Invasive Aspergillosis in the Intensive Care Unit

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Data regarding the incidence of invasive aspergillosis (IA) in the intensive care unit (ICU) are scarce, and the incidence varies. An incidence of 5.8% in a medical ICU has been reported. The majority of patients did not have a hematological malignancy, and conditions such as chronic obstructive pulmonary disease and liver failure became recognized as risk factors. Diagnosis of IA remains difficult. Mechanical ventilation makes it difficult to interpret clinical signs, and radiological diagnoses are clouded by underlying lung pathologies. The significance of a positive respiratory culture result is greatly uncertain, because cultures of respiratory specimens have low sensitivity (50%) and specificity (20%–70%, depending on whether the patient is immunocompromised). The use of serologic markers has never been validated in an ICU population. Limited experience with the detection of galactomannan in bronchoalveolar lavage fluid specimens has yielded promising results. Because of a delay in the diagnosis of IA, the mortality rate exceeds 50%. Recently, our therapeutic armamentarium against IA has improved. Data concerning the safety and efficacy of new antifungal agents in the ICU setting, however, are lacking.

Aspergillus species are ubiquitous soil inhabitants; if the conidia are inhaled into the respiratory tract, they can cause life-threatening disease. Invasive aspergillosis (IA) is a major cause of morbidity and mortality in severely immunocompromised patients. The bulk of literature about IA involves patients with classic risk factors for IA, such as prolonged neutropenia and hematopoietic stem cell transplantation [1–3]. However, a broad group of patients who are admitted to intensive care units (ICUs) may also be susceptible to these infections.

IS IA A PROBLEM IN THE ICU?

Autopsy studies have revealed the emergence of *Aspergillus* species as major pathogens, as well as the expansion of the spectrum of patients at risk for IA. In a nonselected patient population at an academic hospital, the prevalence of invasive fungal infection increased from 2.2% to 5.1% over a 12-year period, largely in association with an increase in the rate of *Aspergillus* infection [4]. However, estimates about the incidence of IA among critically ill patients are sparse and variable. For various reasons, figures about the true incidence of IA are difficult to generate. First, with cultures that are positive for *Aspergillus* species, discriminating between colonization and infection remains challenging. Second, very few institutions perform postmortem examinations routinely, although in most cases, this is the only way to prove the definite nature of the diagnosis [5–7]. Third, characteristic radiological signs of IA are usually absent in the nonneutropenic ICU patient. Finally, to date, the diagnostic utility of recently available non–culture based microbiological tools, including PCR for the detection of fungal antigens and the detection of *Aspergillus*-specific DNA, has not been properly validated in the nonhematology ICU population. In addition, the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) guidelines were not designed for patient categories other than patients with cancer and patients who have undergone bone marrow transplantation [3].

The available studies of ICU patients are summarized in table 1 [4–6, 8, 10–14]. In our medical ICU, we

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Table 1. Relevant epidemiological studies of invasive aspergillosis (IA) in the intensive care unit (ICU).

Study type, study	Year	No. of patients	Duration of study	Type of study	Aim of the study	Autopsy protocol[a]	Incidence of IA	Important findings
Studies that examined the incidence of IA that was widespread in hospital (and not confined to the ICU)								
Groll et al. [4]	1996	8000	12 years	Retrospective, single-centre	Describing trends in postmortem epidemiology of IFI	Yes	3.1%	Increasing trends in incidence of IA, compared with invasive candidiasis
Cornillet et al. [8]	2006	88	6 years	Combined retrospective and prospective cohort, with 47% ICU patients	Comparing features of IA in neutropenic and nonneutropenic patients	No	15 cases/year	Overall mortality rate, 71%; rate for nonneutropenic patients, 89%
Studies that specifically examined the incidence of IA in the ICU								
Bulpa et al. [9]	2001	23	4 years	Case series of patients with COPD in a mixed ICU	Describing IA in patients with COPD who were admitted to the ICU	Yes	…	Mortality in patients with COPD who underwent ventilation, 100%
Meersseman et al. [10]	2003	127	3 years	Retrospective, single-center, medical ICU	Determining the incidence of IA in a medical ICU	Yes	5.8%	IA increasingly recognized in patients without classic risk factors
Garnacho-Montero et al. [11]	2005	1756	9 months	Multiple-centre prospective study of 73 mixed ICUs	Describing characteristics of patients with sputum samples positive for *Aspergillus* species in 73 ICUs	No	1.1%	Mortality rate for patients colonized with *Aspergillus* species, 50%; rate for patients considered to have IA, 80%
Vandewoude et al. [12]	2006	172	7 years	Retrospective, single-center, mixed ICU	Describing characteristics of patients with sputum samples positive for *Aspergillus* species	No	0.33%	Mortality rate for nonhematology patients, 60%; for patients with IA, 77%; for colonized patients, 40%
Other studies[b]								
Roosen et al. [5]	2000	100	1 year	Retrospective, single-center, medical ICU	Comparing premortem diagnosis and autopsy findings (all causes of death)	Yes	15%	IA is a more important missed diagnosis in a medical ICU than any other illness
Valles et al. [13]	2002	67	7 years	Prospective cohort study at 2 mixed ICUs	Describing patients with hospital-acquired pneumonia who were admitted to the ICU	No	19%	IA was the second most frequent cause of HAP requiring ICU admission; COPD was a significant risk factor
Dimopoulos et al. [6]	2004	222	1 year	Retrospective, single-center, mixed ICU	Comparing premortem diagnosis and autopsy findings (all causes of death)	Yes	3.7%	In 6 of 14 cases with major missed diagnoses, IA was responsible
Kumar et al. [14]	2006	2154	15 years	Retrospective, multiple-centre cohort	Determining the impact of antimicrobial therapy for all patients with septic shock who were admitted to the ICU	No	0.7%	No data for proven cases; inclusion was based solely on culture results

