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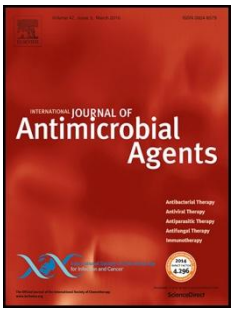

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Drivers and Impact of Antifungal Therapy in Critically Ill Patients with *Aspergillus*-Positive Respiratory Tract Cultures

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- **Abbreviations**

-AFT: Antifungal Therapy

-APACHE: Acute Physiology and Chronic Health Evaluation

-ARDS: Acute Respiratory Distress Syndrome

-BAL: Bronchoalveolar Lavage

-CT: Computed Tomography

-EORTC/MSG: European Organisation for the Research and Treatment of Cancer/Mycosis Study Group

-FOB: Fiberoptic Bronchoscopy

-GM: Galactomannan

-ICU: Intensive Care Unit

-IPA: Invasive Pulmonary Aspergillosis

-SMR: Standardised Mortality Ratio

-SOFA: Sequential Organ Failure Assessment

Highlights:

- Diagnostic and treatment decisions appear to be based both on recognition of risk factors for IFI and disease severity.
- Mortality of suspected pulmonary aspergillosis in critically ill patients is appallingly high.
- Initiation of AFT does not seem to significantly alter the prognosis. Better diagnostic tools and strategies are needed.

Abstract

***Background*:** Invasive pulmonary aspergillosis (IPA) is an increasingly recognized problem in critically ill patients. Little is known about how intensivists react to a *Aspergillus*-positive respiratory sample and about the efficacy of antifungals. Our goal was to identify drivers of antifungal therapy (AFT) prescription and diagnostic workup in patients with *Aspergillus* isolation in respiratory specimens as well as the impact of AFT in these patients.

***Methods*:** ICU patients with a *Aspergillus*-positive respiratory sample from the database of a previous observational multicenter study were analysed. Cases were classified as proven/putative IPA or *Aspergillus* colonization. Demographics, microbiological, diagnostic and therapeutic data were collected. Outcome was recorded 12 weeks after *Aspergillus* isolation.

***Results*:** Patients with putative/proven IPA were more likely to receive AFT than colonized patients (78.7% vs. 25.5%; p<0.001).

Patients with host factors for invasive fungal disease or multiorgan failure (SOFA score >7) were more likely to receive AFT (72.5% vs. 37.4%; p<0.001) (68.4% vs. 29.8%; p<0.001).

Once adjusted for disease severity, initiation of AFT did not alter the odds of survival (**HR** 1.40 95% CI [0.89-2.21]). Likewise, treatment within 48 hours following diagnosis did not change the clinical outcome (75.7% vs. 61.4%; p=0.63).

***Conclusions*:** Treatment decisions appear to be based on diagnostic criteria and underlying disease severity at the time of *Aspergillus* isolation. IPA in this population has a dire prognosis and

AFT is not associated with reduced mortality. This may be explained by delayed diagnosis and an often inevitable death due to advanced multiorgan failure.

Keywords: invasive pulmonary aspergillosis; delayed diagnosis; therapy; critical illness

Introduction

Aspergillus spp. is a saprophytic filamentous and potentially pathogenic fungus that is widespread in the environment (1). The main pathogenic mechanism is inhalation of *Aspergillus* spores or conidia. As such, the respiratory tract is affected in the vast majority of cases of invasive aspergillosis. *Aspergillus* is mainly considered a pathogen affecting immunocompromised hosts and the European Organization for the Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) developed well-defined diagnostic criteria for such patients (2). In recent years, however, *Aspergillus'* importance as a potential pathogen in critically ill patients has been repeatedly emphasized (3,4). Underlying conditions such as chronic obstructive pulmonary disease or cirrhosis, as well as high severity of acute illness, as evidenced by acute respiratory distress syndrome (ARDS), sepsis and multiorgan failure, add to the risk profile of invasive aspergillosis in ICU patients (5,6,7). In critically ill patients, the diagnosis of invasive pulmonary aspergillosis (IPA) is challenging as it often depends on histological samples, which may be risky to obtain in patients with severe physiological instability.

