill; mortality

Over the last decade, invasive aspergillosis (IA) has emerged as a severe infection in neutropenic patients, bone marrow or stem cell transplant recipients, in solid organ transplant patients, and in patients with chronic granulomatous disease (1). Initial reports on IA described an overwhelming, progressive disease in hematologic patients with a very high mortality that was often only recognized at autopsy (2). Since these reports, definitions have been developed that facilitate clinical research and the diagnosis of invasive fungal infections in immunocompromised patients with cancer (3). Also, new diagnostic tools such as the circulating galactomannan antigen test (4) and the high-resolution computed tomography (CT) scan (5), which are validated in patients with malignant hematological diseases, are becoming widely available. New antifungal agents such as voriconazole (6) and echinocandins (7) have been developed.

Despite these advances, IA remains an underdiagnosed disease that often has an insidious onset but a fatal outcome (1). Current advances in medicine result in an increasing population of severely immunocompromised patients at risk for this infection. During recent years, several publications indicate that the population at risk for pulmonary or disseminated IA can be expanded to patients with chronic obstructive pulmonary disease (COPD) (8, 9) and possibly also to nontransplant intensive care patients (8, 10, 11). In our medical intensive care unit (MICU) we regularly encountered patients with IA that did not have classical risk factors such as neutropenia. The impact of IA in these apparently less immunocompromised patients is, however, not well known. There is also a lack of data on the applicability of the new diagnostic tools to this population or the optimal treatment for these patients.

Using the widely accepted definitions of IA in hematopoietic stem cell transplants and patients with cancer (3), the present study aimed to determine the impact of IA in patients without malignancy hospitalized in a MICU, and to describe the difficulties associated with the diagnostic process of IA in this patient population. Preliminary data of this study were previously published in abstract form (12).

## METHODS

This study is a retrospective cohort study, including all adult patients (≥ 16 years old) that were hospitalized in the 17-bed MICU of the University Hospital Leuven, Belgium between January 1, 2000 and January 1, 2003. The University Hospital Leuven is a 1,700-bed tertiary care center. There are four solid organ transplant units (liver, lung, kidney, and heart), a large department of oncology, and a referral unit for hematologic malignancies in the hospital.

### Inclusion Criteria

Any MICU patient fulfilling one or more of the following criteria was included as a case in the study: (*1*) microbiological evidence of *Aspergillus* infection during the stay in the MICU (any positive culture or two positive circulating galactomannan tests by means of sandwich ELISA test), or (*2*) histopathologic evidence of aspergillosis (including autopsy). Surveillance cultures (tracheal aspirate) were performed on a weekly basis in all patients.

All fungi recovered were subcultured on Sabouraud agar and identified using standard phenotypical techniques. High-resolution CT scan of the lung was done for cases of nonresolving infiltrates despite antibiotic treatment. Galactomannan serum antigen detection was done when IA was considered as a potential cause of the clinical picture. The galactomannan ELISA (Platelia Aspergillus; Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France) was performed according to the instructions of the manufacturer. An optical density index of 1.0 or more was considered positive; a result was considered "true-positive" when two consecutive samples for the same patient tested positive.

When a patient had a positive culture for *Aspergillus*, or a bronchial biopsy showing hyphael invasion, or a CT scan showing the halo sign or a positive galactomannan was obtained before or within the first 48 hours of admission, we considered IA to have occurred before admission to the MICU. Autopsies were performed at the request of the treating physician. If the family objected, no autopsy was performed.

### Classification of the Patients

Fungal disease was classified as proven, probable or possible, according to European Organization for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycosis Study Group (EORTC/MSG) definitions (3). "Proven IA" referred to the histopathologic evidence of tissue invasion (needle aspiration or biopsy and/or autopsy specimen) that disclosed septated, acutely branching hyaline hyphae compatible with *Aspergillus* or positive results of culture for

