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# Report of 38 cases of tracheobronchitis in non-immunocompromised patients with dual isolation of *Aspergillus* in lower respiratory tract samples

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## ABSTRACT

**Introduction.** *Aspergillus* tracheobronchitis is an uncommon manifestation of *Aspergillus* infection. This study retrospectively analysed patients presenting tracheobronchitis among non-neutropenic/non-transplant adult patients with at least two valuable cultures of respiratory samples yielding *Aspergillus* spp. in Spanish hospitals.

**Methods.** Clinical records were retrospectively reviewed. Simple tracheobronchitis was considered when the bronchoscopy report described mucosal inflammation and mucus secretions and invasive tracheobronchitis when ulceration and pseudomembrane formation was reported. Cases were considered "proven" (histopathological confirmation) or "probable" aspergillar tracheobronchitis.

**Results.** A total of 38 cases of tracheobronchitis (26 simple, 12 invasive) were identified, all considered probable aspergillar tracheobronchitis. Patients were elderly (89.5% patients were ≥65 years), males (76.3%), presented advanced COPD (GOLD III+IV in 81.3%) and heart insufficiency (55.3%), with higher APACHE II score in those with invasive tracheobronchitis (10.17±7.38 vs. 4.32±4.39, p=0.019). Up to 50% patients were taking steroids (accumulated doses >100 mg in 89.5% of them) and 34.2% antibiotics pre-admission. Antifungals were administered to 60.5% patients (57.7% with simple and 66.6% with invasive tracheobronchitis). Voriconazole was the most frequent antifungal (alone or in combination): 69.6% in the 23 treated patients (60.0% simple and 87.5% invasive tracheobronchitis). Mortality was 23.7% (15.4% in simple and 41.7% in invasive tracheobronchitis).

**Conclusions.** The results of the present studty suggest that aspergillar tacheobronchitis should be considered in the differential diagnosis of non-immunocompromised patients with deteriorating chronic airway limitation.

**Key words: Tracheobronchitis; aspergillosis; COPD; voriconazole; non-immunocompromised patients**

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## Análisis de 38 casos de traqueobronquitis en pacientes inmunocompetentes con doble aislamiento de *Aspergillus* en muestras de tracto respiratorio inferior

## RESUMEN

**Introducción.** La traqueobronquitis aspergilar es una manifestación poco frecuente de la infección por *Aspergillus*. Este estudio analiza de forma retrospectiva los pacientes que presentaron traqueobronquitis entre pacientes adultos no neutropénicos y sin trasplante con al menos dos cultivos de muestras respiratorias del tracto inferior mostrando crecimiento de *Aspergillus* spp. en hospitales españoles.

**Métodos.** Se revisó retrospectivamente las historias clínicas y se consideró traqueobronquitis simple cuando el informe de la broncoscopia describía inflamación de la mucosa y secreción mucosa y traqueobronquitis invasiva ante la presencia de ulceraciones y pseudomembranas. Los casos se consideraron "probados" (confirmación histopatológica) o "probable traqueobronquitis aspergilar".

**Resultados.** Se identificó un total de 38 casos de traqueobronquitis (26 simples, 12 invasivas), todos ellos considerados probable traqueobronquitis aspergilar. Los pacientes presentaban edad avanzada (89,5% de los pacientes con ≥65 años), eran varones en la mayoría de casos (76,3%), y presentaban enfermedad pulmonar obstructiva crónica avanzada (GOLD III+IV en el 81,3% de los casos) e insuficiencia cardiaca (55,3%), con una mayor puntuación en el APACHE II en aquellos pacientes con traqueobronquitis invasiva (10,17±7,38 vs. 4,32±4,39, p=0,019). Un 50% de los pacientes recibía esteroides (con dosis acumuladas >100 mg en el 89,5% de ellos) y un 34,2% antibióticos previos al ingreso. Se administró antifúngicos al 60,5% de los pacientes (al 57,7% de aquellos con traqueobronquitis simple y al 66,6% de los pacientes con traqueobronquitis invasiva). Voriconazol fue el antifúngico más utilizado (solo o en combinación): 69,6% de los 23 pacientes tratados (60,0% de los pacientes con traqueobronquitis simple que recibieron tratamiento y 87,5% de aquellos con traqueobronquitis invasiva que fueron tratados con antifúngicos). La mortalidad fue

del 23,7% (15,4% en traqueobronquitis simple y 41,7% en traqueobronquitis invasiva).

