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Original articles

INVASIVE ASPERGILLOSIS IN CRITICALLY ILL PATIENTS: ANALYSIS OF RISK FACTORS FOR ACQUISITION AND MORTALITY

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Key words: invasive aspergillosis – intensive care – outcome

ABSTRACT

Objective: To investigate outcome in patients who develop invasive aspergillosis in the ICU, and to evaluate whether specific risk factors for the acquisition of invasive aspergillosis are associated with mortality.
Design: Retrospective cohort study (07/1997–12/1999) with screening of 8988 admissions.
Setting: 54-bed ICU of the 1060-bed Ghent University Hospital.
Patients: 38 ICU patients with invasive aspergillosis. Invasive aspergillosis was defined as proven by positive histology and tissue culture and as probable by a combination of clinical suspicion as well as microbiological and radiological data. Seventeen patients had risk factors (neutropenia, haematological malignancy, immunosuppressive therapy). In the other 21 apparently immunocompetent patients, invasive aspergillosis was a complication following ARDS, COPD, pneumonia, acute liver failure, burns, severe bacterial infection and malnutrition.
Measurements: Population characteristics and outcome were compared for patients with and without risk factors for the acquisition of invasive aspergillosis.
Results: Patients with risk factors had higher APACHE II scores. No difference was found between patients with and without risk factors in in-hospital mortality (82% vs. 71%; p=0.431). In patients with specific risk factors, the observed mortality was not different from the mortality as expected on basis of the APACHE II (p=0.940). In patients without risk factors the observed mortality exceeded the expected mortality (p<0.001).

Conclusion: The incidence of invasive aspergillosis in this series is 4/1000 admissions. No difference in mortality was found between patients with and without risk factors for the acquisition of invasive aspergillosis. Yet, the prognosis of the patients without risk factors seems to alter more seriously by the development of this infection.

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INTRODUCTION

Invasive aspergillosis is a rare disease in intensive care unit (ICU) patients. However, because of the continuously expanding proportion of immunosuppressed

patients and advances in life support systems, it is an emerging opportunistic fungal infection. Invasive aspergillosis is particularly problematic in ICU patients because diagnostic management is often difficult, and therapy is often suboptimal due to concurrent disease and organ failure. The most commonly described risk factors for the acquisition of invasive aspergillosis are prolonged profound neutropenia due to haematological malignancy or aplastic anemia, allogeneic bone marrow and stem cell transplantation, and immunosuppression in solid organ transplantation and vasculitis. However, invasive aspergillosis has also been reported before in apparently immunocompetent patients with a range of underlying diseases, including chronic obstructive pulmonary disease (COPD), primary viral pneumonitis, acute liver failure and alcohol abuse (1-4). Severe medical and surgical illnesses are associated with impaired phagocytic function, which per se is a risk factor for invasive mycotic infections (5,6). Despite the advances in diagnosis and treatment, invasive aspergillosis implicates a bad prognosis in critically ill patients with mortality up to 95% (7).

The purpose of this paper is to evaluate whether presence or absence of generally accepted risk factors for the acquisition of invasive aspergillosis had an impact on the prognosis of these patients. This hypothesis is based on the assumption that patients with invasive aspergillosis but without the classic hemato-immunological risk factors could have a better survival rate.

PATIENTS AND METHODS

Setting

This retrospective study was conducted in the Ghent University Hospital, a 1060-bed tertiary care centre with a 54-bed ICU including both a surgical and medical ICU, an ICU for cardiac surgery and a unit for severely burned patients. Approximately 3300 patients are admitted to the ICU each year. The surgical ICU serves all kinds of surgery with the need for intensive care management, including multiple trauma and solid organ transplantations (kidney, liver and pancreas). The medical ICU serves all patients with internal diseases requiring intensive care including patients with haematological malignancies and bone marrow transplant recipients. In the ICU for cardiac surgery, approximately 10 heart transplantations are performed each year. For immunocompromised patients or patients colonized or infected with epidemiologically important microorganisms, each unit is equipped with several isolation rooms. The burns unit consists of 6 separate isolation rooms with shower and bathing installations within. No significant changes in age, length of ICU stay or acute physiology and chronic health evaluation (APACHE) II scores were observed during the study period (8).