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*Aspergillus* species from a sample from a normally sterile but clinically infected body site (excluding bronchoalveolar lavage fluid and sinus aspirate) obtained by a sterile procedure. "Probable IA" implied an appropriate host setting as defined by the EORTC/MSG definitions (3) and the presence of positive culture results or cytological evidence for *Aspergillus* species from a lower respiratory tract specimen, in conjunction with 1 major (halo sign or "air crescent" sign on CT scan) or at least two minor (signs of lower respiratory tract infection, pleural rub, and presence of any new infiltrate in a patient who did not fulfill the major criterion but for whom no alternative diagnosis was available) clinical findings. If there was one microbiological criterion or one major clinical criterion (or two minor clinical criteria) in the appropriate host setting without other clear diagnosis for the symptoms, patients were considered to have "possible IA." The final group of patients ("colonization") were those with positive culture for *Aspergillus* from a nonsterile site in patients without any other evidence of fungal infection.

## RESULTS

A total of 127 patients with microbiological or histopathologic evidence of infection with *Aspergillus* were identified. In 102 of these patients (80%) there was a positive culture for *Aspergillus* (100 bronchial aspirates, 1 cerebrospinal fluid, and 1 brain biopsy specimen). The remaining 25 patients had no positive cultures but were included because of at least two positive galactomannan assays (n = 8), two positive galactomannan assays and an autopsy showing hyphael invasion with *Aspergillus* (n = 7), or an autopsy showing hyphael invasion with *Aspergillus* without positive galactomannan assay (n = 10). The vast majority of isolates were *Aspergillus fumigatus* (96%), three were *A. niger*, and one was *A. flavus*.

Of 1,850 admissions to the MICU during the study period, 527 patients died (28%) and 357 underwent autopsy (68%). Autopsy with hyphael invasion with *Aspergillus* was found in 52 cases or 15% of all autopsies. Of the 127 patients included in the present study, 109 died (86%) and 76 underwent autopsy (70%). Hyphael invasion was found in 52 cases (66%). Table 1 gives an overview of the characteristics of all 127 cases. The 127 patients were divided into two groups: a group of 38 patients who had a hematologic malignancy (n = 37) or another cancer (n = 1, seminoma), and a group of 89 patients without cancer.

### Patients with Malignancy

Mean SAPS II score in the 38 patients was 61, with a predicted mortality of 69%. The observed ICU mortality was 100%. Mean ICU length of stay was 14 days. According to the EORTC/MSG criteria, these patients were classified either as proven IA (n = 26, 68%) or as probable IA (n = 12, 32%). Autopsy was done in 30 of 38 patients (79%). Twenty-five autopsies (83%) showed hyphael tissue invasion with *Aspergillus.* One patient had tissue invasion on a small bowel biopsy.

In 29 patients (76%), antifungal treatment was given.

During their stay in the MICU, galactomannan testing was performed in 35 of 38 patients (92%). This test was positive at least twice in 28 patients (80%). All of them died, and autopsy showed hyphael invasion in 18 patients. The other 10 patients did not get an autopsy (n = 7) or were treated for more than 7 days with antifungals and, hence, had a negative autopsy (n = 3). In four patients, galactomannan testing was negative, although autopsy showed hyphael tissue invasion. Three patients had negative galactomannan testing and did not get an autopsy.

In 20 out of the 38 patients (53%), there was a high suspicion of IA before or within 48 hours of admission to the MICU.

### Patients without Malignancy

This group comprised 89 patients. Among the 89 cases, 35 patients had COPD (42%), 9 were solid organ transplant recipients (10%), 17 had a broad range of autoimmune diseases requiring immunosuppressive therapy (19%), 6 had liver cirrhosis (7%), and 22 were classified as miscellaneous (22%). In this last group, 14 patients were colonized with *Aspergillus* without evidence of fungal disease. The patients were classified as proven IA (n = 30, 34%), probable IA (n = 37, 42%), possible IA (n = 2, 2%), and colonization (n = 20, 22%).

The mean SAPS II score was 52, with a predicted mortality of 48%. The observed mortality was not as high as in the group with malignancy, but was still substantial (80%, n = 71). Mean length of ICU stay was 23 days. Among the 18 patients that survived, 10 had only "colonization" with *Aspergillus*, and none of them had risk factors for IA. Postmortem examination was done in 46 out of the 71 patients who died (65%), and 27 out of the 46 autopsies (59%) showed hyphael invasion with *Aspergillus*. Nineteen patients had disseminated aspergillosis (at least two organs invaded). One patient had a positive bronchial biopsy. In 23 patients (26%) there was a high suspicion of IA before or within 48 hours of admission to the MICU.

