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Invasive aspergillosis in critically ill patients: An autopsy study

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Summary

Autopsy studies show that IA is among the most commonly missed diagnoses in critically ill patients. And, because of lack of unequivocal diagnostic criteria, a timely diagnosis remains challenging. We investigate the epidemiology of and the clinical risk factors for IA in critically ill patients. We conducted a retrospective, observational study of all consecutive ICU patients with evidence of IA in the postmortem examination. During the period of the study (25 years), 893 postmortem examinations were performed in the ICU. Twenty-five patients (2.8%) were diagnosed with IA in autopsy. Only ten (40%) were classified as IA ante-mortem, based on the initiation of antifungal treatment. The most common comorbid conditions were corticosteroid treatment (n = 14, 56%), chronic obstructive pulmonary disease (COPD) (n = 11, 44%), immunosuppression (n = 6, 24%) and haematological malignancy (n = 5, 20%). Twenty-three patients (92%) had three or more risk factors for IA. Critically ill patients with pulmonary infiltrates, treated with high doses intravenous corticosteroids (even for a short period of time), particularly COPD patients who developed worsening respiratory insufficiency despite appropriate treatment were at the highest risk of IA.

KEYWORDS
healthcare quality assurance, intensive care unit, invasive aspergillosis, misdiagnosis, postmortem examination

1 | INTRODUCTION

Invasive aspergillosis (IA) is a serious opportunistic infection generally occurring in severely immunocompromised patients. However, recent data indicate that IA should be considered as an emerging and life-threatening infectious disease in intensive care unit (ICU) patients.[1-6] In this setting, clinical diagnosis of IA remains a challenge, as the revised definition of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG)[7] can not necessarily be extrapolated to critically ill patients without classic host factors.[8]

Previous autopsy findings suggest that invasive fungal infections are among the most commonly missed diagnoses in ICU patients.[9-12] The unspecific clinical and radiological signs, lack of reliable diagnostic test, and difficulties of diagnosing unexpected or new pathogens in patients with existing infections probably account for the observation that IA was missed on many occasions. Moreover, the clinical relevance of *Aspergillus* species isolates, particularly from tracheal and bronchial aspirates, in ICU patients is unknown, and presents a dilemma, as it may represent only colonisation rather than infection.[5,6,13,14]

In several cohorts, risk factors for IA in ICU patients were comorbid conditions, such as chronic obstructive pulmonary disease (COPD), diabetes, liver cirrhosis or severe sepsis, and previous corticosteroid administration.[14-16] ICU patients with aspergillosis were also found to have a high mortality rate.[2,14,15] In this context, initiation of early appropriate antifungal therapy may be justified and may improve the odds of survival. A proper identification of a clinical profile for patients at higher risk of IA may aid clinicians to manage critically ill patients.

The aim of this study was therefore to analyse data from autopsies of ICU patients with a pathologic diagnosis of IA in order to evaluate clinical features and to assess the presence of risk factors that could be helpful in identifying patients at higher risk of missed diagnosis.

2 | MATERIAL AND METHODS

2.1 | Study population

We conducted a retrospective, observational study of all consecutive autopsies performed on patients who died in the ICU of the Hospital Universitario de Getafe, Madrid, Spain, between January 1991 and December 2016. We included those ICU patients with evidence of invasive aspergillosis in the postmortem examination.

The present study was conducted in a 24 bed ICU including a surgical and medical ICU. We routinely approached the families and requested an autopsy for all patients who died, except those who became organ donors (because donated organs were not available for autopsy) and those whose autopsies were legally mandated (because these autopsies were performed in an off-site facility and we could not access their results). The institutional ethics committee approved the study.

2.2 | Data collection

For each patient with histopathological findings consistent with IA in autopsy, data included demographics, comorbidities and underlying diseases, and acute illness severity scores (Simplified Acute Physiology Score, SAPS II score on admission and the Sequential Organ Failure Assessment, SOFA on the day of clinical worsening) were retrospectively recorded. Data were also collected on antifungal therapy as well as length of hospital stay prior to admission to ICU, length of ICU stay, days of mechanical ventilation, need for vasopressor or inotropic treatment, and need for renal replacement therapy.