NOTE. COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; IFI, invasive fungal infection.

[a] Studies in which autopsy was performed in >50% of cases.

[b] More general autopsy studies or studies that examined the etiology of pneumonia in the ICU.

Table 2. Risk of invasive aspergillosis among patients admitted to the intensive care unit (ICU; medical, mixed or surgical).

High-risk category
Neutropenia (neutrophil count, <500 neutrophils/mm^3)
Hematological malignancy
Allogeneic bone marrow transplantation
Intermediate-risk category
Prolonged treatment with corticosteroids before admission to the ICU
Autologous bone marrow transplantation
Chronic obstructive pulmonary disease
Liver cirrhosis with a duration of stay in the ICU >7 days
Solid-organ cancer
HIV infection
Lung transplantation
Systemic diseases requiring immunosuppressive therapy
Low-risk category
Severe burns
Other solid-organ transplant recipients (e.g., heart, kidney, or liver transplant recipients)
Steroid treatment with a duration of ⩽7 days
Prolonged stay in the ICU (>21 days)
Malnutrition
Post–cardiac surgery status

observed a high incidence of IA in 2 separate, retrospective, autopsy-controlled studies. In the larger study, 127 (6.9%) of 1850 hospitalized patients had microbiologic or histopathologic evidence of aspergillosis during their ICU stay, including 89 cases (70%) in which there was not an underlying hematological malignancy. The observed mortality rate of 80% was much higher than the mortality rate predicted on the basis of the Simplified Acute Physiology Score II (48%) [10]. An earlier study sought unsuspected causes of death in the same medical ICU and revealed that, among 100 autopsies, there were 15 cases of IA, of which 5 were missed before death [5]. These data are in line with previous autopsy findings, suggesting that invasive fungal infections are among the most commonly missed diagnoses in ICU patients [15–17]. In a recent study that examined the etiology of patients with septic shock, the prevalence of IA was 0.3% [12]. Valles et al. [13] reported 13 (19%) of 67 episodes of IA with pathologic and/or microbiologic evidence of aspergillosis in a cohort of patients with severe hospital-acquired pneumonia who had been admitted to the ICU. During a 6-year period, Cornillet et al. [8] found that a mean number of 15 patients per year received a diagnosis of IA; approximately one-half of these patients were in the ICU. These intercenter differences can be explained by differences in underlying patient characteristics, case mixes, and autopsy policies.

WHO IS AT RISK OF DEVELOPING IA IN THE ICU?

Over the past 2 decades, IA has emerged as a life-threatening fungal infection in patients with hematological diseases [1, 2, 18, 19]. Although many infected patients will eventually be admitted to the ICU for advanced supportive care, it seems that IA has also gained a foothold in less severely immunocompromised ICU patients [10]. So, can a threshold of immunosuppression needed for the development of IA be defined? We grouped the risk factors for IA in the ICU into 3 categories: high, intermediate, and low (table 2).

Various factors, including the prolonged use of antibiotics and the use of central venous catheters and/or mechanical ventilation, adversely affect the defense systems of previously healthy individuals [20]. Although these factors are present in most ICU patients, many of these patients do not develop IA. One of the intriguing hypotheses for immunosuppression in the apparently immunocompetent patient with multiple-organ dysfunction relates to the biphasic response to sepsis [21]. The initial hyperinflammatory phase is followed by relative immunoparalysis [22]. This latter process is characterized by neutrophil deactivation, and it may put the patient at risk of developing opportunistic infections, such as IA. Additional epidemiological studies are warranted to better delineate this phase of immunoparalysis.

Table 3. Tools for diagnosis of invasive aspergillosis and applicability in the intensive care unit (ICU).