Aspergillus spp. isolation in respiratory samples occurs in up to 2% of ICU patients (4,5,8) and its interpretation is equivocal. If the culture represents IPA, antifungal therapy (AFT) should be initiated promptly as this disease is ultimately fatal in the absence of appropriate therapy. However, if the isolate represents *Aspergillus* colonization, initiating AFT could be deemed antimi-

crobial misuse with deleterious effects for patient and fungal ecology (9,10,11,12). As such, the finding of an *Aspergillus*-positive respiratory tract aspirate creates a dilemma: should AFT be started or not? An important element is the urgency with which decisions need to be taken. In a large multicentre cohort of patients with IPA, mortality at 1 week following the initial *Aspergillus*-positive culture was about 35% (13). This observation illustrates that there is neither room for a watchful waiting strategy nor for an extensive diagnostic workup. Moreover, it is likely that at least some uncertainty about the diagnosis will remain, as diagnosing IPA in unstable critically ill septic patients is particularly problematic (14). In non-critically ill immunocompromised patients, early initiation of appropriate antifungal therapy has lead to improved survival rates (15,16) and there is no reason whatsoever to assume that this would be different in ICU patients with IPA.

In order to support medical decision-making in case of an *Aspergillus*-positive respiratory tract isolate, Vandewoude et al (5) developed a simple algorithm to discriminate colonization from invasive disease. This algorithm was externally validated in a large multicentre study and led to the diagnostic category of "putative IPA" (13). There is, however, scant data about the way intensivists react to the isolation of *Aspergillus* spp. in a clinical sample and about the impact of AFT use.

The present study aims at describing the decision-making process of intensivists in the setting of *Aspergillus* spp. recovery from a respiratory tract sample and to ascertain the impact of AFT on short-term outcome of ICU patients with putative or proven IA.

Methods

This is a secondary analysis based on the *Asp*ICU database. The cohort consisted of patients admitted to one of the participating ICUs (27 from Europe, 2 from Asia and 1 from Brazil).

Patients were eligible for inclusion in the original study if they had at least one *Aspergillus*-positive culture on any body site, sampled during the ICU course. Due to the low frequency of this event, retrospective data from historical cohorts was also accepted provided that all the required information was available. Clinical suspicion of invasive aspergillosis prior to ICU admission was an exclusion criterion.

The local ethics committee/institutional review board of each participating center approved the study. Because of the observational nature of the study and the lack of any modification in the general management of these patients, the need for informed consent was waived. A complete and detailed description of the study methodology has been reported elsewhere (13). Basic demographic and admission data, acute and underlying conditions and the presence of signs suggestive of invasive fungal disease were noted. Data regarding diagnosis and treatment, including sampling techniques, mycological tests, and test results, as well as radiological tests performed were also recorded.

For the purpose of this analysis we exclusively considered patients who had *Aspergillus* recovered from the respiratory tract, whatever the number of respiratory specimens with *Aspergillus*, as they represented the vast majority of the cohort and allowed for a more homogenous study population. Patients were categorized as either proven or putative IPA or *Aspergillus* colonization, according to validated criteria (2,8,13). According to these criteria suggestive clinical signs and symptoms are fever despite more than 3 days of antibiotic therapy, new onset fever despite

antibiotic therapy, pleuritic chest pain, pleural rub, dyspnoea, haemoptysis, and worsening respiratory failure (8,13). Suggestive features on chest CT-scan include dense, well-circumscribed lesions with or without a halo-sign, air-crescent sign, or cavitation (2). We sought to analyse diagnostic-related procedures, namely comparing patients that were deemed to require treatment (IPA) and those that were considered to be simply colonised. When analysing the use of diagnostic tests and impact of AFT, we further excluded patients that did not receive treatment due to decisions of limitation of care or in whom the diagnostic suspicion of IPA occurred *post-mortem*. From a treatment perspective, we analysed the choice of first-line AFT and the outcomes associated with different agents. The need to switch to an alternate agent was also considered as was the use of combination therapy. Finally, the impact of AFT in the different diagnosis categories defined by the clinical algorithm (i.e. colonisation or putative/proven IPA) was assessed.

For continuous variables, median and interquartile ranges (IQRs) are presented. Group comparisons were carried out using chi-square and Mann-Whitney U tests, as appropriate. Cox proportional hazards regression model was used for survival analysis. Hazards ratio (HR) and 95% confidence intervals (95%CI) were calculated in univariate analysis and a multivariate stepwise model was designed to include baseline variables associated with mortality and other known risk factors. IBM SPSS Statistics (version 20) was used. P values <0.05 were considered statistically significant.