**Conclusiones.** Los resultados del presente estudio sugieren que la traqueobronquitis aspergilar debe considerarse en el diagnóstico diferencial en pacientes no inmunocomprometidos con deterioro crónico de la función respiratoria.

**Palabras clave: Traqueobronquitis; aspergillosis; EPOC; voriconazol; pacientes inmunocompetentes**

## INTRODUCTION

The risk of developing disease depends on the interplay between the organism virulence and the host ability to resist infection. *Aspergillus* tracheobronchitis is an uncommon manifestation of *Aspergillus* infection, which in this case is confined to larger airways[1]. As an explanation of this location it has been suggested, although not proven, that *Aspergillus* tracheobronchitis is more common in mildly to moderate immunocompromised patients[2]. In this sense it has also been reported in patients with chronic obstructive pulmonary disease (COPD) as a complication of treatment of exacerbations with broad-spectrum antibiotics and corticosteroids[3,4]. Patients may be initially asymptomatic or present complaints of unspecific symptoms as cough, fever, dyspnoea and chest pain[5]. These facts together with an unremarkable chest radiograph (unless there is associated with bronchopneumonia and atelectasis)[6] delay diagnosis[7]. Within the spectrum of the disease the mildest form is tracheobronchitis with mucosal inflammation and mucus secretions containing *Aspergillus*[8], whereas in later stages ulceration and pseudomembrane formation are usually widespread[7]. Antifungal treatment is problematic as no studies have addressed this subgroup of patients specifically.

The aim of this study was to describe the subgroup of 38 patients with tracheobronchitis among a series of patients with dual isolation of *Aspergillus* from lower respiratory tract samples recently reported in Spain[9].

## PATIENTS AND METHODS

A retrospective study analysing clinical records of adult patients presenting at least two valuable cultures of respiratory samples yielding *Aspergillus* spp. in 29 Spanish hospitals (the 10 most recent valuable patients in each centre) was performed[9]. Transplant recipients and patients presenting neutropenia (<1000 neutrophils/mm$^3$), diagnosis of aspergilloma or allergic bronchopulmonary aspergillosis were excluded. The study protocol was approved by the Ethics Committee of Hospital Central de la Defensa Gomez Ulla, Madrid, Spain.

Only patients with a bronchoscopy report of tracheobronchitis in clinical records were considered for the present study. Simple tracheobronchitis was considered when the bronchoscopy report described mucosal inflammation and mucus secretions and invasive tracheobronchitis when ulceration and pseudomembrane formation was observed. Cases were considered as "probable" aspergillar tracheobronchitis based on the presence of at least two cultures of lower respiratory tract samples yielding growth of *Aspergillus* except when there was histopathological confirmation ("proven" cases). Demographic data, underlying illnesses, clinical and radiological data, laboratory data, previous treatments (corticosteroids, antibiotics, antifungals...), antifungal treatment and outcome were recorded. The age-unadjusted Charlson comorbidity index[10] (age was considered in separate), the modified McCabe score (Sabadell score)[11], the functional classification according to the New York Heart Association (NYHA)[12] and the Acute Physiologic and Chronic Health Evaluation (APACHE) II score were calculated with recorded data, as well as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification for COPD patients[13].

Comparisons between proportions were performed by the $\chi^2$ test and the Fisher's exact test, when necessary. For quantitative variables, since data did not showed normality in the Kolmogorov – Smirnoff test, the Kruskal-Wallis and Mann-Whitney tests, when necessary, were used. A $p<0.05$ was considered statistically significant.