Diagnostic tool	Characteristic finding	No. of patients [reference]	Applicability for the ICU	Comments
CT	Halo sign	25 proven cases [53]	No; sign arrives too early (5 days before the onset of disease) (figure 1)	Not specific for *Aspergillus* species (also other molds)
CT	Crescent sign	25 proven cases [53]	No; obscured by atelectasis, ARDS, and/or pleural effusion (figure 1)	CT often not feasible in a patient with a high fraction of inspired oxygen
Histopathologic evidence	Acutely branching (45°), septated hyphae mainly in lung tissue	129 (56 proven) [10];[a] 100 (15 proven) [5][a]	Yes, global standard	Biopsies often not feasible in patients with thrombocytopenia or a high fraction of inspired oxygen
Culture	Growth on Sabouraud agar	172 (17 proven) [12];[a] 36 (5 proven) [11];[a] 1209 (24 centers) [55]; 260 (31 proven) [30]	Moderate applicability for both culture and microscopy as a result of poor sensitivity and specificity	Isolation of the species takes several days; 50% of cases are missed on the basis of culture and microscopy findings; discrimination of colonization versus invasive disease is difficult; positive predictive value increases with increased immunosuppression
Direct microscopy	PAS, Grocott stain, calcofluor visualization of hyphal elements (not only *Aspergillus* species), rapid test	172 (17 proven) [12];[a] 36 (5 proven) [11];[a] 1209 (24 centers) [55]; 260 (31 proven) [30]	Same as above	Same as above
Galactomannan serum assay	Polysaccharide released by the fungus in the event of invasiveness (threshold, 0.5–1.5 ng/mL)	[56]	Not tested in the ICU	In the nonneutropenic, critically ill patient, bronchoalveolar fluid may perform better than serum
PCR	DNA material of *Aspergillus fumigatus*	[57]	Not tested in the ICU	In the nonneutropenic, critically ill patient, bronchoalveolar fluid may perform better than blood
β-(1,3)D-glucan	Fungal cell wall component	61 [58]	Only 1 study	Not specific for *Aspergillus* species; also present in yeasts and bacteria; may be useful as a negative predictor of fungal infection

NOTE. ARDS, acute respiratory distress syndrome; PAS, periodic acid Schiff.

[a] Studies confined to the ICU.

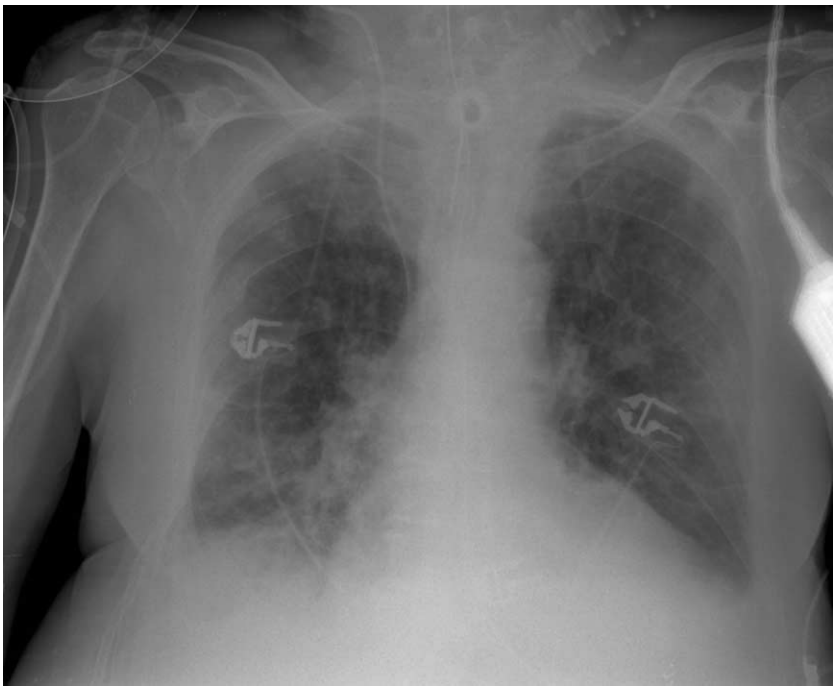

Figure 1. Chest radiograph for a patient with chronic obstructive pulmonary disease (COPD) who was receiving steroids and who was admitted to the intensive care unit because of an exacerbation of COPD with respiratory failure. Patchy, hazy infiltrates with a predominantly peripheral localization and a right-side pleural effusion were seen. Bronchoalveolar lavage (BAL) culture was positive for *Haemophilus influenzae* and negative for fungi. The results of a serum galactomannan test were negative but revealed a value of 2.6 ng/mL in the BAL fluid specimen. Despite administration of caspofungin (the patient was experiencing renal failure), the patient died. Autopsy revealed invasive aspergillosis that was confined to the lungs.

Patients in the ICU (medical and surgical) are often treated with steroids. Recent work concluded that the mortality rate is reduced if patients with septic shock who have adrenal dysfunction receive hydrocortisone for a 7-day period [23]. However, in vitro pharmacological concentrations of hydrocortisone accelerate the growth of *Aspergillus* species [24]. Clearly, high steroid intake diminishes both lines of cellular defense against IA (i.e., macrophages and neutrophils). This has been demonstrated in hematopoietic stem cell transplant recipients who received prolonged courses of steroids for the treatment of graft-versus-host disease [25, 26]. Palmer et al. [27] reported that the threshold steroid concentration varies according to the type of patient, and they emphasized that underlying lung disease is a risk factor for IA even when low doses of steroids are administered. Cases of IA have even been reported in association with inhaled steroids [28]. Additional studies are needed to investigate whether administration of the 7-day course of hydrocortisone (200 mg/day) to patients with septic shock puts them at risk of developing IA, knowing that recognition of fungal infection may be delayed, because the anti-inflammatory properties of steroids blunt the signs of infection [29].