We also analysed the presence of major risk factors for acquiring IA involved in immunosuppression as recent history of neutropenia (<500 neutrophils/mm^3), receipt of a transplantation (solid organ, and bone marrow), malignant haematologic process (leukaemia, myelodysplastic syndrome and lymphoma) or other active neoplastic process, chemotherapy, treatment with other immunosuppressants, use of corticosteroids (systemic, chronic inhalational, stress doses of hydrocortisone for sepsis) and severe inherited immunodeficiency; and in underlying disease as chronic liver disease, chronic obstructive pulmonary disease (COPD/asthma), insulin-dependent diabetes, chronic renal insufficiency and chronic heart failure; and coexisting conditions as alcoholism and malnutrition.

In addition, we evaluated the following features: fever refractory to at least 3 days of appropriate antibiotics or fever relapsing after a period of defervescence of at least 48 hours while still receiving antibiotics; one of the following clinical signs and/or symptoms of lower respiratory tract infection (dyspnoea, or hemoptysis), or worsening previous symptoms of respiratory failure. We also collected any lung abnormalities (diffuse reticular or alveolar opacities, consolidation, pleural fluid, wedge-shaped infiltrate, well-shaped nodule, air-crescent sign, halo sign or cavitation) detected on chest X-ray or (computed tomography) CT scan.

2.3 | Pathological features

We used a predefined protocol, described previously,[17] for the pathologic examination. Postmortem study was performed within 12 h of death. We took samples for microscopic analysis from each pulmonary lobe and additional samples from other areas with macroscopic injuries. Tissue sections for histologic examinations were stained routinely with haematoxylin and eosin (H&E) and, when indicated, with Gomori methenamine silver. The diagnosis of invasive *Aspergillus* infection was made when slender septate hyphae with a pertinent background of inflammation, necrosis or granuloma and demonstrating acute 45° dichotomous branching were observed histologically.

Misdiagnoses cases of IA were classified as class I errors according to Goldman criteria,[18] as they did not receive antifungal therapy which might have changed the course of the disease.

2.4 | Microbiological features

Surveillance samples (pharyngeal and rectal exudates) were routinely obtained once a week in all ICU patients with mechanical ventilation for at least 72 h as part of a selective digestive decontamination protocol. Clinical respiratory samples, galactomannan (GM) serum and/or bronchoalveolar lavage fluid (BAL) or cultures of tissue specimens were obtained at the discretion of the attending physician. The circulating GM test for *Aspergillus* antigen was not routinely available in our institution during the whole study period (just since 2008). Mycologic test results were interpreted as positive if they met international consensus criteria. An optical density index (ODI) of 0.5 or greater for GM in serum and BAL was considered positive.[7,8,19]

Antifungal therapy was initiated on an individual basis by the clinician in charge and was not protocol defined. Since the availability of various antifungals has changed over the 25-year course of the study, their use may reflect what was available at the time of each case.

2.5 | Statistical analysis

Qualitative variables are expressed as the percentage distribution in each category, and quantitative variables are expressed as mean ± standard deviation (SD) or median ± interquartile range (IR). Differences between groups were assessed using the χ^2 test, Fisher's exact test, Student's *t*-test or the Mann-Whitney U-test as appropriate. A comparison of baseline characteristics and risk factors of patients with IA in autopsy between groups of patients correctly diagnosed and patients misdiagnosed was conducted.