All patients admitted to the ICU underwent routine surveillance screening cultures of sputum or tracheal aspirates (if intubated), mouth, urine and perineum thrice weekly. Furthermore, cultures from the above mentioned or other sites were taken whenever clinically indicated. In a retrospective study from July 1997 onwards till December 1999, the charts of all patients with any positive culture for *Aspergillus* spp. were reviewed. Cystic fibrosis patients were excluded from the study population.

The definitions for documented and probable aspergillosis were in part derived from the European Organisation for the Research and Treatment of Cancer / Mycosis Study Group (EORTC/MSG) consensus data on opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoetic stem cell transplants (9).

Definite invasive aspergillosis was defined as (I) positive microscopic examination with septate hyphae and positive results of a culture for *Aspergillus* spp. of a tissue biopsy or autopsy specimen, or (II) positive culture of a specimen of a normally sterile site obtained by aseptic invasive techniques.

Diagnostic criteria for probable invasive aspergillosis were: (I) compatible clinical signs and symptoms, (II) any positive culture from a contiguous nonsterile site, including sputum, nares, sinuses, throat, (III) abnormal chest X-ray and/or computed tomography of lungs (thoracic CT) or suggestive imaging of other body sites, and (IV) either (a) host risk factors or (b) positive results of microscopic examination and culture of a bronchoalveolar lavage (BAL) fluid specimen. The presence of host risk is defined as at least one of the following: (a) neutropenia (absolute neutrophil count less than 500/mm^3), (b) underlying hematologic or oncologic malignancy treated with cytotoxic agents, (c) prolonged corticosteroid use in a dose of 20 mg. of prednisone or equivalent and/or use of steroids in combination with other immunosuppressive drugs ,-(d) congenital immunodeficiency. All criteria needed to be fulfilled for the diagnosis of probable invasive aspergillosis (I + II + III + either IVa or IVb). The circulating galactomannan specific for *Aspergillus* spp. was not available in our institution during the study period.

Outcome evaluation was based upon mortality 14 days and 28 days after the first culture positive for *Aspergillus* spp. and in-hospital mortality. In-hospital mortality is defined as death within the same hospital admission (ICU and general wards).

Definitions of risk factors

Risk factors for the acquisition of invasive aspergillosis were defined as hematologic or oncologic malignancy, neutropenia < 500 neutrophils/mm³, solid organ transplant, chronic glucocorticoid use in daily dose equivalent to or higher than 20 mg. of prednisolon, and congenital immunodeficiency. Apparently immunocompetent critically ill patients with invasive aspergillosis were designated to the group without risk factors.

Other definitions

Acute renal failure is defined as the need for renal replacement therapy, acute respiratory failure as the need for mechanical ventilation, and cardiovascular failure as the need for inotropic or vasopressor support (10-14).

Statistical analyses

Continuous variables are described as mean ± standard deviation (SD) and median (lower quartile – upper quartile). Comparative analyses are executed with Mann-Whitney U test or Chi-square test when appropriate. A multivariate analysis is performed following a logistic regression model; hereby odds ratios (OR) and 95% confidence intervals (CI) are reported. In order to compare the observed in-hospital mortality with the mortality as expected on basis of the APACHE II scoring system, the Chi-square test for observed vs. expected frequencies was used. Statistical analyses are executed with STATISTICA 4.5 (StatSoft Inc. Tulsa, OK, USA) and SPSS 9.0 (SPSS Inc. Chicago, IL, USA). All tests used are two-tailed and statistical significance is defined as $p<.05$.

Results

During the study period there were 8988 admissions in the ICU. Of these patients, 71 were identified with positive cultures for *Aspergillus* spp. According to the predefined criteria 38 were classified as cases with either definite or probable invasive aspergillosis, representing an incidence of 4/1000 ICU admissions. All but two patients received appropriate antifungal therapy consisting in either itraconazole or amphotericin B.