Two at-risk groups not included in the EORTC/MSG definitions stand out with regard to IA: patients with chronic obstructive pulmonary disease (COPD) and patients with cirrhosis. Patients with COPD have an increasingly recognized risk of developing IA, and in some institutions, cases of IA among patients with COPD outnumber those cases in "classic" patients [30]. Bulpa et al. [9] analyzed a group of 16 patients with COPD who had proven or probable IA and who required ICU admission. All patients were receiving steroid treatment. The outcome was invariably poor. This is in accordance with the findings of Rello et al. [31], who described another 8 patients with COPD and IA, among whom the outcome was universally fatal.

Hepatic failure is generally not recognized as a risk factor for IA. A literature review revealed that 5 of 14 previously reported cases of IA in seemingly immunocompetent hosts were associated with liver disease [32]. Our study revealed 3 fatal cases of IA [10]. Patients with cirrhosis experience depressed phagocytosis, which may increase their risk for severe infections [33].

It is expected that new risk categories of IA will arise as new immunosuppressive agents, such as alemtuzumab and etanercept (a TNF-α blocker), are made available [34, 35].

DO PATIENTS ACQUIRE IA IN THE ICU?

There are numerous sources of *Aspergillus* species for patients in the ICU. Some studies suggest that fungal colonization of the lungs is present before entry into the hospital [36]. It is believed that the primary ecological niche is decomposing ma-

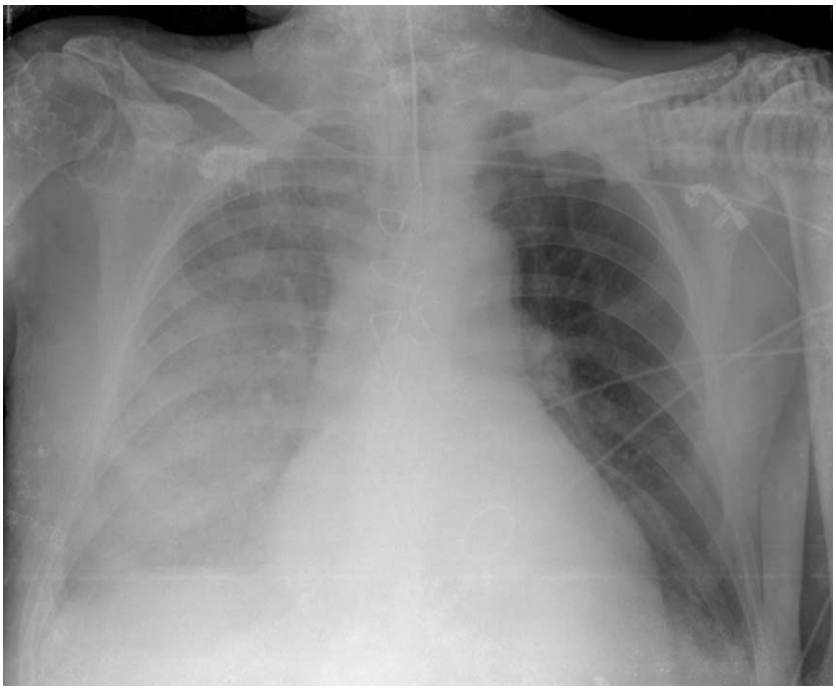

Figure 2. Chest radiograph for a liver transplant recipient revealing predominantly right-side air-space disease. No nodular lesions are seen. Findings are compatible with the diagnosis of pneumonia. Chest CT was not feasible because of the high fraction of inspired oxygen requirements. Bronchoalveolar lavage culture results were negative for bacteria and fungi (while the patient was receiving broad-spectrum antibiotics). Results of tests for galactomannan in serum were negative. The patient died, and autopsy revealed disseminated aspergillosis.

terial. However, aerosolized spores may become a potential source of infection through improperly cleaned ventilation systems, water systems, or even computer consoles [37]. The use of high-efficiency particulate air filtration reduces the risk of IA but does not reduce it to zero, probably in part because patients may be colonized before admission to the ICU, and partly because of breaks in airflow [38]. Pittet et al. [39] described 2 patients who developed fatal IA in the ICU. In retrospect, high concentrations of airborne *Aspergillus* spores could be found in close proximity to an air filter change in the ICU. In addition to the airborne route, contaminated water has been implicated as a source of infection [40, 41]. To our knowledge, a study of ventilators as a source of infection has not been undertaken. Of note, the development of IA depends on an interplay between the inoculating dose, the ability of the host to resist infection, and the virulence of the organism.

