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Aspergillosis in the ICU – The new 21st century problem?

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Invasive pulmonary aspergillosis (IPA) is a serious opportunistic infection mainly affecting seriously immunocompromised patients. The major risk factor is prolonged granulocytopenia. Most literature on the epidemiology and clinical impact of *Aspergillus* spp. infections concern patients with hematological malignancies, cancer, stem cell transplantation and solid organ transplant patients. However, evidence from recent literature indicates that *Aspergillus* spp. may cause invasive disease in other categories of patients without apparent immunodeficiency, including patients in intensive care units (ICUs). Clinical diagnosis of IPA in non-immunocompromised patients is difficult. Standardized diagnostic definitions, developed by the European Organization for the Research and Treatment of Cancer/Mycosis Study Group for research purposes in patients with cancer and in recipients of haematopoietic stem cell transplants, are not feasible for patient categories with an intermediate to low probability for acquiring IPA. In routine clinical practice, most *Aspergillus* isolates from non-sterile body sites do not represent disease. Invasive diagnostic procedures are often not feasible in patients with severe respiratory insufficiency and critical illness. The presence of systemic risk factors, or underlying predisposing lung disease or general debilitation, may enhance the clinical relevance of a positive culture. The finding of an *Aspergillus* spp. positive respiratory specimen in an ICU patient should not be discarded; pre-emptive antifungal treatment should be considered, while attempting to substantiate the diagnosis.

Keywords Intensive care, invasive *Aspergillosis*, risk factors, outcome

Introduction

Aspergillus spp. can cause a wide spectrum of diseases in humans, including allergy, superficial infection related to (surgical) trauma, and invasive disease [1,2]. Sinopulmonary involvement is most common, but systemic dissemination with invasion of other organs and tissues may occur. The most important defence mechanisms against *Aspergillus* spp. are neutrophils and alveolar macrophages. Lowered host resistance due to underlying disease, neutropenia, treatment with cytostatic drugs, corticosteroids and other immunosuppressive agents, may predispose patients to develop infection after exposure. Invasive pulmonary aspergillosis has emerged as an important cause of morbidity and mortality in patients receiving intensive chemotherapy and allogeneic stem cell transplantation, and may complicate solid organ transplantation. However, recent literature evidence data indicates that *Aspergillus* spp. may cause invasive disease in other patient categories, without apparent severe immunodeficiency, such as patients with critical illness. Difficulties of establishing the diagnosis pose a major problem to assess the true incidence of *Aspergillus* spp. infection outside the population of severely immunocompromised patients. Incidence figures in intensive care range from 0.3% to as much as 5.8% [3–5]. The prognosis is grim with a mortality rate exceeding 80%.

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Clinical spectrum of *Aspergillus* spp. infections

The clinical manifestations and severity of *Aspergillus* spp. pulmonary disease depend upon the immune status of the patient [6]. Airway colonization without evidence of tissue invasion can be found in COPD patients, smokers and even healthy individuals. It is unclear whether colonization predisposes to invasive disease if the immunological status of the host changes. In the tracheobronchial tree, *Aspergillus* spp. may cause tracheobronchitis with superficial invasion, ulcerative lesions, formation of pseudomembranes or frank tissue invasion. Severe *Aspergillus* tracheobronchitis is characteristically associated with bronchoconstriction; acute respiratory failure may evolve with impaction of plugs in the airways [7]. Mechanical ventilation can be difficult to impossible because of airway obstruction. It has been described in severely immunocompromised patients, patients with HIV infection as well as after influenza. In lung transplant patients, *Aspergillus* spp. may cause ulcerative anastomotic infections. Pulmonary aspergilloma is characterized by histologic evidence of hyphae in cavities but not in tissues, and a chronic inflammation with fibrosis in the tissue surrounding the cavity [8]. A variety of terms such as chronic necrotizing pulmonary aspergillosis, semi-invasive aspergillosis, chronic invasive aspergillosis, and symptomatic aspergilloma are described; the distinction between these entities is not rigorously defined and overlap in clinical and radiological features probably exists. It can be speculated that such indolent forms of *Aspergillus* spp. disease may become invasive and cause life threatening disease when host immunity weakens due to underlying or intercurrent diseases. Acute invasive pulmonary aspergillosis is characterized by invasion of lung parenchyma. Acute IPA develops over period of days or weeks after exposure, typically in patients with severe immunologic derangements.