Forty-five % (n=17) of the patients had underlying conditions known to be risk factors for the acquisition of invasive aspergillosis: 11 patients had hematological malignancy (7 with neutropenia). Four patients received immunosuppressive therapy following solid organ transplantation (1 with neutropenia). One patient had polymyalgia rheumatica with neutropenia and one patient had aplastic anaemia due to thiamazol. Other underlying conditions included COPD (n=7), liver cirrhosis (n=3), severe bacterial infection (n=3), malnutrition (n=1), fulminant liver failure (n=1), viral pneumo-myocarditis (n=1), ARDS following multiple trauma (n=1), extensive burns (n=1), bacterial pneumonia (n=1), heat stroke with liver failure (n=1) and near drowning (n=1). None of the patients was HIV positive.

Characteristics of both patient groups are summarized in table 1. All patients with invasive aspergillosis were mechanically ventilated. Patients with risk factors had higher APACHE II scores and related expected mortality. No difference between patients with and without factors were found in age, acute renal failure, cardiovascular failure, length of ICU stay prior to the first positive culture, total length of ICU stay, length of ventilator dependence prior to the first positive culture and total length of ventilator dependence. Ninety-four% of patients with the predefined risk factors received appropriate antifungal therapy vs. 86% of patients without risk factors (p=0.401).

For the outcome comparison, no difference was found between patients with and without specific risk factors in 14-days mortality, 28-days mortality and in-hospital mortality. In a logistic regression analysis no variables were found to be independently associated with mortality.

An outcome evaluation was also performed by comparing the observed mortality rate with the mortality as expected on basis of the APACHE II scoring system. When all ICU patients were taken into account the difference between observed (73.7%) vs. expected mortality (54 ± 26.8%) was statistically significant (p<0.001). When only ICU patients with risk factors for the acquisition of invasive aspergillosis were considered, no difference in observed (82.4%) vs. expected mortality (70 ± 20.7%) was noted (p=0.940). In patients without risk factors, the observed mortality (71.4%) significantly exceeded the expected mortality (40 ± 23.9%), (p<0.001).

Discussion

In the last decades, invasive aspergillosis has been recognized, mainly in autopsy studies, as an emerging infection. (15, 16, 17). An incidence of 12.4 cases/million/year was reported in a prospective population-based laboratory surveillance study (18). In the particular setting of critical care, few epidemiological data are available. In a recent autopsy study of ICU patients, an incidence of invasive aspergillosis of 2.7% of the patients undergoing post-mortem examination was found (19). In this retrospective study, the incidence of invasive aspergillosis in general ICU patients was found to be 4/1000 admissions.

Furthermore, in our series, a clinical algorithm, derived from the EORTC/MSG criteria, considering host factors, bronchoscopy, radiological data, results of cytological and/or histological samples, and microbiological data of bronchoalveolar lavage specimens was used to discriminate colonisation from invasive infection (20). The clinical significance of *Aspergillus* spp. isolated from any specimen and especially from sputum and lower respiratory tract secretions is difficult to assess. The immune status of the patient is considered the most important determinant in the interpretation of the clinical relevance of a positive respiratory tract sample. Risk factors for invasive aspergillosis are mainly found in high risk hemato-oncological patients. They are a component of the EORTC/MSG definitions for probable and possible aspergillosis, a far more frequent clinical diagnosis than proven invasive aspergillosis, which requires histological confirmation and a positive culture from an otherwise sterile body site (9). In fact, the EORTC/MSG criteria were developed in order to have diagnostic conformity in clinical trials with antifungals in hemato-oncological and bone marrow or stem cell transplant patients. In apparently

Table 1. Population characteristics of ICU patients with and without specific risk factors for the acquisition of invasive aspergillosis.

