Aspergillus Fungemia: Report of Two Cases and Review

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We present two cases of aspergillus infection confirmed by blood culture and review 30 other cases of genuine aspergillus fungemia and 34 cases of aspergillus pseudofungemia. Multiple different media and blood culture systems were used to isolate *Aspergillus*. The median time to positive blood culture was 8.5 days (range, 1–27 days) in the genuine cases. Genuine aspergillus fungemia was observed more often after cardiac surgery (*n* = 11 [34%]) or during neutropenia (*n* = 9 [28%]) than in other settings. In a recent series of fungemia during neutropenia, 7.6% of all episodes were due to *Aspergillus*. Other patients at risk for aspergillus fungemia were similar to those at risk for invasive aspergillosis, including patients with AIDS. Seven (44%) of 19 patients who were treated survived. In the group of patients with aspergillus pseudofungemia, there were no deaths, and cultures of additional specimens from the same patient were not positive. Criteria that may be applied to ascertain whether the isolation of *Aspergillus* from blood cultures is clinically significant are put forward.

Aspergillus fungemia is encountered infrequently. In most published studies of blood culture methods, it is seldom mentioned [1]. More restrictive series of only fungal blood cultures still rarely report its occurrence [2, 3]. A vascular origin or dissemination is indicative of true aspergillus fungemia. In most cases aspergillus fungemia is associated with a high mortality rate unless treatment is initiated urgently [4], although non–respiratory tract, noncutaneous disease—such as osteomyelitis in patients with chronic granulomatous disease, isolated renal disease, or cerebral disease—may develop occasionally secondary to this fungal infection. Since media contamination yielding false-positive results of cultures can occur, problems in the interpretation of the significance of aspergillus fungemia in individual cases may arise [5–7]. Therefore, determining the importance of aspergillus fungemia in the immunocompromised patient is particularly difficult.

We present two cases of aspergillus fungemia and review 30 cases of genuine aspergillus fungemia. These cases are compared with 34 cases of contamination of blood cultures with *Aspergillus* species (aspergillus pseudofungemia). We present criteria for distinguishing genuine aspergillus fungemia from aspergillus pseudofungemia.

Methods

We reviewed the English-language literature from 1960 to date for cases in which *Aspergillus* species were isolated in cultures of human specimens of blood. We recorded the underlying diseases, predisposing factors, organs involved, other sites positive for *Aspergillus* (both before and after death) in culture, blood culture methods, time to positive culture, species, treatment, and, if described, outcome. Criteria for genuine aspergillus fungemia (definite and probable) and aspergillus pseudofungemia are listed in table 1. The source of contamination for aspergillus pseudofungemia was noted.

Case Reports

Case 1

A 76-year-old woman with a history of temporal arteritis managed with high doses of prednisolone presented with a history of right orbital swelling, pain in the right eye, and cough. Computerized axial tomography and magnetic resonance imaging demonstrated a right orbital mass on both sides of the lateral orbital wall that extended to and invaded the soft tissues of the right infratemporal fossa. Small additional lesions were noted in the left mastoid region on the right and in the left cerebellum. Gallium 67 scanning at 72 hours also demonstrated an abnormal accumulation in the right orbit. Biopsy of the accumulation showed only granulomatous inflammation and no hyphae. A sputum culture yielded *Aspergillus fumigatus*, and treatment with amphotericin B (total dose, 500 mg) was initiated. The patient was then discharged and continued therapy as an outpatient. She failed to tolerate this therapy and was readmitted for stabilization of her condition. The dose of amphotericin B was reduced from 50 mg to 35 mg daily. During this admission *Staphylococcus aureus* pneumonia developed. After a total dose of amphotericin B of 1,510 mg was administered, her signs and symptoms resolved, and she was discharged. She

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Table 1. Criteria for definition of genuine aspergillus fungemia and of aspergillus pseudofungemia.