### Patients without Malignancy with Proven or Probable IA

Table 2 summarizes the characteristics of the 67 proven (n = 30) and probable (n = 37) cases. In 14 patients with proven IA

**TABLE 1. CHARACTERISTICS OF ALL OBSERVED CASES**

| | All (*n = 127*) | Proven IA (*n = 56*) | Probable IA (*n = 49*) | Possible IA (*n = 2*) | Colonization (*n = 20*) |
|---|---|---|---|---|---|
| Age, yr, mean | 61 | 59 | 63 | 61 | 64 |
| Sex, male, n | 84 | 39 | 35 | 2 | 8 |
| Patients with hematologic malignancy, n | 38 | 26 | 12 | 0 | 0 |
| Patients without hematologic malignancy, n | 89 | 30 | 37 | 2 | 20 |
| COPD, n | 35 | 12 | 21 | 2 | 0 |
| Solid organ transplants, n | 9 | 4 | 5 | 0 | 0 |
| Systemic disease, n | 17 | 6 | 8 | 0 | 3 |
| Cirrhosis, n | 6 | 3 | 0 | 0 | 3 |
| Other, n | 22 | 5 | 3 | 0 | 14 |
| SAPS II, mean | 54 | 57 | 52 | 43 | 54 |
| Predicted mortality, % | 53 | 58 | 49 | 31 | 51 |
| Observed mortality, % | 86 | 98 | 90 | 0 | 50 |
| ICU length of stay, d | 20 | 14 | 23 | 32 | 28 |
| Hemodialysis in ICU, n | 54 | 27 | 20 | 0 | 7 |
| Mechanical ventilation, n | 123 | 56 | 47 | 2 | 18 |
| Neutropenia, n | 19 | 12 | 6 | 0 | 1 |
| Autopsy, n | 76 | 52 | 19 | 0 | 5 |

and in 7 patients with probable IA, *Aspergillus* was cultured before or within 48 hours of admission. The mean SAPS II score in these 67 patients was 52, with a predicted mortality of 48%. The observed ICU mortality was 91% (proven IA, 97%; probable IA, 87%). Of the 30 patients with proven IA, there were 5 cases without any compromising host factors as defined by the EORTC/MSG: three patients with Child C alcoholic liver cirrhosis, one 95-year-old man with pneumonia, and one patient with septic shock and multiorgan failure. Four out of five had bacterial infections (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Streptococcus pneumoniae*) and the positive culture for *Aspergillus* was thought to be colonization. They died during their first week of intensive care. Nine patients had a bronchial aspirate with *Aspergillus* and a positive serum galactomannan assay, but were classified as probable IA, because there was no autopsy, and hence no histologic proof was obtained. Six of them were patients with COPD, two were patients with autoimmune diseases, and one was a solid organ transplant recipient.

Galactomannan testing was performed in 51 of the 67 patients with proven or probable IA (76%). Twenty-seven patients tested positive at least twice (53%). Of the 30 patients with proven IA, 20 patients were tested (66%) and 14 were positive (70%). Of the 37 patients with probable IA, 31 were tested (84%) and 13 were positive (42%). Of the 27 patients with positive galactomannan testing, 26 died, and autopsy was done in 21 patients. There was hyphael invasion in 14 of those patients. Three patients with positive galactomannan assays but without positive culture were being treated simultaneously with piperacillin-tazobactam; one of these patients had an autopsy, which did not show hyphael tissue invasion.

Postmortem examination was done in 41 out of 67 patients (61%). 27/41 (66%) autopsies showed hyphael invasion with *Aspergillus*.

Because of suspicion of nodules or cavities on plain chest X-rays, in 17 out of 67 patients with proven or probable IA (25%), the attending physician decided to do a CT scan. Only three patients had a halo sign (all three solid organ transplant recipients). Nine patients had a cavity in an already present pulmonary infiltrate. Five patients had a broad differential diagnosis on CT scan, of which fungal disease was one of them.

