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Ulcerative and Plaque-Like Tracheobronchitis Due to Infection with Aspergillus in Patients with AIDS

Carol A. Kemper, John S. Hostetler, Stephen E. Follansbee, Peter Ruane, DeCarr Covington, Stewart S. Leong, Stanley C. Deresinski, and David A. Stevens

Tracheobronchitis is an uncommon manifestation of infection due to Aspergillus species, occurring in <7% of cases of pulmonary aspergillosis. At least 58 cases of invasive aspergillus tracheobronchitis have been described since 1962. We describe four patients with AIDS, all of whom were severely immunocompromised, who had ulcerative tracheobronchitis due to Aspergillus species demonstrated histologically. Three patients had received corticosteroids or were neutropenic at presentation. At bronchoscopy, three patients had some degree of diffuse tracheobronchitis, multiple ulcerative or "plaque-like" inflammatory lesions, and occasionally nodules involving the mainstem and segmental bronchi. The remaining patient had a single deep ulceration of the proximal trachea. Aspergillus was isolated from biopsy specimens from all four patients. There were varied degrees of invasion of the mucosa, submucosa, and cartilage on histological examination in three patients, one of whom had evidence of disseminated aspergillosis. Two patients subsequently developed pulmonary parenchymal disease due to Aspergillus. A review of aspergillus tracheobronchitis, including a discussion of airway disease in patients infected with human immunodeficiency virus, is presented.

Invasive disease of the airways due to infection with Aspergillus is uncommon; in three large series it occurred in only 15 (6.9%) of 217 cases of intrathoracic aspergillosis [1-3]. Mary Lapham provided the original, quite descriptive, report of aspergillus tracheobronchitis in 1926: "the mucous membranes . . . may become almost black from congestion; ulcerations may be eaten out, and patches of membranes formed [4]." Aspergillus infection of the airways, with varied degrees of mucoid impaction and pseudomembrane formation, has been described in five human immunodeficiency virus (HIV)-infected patients, but only three of these patients had evidence of tissue invasion [5-7]. The incidence of invasive aspergillosis in patients with HIV disease is not known, but it is an unusual opportunistic infection in this population. Fungi other than Cryptococcus neoformans caused <1% of all pulmonary infections in patients with AIDS in one large series [8], with none reportedly due to Aspergillus. The low incidence of reported disease may in part be due to the difficulties inherent in the antemortem diagnosis of invasive aspergillosis. However, even in a large autopsy series, aspergillosis was found in only 1.4% of pulmonary infections in patients with AIDS [9]. Nevertheless, aspergillosis in patients with AIDS is being reported with increased frequency [5, 10-19].

We describe four patients with AIDS who developed severe airway infection due to Aspergillus species. The pertinent clinical and demographic characteristics are outlined in table 1. In addition, a review of invasive tracheobronchitis due to infection with Aspergillus, including a discussion of airway disease due to Aspergillus in patients with HIV infection, is presented.

Methods

Three patients presented with ulcerative bronchitis and one presented with ulcerative tracheitis due to Aspergillus species between 17 May 1990 and 21 May 1991. Three patients were referred to the Santa Clara Valley Medical Center (San Jose, CA) for evaluation and treatment, and the other patient was cared for at the Cedars-Sinai Medical Center.
(Los Angeles, CA). The interval between the diagnosis of AIDS and infection with *Aspergillus* ranged from 25 days to 41 months (median, 19 months).

All of the patients underwent bronchoscopic examination with bronchoalveolar lavage (BAL), and one underwent transbronchial biopsies. BAL specimens at each institution were cultured for bacteria (including *Legionella* species), mycobacteria, fungi, and virus (including cytomegalovirus [CMV]). Cytological examinations, including staining with Wright’s and Grocott-Gomori methenamine–silver nitrate (GMS), stains were performed on BAL specimens from all four patients. Sputum specimens were obtained at baseline for fungal culture from two patients. Endobronchial or endotracheal biopsy specimens were cultured for fungus for all four patients. Two of the three patients who died were examined post-mortem. Three patients received itraconazole as part of an open trial of itraconazole in the treatment of invasive aspergillosis by the National Institute of Allergy and Infectious Diseases Mycoses Study Group, and one obtained the drug outside of the study setting. Serum concentrations of itraconazole were determined by bioassay as described elsewhere [20].

A review of the literature was conducted by a MEDLINE search with use of key terms (including aspergillus, bronchitis, tracheobronchitis, airway disease, HIV, and AIDS) as well as by cross-referencing published articles.