Criteria
Aspergillus fungemia
Definite
Presence of *Aspergillus* in blood and histologic evidence of hyphae in tissue from other sites or in a device or culture of tissue from other sites or of a device that was positive for *Aspergillus*
Probable
Presence of *Aspergillus* in blood and clinical condition compatible with disseminated aspergillosis in a typical clinical setting and no record of other positive cultures accounting for clinical condition or no histopathologic evidence of invasive aspergillosis before or after death
Aspergillus pseudofungemia
Presence of *Aspergillus* in blood
Atypical clinical setting or clinical course not compatible with disseminated aspergillus infection, no isolates from any other body site or histologic evidence of invasive aspergillosis, and/or positive cultures of environmental sites in laboratory

relapsed 1 month later and was admitted again with further orbital and maxillary swelling, visual loss, and a left seventh nerve palsy. Repeated magnetic resonance imaging showed extension of the lesions in the left mastoid region and in the left cerebellopontile angle just caudal to the seventh and eighth nerve bundles and extension of the large right orbital mass inferotemporally. Culture of blood obtained during this admission yielded *A. fumigatus.* At the time of surgery, a large inflammatory mass was found in the right orbit. Biopsy of the mass revealed extensive chronic and focal granulomatous inflammation. Total removal of the mass was not possible. She later received therapy with itraconazole (400 mg//d) for 2 weeks and then declined further treatment.

Commentary. This patient suffered an unusual form of invasive aspergillosis that has been infrequently described [8, 9]. Histologic evidence of scanty hyphae, which may not be present at all in a small biopsy sample, has been previously noted in cases of this disease entity, perhaps reflecting a vigorous local immune response. The response to amphotericin B therapy and relapse are also characteristic of this form of invasive aspergillosis.

Case 2

A 62-year-old woman was admitted to the hospital for evaluation of an indwelling vascular device (Mediport) infection. She had been dependent on total parenteral nutrition for 10 years following radical pelvic surgery and radiotherapy for endometrial carcinoma. This Mediport was her sixth, the previous five having been infected with various bacteria. Six weeks before admission a routine culture of blood drawn through the Mediport had yielded *Aspergillus niger.* Cultures of blood obtained 2 weeks later were negative. She was weak with malaise, anorexia, headache, and light-headedness. She had lost 15–20 lb. Her maximum temperature was 37.6°C during hospitalization. No evidence of aspergillus infection was found at any other site. Her total white blood cell count was 7.6×10^9/L. Five days later a repeated aerobic and anaerobic bacterial blood culture was positive for *A. niger.* Therefore, the Mediport was removed and examined. It was not damaged or cracked. There was a brown-black, furry, friable lining that covered the entire chamber of the Mediport. The catheters were clear of fungus macroscopically. Microscopy of the slit tubing of the Mediport showed a few mononuclear cells and rare granulocytes, and culture of the tubing yielded a light growth of *A. niger.* Subsequently, venous access became impossible, and the patient died 1 year later of malnutrition.

Commentary. To our knowledge aspergillus fungemia from an infected intravascular catheter has not been previously described, although infection of the catheter insertion site and tunnel by *Aspergillus* species has been reported [10, 11].

Results

A total of 30 cases of genuine aspergillus fungemia have been previously reported. We recorded the following underlying conditions: AIDS (1), steroid therapy (2), renal transplantation (3), bone marrow transplantation (3), cancer and/or neutropenia (11), and cardiac surgery (11) (table 2). Of the 32 cases of genuine aspergillus fungemia, 23 fulfilled the criteria for definite cases and nine fulfilled the criteria for probable cases. The following organs were involved in the infection: kidney (1), musculoskeletal system (1), gastrointestinal tract (1), eye (1), nose (1), brain (6), lung (17), and heart (12). For five patients there was no record of any other positive culture before or after death. Thirty-three specimens from the other 27 patients that were positive in culture were as follows: cardiac tissue (8), lung tissue (8), sputum (5), brain tissue (4), embolectomy specimen (2), nasal specimen (2), skin (1), sinus washout (1), bronchoalveolar lavage fluid specimen (1), and unspecified postmortem tissue (1).

Nineteen patients were treated systemically with antifungal therapy, and seven (44%) of these patients survived. Of eight patients who did not receive treatment, all died. One patient (case 3) underwent a valve replacement only and survived [13]. Among the other 10 patients who underwent cardiovascular surgery, two were treated, but all died. Of the 12 patients with cancer and/or neutropenia, 10 were treated, and six (50%) survived. Our second patient (case 32) simply had the Mediport removed.

Aspergillus was isolated in 21 (66%) of the 32 genuine cases of fungemia while the patient was alive and in eight cases (25%) after the patient died; no data were available for three cases. The median time to positive culture was 8.5 days (range, 1–27 days) in the eight genuine cases in which it was recorded. Concurrent bacteremia was uncommon but occurred in four patients with leukemia [28]. In most instances

Table 2. Summary of data on genuine cases of aspergillus fungemia.