## RESULTS

Among the 245 patients with at least two valuable cultures of respiratory samples yielding *Aspergillus* spp. identified from October 2002 to July 2010 in 29 Spanish hospitals, 38 presented tracheobronchitis (26 simple tracheobronchitis and 12 invasive tracheobronchitis) in 16 centres. All cases were classified as probable aspergillar tracheobronchitis due to the absence of histopathological analysis. Of the 38 patients, 55.3% had been admitted in Pneumology (65.4% of those patients with simple tracheobronchitis and 33.3% of those patients with invasive tracheobronchitis, p=0.065), 18.4% in the ICU as initial ward (15.4% of those patients with simple tracheobronchitis and 25.0% of those with invasive tracheobronchitis, p=0.656), 13.2% in Internal Medicine and 13.2% in other medical wards. A total of 47.4% patients had been hospitalized within the previous three months.

Table 1 shows demographics and comorbidities of patients included in the study distributed by clinical diagnosis. Most patients were elderly (89.5% patients ≥65 years, 73.7% patients ≥70 years; 57.9% patients ≥75 years), males (76.3%), and presented advanced COPD (GOLD III+IV in 81.3%) and heart insufficiency (55.3%) with marked limitation or incapacity for physical activities (71.4% classes III + IV in the NYHA classification), without differences between simple and invasive tracheobronchitis. However the APACHE II score was significantly higher in invasive tracheobronchitis (10.17 ± 7.38 vs. 4.32 ± 4.39, p=0.019). Most patients (71.1%) presented exacerbation of COPD with dyspnoea (73.7%), increase in secretions (71.1%), increase in oxygen requirements (68.4%) and bronchospasm (42.1%), without differences between patients with simple tracheobronchitis and those with invasive tracheobronchitis.

Imaging data (table 2) showed concomitant infiltrates in

**Table 1** Demographical data and comorbidities of patients included in the study distributed by clinical entity; [n (%)] except where indicated

| | Total | Simple | Invasive |
|---|---|---|---|
| n | 38 | 26 | 12 |
| Age (mean ± SD) | 72.2 ± 10.6 | 71.5 ± 12.2 | 73.5 ± 5.8 |
| Males | 29 (76.3) | 20 (76.9) | 9 (75.0) |
| Comorbidities[a] | | | |
| COPD | 34 (89.5) | 23 (85.5) | 11 (91.7) |
| Gold III + IV[b] | 26 (81.3) | 18 (85.7) | 8 (72.7) |
| Heart failure | 21[c] (55.3) | 15 (57.7) | 6 (50.0) |
| Diabetes mellitus | 9 (23.7) | 7 (26.9) | 2 (16.7) |
| Malignancies | 7 (18.4) | 4 (15.4) | 3 (25.0) |
| Charlson (mean ± SD) | 2.84 ± 2.22 | 2.85 ± 2.05 | 2.83 ± 2.66 |
| APACHE (mean ± SD) | 6.16 ± 6.07 | 4.32 ± 4.39 | 10.17 ± 7.38[d] |
| NYHA (III+IV)[e] | 20 (71.4) | 11 (68.8) | 9 (75.0) |
| McCabe | | | |
| Fatal >6 months | 14 (36.8) | 10 (38.5) | 4 (33.3) |
| Fatal <6 months | 3 (7.9) | 2 (7.7) | 1 (8.3) |
| Rapidly fatal | 2 (5.3) | 0 (0.0) | 2 (16.7) |
| ICU admission at any time during hospital stay | 11 (28.9) | 7 (26.9) | 4 (33.3) |

[a]present in ≈>10% total patients;
[b]among the 32 patients with available data (21 simple and 11 invasive)
[c]includes 9 acute heart failure and 12 congestive heart failure
[d]p=0.019 vs. simple tracheobronchitis
[e]among the 28 patients with available data (16 simple and 12 invasive)

50.0% patients and pleural effusion in 15.8% patients in the radiographs performed, without cavitations, halo or air crescent signs in the CT Scan. In 18.4% patients a worsening of radiological findings was found, with significantly higher frequency in patients with invasive tracheobronchitis (45.1% vs. 7.7%, p=0.022).