In the retrospective study performed in our unit, 63 (62%) of 102 patients with a culture positive for *Aspergillus* species had received the positive culture result within 1 week after admission to the ICU. Almost all patients were undergoing mechanical ventilation, and the mean duration of ICU stay was 20 days. Of the patients with proven cases, 18 (69%) of 26 with an underlying hematological malignancy and 11 (37%) of 30 without a malignancy had clinical evidence of IA at the time of admission to the ICU [10]. However, there is no consensus about the incubation period; estimates range from 2 days to 3 months [42]. Moreover, culture results and clinical evidence alone are not reliable predictors for invasive disease. The concept that increasing fungal burden associated with specific ICU treatments for diseases other than IA (e.g., steroid therapy for septic shock) parallels the progression from subclinical to clinical aspergillosis needs to be explored using more-sensitive markers (e.g., PCR). PCR of respiratory secretion specimens as a modality for surveillance is an interesting topic for research.

DISEASE MANIFESTATIONS IN THE ICU

There are several manifestations of IA disease in the ICU [43–52]. There are 3 types of pulmonary pathogen–host interactions [43]. The most frequent interaction is colonization of the airways; this can be present in patients with defective mucociliary clearance and structural changes in the bronchial wall [44]. These changes are present in almost every patient who is undergoing mechanical ventilation, making them particularly susceptible to colonization. IA will not develop in these patients unless a critical level of immunodeficiency has been reached. The second type of interaction is "allergic" in nature and is beyond the scope of this review. The most relevant form of interaction for ICU physicians is the invasive disease that develops in persons with impaired immunity. The lungs and sinuses are implicated in >90% of these cases. The aggressive angioinvasive form of IA is frequently encountered in neutro-