TABLE 1 Baseline characteristics of patients with invasive aspergillosis in autopsy

Baseline characteristics of patients with IA in autopsy	Diagnosed (n = 10)	Misdiagnosed (n = 15)	*P*
Age, mean (SD)	63 (14)	68 (11)	0.329
Sex, female, n (%)	5 (50)	5 (33)	0.426
SAPS II, mean (SD)	63 (22)	57 (18)	0.423
Severity of acute illness at time of clinical worsening prior to death			
SOFA score, mean (SD)	10 (4)	11 (4)	0.437
Vasopressive or inotropic agents, n (%)	8 (80)	11 (73)	0.936
Mechanical ventilation, n (%)	10 (100)	13 (87)	0.410
Renal replacement therapy, n (%)	3 (30)	3 (20)	0.650
Length of ICU stay before death, median (IR)	10.5 (4.25-24.75)	6 (3-19)	0.397
Duration of mechanical ventilation before death, median (IR)	8 (2-21)	5 (1-19)	0.338
Length of hospital stay before death, median (IR)	17 (1-28.25)	12 (2-22)	0.892
Last admission unit, n (%)			
Emergency room	2 (20)	1 (7)	0.335
Medical wards	7 (70)	9 (60)	0.627
Surgical wards	1 (10)	5 (33)	0.196
Main reason for ICU admission, n (%)			
Acute respiratory failure	7 (70)	9 (60)	0.627
Sepsis	2 (20)	3 (20)	1.000
Coma	1 (10)	1 (7)	0.775
Cardiovascular failure	0	1 (7)	0.426
Gastrointestinal disorder	0	1 (7)	0.426

Multivariable logistic regression analysis was performed in a stepwise manner to search for risk factors associated with an accurate diagnose of IA in critically ill patients. Variables with a level of significance <0.2 in the univariate analysis were included in the model. Results are expressed as odds ratio (OR), 95% confidence interval (CI). $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 22.0; SPSS Inc.).

3 | RESULTS

3.1 | Characteristics of the study cohort

During the observation period (25 years), 893 postmortem examinations were performed in deceased patients in the ICU. Twenty-five patients (2.8%) were diagnosed with IA in autopsy. Only ten (40%) were classified as IA ante-mortem, based on the initiation of antifungal treatment. Five patients were treated with Amphotericin B, whereas five were treated with other antifungal agents (four with Voriconazole and one with Caspofungin).

Baseline characteristics of patients with IA in autopsy are shown in Table 1. Most patients were medical admissions (n = 16, 64%). The most common reason for ICU admission was acute respiratory failure (n = 16, 64%) and sepsis (n = 5, 20%). Patients were admitted to the ICU with a high score on the SAPS II scale (59.5 ± 19, mean ± SD). And, at the time of clinical worsening prior to death, most patients needed vasopressive agents (n = 19, 76%) and also presented with a high SOFA score (10 ± 4, mean ± SD). We did not observe any statistically significant difference in baseline characteristics between correctly diagnosed and misdiagnosed patients with IA.

At the time of death, most patients had signs of septic shock and/or severe hypoxaemia.

3.2 | Risk factors for IA

Risk factors of patients with IA in autopsy are shown in Table 2. The most common comorbid conditions were corticosteroid treatment (n = 14, 56%), chronic obstructive pulmonary disease (COPD) (n = 11, 44%), immunosuppression (n = 6, 24%) and haematological malignancy (n = 5, 20%). Fourteen patients (56%) were receiving systemic corticosteroids prior to ICU admission, with an accumulated steroid use of >700 mg methylprednisolone or its equivalent in seven patients (28%), and only two (8%) were on prolonged (>30 days) corticosteroid therapy. Twenty-three patients (92%) had three or more risk factors for IA. The most frequent combinations of risk factors for IA in our series were COPD receiving intravenous corticosteroids and haematological malignancy with neutropenia. Other combinations mainly include chronic organic pathology (chronic heart and renal failure). IA occurred