Incidence and impact of invasive aspergillosis in critically ill patients

In recent years, both observational and autopsy findings indicate a further emergence of *Aspergillus* spp. as a major pathogen affecting mainly severely immunocompromised patients [8]. However, IPA may also develop in patients without apparent immunodeficiency [9–14]. Recent literature suggest that IPA may even be an emerging disease in critically ill patients [3,4,15]. Table 1 summarizes literature data on invasive aspergillosis in critically ill patients.

Epidemiological data about the true incidence and outcome of invasive pulmonary aspergillosis in the critically ill, non-neutropenic and apparently immunocompetent patients are scarce. Interpretation of data is difficult, because of the differences in diagnostic approach. In a prospective, cohort observational multicenter study in Spain, an incidence of 11/1000 admissions was noted [4]. Diagnosis was based upon a positive culture for *Aspergillus* spp. in respiratory tract secretions and the presence of pneumonia. Mortality in infected patients was 80%, versus 50% in colonized patients. In a retrospective study, using a sole entry criterion of an *Aspergillus* positive respiratory specimen and an adapted diagnostic algorithm, an incidence of invasive pulmonary aspergillosis of 3.2/1000 ICU admissions was found [15]. In the subgroup of medical patients, the incidence was thrice as high (10.2/1000). Mortality in the patient group categorized as invasive disease was significantly higher than in the patient group considered colonized (77% versus 40%). In a recent retrospective study in a medical ICU, with strict application of the EORTC/MSG criteria, an incidence of invasive aspergillosis of 5.8%, was found, with pulmonary involvement in most cases [3]. The majority of the patients did not have an underlying hematological malignancy. The observed mortality in these patients (91%) was far higher than predicted by the SAPS II score. It can be speculated that the incidence of invasive aspergillosis in intensive care may be underestimated, since most institutions do not have a per protocol autopsy policy, and since culture sensitivity is only approximately 30% [16].

Risk factors for IPA in the context of critical illness

In a retrospective analysis of medical and microbiological records of patients with pulmonary fungal infection in Taiwan [17], it was shown that other host factors that those described by the EORTC/MSG, may play a role in the acquisition of invasive fungal disease. Underlying malignant disease was only present in 27%, other immunocompromising conditions were diabetes mellitus, cytostatic treatment, long term steroid use, organ transplantation, AIDS, uraemia and liver cirrhosis; 5% of patients had COPD. In 15% of patients, no predisposing underlying condition could be identified. Various small series and case reports have shown that invasive aspergillosis commonly occurs in critically ill patients admitted to the ICU because of acute exacerbation of COPD and treatment with intravenous corticosteroids [11,12,14,18].

Table 1 Studies of invasive aspergillosis in ICU patients.

Author	Year	Type of study	Patient category	No. with invasive disease	Incidence	Mortality
Lewis [9]	1985	Case series	IPA complicating influenza pneumonia Case report and literature review	6	–	100%
Karam [10]	1986	Cases series	Non-neutropenic patients 10 structural lung disease 7 steroid treatment			
Janssen [36]	1996	Monocentric Retrospective	Medical ICU pts with hematological malignancy, immunosuppression for mixed connective tissue disease, ARDS	25	–	92%
Pittet [11]	1996		COPD patients in MICU Acquisition of IPA during mechanical ventilation due to high grade airborne inoculation	2	–	100%
Rello [12]	1998	Monocentric	Series of COPD patients and literature review	24	–	100%
Valles [13]	2002	Two centres Observational, prospective study	Hospital acquired pneumonia requiring ICI admission *Aspergillus* spp. identified in 17% of pts Mainly COPD pts			77%
Bulpa [14]	2001	Monocentric Case series	COPD patients admitted to ICU diagnosed with IPA	23	–	100%
Meersseman [3]	2004	Monocentric Retrospective	Medical ICU 70% cases without malignancy 5 pts with IA without known predisposing condition (of whom 3 Child C cirrhosis)	107	5.8%	91%
Garnacho-Montero [4]	2005	Multicentric Prospective	73 ICUs in Spain patients with LOS >7 days	20	1.1%	80%
Vandewoude [15]	2006	Retrospective	Mixed ICU 40% haematological pts	83	3.3/1000	77%

Malnutrition, diabetes mellitus, pulmonary disorder, liver cirrhosis and corticosteroid use were found as underlying predisposing conditions for the development of IPA in patients without hematological disease [3,16,19]. In the setting of persistent septic shock, steroids are frequently used since a beneficial effect has been demonstrated [20]. Corticosteroids substantially impair macrophage killing of *Aspergillus* spores and mononuclear cell killing of *Aspergillus* hyphae [21]. In patients with underlying lung disease steroid therapy should be considered as a risk factor for invasive aspergillosis, even at low doses and short courses [21–23].