Twenty-six out of 30 patients with proven IA (87%) and all 37 (100%) patients with probable IA received steroids. Nineteen patients (28%) were started on steroids after their admission to the MICU (within 4 days of admission with an average stay of 21 days in this group). The most frequent reasons for starting steroids were severe, persistent bronchospasm or suspicion of relative adrenal insufficiency due to septic shock. All the patients in the proven and probable group who were started on steroids after admission to the ICU died.

Antifungal treatment was given to 18 patients (60%) in the proven group, of which 17 died, and 21 patients in the probable group (57%), including 14 patients who underwent autopsy. Amphotericin B and the lipid-based formulations were used. Eleven of those 14 autopsied cases (79%) were treated with antifungal agents for at least 4 days before death. Due to the high mortality rate, the mean duration of treatment was only 7 days.

### Patients without Malignancy with Possible IA or with Colonization

Only two patients were classified as "possible" IA. Both had COPD. The bilateral infiltrates on chest X-ray could be explained by causes other than aspergillosis, and there were no suggestive CT findings; hence, there were no clinical criteria. Both patients had serum galactomannan assays, but neither of them were positive.

Twenty cases were considered to be "colonized" with *Aspergillus.* In none of these cases was a host factor according to the EORTC/MSG definitions present. In two of these patients, *Aspergillus* was cultured within 48 hours of admission. In these 20 patients mean SAPS II score was 54, with a predicted mortality of 51%. The observed mortality was 50%. Autopsy was performed in five patients (50% autopsy rate). One patient was a Child C liver cirrhosis patient, who had bilateral infiltrates, a very high galactomannan level in his serum in the absence of treatment with piperacillin-tazobactam and amoxicillin-clavulanate, several bronchial aspirates that yielded *Aspergillus*, and subsequently evolution to intractable shock. No tissue biopsy was available due to the severe thrombocytopenia. No autopsy was performed, and the patient could not be classified as proven, probable or possible according to the EORTC/MSG definitions, because liver cirrhosis is not as yet considered a host factor. This patient, classified as colonization, may in fact have had true IA.

## DISCUSSION

In this study we report a population of 1,850 patients in a medical ICU of which 6.9% had microbiological or histopathologic evidence of infection with *Aspergillus*. Excluding patients with hematologic malignancies or cancer, the rate of proven or probable IA was 3.7%. The mortality exceeded 90% and was much higher than predicted by the SAPS II score. *Aspergillus* infections occurred in five critically ill patients with proven IA who did not have any predisposing factors according to the currently available

**TABLE 2. CLINICAL CHARACTERISTICS OF PATIENTS WITHOUT HEMATOLOGICAL MALIGNANCY WITH PROVEN OR PROBABLE IA**

| | All (*n* = 67) | COPD (*n* = 33) | Systemic Disease (*n* = 14) | Liver Cirrhosis (*n* = 3) | Solid Organ Transplants (*n* = 9) | Other (*n* = 8) |
|---|---|---|---|---|---|---|
| Age, yr, mean | 65 | 69 | 60 | 55 | 51 | 73 |
| SAPS II, mean | 52 | 49 | 50 | 64 | 47 | 66 |
| Predicted mortality, % | 48 | 43 | 44 | 71 | 40 | 73 |
| Observed mortality, % | 91 | 85 | 93 | 100 | 100 | 100 |
| Length of stay, d | 21 | 23 | 18 | 13 | 22 | 14 |
| Culture positive* | 56/67 | 31/33 | 10/14 | 1/3 | 6/9 | 8/8 |
| Asp Ag** Positive* | 27/51 | 12/25 | 7/11 | 0/0 | 4/9 | 4/6 |
| Autopsy positive* | 27/41 | 12/19 | 6/9 | 3/3 | 3/6 | 3/4 |

*Tested positive/tested.
**Serum aspergillus antigen (galactomannan assay by means of ELISA).

definitions. In particular, patients with Child C liver cirrhosis seem to be a risk group.