Results

Description of the cohort

The total cohort of the *Asp*ICU study consisted of 563 patients of whom 529 had evidence of respiratory infection or colonisation. Of these, 20 were not considered as they had another probable source of infection and another 5 were excluded as the diagnosis was made post-mortem and they had no previous *Aspergillus* isolation. Basic demographic characteristics of the remaining 504 patients are presented in Table 1. Overall mortality after 12 weeks was 54.8%.

Patient profile and antifungal therapy

Of the 504 patients analysed, 38 were excluded from further analysis due to limitation of care decisions.

Of the remaining 466 patients, 246 (52.7%) were put on AFT. Patients with criteria for putative or proven aspergillosis were more likely to be treated with AF than patients without those criteria (78.7% vs. 25.5%; p<0.001). Figure 1 shows rates of AFT according to patient's profiles, in terms of presence of clinical signs and symptoms, host risk factors, disease severity and additional diagnostic procedures performed.

The majority of patients had at least one sign or symptom present (75.3%). The most common findings in putative / proven cases were worsening respiratory failure or dyspnoea and persistent fever despite > 3 days of antibacterials. Of note, the presence of haemoptysis, despite uncommon, was much more frequent in putative or proven cases (1.8% vs 8.4%; p<0.001 when compared with colonised cases).

Almost 90% of patients were mechanically ventilated. The majority of patients had at least one sign or symptom present (75.3%). The rate of AFT given in patients with symptoms was signifi-

cantly higher compared with patients without suggestive signs and symptoms (p<0.001) (Figure 1). EORTC/MSG host factors were present in 204 patients (43.8%). The rate of AFT initiated in patients with host factors was higher compared with those without (72.5% vs. 37.4%; p<0.001) (Figure 1). Regarding severity of disease, Figure 1 presents AFT rates according to SOFA scores at the time of diagnosis. Patients receiving AFT had similar APACHE II scores when compared with untreated patients but a significantly higher SOFA score (10 vs. 5; p<0.001) at the time of *Aspergillus* isolation. This remains true irrespective of the diagnostic classification of patients (**Table 2**). Colonised patients put on AFT were more frequently on mechanical ventilation (93.9% vs. 75.0%), on renal replacement therapy (35.0% vs. 15.9%) and in shock (70.7% vs. 50.0%) (p<0.001, for all comparisons).

Additional diagnostic workup and antifungal therapy

With regard to diagnostic procedures, thoracic CT-scan, fiberoptic bronchoscopy (FOB), lung biopsy, galactomannan (in serum or BAL), serum β-D-glucan or polymerase chain reaction were performed in, respectively, 41.6%, 42.9%, 20.2%, 12.9%, 0.6% and 0.6% of the cases. All these tests were more frequently used in patients that were deemed to require AFT (**Table 3**). Patients undergoing any diagnostic test had a significantly higher SOFA at the time of diagnosis (9 vs. 5; p<0.001). However, information on timing of these procedures is not available, namely if they were performed before or after the initiation of treatment.

Lung biopsies were performed significantly more often in patients with an overt risk profile for invasive fungal disease as evidenced by the presence of EORTC/MSG host factors. Biopsies established the diagnosis of IPA (positive culture and evidence of tissue invasion) in 60 patients

(63.8% of the patients that underwent a biopsy). Rates of AFT in patients with proven IPA were 96.7%, compared to 52.9% in patients with negative histopathologic examination (p<0.001). BAL was carried out in 200 patients (42.9%). In 75.5% of these microscopy or culture were positive for *Aspergillus*. Specific findings on CT-scan (nodules with/without halo sign, air crescent, and cavity formation) seldom occurred (**Table 4**). In total, 66 patients (34.0% of the patients that performed CT-scan) demonstrated at least 1 clinical feature on chest CT-scan. The rate of AFT in these patients was higher compared with patients without suggestive CT-scan findings (p<0.001).