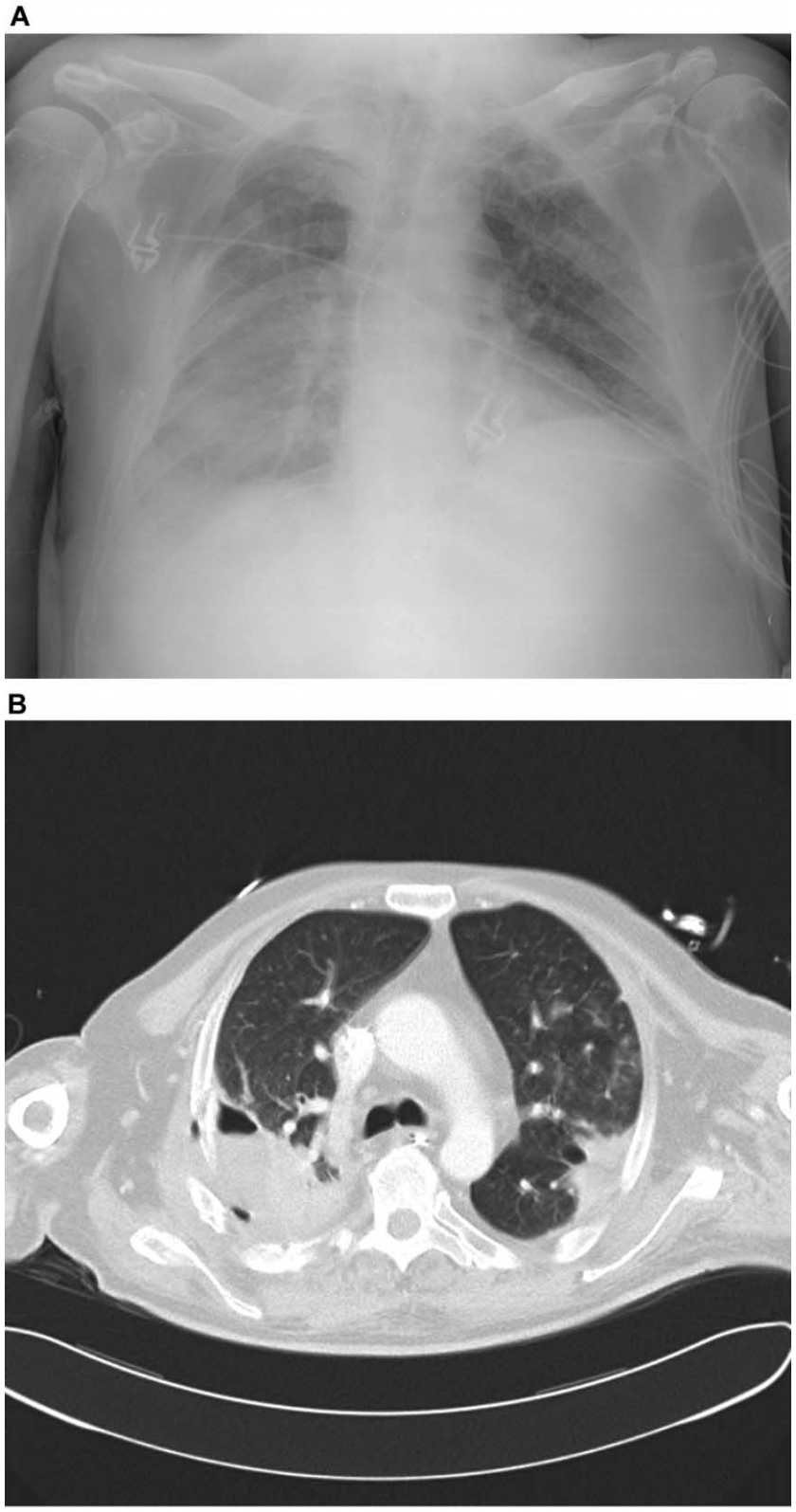

Figure 3. Chest radiograph *(A)* and CT *(B)* for a patient who was receiving high-dose steroids because of graft-versus-host disease 4 months after undergoing bone marrow transplantation for acute myeloid leukemia. Chest radiography revealed a right-side pleural effusion and adjacent lung infiltrate. CT confirmed a right-side complicated parapneumonic effusion, a mass filled partially with air between the fourth and fifth rib (with partial destruction of the bone), and a wedge-shaped infiltrate on the left side. The pleural fluid culture grew *Aspergillus fumigatus*. Findings are compatible with a bronchopleural fistula, secondary to rupture of a cavitating infiltrate and adjacent bone destruction.

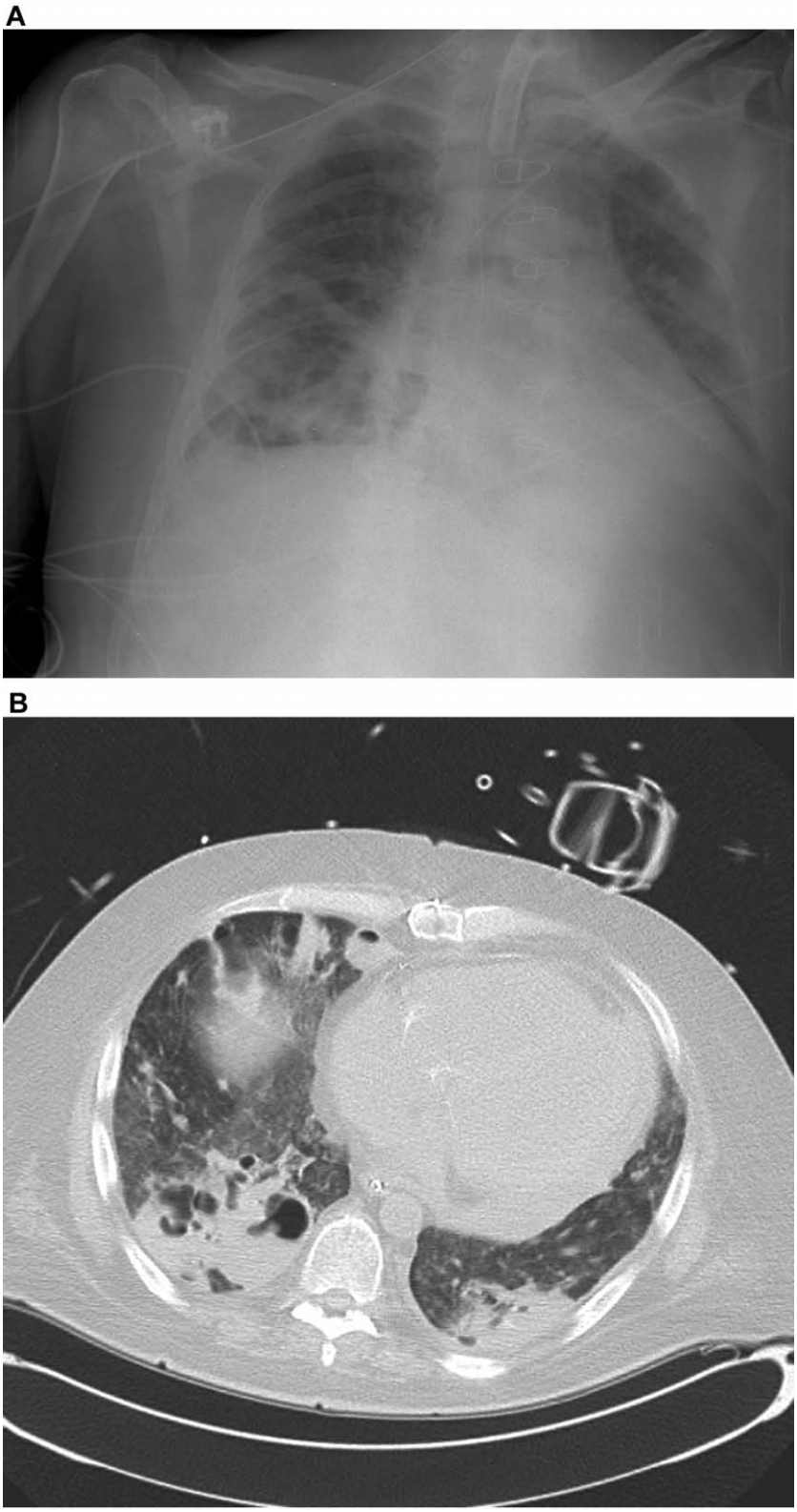

Figure 4. Chest radiograph *(A)* and CT *(B)* obtained 2 months after kidney transplantation in a patient with end-stage diabetes. Bilateral lower lobe cavities with adjacent pleural effusion on the right side are seen. Transbronchial biopsy revealed *Aspergillus fumigatus.* The serum and bronchoalveolar lavage galactomannan levels were 0.1 and 5.7 ng/mL, respectively. Despite the administration of antifungal treatment, the patient died of proven *Aspergillus* endocarditis of the tricuspid valve.