### Results

#### Report of Cases

Details of bronchoscopic findings, results of histological examination of biopsy specimens, and autopsy findings are grouped at the conclusion of this section.

**Case 1.** A 48-year-old homosexual man with serological evidence of HIV infection presented with a 3-week history of progressive dyspnea and fever. He had a 20-pack-year history of smoking but no known pulmonary disease. His CD4 count was 90/mm³. Chest roentgenographs revealed diffuse bilateral interstitial infiltrates, and *Pneumocystis carinii* was demonstrated on examination of a BAL specimen. He was treated with trimethoprim-sulfamethoxazole (TMP-SMZ) and tapering doses of corticosteroids, with resolution of his symptoms.

Twenty-five days after his initial presentation, he developed recurrent fever (temperature to 104°F), dyspnea, and nonproductive cough. Physical examination revealed diffuse rales and inspiratory wheezes in the right lower lobe and hyperinflation. Chest roentgenograms revealed patchy perihilar interstitial infiltrates, with increased infiltrate and possible cavitation in the right lower lobe. Computed tomographic (CT) scan of the chest demonstrated bilateral hilar adenopathy and perihilar infiltrates without unequivocal cavitation. TMP-SMZ and amphotericin B (total dose, 70 mg) were administered. Bronchoscopic examination of the airways revealed diffuse mucosal inflammation and ulceration, and GMS stain of BAL fluid revealed *P. carinii*. Cultures yielded *Aspergillus* species (see table 2), and treatment with itraconazole, 200 mg twice daily, was initiated. The patient’s fever and dyspnea gradually resolved during the following 2 weeks. Chest roentgenography performed during the following 3 months demonstrated gradual resolution of the perihilar densities. His subsequent course was complicated by progressive encephalopathy and CMV esophagitis and enteritis. He continued to have intermittent nonproductive cough and occasional dyspnea but had no evidence of recurrent pulmonary infiltrates; sputum cultures were negative for *Aspergillus*. He died 11 months after his initial presentation, and postmortem examination showed a small focus of pulmonary aspergillosis infection.

**Case 2.** A 39-year-old homosexual man with a 17-month history of AIDS who was receiving maintenance therapy with zidovudine, TMP-SMZ, and ketoconazole presented with a 10-day history of mildly productive cough, dyspnea,
and fever. His medical history was remarkable for two episodes of *P. carinii* pneumonia (PCP) with the development of small bilateral cavities in the upper lobes. Non-Hodgkin's lymphoma of the palate had been diagnosed 2 months before admission, for which he had received three cycles of methotrexate, doxorubicin hydrochloride, cyclophosphamide, vincristine, bleomycin, and prednisone; the administration of these agents was complicated by neutropenia. A central intravenous catheter had been placed 1 month before admission for daily administration of total parenteral nutrition. A recent CD4 count showed no CD4 cells.

Physical examination revealed a chronically ill appearing man with a temperature of 39.3°C, bibasilar rales with occasional expiratory wheezes, hepatomegaly, and splenomegaly. Funduscopic examination revealed hemorrhagic exudates consistent with a diagnosis of CMV retinitis. Neurological examination revealed slow but intact speech, impaired cognition and memory, and hyperreflexive deep tendon reflexes at the knees and ankles. A chest roentgenogram revealed patchy multinodular infiltrates. Cultures of BAL fluid were positive for *Aspergillus* species and CMV.

Amphotericin B therapy was initiated (total dose, 100 mg), but 3 days later the therapy was changed to itraconazole, 200 mg twice daily. That evening, the patient experienced a grand mal seizure, and therapy with phenytoin and carbamazepine was initiated. CT scans of the head revealed a large right parietal lesion consistent with tumor or abscess. The serum itraconazole concentration 4 days later was 0.4 \( \mu g/mL \). The following day, he became acutely hemiplegic and obtunded. A repeated CT scan of the head revealed a large right parietal hematoma. Medical support was gradually withdrawn, and the patient died.