Antifungal therapy and survival

Two hundred and forty-six patients were put on AFT (**Table 5**), and outcome data exists regarding 241. Mortality of treated patients was 68.7% and that of patients deemed not to require AFT was 36.4% (standardised mortality rate (SMR) =0.84) (p<0,001), very similar to the mortality of patients deemed to be colonised according to the clinical algorithm by Vandewoude et al (38.6%; SMR=0.90). Out of 188 patients with putative or proven aspergillosis receiving AFT, 73 (38.8%) got voriconazole as first line treatment (alone or in combination with other antifungal agents) and 51 (27.1%) got a form of amphotericin B. An echinocandin was used in 28 (15%) cases. Survival rates were respectively 34.2%, 27.4% and 25% for these classes of AFT.

Factors associated with 12-week mortality were SOFA score, presence of shock and presence of **multiple organ dysfunction syndrome**. Mortality according to diagnostic classification and decision to start AFT is shown in figure 2.

In the overall sample, use of AFT was found to be an independent predictor of mortality (adjusted HR 1.760 [1.307-2.370]) but this association was lost when looking only at putative or proven cases (adjusted HR 1.400 [0.885-2.213]).

Considering patients with known survival status, no significant differences in mortality were noted in association with the different choices of initial AFT, after adjustment for disease severity and organ failure.

Of the 242 patients colonized, according to the Vandewoude clinical rule, data regarding the decision to start AFT and outcomes are available for 227 patients. Of these, 58 were given antifungal treatment. The mortality of this subgroup was 51.7% (SMR=1.29) and that of the group left untreated (n=169) was 32.5% (SMR=0.76 - p=0.018). Using multivariate analysis, to correct for disease severity, namely for SOFA, shock and mechanical ventilation, the mortality difference was no longer significant (HR 1.25 [0.77-2.02]).

The timing of initiation of therapy, counted from the day that diagnostic criteria were met, was available for 182 patients with putative or proven IA. Mortality tended to be higher in the 144 patients that started therapy in the first 48 hours after clinical diagnosis when compared with those beginning therapy at a later time (75.7% vs. 61.4%; p=0.063). SOFA scores were similar in both groups (10 vs. 9.5; p=0.439). Combination therapy was used as the initial choice in 8 patients (3.4%), but its use increased as further changes in therapy were deemed necessary. Four received amphotericin B plus itraconazole, 3 voriconazole plus echinocandin and 1 voriconazole plus amphotericin B. These 8 patients had a median admission APACHE II score of 23.4 and a

median SOFA score on the day of *Aspergillus* isolation of 9 [2-15]. Mortality in this group was 62.5%. Out of 21 patients who had combination therapy at any moment during their ICU stay, eight received an echinocandin combined with an azole or a polyene and 13 received azole/polyene combinations (mainly amphotericin B deoxycolate + itraconazole).

Discussion

This study gives us a clearer picture of how ICU physicians deal with patients in whom *Aspergillus* is isolated from respiratory tract samples. The decision-making process appears to depend mainly on the presence of aspergillosis diagnostic criteria and on severity of disease expression, namely organ dysfunction. Thus, patients with putative/proven IPA are more likely to receive AFT and, at the same time, patients put on AFT have significantly higher SOFA scores at the time of clinical diagnosis. Similarly, patients treated with AFs more often undergo diagnostic procedures. Using multivariate analysis to correct for disease severity, there is no significant mortality difference between patients treated and not treated with AF, both for the colonized and the putative/proven populations.

Taken together, these aspects may be interpreted as meaning that the decision to start AFT is often based not only on detailed microbiological, radiological and clinical examination, which are the main components of the Vandewoude criteria (8), but also on the perception of patient's disease severity. As for bacterial disease, in the setting of an acutely deteriorating patient with suspected IPA, therapy might be started empirically while awaiting further test results, while in a more stable patient one might postpone the decision until a more detailed diagnostic assessment is completed. One caveat, however, is that a true causal relationship between the ordering of diagnostic procedures and the start of AFT cannot be determined, as it is impossible to establish a detailed timeline of events.