Case no. [reference]	Age (y)/ sex	Status	Underlying disease	Possible predisposing factor(s)	Organ(s) involved	Positive culture specimens from other sites	Blood culture method	Species/ time of isolation	Treatment	Outcome
1 [12]	31/M	D	Mitral stenosis	Mitral valve replacement, antibiotics	Heart valve	PM vegetation	Terminal subculture	*Aspergillus* species/ AM, PM	None	Died
2 [13]	13/M	D	CHD	Cardiac surgery	Heart valve	Lung, brain	NR	*A. fumigatus*/PM	AmB	Died
3 [13]	14/F	D	CHD	Valve replacement	Heart valve	Vegetations	NR	*Aspergillus* species/AM	Valve replacement	Cured
4 [13]	13/F	D	CHD	Starr-Edwards mitral valve	Heart valve	Lung, brain	NR	*A. flavus*/AM	AmB	Died
5 [14]	11/F	D	Rheumatic heart disease	Mitral valve replacement	Heart valve	Abscess, PM vegetation	NR	*A. fumigatus*/AM	None	Died
6 [15]	47/M	D	Aortic regurgitation	Cardiac bypass, valve replacment, OT contamination, multiple antibiotics	Vascular wall	AM embolus	Culture with Castaneda bottle, BHI broth/agar	*Aspergillus* species/AM	AmB	Died
7 [16]	47/M	D	Aortic valve disease	Cardiac surgery	Heart	AM embolus	NR	*Aspergillus* and Zygomycetes/AM/ PM	AmB	Died
8 [17]	0.2/?	D	Erythroblastosis	Endocarditis (?)	Heart, brain, kidney	PM vegetation	NR	Repeated isolates of *A. fumigatus*/AM 7 d	None	Died
9 [18]	58/M	D	Aortic valve disease	Cardiac surgery, aortic valve repair	Heart valve	PM heart valve	NR	*A. fumigatus*/AM/PM	None	Died
10 [19]	24/M	D	Valvular heart disease	Cardiac surgery, steroids, mitral valve	Brain, leg, hand	PM major organs and vegetations	NR	*A. fumigatus*/AM/PM 14 d	None	Died
11 [20]	51/M	D	Aortic dissection	None	Lung, heart, brain	AM sputum, PM heart, lung	Pour plate with Sabouraud medium	*Aspergillus* species/AM 2 d	Natamycin, inhalations	Died
12 [21]	24/M	D	Valvular heart disease	Aortic valve replacement	Heart valve, emboli	None	NR	*A. fumigatus*/AM/PM	None	Died
13 [2]	NR	P	NR	NR	NR	NR	Culture with 10-mL aerobic Septi-Chek bottles*	*Aspergillus* species/NR	NR	NR
14 [22]	NR	D	Malignancy	Several nasal cultures positive for *Aspergillus*, antibiotic treatment, environmental specimen positive for *Aspergillus*	Nasal sinuses	Sinus biopsy specimen	NR	*Aspergillus* species/AM	AmB	Lived
15 [23]	49/M	D	Renal transplant	Pneumonia with cavitation	Lung, gastrointestinal tract	Lung	Subculture with Sabouraud medium	*A. fumigatus*/AM 14 d	AmB	Died

Table 2. (*Continued*)