Respiratory samples yielding growth of *Aspergillus* were sputum (86.8%), bronchial aspirates (10.5%) and bronchoalveolar lavage (2.6%) for the first culture, and sputum (84.2%) and bronchial aspirates (15.8%) for the second culture. *Aspergillus fumigatus* was the most frequent dual isolated species both in simple (69.2%) and invasive tracheobronchitis (75.0%).

Table 3 shows steroids and antibiotics before admission, antifungals administration after culture request and outcome by clinical entity. Up to 50% patients were taking steroids (with accumulated doses >100 mg in 89.5% of them) and 34.2% antibiotics prior to hospital admission. During hospitalization 89.5% patients received corticosteroids, with accumulated doses >100 mg in 97.1% of them and >700 mg in 50.0% of them, without statistical differences between both entities. After admission, antibiotics were administered to 89.5% patients, being quinolones (55.3%), β-lactams (36.8%) and carbapenems (31.6%) the most common antibiotics used, without differences between simple and invasive tracheobronchitis except in carbapenems that were more frequently administered in patients with invasive tracheobronchitis (58.3% vs. 19.2%, p=0.026). Antifungals were administered to 60.5% patients after culture request: 57.7% of those with simple tracheobronchitis and 66.6% of those with invasive tracheobronchitis. Voriconazole was the antifungal most frequently administered alone or in combination, with rates of 69.6% in the 23 treated patients (60.0% of simple and 87.5% of invasive tracheobronchitis).

Mortality was 23.7% in the complete series, with higher (but non-significant) mortality rates among patients presenting invasive tracheobronchitis (41.7% vs. 15.4% for simple tracheobronchitis, p=0.073).

## DISCUSSION

Aspergillar tracheobronchitis has been rarely seen in immunocompetent patients[3,14], with very few cases as isolated disease[14]. In this study we describe 38 cases of probable aspergillar tracheobronchitis (12 of them invasive). Although the term "probable" denotes a relatively high degree of certainty of infection due to *Aspergillus* (recovered in at least two lower respiratory samples), the characteristics of the patients suggest that the tracheobronchitis was a superimposed infection. Local damage of the airway wall and non fungal infections may be predisposing factors for *Aspergillus* infection; the fungal infection of the tracheobronchial tree negatively contributing to the respiratory impairment of the patient. In our series the most frequent comorbidity was advanced COPD (GOLD III+IV) and, at admission, most patients (71.1%) presented exacerbation of COPD, with dyspnoea (73.7%) and infiltrates in the radiography in 50% patients. Clinical signs and radiological findings are often clouded by concurrent viral or bacterial infection in COPD patients. Moreover, it is difficult to differentiate *Aspergillus* tracheobronchitis in COPD patients and acute exacerbations caused by COPD itself. A high index of suspicion is needed for early performance of bronchoscopy since clinical and radiographic findings rarely point to aspergillar tracheobronchitis[15]. In fact, even in the presence of at least two respiratory cultures yielding *Aspergillus*, all cases in this series could only be classified as probable since histopathological analyses had not been requested.

It has been reported that therapy with high-dose corticosteroids with or without broad-spectrum antibiotics for as little as one to two weeks can result in aspergillosis in patients with COPD[4]. In our series, 34.2% patients received antibiotic treatment before admission and, more importantly, 50% patients were treated with corticosteroids with high accumulated doses (89.5% of them) before admission. Although there were no differences in the percentage of patients with advanced COPD, infiltrates in X-ray or heart disease (the second most frequent comorbidity present in up to 55.3% patients, with advanced classes in the NYHA classification) between