In our population, both the occurrence of specific IPA findings and the proportion of patients undergoing FOB are rather low and GM measurement was used even less often than FOB. The use

of diagnostic tests in the setting of suspected IPA is well described for the neutropenic population, but sensitivity seems to be lower in non-neutropenic patients. The identification of a halo sign in non-neutropenic patients is rare (17), limiting its utility as a diagnostic tool. Other radiological features, like the presence of a "reverse halo", particularly with a thick outer rim, central reticulation and concomitant pleural effusion, (18,19), or the combination of pulmonary CT and arteriography (20) may also be helpful. As for GM, it is particularly useful when measured in BAL fluid, in the setting of neutropenia and suspected IPA (21), as a persistently positive optical density index may be a trigger for early "pre-emptive" therapy (22). Its use in non-neutropenic, critically ill patients is less well established. Meersseman (23) suggested that BAL GM assays might have adequate sensitivity and specificity for the diagnosis of IPA in the ICU, but one third of the patients in his series had haematological malignancies. More recently, Acosta *et al.* reported a 21-month prospective study on 51 medical ICU patients with lung infection and at least one risk factor for invasive fungal disease (24). When compared with serum GM measurements, BAL GM had a better diagnostic performance, with an area under the ROC curve of 0.98. Together, these data suggest that there is room for improving the use of diagnostic tests in ICU patients with suspected IPA.

Regarding the efficacy of AFT, our main finding is the apparent increase in mortality of the global population after adjusting for the concomitant presence of organ failure and regardless of the initial choice of AFT. In spite of this fact, this effect was not seen when the analysis was restricted to putative/proven cases. Analogously with IPA patients, *Aspergillus*-colonised patients receiving AFT also tended to have a higher mortality. Patients receiving AFT had more severe organ failure but this does not seem to account for all of the observed difference in outcome. We

suggest that factors such as delayed diagnosis, antifungal-related adverse events, missed diagnoses other than IPA and mortality associated with other underlying conditions may contribute to this observation. As such, one should strive to make as firm a diagnosis as feasible, even if empirical treatment has been initiated.

The absence of a clear advantage of AFT in patients with IPA stresses the limitations of current approaches to diagnose IPA in critically ill patients. The present cohort includes exclusively patients with an *Aspergillus*-positive respiratory tract sample. As such, the time-point at which mycological culture results are reported may be too late to guarantee a beneficial effect of AFT. An earlier diagnosis of IPA or the identification of high-risk patients potentially benefiting from a pre-emptive approach seems the challenge for further clinical research. However, on the other hand, it should be kept in mind that most antifungals in current clinical practice have potentially serious side-effects and drug-drug interactions and also that initiating treatment for an infection that is not present may induce a false sense of security contributing to a delay in the right diagnosis, as critically ill patients have been shown to be at increased risk for opportunistic infections other than IA (25).

The most commonly used AFs (either alone or in combination), as first line treatment, were voriconazole and amphotericin B. The fact that there is no significant difference in mortality associated with the choice of initial AFT is most probably related to the severity of the underlying disease and to the severe acute physiological derangements at the onset of infection, as shown by APACHE II and SOFA scores. In this setting, small differences of efficacy would be unlikely to independently influence the prognosis. The choice of voriconazole as the preferred first-line

agent for this patient population is not surprising in light of the available data suggesting the superiority of this drug over amphotericin B for the treatment of IPA (26). In addition, in a cohort of mechanically ventilated haematology patients with invasive aspergillosis (27), voriconazole treatment was independently associated with reduced mortality risk (hazard ratio 0.5, 95% CI, 0.3-0.9). Until the publication of the Herbrecht trial (19), amphotericin B was the cornerstone of treatment of invasive aspergillosis and it is still frequently used. Although there are concerns about the tolerability of the classical deoxycholate formulation, some evidence exists suggesting that adequate use of this drug can effectively prevent most of its side effects (28, 29). In this sample, of the 67 patients that were given a polyene as initial treatment, the majority got the classical formulation and only 21% (14/67) received any of the lipid formulations, suggesting that it is still considered an adequate option in many ICUs but also possibly reflecting limitations to the use or reimbursement of the lipid forms in certain countries. The fact that a significant proportion of patients received echinocandins as initial treatment may raise some questions as these agents are only approved for salvage therapy of IPA in patients with hematological malignancies (30, 31) and reports exist of breakthrough IPA in patients receiving echinocandins for empirical treatment of febrile neutropenia (32). Combination AFT has been suggested as a possible alternative for severe IFI and the advent of the candins promoted a renewed interest in this matter, as candins and voriconazole act at different structures of the fungal cell. Two Spanish scientific societies suggest combination AFT should be used in severely ill patients (33), despite stating that the evidence for this recommendation is weak. One recent large randomized study (34) reports a decreased mortality using a combination of voriconazole and anidulafungin over voriconazole monotherapy in subgroups of patients with proven or probable invasive aspergillosis.