In patients with sepsis, a biphasic immunological pattern has been described: an early hyper inflammatory phase followed by an anti-inflammatory response, leading to a hypo-inflammatory state, the so-called compensatory anti-inflammatory response syndrome (CARS or immunoparalysis). This should be considered as a temporary form of acquired immunodeficiency, and has been associated with the development of IPA in critically ill patients [24]. In critically ill patients, acquired disorders of phagocytic function complicating severe medical and surgical illness are recognized as a contributing cause for the development of opportunistic infection [25].

Diagnosis of invasive aspergillosis in critically ill patients

Timely diagnosis of invasive aspergillosis, in early stage, remains difficult in immunocompromised patients. In patients with critical illness, the diagnostic process is even more difficult, because symptoms and signs are atypical, and the initiation of additional diagnostic examinations is often delayed because a low index of suspicion. The diagnosis of invasive aspergillosis in apparently immunocompetent patients is often discarded, or considered as not plausible. The publication of the EORTC/MSG guidelines for invasive fungal infection has paved the way to a systematic diagnostic approach. However, these guidelines are intended for

use in clinical trials and for epidemiologic research; they should not be used for routine clinical practice, or to guide therapy in individual patients. Moreover, they are not designed for patient categories other than patients with cancer and bone marrow transplantation.

Although a positive *Aspergillus* spp. culture in a respiratory tract specimen is not sensitive, nor specific, it is often the first clue for the diagnosis in critically ill patients [4,15]. Excluding the possibility of contamination during the pre-analytical phase of a sample, isolation of *Aspergillus* spp. in the respiratory tract may represent one of the three scenarios: (1) evidence of current disease, (2) true colonization, or (3) a marker for the future development of invasive disease. In a multicenter, hospital-based survey, most *Aspergillus* spp. culture isolates from non-sterile body sites did not represent disease [16]. However, for high-risk patients, a positive culture result was associated with invasive disease, such as in allogeneic bone marrow transplant recipients (60%), persons with hematologic cancer (50%), and those with signs of neutropenia (60%) or malnutrition (30%). Diagnosis of invasive aspergillosis on the basis of an *Aspergillus* spp. positive culture of a specimen obtained from a non-sterile body site remained most difficult in the group of patients with an intermediate risk for invasive aspergillosis (10–30%): human immunodeficiency virus infection (20%), solid-organ transplantation (20%), corticosteroid use (20%), or an underlying pulmonary disease (10%). Tissue sampling remains the golden diagnostic standard; however, tissue sampling in critically ill patients is often impossible because of high-grade ventilatory and inotropic support, and coagulation deficiencies. Hence, the clinical diagnostic process is often dependent on indirect circumstantial data enhancing the probability of invasive disease. Fiberbronchoscopy with inspection of the tracheobronchial tree, sampling of deep airway secretions and bronchoalveolar lavage can be helpful. The macroscopic finding of ulcerative lesions and/or pseudomembranes together with a positive culture for *Aspergillus* spp., is highly suggestive for tracheobronchitis and warrants appropriate antifungal therapy. Direct microscopic examination is important in the appreciation of a culture positive sample; the demonstration of septate hyphae increases the probability of invasive disease. In a retrospective study addressing the significance of *Aspergillus* spp. in respiratory samples in nongranulocytopenic patients, detection of septate hyphae was significantly higher in infected patients than in colonized patients [26]. In another retrospective study, the combination of a positive culture and the presence of septate hyphae in lower respiratory tract samples was used to discriminate colonization from true disease in nongranulocytopenic patients. This approach resulted in the identification of two cohorts of patients (infected versus colonized), with a significant difference in outcome: in-hospital mortality of patients with invasive disease was 77% versus 40% of patients considered as colonized. Moreover, the diagnosis of infection using this criterion was confirmed by histopathological data in a limited number of patients. The use of quantitative cultures to discriminate infection from colonization has not been studied. However, in critically ill patients with pneumonia, it seems plausible that a (semi) quantitatively highly positive culture in the absence of bacterial isolates, increases the probability of invasive disease.