Case no. [reference]	Age (y)/ sex	Status	Underlying disease	Possible predisposing factor(s)	Organ(s) involved	Positive culture specimens from other sites	Blood culture method	Species/ time of isolation	Treatment	Outcome
16 [23]	29/F	D	Renal transplant	CMV pneumonia	Lung	Lung	Subculture with Sabouraud medium	*A. fumigatus*/AM 7 d	AmB	Died
17 [24]	NR	D	ANLL	Prolonged granulocytopenia	Lung	Lung biopsy specimen	NR	*A. fumigatus*/NR	None	Died
18 [3]	NR	D	NR	Antibiotics, steroids, CVC	NR	PM spread	NR	*A. fumigatus*/AM/PM	None	Died
19 [25]	48/M	D	Lymphoma of eye	Chemotherapy, BMT, prednisolone, splenectomy	RUL lung	AM sputum	Culture with BHI medium plus dextran, 40 mL of blood	*A. fumigatus*/AM 4 d	AmB	Lived
20 [26]	NA	D	Aplastic anemia	BMT	Brain, lung	Sputum, BAL fluid, brain	NR	*Aspergillus* species/AM	AmB	Died
21 [26]	NA	P	Acute leukemia	BMT	Lung	NR	NR	*Aspergillus* species/AM	AmB	Lived
22 [27]	60/F	D	Acute myelogenous leukemia	Neutropenia	Lung	PM lung	NR	*Aspergillus* species/NR	AmB, white blood cell transfusions	Died
23 [28]	NR	D	Acute leukemia	Neutropenia	Lung, skin	Skin	BCB	*A. fumigatus*/AM	AmB	Lived
24 [28]	NR	D	Acute leukemia	Neutropenia	Lung	Sputum	BCB	*A. fumigatus*/AM	AmB	Lived
25 [28]	NR	D	Acute leukemia	Neutropenia	Lung	Nose	BCB	*A. fumigatus*/AM	AmB	Lived
26 [28]	NR	P	Acute leukemia	Neutropenia	Lung	Nose	BCB	*A. fumigatus*/AM	AmB	Died
27 [28]	NR	P	Acute leukemia	Neutropenia	Lung	None	BCB	*A. fumigatus*/AM	AmB	Died
28 [28]	NR	P	Acute leukemia	Neutropenia	Lung	None	BCB	*A. fumigatus*/AM	AmB	Died
29 [29]	?/M	D	Myocarditis, HIV+	AIDS, non-Hodgkin's lymphoma, cytotoxic treatment	Heart	Myocardium	NR	*A. fumigatus*/AM 10 d	Withheld because of clinical condition	Died
30 [30]	NR	D	Renal transplant	NR	Lung	NR	NR	*A. flavus*/AM	AmB	Died
31 [PR]	76/F	P	Temporal arteritis	Corticosteroid therapy	Orbit	Sputum	NR	*A. fumigatus*/AM	Itr, not compliant	Unevaluable
32 [PR]	62/F	D	Mediport, TPN	None	Mediport only	None	Culture with routine bacterial media	*A. niger*/AM 5 d	Mediport removal	Responded

NOTE. D = definite; PM = postmortem; AM = antemortem; CHD = congenital heart disease; NR = not recorded; AmB = amphotericin B; OT = operating theater; BHI = brain-heart infusion; AM/PM = specimen for culture obtained antemortem, and culture positive postmortem at the stated time; ? = unknown; P = probable; CMV = cytomegalovirus; ANLL = acute nonlymphocytic leukemia; CVC = central venous catheter; BMT = bone marrow transplant; RUL = right upper lobe; NA = not available; BAL = bronchoalveolar lavage; BCB = BCB Combi Set (trypticase soy broth, Hoffmann-La Roche); HIV+ = human immunodeficiency virus seropositive; PR = present report; Itr = itraconazole; and TPN = total parenteral nutrition.

* Hoffmann-La Roche (Basel, Switzerland).

Table 3. Reported episodes of contamination of blood cultures by *Aspergillus* species (aspergillus pseudofungemia).

No. of cases [reference]	Underlying disease	Predisposing factor(s)	Organ involved	Other positive culture specimens	Blood culture method	Species/time of isolation	Treatment	Outcome	Source of contaminant
10 [5]	BMT	Post-BMT	None	≥1 sputum specimen from a patient with cavitary pneumonia (laboratory source for this result)	BCB with agar slide	6 cases, *A. fumigatus*; 2 cases, *A. flavus*; 2 cases, not stated	None	All lived	Mishandling of mycology cultures in main laboratory; placement of BC agar slants on BC bottles in main laboratory
1 [31]	Aortic stenosis with Starr-Edwards prosthesis	Cardiac surgery, multiple antibiotics	None	None	Not stated	*A. glaucus*/10 d	None	Lived	Contamination from ward sampling; (?) OT air (other cases in series)
1 [3]	Not stated	Not stated	Lung	None	Not stated	*A. niger*	None	Recovered	Not stated
6 [32]	Immunocompromised	None	None	Pleural fluid	Not stated	*Aspergillus* species	None	Lived	Not stated
3 [7]	Not stated	Not stated	None	Not stated	Culture with BHI broth,* 30°C, in biphasic bottles	*Aspergillus* species	None	Lived	Not stated
13 [6]	Various illnesses requiring blood culture as a diagnostic procedure	None	None	Laboratory samples	Anaerobic culture, BACTEC,† CBA culture, lysis-centrifugation system	*Aspergillus* species and *Penicillium*	None	All lived	Culture plates left open on bench; *Aspergillus* in laboratory ceiling

NOTE. BMT = bone marrow transplant; BCB = BCB Combi Set (trypticase soy broth, Hoffmann-La Roche, Basel, Switzerland); BC = blood culture; ? = unknown; OT = operating theater; BHI = brain-heart infusion; and CBA = Columbia blood agar.