TABLE 2 Risk factors of patients with invasive aspergillosis in autopsy

Risk factors for invasive aspergillosis, n (%)	Diagnosed (n = 10)	Misdiagnosed (n = 15)	*P*
Corticosteroids			
Systemic	4 (40)	10 (67)	0.204
In combination with other immunosuppressants	1 (10)	2 (13)	0.228
Chronic inhalational corticosteroids	4 (40)	3 (20)	0.295
Stress doses of hydrocortisone for sepsis	0	2 (13)	0.137
Chronic obstructive pulmonary disease	3 (30)	8 (53)	0.877
Immunosuppresive therapy	3 (30)	3 (20)	0.137
Haematological malignancy	4 (40)	1 (7)	0.137
Neutropenia			
<500 neutrophils/mm^3	3 (30)	2 (13)	0.129
<500 neutrophils/mm^3 for 10 days	3 (30)	0	0.023
Chronic heart failure	0	4 (27)	0.524
Solid tumours	2 (20)	1 (7)	0.672
Chronic renal failure	1 (10)	2 (13)	0.228
Insulin-dependent diabetes	0	2 (13)	0.246
Alcoholism	0	2 (13)	0.246
Malnutrition	0	2 (13)	0.246
Chronic liver failure	0	1 (7)	0.426
No of risk factors, n (%)			
0	0	2 (13)	0.426
1	1 (10)	1 (7)	0.811
2	3 (30)	5 (33)	0.811
3	5 (50)	3 (20)	0.868
4	1 (10)	3 (20)	0.524
6	0	1 (7)	0.426

in seven patients (28%) with COPD treated with systemic steroids immediately before ICU admission (n = 7/7, 100%) and during their ICU stay (n = 4/7, 57%), and the other seven patients received intravenous steroids for different pathologies (neoplasm, acute interstitial pneumonia, Stevens-Johnson syndrome). The proportion of COPD patients receiving inhaled corticosteroid treatment was 86% (n = 6/7). Duration and dose of systemic corticosteroids are shown in Table 3. Neutropenia was present in five patients (20%), and it was prolonged (>10 days) in three patients. We did not observe any statistically significant difference in risk factors between correctly diagnosed and misdiagnosed patients with IA. We did not identify any risk factor significantly associated with an accurate diagnosis of IA either.

3.3 | Clinical signs, medical imaging and microbiological data

Clinical, radiologic and microbiological findings are reported in Table 4. Nineteen patients (76%) had two or more compatible signs and symptoms, and worsening respiratory insufficiency was the most common clinical sign (n = 20, 80%)

Abnormal thoracic medical imaging was present in nearly all patients (19 of 20, 95%), but there were radiologic findings typical of IA on chest X-ray in only two patients (two of 20, 10%) (radiological images were available in 20 patients).

The most commonly affected site was the lung (n = 23, 92%). Nine patients (36%) had semi-quantitative bronchial aspirate (BAS) or BAL fluid cultures positive for *Aspergillus*. *Aspergillus fumigatus* was the most commonly isolated species (n = 6, 24%). GM was measured in only six patients, with a positive result in 75% of GM in serum and 100% of GM in BAL fluid.

The detection rate for other pathogens (eg *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Stenotrophomonas maltophilia* and *Candida lusitaniae*) was 36%, and sixteen patients (64%) were treated with broad-spectrum antibiotics.

4 | DISCUSSION

In our study, IA was diagnosed in 2.8% of autopsies. And, it was still a clinical entity frequently misdiagnosed as evidenced by the

TABLE 3 Systemic corticosteroids as risk factor for invasive aspergillosis

Systemic corticosteroids treatment	
Prior to ICU admission, n (%)	14 (56)
Duration, days, median (IR)	12 (2-36.75)
Accumulated dose, (mg of methylprednisolone, or equivalent), median (IR)	540 (15-1360)
COPD, n (%)	7 (28)
Duration, days, median (IR)	30 (20-365)
Accumulated dose, (mg of methylprednisolone, or equivalent), median (IR)	900 (16-1840)
During ICU stay, n (%)	12 (48)
Duration, days median (IR)	5 (2-20.75)
Accumulated dose, (mg of methylprednisolone, or equivalent), median (IR)	780 (170-1590)

fact that only 40% of our patients with IA in autopsy received antifungal treatment. High cumulative doses of corticosteroids prior and/or during ICU stay were the major risk factor associated with IA, even for a short period of time. IA mostly occurred in critically ill patients admitted to the ICU because of acute exacerbation of COPD (44%), all of them received systemic corticosteroid treatment and 86% were also under chronic inhalational corticosteroids. However, up to 92% of patients had a combination of three or more risk factors.