Although, some studies have linked early treatment to better outcomes (15,16,35), in our population an earlier start of AFT appears to be associated with increased mortality, at an almost significant level, but this may be a mere reflection of a higher underlying disease severity of the patients treated earlier.

Our study has some limitations that should be noted. First, it is a secondary analysis of the AspICU multicenter study and, due to its prospective design, we cannot be sure that the study protocol itself did not influence management decisions.

Secondly, the algorithm used has flaws, as shown by the fact that a fair number of untreated putative/proven patients survived.

We cannot establish a detailed timeline of diagnostic procedures and treatment decisions thus limiting our conclusions.

Furthermore, loss of some patients due to incomplete data collection further reduced certain subgroup sample sizes. It should also be recognised that dosing in critically ill patients can be particularly problematic (36) and that the dataset used does not allow us to look into this, namely lacking information on doses used and achieved concentrations. Finally, due to the rapidly evolving nature of the field of invasive fungal infections, medical decision processes by intensivists may have already changed.

of untreated putative/proven patients survived. Furthermore, loss of …

Conclusions:

In this large cohort of patients, the dismal prognosis of *Aspergillus* isolation in respiratory samples from ICU patients, either reflecting colonization or infection, becomes evident. Therapeutic decisions seem to be driven by both the presence of diagnostic criteria and by underlying disease severity/organ failure at the time of *Aspergillus* isolation.

A large proportion of these patients received AFT with no apparent reduction of mortality, regardless of AF used or timing of initiation of therapy. This is probably caused by a combination of late diagnosis and an often inevitable death due to advanced multiorgan failure.

In accordance with recommendations, voriconazole is the first-line agent most commonly used. The lack of outcome difference with different choices and variable timing of initial treatment probably reflects the major difficulty of establishing a consistent diagnosis in this population. The high mortality of patients receiving seemingly unneeded treatment should be regarded as demonstrative of the need to carefully evaluate these patients, namely increasingly incorporating recent advances in the radiological and laboratorial diagnosis of IPA in our decision-making process.

412

413 **Declarations**

414 **Funding:** The original AspICU project was supported by an unrestricted educational grant from
415 Pfizer Belgium and a research grant from the Special Research Fund of Ghent University.

416 **Competing Interests:** Jordi Rello reports having received a research grant from Astellas and
417 having done consultancies for Astellas and Pfizer
418 Paulo Mergulhão reports having received speaker fees from Astellas and MSD
419 All other authors have no conflicts of interest to report

420 **Ethical Approval:** This is a secondary analysis of the AspICU dataset for which a waiver of in-
421 formed consent was obtained from each participating centre ethics committee due to its observa-
422 tional nature.

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425 **Availability of supporting data**

426 The datasets during and/or analysed during the current study available from the corresponding
427 author on reasonable request

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-**Figure 1 title:** Rates of antifungal therapy according to patient's profiles, in terms of presence of clinical signs and symptoms, host risk factors, disease severity and additional diagnostic procedures performed.

-**Figure 1 legend:** IPA, invasive pulmonary aspergillosis; EORTC, European Organisation for the Research and Treatment of Cancer-Mycosis Study Group; SOFA, sequential organ failure assessment score

Bronchoscopy positive on microscopy (mycelium, branching hyphae) and culture.

-**Figure 2 title:** Mortality according to diagnostic classification and decision to start antifungal therapy

-**Figure 2 legend:** AFT, antifungal therapy; IPA, invasive pulmonary aspergillosis

542 **Table 1 - Basic demographic characteristics of the population**

	Patients (n=504)
Male sex - n (%)	306 (60.7%)
Age, years – median (IQR)	65 [53-74]
BMI Kg/m2 – median (IQR)	24.1 (20.7-27.3)
Admission data	
Admission type medical - n (%)	354 (70.4%)
Admission type elective surgery - n (%)	69 (13.7%)
Admission type emergency surgery / trauma - n (%)	81 (16.1%)
APACHE II score – median (IQR)	23.0 (17.0-28.0)
Organ dysfunction at diagnosis	
Vasopressor or inotropic use - n (%)	380 (75.4%)
Mechanical ventilation - n (%)	453 (89.9%)
Renal replacement therapy - n (%)	157 (31.2%)
Median SOFA score at diagnosis (IQR)	7 [4-12]

543 *SOFA, Sequential Organ Failure Assessment*
544 *IQR, interquartile range*
545