Table 4. Prediction scoring model and probability of invasive aspergillosis (IA).

Score	No. of patients	No. (%) of patients with IA
0	119	3 (2.5)
1–2	106	11 (10.3)
3–4	25	10 (40)
⩾5	10	7 (70)

NOTE. Scoring model: ⩾2 consecutive, positive airway samples, 1; sample obtained by invasive procedure, 1; leukemia, 2; corticosteroid treatment, 2; neutropenia, 5. Data are from [30].

penic patients, whereas cavitating infiltrates are observed most frequently in patients who are receiving steroids, patients with COPD, patients with cirrhosis, solid-organ transplant recipients, et cetera. In lung transplant recipients, anastomotic infections are the most frequently occurring presentations [45, 46]. Other, rarer presentations include endocarditis, wound infection, mediastinitis (after cardiac surgery), infection of vascular grafts, and osteomyelitis; these are occasionally a problem in immunocompromised patients or during epidemic outbreaks. A detailed description of all disease entities is beyond the scope of this article and was recently reviewed elsewhere [47, 48]. Infection of the CNS is frequently an ominous sign and may arise from hematogenous seeding (for which the lung is the most common primary site), from spread of the pathogen from the sinuses, or after neurosurgery.

The pathogenesis of IA in patients with steroid-associated immunosuppression differs greatly from that in neutropenic patients. Data demonstrate that pathologic lesions are often widespread and that death is related to a high fungal burden in neutropenic animals, whereas the pathogenesis in nonneutropenic, steroid-treated animals is driven by an adverse inflammatory host response that is frequently confined to the lungs, with a low fungal burden in the lung parenchyma and other organs [53, 54].

Clinical signs are usually nonspecific and do not necessarily differ from those for other causes of nosocomial pneumonia. In addition, critically ill patients with prolonged stays in the ICU often develop pulmonary infiltrates, atelectasis, and/or acute respiratory distress syndrome (ARDS), whereas patients with prior lung disease (e.g., COPD) may present with preexisting cavities noted by conventional chest radiography.

ARE THE AVAILABLE DIAGNOSTIC TOOLS APPLICABLE TO PATIENTS IN THE ICU?

Making a timely diagnosis of IA in the ICU population is probably even more challenging than establishing an early diagnosis in patients with hematologic disease. Basically, this is because the index of suspicion is lower in the ICU population, because most patients do not belong to one of the well-established risk groups. Moreover, the diagnostic tools were developed in hematology patients. In general, a diagnosis is made on the basis of a combination of compatible clinical findings, abnormal radiologic findings, and microbiologic confirmation or on the basis of histologic proof of tissue invasion by the fungus [55]. Table 3 presents an overview of the available diagnostic tools.

Over the past few years, lung CT has become one of the most important diagnostic tools. Diagnostic signs of angioinvasive pulmonary mycosis—not only that due to *Aspergillus* species, but occasionally that due to *Mucorales* species—include single or multiple small nodules with the halo sign. It should be recognized that the utility of this sign has been evaluated almost exclusively in neutropenic patients [61]. In other groups, including ICU patients, similar CT findings are frequently absent, and if the signs are present, they are far less specific [10, 12]. Many ICU patients have nonspecific interfering radiologic abnormalities associated with atelectasis or ARDS (figures 1–4).

A positive result of a culture of a respiratory specimen or positive findings of a direct microscopic examination is present in only one-half of patients with IA [55, 59]. The predictive value of a positive culture result depends largely on whether the patient is immunocompromised and ranges from 20% to 80% [60]. Given the ubiquitous nature of *Aspergillus* spores, differentiation of colonization from infection remains problematic. Two studies have examined the significance of isolation of *Aspergillus* species in ICU patients and have confirmed the poor positive predictive values [12, 61]. However, although culture and microscopic examination of respiratory tract samples are performed on a regular basis in most ICUs (once or twice weekly, as a means of surveillance), it is not an appropriate guide for clinical practice.