TABLE 4 Diagnostic features of patients with invasive aspergillosis in autopsy

Diagnostic features	
Clinical signs, n (%)	
Worsening respiratory insufficiency	20 (80)
Fever refractory to at least 3 days of antibiotic therapy	9 (36)
Recrudescent fever after ≥ 48 h of defervescence	6 (24)
Dyspnoea	4 (16)
Hemoptysis	4 (16)
No clinical signs, n (%)	
1	5 (20)
2	16 (64)
3	3 (12)
Abnormal thoracic imaging on X-ray or CT scan, n (%) (available in 20 patients)	
Diffuse reticular or alveolar opacities	19 (95)
Consolidation	0
Pleural fluid	0
Wedge-shaped infiltrate	1 (5)
Well-shaped nodule	0
Air-crescent sign	0
Halo sign	0
Cavitation	2 (10)
Microbiological data, n (%)	
Surveillance samples *Aspergillus*-positive	2 (8)
Semi-quantitative *Aspergillus*-positive culture of BAS or BAL fluid (available in 20 patients)	9/20 (45)
Aspergillus fumigatus	6 (67)
Aspergillus niger	1 (11)
Other specie	2 (22)
Galactomannan in serum positive (available in 4 patients)	3/4 (75)
Galactomannan in BAL fluid positive (available in 2 patients)	2/2 (100)

Different incidence rates have been reported (ranges from 0.3% to as much as 5.8%) and may vary according to the risk profile of subsets of ICU patients. Furthermore, a significant attributable mortality has been reported,[2-5,15,20] and prognosis may be related to overall severity of underlying disease and acute illness. In our cohort, scores on the clinical severity scales were high both at admission to ICU (mean SAPS II, 59.5) and at the time of clinical worsening (mean SOFA, 10). However, high mortality in ICU patients with IA is, at least partially related to difficulties in timely diagnosis.[21] In the present study, because of the lack of reliable diagnostic tools or of an insufficiently high clinical suspicion index, up to 40% of patients with IA diagnosed at autopsy had not received antifungal treatment. This fact has been previously reported at a percentage even higher of up to 60%.[22]

Of concern, several studies have determined the clinical significance of isolating *Aspergillus* from respiratory samples of critically ill patients, and the differentiation between invasive disease or colonisation remains difficult.[4-6,13,19] In our cohort, *Aspergillus* species were detected in only 45% of processed respiratory samples. Moreover, the sensitivity of other diagnostic tests such as GM antigen detection on serum is also limited, and although the detection of antigen GM in BAL fluid has an increased sensitivity in critically ill, it implies performing bronchoscopy, an invasive procedure not always feasible in critically ill patients due to severe hypoxaemia.[4,19,23]

Concerning radiological abnormalities suggestive for invasive pulmonary aspergillosis are less apparent in critically ill ventilated patients and, of the typical imaging findings observed in neutropenic patients, the air-crescent sign was seen in only a small proportion of cases, while the halo sign was very rarely observed.[2,3,13,19,23] In our series, most patients had non-specific radiologic findings. The most frequent radiographic findings were bilateral pulmonary infiltrates and pleural fluid effusions. Cavitation was only found in two patients and a wedge-shaped infiltrate in one patient. Our findings agreed

with prior studies in critically ill patients. In a recent study,[23] typical radiological lesions suggestive for invasive fungal disease were absent in up to 69.6% of proven invasive pulmonary aspergillosis cases in ICU patients. In other previous ICU cohort,[2] only 12 of 67 patients with proven IA had a halo sign or cavitation visualised on chest CT scans.