* Difco (Detroit).

† Becton Dickinson (Cowley, Oxfordshire, United Kingdom).

only one positive blood culture was reported, but in one collected series of six cases, cultures were persistently positive in five cases, some of which persisted over 3–5 days [28].

We found 34 published cases of aspergillus pseudofungemia in the literature (table 3). In three reports several cases occurred in a single institution. The reasons for contamination are listed in table 3. Multiple different blood culture systems were used.

Microbiological details provided in the reports were scanty. Methods used for blood culture are outlined in table 4. In addition to these methods, we are aware of a number of instances of both true and false-positive isolation of *Aspergillus* related to the lysis-centrifugation system.

Discussion

Disseminated aspergillosis is an increasing problem in the severely immunocompromised patient. Aspergillus infections develop in ~5%–12% of bone marrow transplant patients [26, 33], 13% of heart transplant recipients [34], and 4% of patients with AIDS [35, 36]. A recent survey of cancer centers in Europe [37] showed that at least 13 cases of invasive aspergillosis occurred annually in up to one-quarter of the centers. Among the affected patients the rates of response to amphotericin B treatment varied from 6% to 87%; the overall response rate was ~55% among those who received therapy for at least 2 weeks [34]. Delayed intervention is associated with higher mortality; therefore, early recognition of the infection is important [4]. Present diagnostic modalities for aspergillus infection are inadequate. The role of blood culture has been little explored.

Although several investigators have examined the problems involved in interpreting the importance of pulmonary isolations of *Aspergillus* species [38–40], the significance of isolations of *Aspergillus* species in blood cultures is less clearly enunciated. Aspergillus fungemia is apparently a rare infection; it represents only 0.5%–2% of all fungemias [2, 3]. However, in a recent series of cases of fungemia from a leukemia and bone marrow transplant unit [28], 7.6% were due to *A. fumigatus*.

Review of the literature and comparison of the circumstances surrounding genuine aspergillemia and aspergillus pseudofungemia suggest that both clinical and laboratory criteria can be used to evaluate the likely significance of asper-

Table 4. Blood culture systems used in cases of aspergillus fungemia.

Blood culture system	No. of cases in which indicated method was used	
	Genuine aspergillus fungemia	Aspergillus pseudofungemia
Not stated	18	8
Culture with BHI broth in biphasic bottles	1	3
Culture with BHI broth plus dextran (40% blood)	1	0
BCB with agar slide	6	10
Pour plate with Sabouraud medium	1	0
Culture with bacterial media (unspecified)*	5	13
Total	32	34

NOTE. BHI = brain-heart infusion; BCB = BCB Combi Set (trypticase soy broth, Hoffmann-La Roche, Basel, Switzerland).
* Some with subculture to Sabouraud medium.

gillus fungemia (table 5). To prove that these features are significant would require a complex case-control study with multivariate analysis, which is difficult to undertake given the rarity of the problem. Certain features deserve emphasis. Clusters of *Aspergillus* isolates in the laboratory together with a possible laboratory source should suggest aspergillus pseudofungemia, whereas isolation of *Aspergillus* from surfaces or air in clinical areas [15, 41–43] suggests the possibility of genuine aspergillus fungemia. A useful clue to contamination on solid media is the position of the colony on the agar. If the colony is not on the streak, then the suspicion of a false-positive isolation should be higher. If aspergillus pseudofungemia occurs in high-risk patients [5, 6], the distinction between pseudofungemia and genuine fungemia can be difficult.

Theoretically, the recent development of molecular typing systems makes it possible to trace the origin of *Aspergillus* isolates from blood, other body sites, and the environment. The present systems are not yet adapted to routine use in laboratories but can be used retrospectively [44]. However, isolates with particular DNA types in particular hospitals may be found in the environment in the clinical areas, in patients, and in the microbiology laboratory. Thus, genuine aspergillus fungemia may not be distinguished from aspergillus pseudofungemia on the basis of common DNA types, although the finding of different DNA types may be helpful.

The infrequency of aspergillus fungemia, even in cases of endocarditis when blood and the organism are in proximity, is difficult to understand. After all, disseminated disease is common. Limited studies examining relative numbers of colonies in venous and arterial blood report no increase in cfu in arterial blood, thus suggesting that the capillary bed is not responsible for clearance. Even examination of cardiac blood samples may fail to detect organisms [45, 46]. Intermittent release of hyphae may be responsible for these findings, particularly if there are few cfu. It is unlikely that blood contains inhibitory factors preventing hyphal growth because several different media have yielded pseudoaspergillemia and blood agar is an excellent culture medium for *Aspergillus. Aspergillus* invades blood vessels, which results in thrombosis and distal infarction. This invasion occurs in both the arterial and the venous blood and thus may prevent blood flow through the affected areas, possibly accounting, in part, for the rarity of isolation of *Aspergillus* in blood cultures.