**Table 2** **Imaging data corresponding to patients included in the study distributed by clinical entity; [n (%)]**

| | Total | Simple | Invasive |
|---|---|---|---|
| **No. patients with X-ray** | 38 | 26 | 12 |
| Infiltrates | 19 (50.0) | 12 (46.2) | 7 (58.3) |
| Nodules | 3 (7.9) | 3 (11.5) | 0 (0.0) |
| Cavitations | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pleural effusion | 6 (15.8) | 4 (15.4) | 2 (16.7) |
| Worsening radiological findings | 7 (18.4) | 2 (7.7) | 5 (41.5)[a] |
| **No. patients with CT Scan** | 14 (36.8) | 11 (42.3) | 3 (25.2) |
| Infiltrates | 3 (21.4) | 2 (18.2) | 1 (33.3) |
| Nodules | 5 (35.7) | 4 (36.4) | 1 (33.3) |
| Cavitations | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Halo sign | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Air crescent sign | 0 (0.0) | 0 (0.0) | 0 (0.0) |

[a]**p=0.022 vs. simple tracheobronchitis**

simple and invasive tracheobronchitis, patients with invasive tracheobronchitis presented a significantly higher APACHE II score and were more frequently treated with carbapenems (despite antibiotics and antifungals were equally administered in both groups).

A previous study concluded that invasive pulmonary aspergillosis should be excluded in hospitalized patients with COPD that develop severe pneumonia, and antifungal therapy considered[4]. Another study indicated that *Aspergillus* tracheobronchitis should be considered in any COPD patient with worsening dyspnea and/or cough who fails to improve with empiric antimicrobial therapy since early diagnosis is essential[15]. In our study, although mortality was 15.4% among patients with simple tracheobronchitis, invasive tracheobronchitis presented higher mortality rates (41.7%).

There is a lack of studies in the literature specifically addressing antifungal treatment in tracheobronchitis in non-neutropenic, non-transplant patients. The present study, a descriptive analysis of cases of aspergillar tracheobronchitis found in a series of patients with dual isolation of *Aspergillus* from lower respiratory tract samples, provides a description of antifungal treatments used in daily practice. In our series only 60.5% patients were treated with antifungals, reinforcing the idea of tracheobronchitis as superimposed infection in severe COPD patients. Voriconazole alone or in combination was the most frequent antifungal used: 87.5% treated patients with invasive tracheobronchitis (vs. 12.5% with other antifungals) and 60% treated patients with simple tracheobronchitis (vs. 40% with other antifungals).

The results of the present analysis suggest that aspergillar tacheobronchitis should be considered in the differential diagnosis of non-immunocompromised patients with deteriorating chronic airway limitation in order to initiate antifungal treatment as early as possible to enhance the success treatment of the highly aggressive form (invasive tracheobronchitis) of the disease.

**Table 3** **Steroids and antibiotics before admission, antifungals administration after culture request and outcome by clinical entity [n (%)]**

| | Total | Simple | Invasive |
|---|---|---|---|
| **n** | 38 | 26 | 12 |
| **Steroids intake before admission** | 19 (50.0) | 11 (42.3) | 8 (66.7) |
| ≥20 mg/day | 11 (57.9) | 7 (63.6) | 4 (50.0) |
| Accumulated dose >100 mg | 17 (89.5) | 11 (100) | 6 (75.0) |
| Accumulated dose >700 mg | 6 (31.6) | 5 (45.5) | 1 (12.5) |
| **Antibiotic treatment before admission** | 13 (34.2) | 9 (34.6) | 4 (33.3) |
| **Antifungal treatment after culture request** | 23 (60.5) | 15 (57.7) | 8 (66.6) |
| Voriconazole as monotherapy | 12 (52.2) | 7 (46.7) | 5 (62.5) |
| Voriconazole + other antifungals | 4 (17.4) | 2 (13.3) | 2 (25.0) |
| Total patients receiving voriconazole | 16 (69.6) | 9 (60.0) | 7 (87.5) |
| Other antifungals | 7 (30.4) | 6 (40.0) | 1 (12.5) |
| **Mortality** | 9 (23.7) | 4 (15.4) | 5 (41.7) |

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