The majority of critically ill patients with IA did not have the classic risk factors (neutropenia, bone marrow transplant, haematological cancer). In previous studies, underlying conditions such as COPD, non-haematological malignancy, diabetes, liver cirrhosis, chronic alcohol abuse, human immunodeficiency virus (HIV) infection, malnutrition and severe burn injury have been described in association with IA in patients requiring ICU admission.[6,9,20] Interestingly, influenza infection has been also reported as an independent risk factor for invasive pulmonary aspergillosis in ICU patients.[23,24] In our series, influenza infection was investigated in only one patient in 2008, with a negative antigen in BAL fluid. This result could be explained by a low overall awareness of influenza-associated aspergillosis, and the lack of availability of PCR test for influenza until recent years. Furthermore, invasive disease can occur even in the absence of any risk factor,[25] and autopsy series indicated that strict interpretation of the host factors for invasive fungal disease contributes to the risk of missed diagnosis.[2,26,27] In the present study, two of 25 proven IA cases (8%) lacked host factors and only 11 (44%) had classic risk factors. This stresses the clinical relevance of an extended interpretation of risk profile.

Among our patient population, 56% of the study cohort received acute high dose corticosteroid therapy prior and/or during the inpatient stay, and COPD was the most frequent underlying condition (44%). Of the COPD patients, 100% were under intravenous corticosteroid and 86% also received inhaled corticosteroid. In previous reports, treatment with immunosuppressive agents was also the major host factor associated with IA in the ICU population, and COPD was the most frequent underlying condition, mostly in association with corticosteroid administration.[2,3,5,13,15,16,25] Immune function is impaired in critically ill patients, with depressed macrophage function and altered cellular immune response, due to immunoregulatory disturbances and immunoparalysis during the late phase of multiorgan dysfunction, disturbing adequate host response to fungal disease.[28] Furthermore, corticosteroids alter distribution and function of neutrophils and macrophages against *Aspergillus* hyphae and directly accelerate the in vitro growth of *Aspergillus* spp.[29]] In our study, patients with IA in autopsy received a median accumulated dose of systemic corticosteroids of 540 mg methylprednisolone (or equivalent) for a median of 12 days prior to ICU admission (0.8 mg/kg/día of prednisolone, approximately). Studies have reported different data on the timing and dose of corticosteroids,[19,30] and some reports suggested that high doses of inhaled corticosteroids might also be a risk factor for IA.[31,32]

This is the largest study to date in which IA was diagnosed on autopsy in a cohort of critically ill patients. But our study has some limitations. First, this is a descriptive study and therefore it is not possible to establish a certain causal relationship between risk factors and the development of the disease. Second, while the vast majority of tissue specimens with evidence of fungal hyphae infection on histologic examination are due to Aspergillus spp, there are other filamentous fungal infections that may be morphologically indistinguishable from the appearance of aspergillosis. Lee et al. found 17% discrepancy rates between histology and culture in filamentous fungal infections. The cultures which differed from histologic data involved *Scedosporium*, *Fusarium*, *Pseudallescheria*, *Phialophora* and *Trichophyton* species.[33] In the present study, fungal culture and serological studies for microbiologic identification of the aetiologic agent were not available in several cases. So, although certainly there was evidence of invasive fungal infection, we cannot assure it was due to *Aspergillus* spp. So, a large multicentre study needs to be performed to further determine risk factors for IA in critically ill patients.

5 | CONCLUSIONS

Although IA was a rare condition among critically ill patients, it was still frequently misdiagnosed in autopsy studies. The lack of a reliable method may delay the obtainment of an early diagnosis and a timely therapeutic intervention. So it should be maintained a high index of suspicion for IA in critically ill patients with pulmonary infiltrates, treated with high doses of intravenous corticosteroids (even for a short period of time), particularly in COPD patients who developed worsening respiratory insufficiency in spite of appropriate therapy. But also it should keep in mind other risk factors (not only the classic ones), since up to 92% of patients with IA in autopsy had a combination of three or more of them that mainly include chronic organic pathology.

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CONFLICT OF INTEREST

All authors declare that they have no relevant conflict of interests.

AUTHOR CONTRIBUTIONS

All persons who meet authorship criteria are listed as authors, and all authors (E.E.T.; E.A., R.P.; C.RR.; A.B.; F.FV.; JA.L.; A.E.) certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing or revision of the manuscript.

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