546

Table 2: SOFA and APACHE II according to diagnosis and treatment decisions

	Aspergillus colonization			Invasive Pulmonary Aspergillosis		
	AFT	No AFT	P	AFT	No AFT	P
SOFA score	6 (4-12)	4 (2-8)	0.001	10 (6-12)	7 (4-10)	0.004
APACHE II score	23 (16-26)	22 (16-28)	0.583	25 (17-29)	22 (15-28)	0.456

AFT, antifungal therapy
SOFA, sequential organ failure assessment at the time of Aspergillus isolation
APACHE, acute physiology and chronic health evaluation

Table 3: Use of diagnostic tests according to treatment decision

	Total population (n=466)	**Received AFT** (n=246)	**No AFT** (n= 220)	p
CT scan	194 (41.6%)	144 (58.5%)	50 (23.7%)	< 0.001
FOB	200 (42.9%)	158 (64.2%)	42 (19.1%)	< 0.001
Biopsy	94 (20.2%)	76 (30.9%)	18 (8.2%)	< 0.001
GM	60 (12.9%)	58 (23.6%)	2 (0.9 %)	0.002
BDG	3 (0.6%)	3 (1.2%)	0	ns
PCR	3 (0.6%)	3 (1.2%)	0	ns

CT scan, computorized tomography scan
FOB, fiberoptic bronchoscopy
GM, galactomannam
BDG, beta-d-glucan
PCR, polymerase chain reaction

Table 4: Specific findings on chest CT scans

	Total	Colonization	Putative/Proven IPA
Nodule	56 (11.1%)	10 (4.1%)	46 (17.6%)
Air crescent sign	4 (0.8%)	0 (0.0%)	4 (1.5%)
Halo sign	13 (2.6%)	3 (1.2%)	10 (3.8%)
Cavity	17 (3.4%)	6 (2.5%)	11 (4.2%)

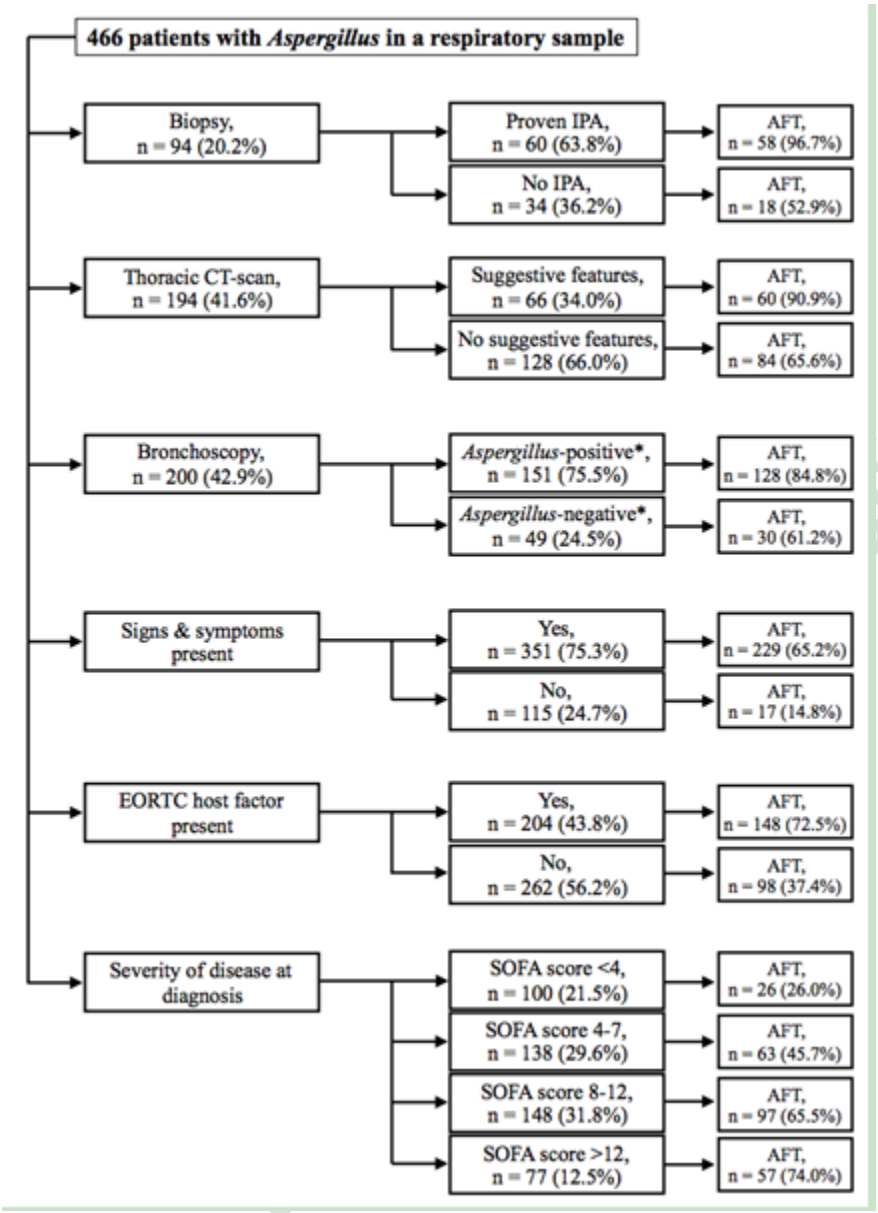
CT scans, computorized tomography scans
IPA, invasive pulmonary aspergillosis