	ICU patients with risk factors (n=17)	ICU patients without risk factors (n=21)	P value
APACHE II score	31.2 ± 7.6	22.1 ± 8.4	.003
	32 (28.5-35)	21 (17-28.5)	-
APACHE II related expected mortality (%)	70.1 ± 20.7	40.1 ± 23.9	.003
	73 (64.5-84.5)	34 (26-60)	-
Age (years)	53.5 ± 15.3	56.1 ± 13.4	0.078
	57 (45-65.5)	59 (48-64.5)	-
Acute renal failure	9 (52.9)	8 (38.1)	.739
Vasopressor support	14 (82.4)	18 (85.7)	.999
Acute respiratory failure	17 (100)	21 (100)	.999
Length of ICU stay prior to first positive culture (days)	7.4 ± 7.6	5.8 ± 6.2	.506
	6 (1-11.5)	4 (1-8.5)	-
Total length of ICU stay (days)	22.8 ± 22.4	25.8 ± 24.0	.638
	12 (7.5-34)	14 (10-36)	-
Ventilator dependency prior to first positive culture (days)	5.9 ± 7.3	5.6 ± 6.2	.975
	4 (1-9)	4 (1-7.5)	-
Total length of ventilator dependency (days)	18.8 ± 17.4	23.2 ± 22.2	.360
	11 (5.5-34)	13 (9.5-31.5)	-
Patients with appropriate antifungal therapy	16 (94.1)	18 (85.7)	.401
Mortality day 14	12 (70.6)	12 (57.1)	.506
Mortality day 28	14 (82.4)	14 (66.7)	.460
In-hospital mortality	14 (82.4)	15 (71.4)	.476

Discrete variables are described as n (%) and continuous variables as mean ± SD and median (lower quartile – upper quartile).

immunocompetent non-neutropenic patients it is even more difficult to diagnose this condition by clinical and microbiological means. The diagnostic criteria that are proposed in this study are less restrictive than the EORTC/MSG criteria. They differ from the EORTC/MSG criteria for invasive aspergillosis by a different appreciation of host risk factors and a less strict interpretation of radiological criteria, including any evidence of pneumonia. The latter is warranted by the fact that typical radiological abnormalities suggestive for invasive pulmonary aspergillosis are less apparent due to many confounding factors such as ventilator associated pneumonia, atelectasis, and pleural fluid effusion in critically ill patients. In the autopsy study of Dimopoulos et al. (19), chest X-ray abnormalities were neither specific nor sensitive for disseminated aspergillosis. Furthermore, in the particular setting of intensive care, diagnostic studies and invasive procedures for tissue sampling are often hampered by high grade ventilatory and inotropic support and coagulation abnormalities. An important argument in favour of the diagnostic algorithm used in this study is the fact that in six patients who in vivo met the diagnosis of probable invasive aspergillosis, this finding was confirmed post mortem. They were accordingly classified as definite invasive aspergillosis.

In the group with risk factors the observed in-hospital mortality was not significantly different from the mortality as expected on basis of APACHE II (p=0.940). In patients without specific risk factors, however, the observed mortality significantly exceeded the expected mortality rate (p<0.001). The excess mortality in the latter group is in favour of the diagnostic algorithm that was used to define invasive aspergillosis, reflecting the true impact of invasive aspergillosis on mortality in a patient population with a lower risk profile for this disease, and possibly later recognition of the disease.

Various risk factors for the acquisition of invasive aspergillosis have been reported. In addition to patients with the generally accepted risk factors, such as prolonged, profound neutropenia due to a haematological malignancy (5-25% risk) or aplastic anemia, allogeneic bone marrow or stem cell transplantation (2-30% risk), acquired immunodeficiency syndrome, severe combined immunodeficiency, or chronic granulomatous disease, and chronic steroid use, invasive aspergillosis has been described increasingly in other patient groups (21). In this retrospective study, less than half of the patients had a typical risk profile; the other patients had risk factors that were not strictly related to hematologic or immunological underlying disease. In study addressing the impact of culture isolation of *Aspergillus* spp., Perfect et al. also found that certain underlying diseases, such as malnutrition, pulmonary disease, diabetes, HIV, steroid treatment, solid organ transplant, and solid organ cancer influence the incidence of the disease (22).

By MEDLINE search (1980 – 2001), only one study addressing outcome of patients with invasive aspergillosis in a medical ICU was found; most patients suffered from malignant hematological disease and neutropenia (23). Despite standard antifungal treatment and maximal available supportive treatment, 92% of patients died.