In patients with malignancies, a conclusive diagnosis of IA is seldom straightforward and remains a significant clinical problem. The context of critically ill patients in which the diagnosis of IA is entertained is possibly even more challenging. The clinical picture is very nonspecific. Suggestive signs and symptoms of angio-invasion are usually absent. In the present study fever was absent in half of the cases. Critically ill patients often have a number of possible alternative explanations for inflammation, new infiltrates, increasing sputum production, arrythmias, or progression toward multiple organ failure. The consensus criteria for IA developed by the EORTC/MSG were intended to provide uniform criteria for inclusion and evaluation of patients with hematologic malignancies or cancer and suspected IA enrolled in clinical trials (3). These criteria were not designed for the clinical diagnosis of IA. However, they incorporate the most recent diagnostic advances such as the galactomannan test and the halo sign, which have proven validity in patients with cancer but have yet to prove their usefulness in other patient populations. In this study we have applied these criteria to our patients in the medical ICU without malignancy, and found that approximately 1 out of 27 admissions has or will develop IA during his or her stay in the MICU.

Even though the true incidence of IA in critically ill patients is not known, the rate of proven or probable IA reported in this study is worrisome. A number of factors may have explanatory power: more awareness of possible IA by clinicians followed by a more intensive diagnostic approach also in patients without hematologic malignancy, longer survival in intensive care, high use of steroids in the population studied, and increasing numbers of solid organ transplant recipients and patients with autoimmune disease. Environmental factors also may play a role. However, during the study period, several air samples taken by the hospital hygiene department did not yield *Aspergillus*. Recently, the hospital water supply has been recognized as a source of *Aspergillus* (13). In our unit, samples were taken in the patient rooms during the study period, and, again, no *Aspergillus* was found. There were no major building or demolition activities during the study period in or nearby the MICU.

As compared with the mortality of 100% in the patients with hematologic malignancy, the mortality in the group with proven or probable IA was only 91%. However, for an infectious disease this is still a very high mortality rate for modern intensive care, and the discrepancy between predicted (48%) and observed mortality confirms previous findings. Bulpa and coworkers (8) retrospectively analyzed a group of 16 patients with COPD with proven or probable IA requiring ICU admission. Despite maximal supportive therapy, the outcome was invariably poor, the mortality rate reaching 100%. This is in accordance with the report of Rello and colleagues (9), who described another eight patients with COPD with IA and fatal outcome.

To our knowledge, this is the first report using serum galactomannan levels in critically ill patients without hematologic malignancy. At our institution, Maertens and colleagues (4) did a prospective study in patients with prolonged neutropenia and in hematopoietic stem cell transplantation recipients. The test showed a sensitivity of 89.7% and a specificity of 98.1% (incorporating postmortem findings) for IA. In the present study, galactomannan testing was performed in 92% of the patients with malignancy and was positive in 80%. All the patients in this group had proven IA and all of them died, with or without positive galactomannan test. In the group of patients without malignancy, galactomannan testing was performed in 66% of patients with proven IA and was positive in 70%. Of those 20 patients, 19 died. 84% of patients with probable IA were tested but only 42% were positive and, of those with a positive galactomannan, all but one died. These data suggest that in critically ill medical patients without malignancy but fulfilling criteria for proven IA, galactomannan testing might be useful as in patients with hematologic malignancy. However, due to the retrospective nature of the study, due to the fact that galactomannan testing was done at the discretion of the attending physician, and due to the absence of mechanisms that control for false-positive tests due to concomitant use of antibiotics (14), no conclusions on the sensitivity and specificity of this test in this patient population can be drawn. A prospective study to validate the galactomannan test in the ICU setting is warranted.

In the present study 17 out of 67 (25%) of patients with proven or probable IA underwent CT scanning of the lungs. Only three patients (17%) had a halo sign. This number is in agreement with the reported sensitivity of the halo sign of only 24% in patients without hematologic malignancy as compared with 82% in patients with neutropenic hematologic malignancy (15). The type and degree of immunosuppression in hematologic patients is often quite different from patients with COPD on steroids, transplant recipients, or patients with liver cirrhosis. In patients in whom neutrophils are still present, a halo sign on CT scan is rarely seen (16). The absence of the halo sign in this population has no negative predictive power. Even though nine patients had a cavity on CT scan, a cavity can only trigger the attention toward IA but has very low specificity (17).