Table 5: Summary of AFs used as first-line treatment#

Antifungal	Treated patients n (%)	Treated Colonized patients n (%)	Treated Putative/Proven patients n (%)
Amphotericin B deoxycholate	53 (22.0)	15 (28.3)	38 (20.2)
Amphotericin B lipid-associated	14 (5.8)	4 (7.5)	10 (5.3)
Echinocandin	34 (14.1)	6 (11.3)	28 (15.0)
Voriconazole	94 (39.0)	21 (39.7)	73 (38.8)
Other	46 (19.1)	7 (13.2)	39 (20.7)
Total	241 (100)	53 (100)	188 (100.0)

 # Data is available, regarding AF used, in 241 out of the 246 patients treated with AFT

574 Figure 1.



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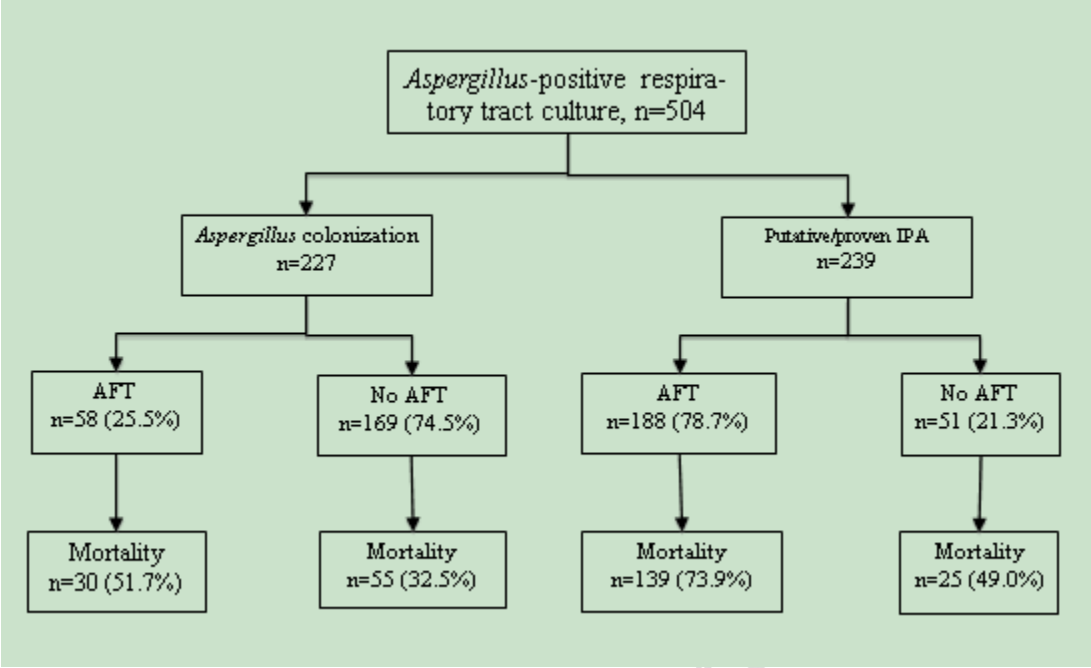
578 Figure 2.



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