Serologic testing techniques based on the detection of circulating fungal cell wall components, such as galactomannan (GM) or β-D-glucan, and detection of circulating fungal DNA by PCR techniques hold promise for patients with hematologic malignancy, but they have not been systematically studied for the diagnosis of IA in the ICU. GM and β-D-glucan are polysaccharide fungal cell wall components that are released during tissue invasion and that can be detected in specimens of body fluids (e.g., serum and bronchoalveolar lavage fluid) obtained from patients with IA [56, 62]. Studies of neutropenic patients have revealed high rates of sensitivity (67%–100%) and specificity (86%–99%) [58, 63–65]. However, in a retrospective observational study of a medical ICU population, serum GM was elevated in only 53% of patients with IA [10]. Detection of serum GM is probably not a sensitive marker for IA (especially in nonneutropenic patients), as demonstrated in lung and liver transplant recipients [57, 66]. Viable fungi can endure in the lung tissue (with encapsulation by an inflammatory process), whereas circulating markers can remain undetectable because

of clearance by circulating neutrophils. Bronchoalveolar lavage fluid could be a better specimen for GM detection. The use of β-D-glucan detection in the ICU is hampered by false-positive results (associated with the use of albumin, wound gauze, hemodialysis, and bacterial infections) [67]. GM detection yields fewer false-positive results, although the use of β-lactam antibiotics, such as piperacillin-tazobactam, may also pose a problem [68]. Thus far, no prospective data on PCR detection are available for ICU patients [69].

Critical care physicians need a helpful instrument to guide clinical practice. We are currently exploring the role of GM in bronchoalveolar lavage in a broad group of critically ill patients who are at risk of acquiring IA. It may result in an algorithm that is able to identify an invasive mold infection at an early stage or that can rule out infection in high-risk, critically ill patients. Meanwhile, the prediction model involving currently available diagnostic tools (i.e., risk factors and culture results) proposed by Bouza et al. (table 4) [30] can be used.

ANTIFUNGALS FOR THE TREATMENT OF IA IN THE ICU

Amphotericin B has been the mainstay of the treatment of IA for a long time. However, this formulation is renowned for being associated with serious adverse effects (e.g., nephrotoxicity, hypokalemia, and fever). These events often result in the use of suboptimal dosing regimens. Fortunately, over the past few years, lipid-based formulations of amphotericin B and new antifungal drugs with more favorable tolerability and safety profiles (including voriconazole, posaconazole, and the echinocandins) have become available as alternatives [1, 2].

Recently, voriconazole, a derivative of fluconazole, has become the new standard of care for treating IA. A significantly better outcome (response rate, 52.8% vs. 30.6%) was demonstrated in a randomized study that compared initial treatment with voriconazole versus conventional amphotericin B [70]. Posaconazole is a new, oral, broad-spectrum triazole that is effective against several fungi that are resistant to most other antifungals; it is well tolerated and holds promise as a prophylactic agent in neutropenic patients [71]. It can be used as an alternative agent in salvage therapy [72]. Caspofungin, micafungin, and anidulafungin belong to a new class of antifungal drugs, the echinocandins, which act by inhibiting the synthesis of β-(1,3)-D-glucan in the fungal cell wall. Echinocandins display activity against *Aspergillus* species, as demonstrated in several studies of salvage therapy, but convincing data on its use as first-line treatment are still lacking [73]. (The latter criticism also applies to first-line treatment with lipid-based formulations of amphotericin B [74].)

However, most patients who were recruited in these first- and second-line treatment studies were experiencing an underlying hematological disorder or were transplant recipients. These studies usually exclude patients with baseline characteristics that are commonly seen in ICU patients, including patients with liver function abnormalities, coagulation disorders, or renal dysfunction and patients in need of advanced cardiovascular or pulmonary support, including mechanical ventilation. Nonneutropenic ICU patients and patients who are not transplant recipients largely tend to be underrepresented in all major trials; given the impact of these comorbidities, lower response rates can be anticipated.

In addition, many aspects of antifungal therapy that are relevant to the ICU population have not been sufficiently addressed in clinical studies, including the pharmacokinetic profile of antifungals in patients with underlying renal, hepatic, and/or cardiac dysfunction; the dose-response relationship; the best route of administration (oral, enteral, or parenteral); the monitoring of drug-related toxicities (e.g., how to monitor voriconazole-induced visual disturbances in sedated patients); and, especially, drug interactions with frequently used "ICU drugs." The echinocandins have not been studied as first-line therapy but offer the advantage of being free of nephrotoxicity; dose adjustments are not required in the event of renal failure or in patients who are undergoing continuous hemofiltration. In addition, few clinically significant drug-drug interactions have been reported.

FUTURE DIRECTIONS

In an era of increased availability of new immunosuppressive drugs and better intensive care, with prolonged patient survival, we can expect a continuing increase in the incidence of IA. The occurrence of IA in the ICU usually entails a poor prognosis, despite major recent improvements in the diagnosis and treatment of IA in patients with hematologic diseases. Multicenter studies are warranted, to explore the exact incidence of IA in the ICU and to better delineate the difference between hospital-acquired, ICU-acquired, and community-acquired aspergillosis. Evaluating the value of galactomannan, β-D-glucan, and PCR in nonneutropenic, critically ill patients with different sample types (and, especially, with respiratory samples) is urgently needed, as is a better delineation of the patient population at risk for IA in the broad group of critically ill patients. Finally, antifungal pharmacokinetics, pharmacodynamics, and interactions with other drugs need to be explored more thoroughly. Meanwhile, all new diagnostic techniques and therapeutic measures must be validated against postmortem findings, because only proven cases of IA offer the most valuable information.

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and is a member of the speakers' bureaus of Merck and Pfizer. K.L.: no conflicts.

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