Sadly enough, the result of the autopsy was the diagnostic criterion to classify patients without hematologic malignancy as having proven IA in 90% of the patients; this underscores the importance of autopsy in studying IA. The autopsy rate in our cohort (70%) is in line with the autopsy rate of all the ICU deaths in our unit during the study period (68%). This figure is significantly higher than at most other institutions (18). Among the 100 autopsies done in 1996 from patients who died at our unit, there were 16 cases of fungal infections with MODS, of which 5 were missed diagnoses (2 patients with COPD, 1 patient with decompensated liver cirrhosis, 1 lung transplant patient, and 1 patient with non-Hodgkin lymphoma) (19). This rate is comparable to the 15% rate at autopsy in our present study and indicates that our present results are not spurious. Dimoupolos and coworkers (11) evaluated cases of IA identified at autopsy over a 1-year period in a 31 mixed-bed medico-surgical ICU. In 222 out of 489 deceased patients, an autopsy was performed. Postmortem examination demonstrated disseminated aspergillosis involving noncontiguous organs in six (2.7%) autopsies, and, of these, five patients (2.3% of total) had COPD. Probable factors that explain the difference in the rate of IA between the study by Dimoupolos and colleagues and our autopsy series are the case-mix and the selection bias introduced with lower autopsy rates.

Among the 14 autopsies done in the group with probable IA, 79% had been treated with antifungal agents. Based on animal work, the limit of detection of *Aspergillus* is probably 104 organisms per gram of tissue (3), and previous treatment may lower the rate of positive autopsies (20). Other factors that may increase the rate of negative autopsies are poor sampling, especially in the sinus region, or failure to use special stains. In fact, because of previous treatment with antifungal agents, several patients in this study classified as probable IA may have had true IA.

Besides neutropenia, the use of corticosteroids for more than 3 weeks is considered a predisposing host factor in the EORTC/MSG criteria. Of the patients without hematologic malignancy, 87% with proven IA and 100% with probable IA were receiving steroids. Twenty-eight percent were started on steroids after their admission to the ICU, and all of them died. In the setting

of persistent septic shock, a condition that may afflict many of the patients at risk for IA, steroids are used frequently as they may improve outcome (21). Corticosteroids substantially impair macrophage killing of *Aspergillus* spores and mononuclear cell killing of *Aspergillus* hyphae (22). Palmer and coworkers (23) reported that the threshold steroid level varies according to the type of patients, and emphasized that in the setting of underlying lung disease there is a risk factor for IA at much lower doses. Our study cannot prove whether short-term steroid use is an additional risk factor for IA in critically ill patients. However, our results clearly suggest that this is likely.

In the cohort of 30 patients with proven IA but without malignancy, there were five cases without any compromising host factor as defined by the EORTC/MSG at all. Three of these were patients with Child C liver cirrhosis. An additional three patients with cirrhosis (Child status) were classified as "colonization" because no autopsy was performed. Patients with cirrhosis have predisposing immune deficits for IA that include impaired phagocytosis and chemotaxis, decreased complement levels, and poor opsonization. IA has long been recognized as one of the most significant opportunistic fungal infections in liver transplant recipients (24). However, case reports of patients with cirrhosis with IA but without liver transplantation are very sparse. Child C liver cirrhosis is not a host factor according to the EORTC/MSG definitions, but our data suggest that this condition may indeed be considered as a host factor.

In conclusion, IA poses a major threat to a broad group of patients in the medical ICU without underlying malignancy. If IA develops in these apparently less immunocompromised patients, the associated mortality is still devastating. The definite diagnosis of IA in these patients is usually made at autopsy. The value of early diagnostic criteria such as the galactomannan test in this population needs to be proven in prospective trials.

***Conflict of Interest Statement***: W.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.J.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.W. has received €400 for a consultancy for GlaxoSmithKline in 2003 relating to a sepsis trial; E.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; W.E.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.V.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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