A variety of blood culture systems have yielded *Aspergillus.* Multiple specimens were cultured on trypticase soy broth, and these cultures became positive in 1 to 5 days [28]. One culture by means of a direct pour plate technique [47] with Sabouraud agar was positive in 2 days [20]. Another experimental method used 40 mL of blood in an impedance detection system, and *Aspergillus* was isolated in 4 days [25].

Table 5. Features favoring genuine aspergillus fungemia and aspergillus pseudofungemia.

Features	Likely genuine aspergillus fungemia	Likely aspergillus pseudofungemia
Clinical history	Immunosuppressive therapy, chemotherapy, steroid dosage of >1.25 mg/kg · d, cardiac surgery	Nontypical host
Clinical features	Prolonged fever unresponsive to antibacterial therapy, clinical site of infection, prolonged neutropenia for >21 days, associated hemorrhagic diathesis, associated embolic episodes, clinical course compatible with focal or disseminated aspergillosis	Clinical course not compatible with focal or disseminated aspergillosis
Microbiological features	Isolation of *A. fumigatus* or *A. flavus*, positive cultures of specimens from other sites (including surveillance cultures and sinus colonization), environmental source in clinical areas, few positive isolates in the laboratory during the same period, autopsy confirming invasive aspergillosis, repeated isolates from the same patient	Isolation of species other than *A. fumigatus* and *A. flavus*, source for environmental contamination in laboratory, several blood cultures positive for *Aspergillus* at one time (cluster of positive cases), change in usual handling procedures of blood cultures

However, the impedance changes produced by *Aspergillus* are small [48]. *Aspergillus* has also been isolated in classical biphasic bottles with brain-heart infusion medium, bacterial broth with Sabouraud medium for subculture, and brain-heart infusion medium with dextran. One study reporting that *Aspergillus* had been isolated with the Roche Septi-Chek system (Hoffmann-La Roche, Basel, Switzerland) in six cases is remarkable. This finding suggests that the trypticase soy broth used in the BCB Combi Set system (Hoffmann-La Roche) may be the preferred fungal medium for isolation of *Aspergillus* from blood, but much more work will be necessary to confirm this suggestion.

Many modifications of classical blood culture systems for optimizing the isolation of fungi have been studied, including increased volumes of blood cultured [49, 50], diagnostic hemoperfusion [51], addition of lysing agents [9], aeration by shaking or adding hydrogen peroxide [52, 53], and use of hypertonic media (such as 10% sucrose) [54]. To our knowledge, none of these modifications have been associated with increased isolation rates of *Aspergillus*. Agitation of the Roche Septi-Chek system improves the isolation of yeast [53] and might be expected to speed the growth of *Aspergillus*. To our knowledge, *Aspergillus* has never been isolated on bacterial media used in the BACTEC system (Becton Dickinson, Cockeysville, MD); however, this finding could reflect the inadequate production of carbon dioxide [55] or the lack of terminal subcultures [56]. Recently, a new fungal medium for the BACTEC system has been introduced; this medium is associated with good isolation rates in the BACTEC 660 system [57], but to our knowledge no *Aspergillus* species have been isolated yet.

Compared with more conventional blood culture systems, use of the lysis-centrifugation system resulted in a significant increase in the isolation of fungi in early studies [57–60]. This system also allows quantitation of cfu. However, the method of processing is prone to contamination [61], and *Aspergillus* is one of the potential airborne contaminants. Processing in a laminar air-flow facility should prevent airborne contamination. Aside from the problem of contamination, isolator systems cannot be automated and therefore are more labor intensive [53, 62].

At present the diagnosis of invasive aspergillosis is based on many factors, including the patient's immune status, results of radiology, and culture and histologic data. Serology may be helpful in the diagnosis, but the sensitivity of this test is still relatively limited [63–65]. Confirmation of the diagnosis can be elusive. If aspergillus fungemia could be detected as often as it occurs clinically, as manifested by disseminated disease, then there would be clear benefits for the management of cases. Development of an optimal blood culture system may be justified for the increasing numbers of high-risk patients.

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