Using the same data set of our retrospective study, in a matched cohort study, we found a statistically significant attributable mortality of invasive aspergillosis of 18.9% (95% CI: 1.1-36.7%), and in a multivariate analysis, following adjustment for disease severity and major organ dysfunction, invasive aspergillosis was recognised as an independent predictor for mortality (24).

In the current analysis of both groups of patients, a statistically significant difference was found in APACHE II score and derived expected mortality, with patients having risk factors being more severely ill upon ICU admission. Organ failure, total length of ventilation before diagnosis of invasive aspergillosis, length of ICU stay and antifungal treatment were comparable in both groups. No difference in observed in-hospital mortality was found between patients with and without risk factors for the acquisition of invasive aspergillosis. However, as the difference between observed and expected mortality in patients with risk factors does not reach statistical significance while it does in patients without the predefined risk factors, it seems that the clinical impact of invasive aspergillosis is higher in the latter group. However, the statistically non-significant difference in in-hospital mortality (11%) can be due to the fact that patients with risk factors for the acquisition for invasive aspergillosis were initially more severely ill. Hence, risk factors that might be helpful to predict the development of invasive aspergillosis had no additional value in predicting mortality among ICU patients with invasive aspergillosis. However, due to the limited number of patients in both groups, study power can be insufficient to demonstrate any association between the

underlying predisposing condition and survival. Yet, based on the results obtained, there is absolutely no reason to presume that invasive aspergillosis carries higher fatality rates in populations with risk factors. On the contrary, as stated before, the pathogenic significance of invasive aspergillosis seems higher in ICU patients without risk factors.

In conclusion, no difference in observed in-hospital mortality was found between patients with and without risk factors for the acquisition of invasive aspergillosis. Yet, the prognosis of ICU patients without risk factors seems to alter more seriously by the development of this infection, whereas in ICU patients with risk factors, the observed outcome matches the expected mortality as based on APACHE II.

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ABSTRACT

Doel van de studie. Het doel van deze studie is de incidentie vast te stellen van invasieve aspergillose bij patiënten op intensieve zorg, en na te gaan of de aan- of afwezigheid van risicofactoren voor aspergillusinfecties geassociëerd is met mortaliteit.
Opzet. Retrospectieve cohort studie (07/1997 – 12/1999) in de Afdeling Intensieve Zorg van het Universitair Ziekenhuis Gent.
Patiënten en methodiek. Tijdens de studieperiode werden op 8988 opnames 38 patiënten herkend met invasieve aspergillose,. Invasieve aspergillose werd als bewezen geacht bij positieve histologie en kweek van normaal steriel weefsel of lichaamsvocht, bekomen door een invasieve aseptische techniek. Waarschijnlijk geachte invasieve aspergillose werd vastgesteld aan de hand van een combinatie van klinische data, microbiologische en radiologische gegevens. Zeventien patiënten hadden gekende risicofactoren voor de acquisitie van aspergillusinfectie. In de overige 21 patiënten was invasieve aspergillose een verwikkeling van ARDS, COPD, leverfalen, pneumonie, sepsis, ondervoeding en ernstige brandwonden.
Metingen. Populatiekenmerken en overleving werden vergeleken voor de patiënten met en zonder risicofactoren voor de acquisitie van aspergillusinfectie.
Resultaat. Patiënten met risicofactoren hadden hogere APACHE II scores. Er werd geen significant verschil gevonden in hospitaal mortaliteit tussen patiënten met en zonder risicofactoren (82% vs. 71%). De geobserveerde mortaliteit bij patiënten met risicofactoren was niet verschillend van de mortaliteit zoals verwacht op basis van de APACHE II score ($P = 0.940$). Bij de patiënten zonder risicofactoren werd een significant verschil vastgesteld tussen de geobserveerde en verwachte mortaliteit ($P < 0.001$).
Besluit. In deze reeks was de incidentie van invasieve aspergillose 4/1000 opnames. Er werd geen verschil in mortaliteit vastgesteld tussen enerzijds patiënten met risicofactoren en anderzijds patiënten zonder risicofactoren voor aspergillusinfectie. Toch lijkt invasieve aspergillose bij patiënten zonder risicofactoren de prognose negatief te beïnvloeden.

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