The value of serological markers for the diagnosis of invasive aspergillosis in non-neutropenic patients remains unclear at this moment. Galactomannan and 1, 3- β-D-glucan are incorporated in the diagnostic guidelines for immunocompromised patients. Galactomannan release may be influenced by the immune status of the patient. In a study of critical care patients without malignancy, the galactomannan test was twice positive in 53% of patients with proven or probable invasive aspergillosis [3]. Extraneous galactomannan and translocation of galactomannan across the gut mucosa, compromises the clinical specificity of this test; false positive tests have been reported in patients receiving piperacillin-tazobactam and other beta-lactam antibiotics. Reproducible assay results with high specificity and high positive predictive value in a multicenter setting demonstrate that use of an assay to detect serum glucan derived from fungal cell walls is a useful diagnostic adjunct for invasive fungal infection [27]. However, glucan is not specific for *Aspergillus* spp. False-positive glucan tests have been found in patients after hemodialysis, cardiopulmonary bypass, high dose immunoglobuline treatment, and after exposure to glucan containing gauze. Hence the use of galactomannan and glucan as serological markers cannot be advocated for routine diagnostic use in critical care patients, and caution is warranted in the interpretation of positive or negative test results.

As far as the amplification of nucleic acid and diagnosis of invasive aspergillosis is concerned, PCR technology has dominated. It can be applied to blood and BAL specimens [28–31]. Experience is limited to patients treated for hematological malignancy.

The demonstration of specific antibody is required to establish the diagnosis of chronic pulmonary aspergillosis [6,32]. Antibodies have been documented in approximately one-third of patients with invasive aspergillosis. The use of antibody testing for diagnostic

use in non-neutropenic critically ill patients has not been explored.

Aspergillus spp. produce a range of extracellular enzymes as well as primary (e.g., D-mannitol) and secondary metabolites (e.g., gliotoxin), all of which have at least the potential to serve as diagnostic markers for invasive aspergillosis. The detection of metabolites produced by *Aspergillus* spp. has not been researched in terms of their potential application as non-invasive diagnostic modalities [28,33].

Chest computerized tomography is an important tool for the diagnosis of invasive aspergillosis in neutropenic, severely immunocompromised patients, even in the absence of evident lesions on a conventional chest X-ray. One or more nodules is the most common finding in early invasive aspergillosis in neutropenic patients and patients after haematological stem cell transplantation [34]. The 'halo sign', a haziness surrounding a nodule or infiltrate, is a characteristic chest CT feature of angioinvasive organisms, and is highly suggestive of invasive aspergillosis in patients with prolonged neutropenia [34]. However, medical imaging of the lungs in ICU patients is less pathognomonic due to many confounding factors such as ventilator-associated pneumonia, atelectasis, and pleural fluid effusions in ventilated patients. Furthermore, it can be speculated that typical radiological lesions may be less apparent because of the difference in severity and nature of the immune derangements. Typical lesions for invasive aspergillosis, such as the halo and the air crescent sign, were only found in 5% in a series of ICU patients [15]. This observation was confirmed in another study, demonstrating that the halo sign was only present in a minority of patients with proven or probable disease; cavitating lesions or atypical infiltrates with a broad differential diagnosis were present in most patients [3]. This is also in agreement with the previous description of the low sensitivity the halo sign/air crescent sign of 24% in patients without hematological malignancy as compared with 82% in patients with neutropenic hematological malignancy [35].

Conclusion

Recent data indicate that invasive pulmonary aspergillosis may be an underestimated opportunistic fungal infection in critically ill patients, even in the absence of severe immunological derangements. Incidence estimates up to 5.8% in patients in a medical ICU have been reported. Apart from the well known high risk factors, other medical conditions predisposing to the development of this often fatal infection may be steroid exposure, malnutrition, diabetes, pre-existing lung disease and liver failure. Diagnosis is difficult. A positive culture is often the first diagnostic clue, but this finding is not specific; furthermore culture of lower respiratory tract specimens may become positive in an already advanced stage of the disease. The use of serological markers, including galactomannan and glucan, is not sufficiently explored in non-neutropenic patients. Medical imaging is less useful since the typical lesions observed in neutropenic patients are rarely observed. Tissue sampling is often impossible because of the critical condition of the patient. Mortality remains high in spite of treatment, due to delay in diagnosis and the severity of disease condition precipitating ICU admission.

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