**Case 3.** A 44-year-old man with an 18-month history of AIDS, *Mycobacterium avium* complex bacteremia, Kaposi's sarcoma, and probable PCP presented with weakness, intermittent epistaxis, and an episode of gross hemoptysis. Physical examination revealed a temperature of 99°F, dried blood along the nasal passages, and coarse expiratory wheezes. Chest roentgenograms were unremarkable, but a CT scan of the chest demonstrated right pleural thickening and a small effusion. Magnetic resonance imaging revealed an air-fluid level in the left maxillary sinus. Laboratory tests were significant for a white blood cell count of 700/mm\(^3\), an absolute neutrophil count of 532/mm\(^3\), and a CD4 count of 2/mm\(^3\). Otolaryngeal examination with indirect laryngoscopy was unremarkable. Bronchoscopy showed ulcerative bronchitis, and the culture of BAL fluid yielded *Aspergillus* species. He received parenterally administered amphotericin B for 8 days and then itraconazole, 400 mg once daily. The patient's fever, cough, and hemothysis rapidly resolved, but he was lost to further follow-up.

**Case 4.** A 35-year-old man had a 41-month history of
AIDS with cryptococcal meningitis, CMV retinitis, recurrent toxoplasmal encephalitis, and intermittent neutropenia. He was receiving maintenance therapy with pyrimethamine and granulocyte colony-stimulating factor. He initially presented in November 1990 with neutropenia (absolute neutrophil count, 154/mm³), neck pain, and hoarseness. Bronchoscopic examination revealed a small mucosal swelling below the vocal cord without apparent ulceration. Biopsy of this area and of the tracheobronchial tree revealed acute inflammation and fragments of necrotic squamous epithelium but no intact epithelium. A GMS-stained preparation revealed pseudohyphae consistent with Candida species in the superficial necrotic material. His symptoms subsequently resolved.

The patient presented 6 months later with 6 weeks of anterior neck pain, odynophagia, and chronic productive cough. He denied fever, chills, or breathlessness. Physical examination and chest roentgenograms were unremarkable. Bronchoscopic examination identified a single deep 1.5-cm tracheal ulceration, and biopsy specimen cultures were positive for Aspergillus species. Despite initial symptomatic abatement with itraconazole therapy, 200 mg twice daily, he developed recurrent throat pain and hoarseness after 3 months of therapy. Repeated bronchoscopy demonstrated evidence of persistent ulceration. Although no biopsies were performed, the BAL fluid culture was positive for one colony of Aspergillus species. A pulmonary nodule was noted shortly thereafter, and a transthoracic fine-needle aspirate yielded Aspergillus species. Pill counts indicated that the patient’s compliance was poor. Therapy with amphotericin B (total dose, 500 mg) was initiated, but the patient died 1 month later. No autopsy was done.

**Bronchoscopic Findings**

Bronchoscopic examination demonstrated mild-to-moderate diffuse tracheobronchitis with erythematous, edematous mucosa in the first three patients. Patient 1 had a 1.0-cm exophytic lesion involving the mucosa at the juncture of the bronchus to the superior segment of the right lower lobe and multiple 2- to 5-mm inflammatory ulcers and white plaque-like lesions involving the mainstem and segmental bronchi. Several ulcers were grossly blackened and necrotic, and some were coated with a shaggy fibrinous exudate. Patient 2 had multiple small 2- to 3-mm raised cream-colored plaques throughout the tracheobronchial tree. Patient 3 had a small amount of blood in the anterior segment of the right upper lobe and the lateral segment of the right middle lobe, with multiple 2- to 3-mm raised creamy-white plaques in the right and left main stem bronchus and bronchus intermedius. Patient 4 had a single 1.5-cm-deep ulceration with overlying fibrinous eschar immediately posterior to the right vocal cord but no evidence of distal airway involvement.

**Pathological Examination and Cultures**

Endobronchial biopsy specimens obtained from the first three patients demonstrated acute and chronic inflammation with reactive mucosal metaplasia and mild atypia. Portions of the surface mucosa were ulcerated and associated with inflammatory debris and necrosis in all three patients. There was histological evidence of inflammation involving the mucosa in patient 1 and inflammation extending to the submucosa in patient 2, with numerous narrow-angle branching septate organisms visualized on GMS- and hematoxylin/eosin-stained specimens from both patients (see table 2). Transbronchial biopsy specimens from patient 1 showed no evidence of invasive aspergillosis, although GMS-stained samples demonstrated P. carinii. A dense fibrinous exudate consisting of hyphal elements and inflammatory cells covered areas of mucosal ulceration in patient 3, but no hyphae were visualized in the intact mucosa adjacent to the ulcerations. Endotracheal biopsy specimens from patient 4 demonstrated acute and chronic inflammation, ulceration, necrosis, and numerous septate branching hyphae invading the tracheal cartilage.

Cultures of sputum were positive for four colonies of Aspergillus species for patient 2 but were negative for fungus for patient 4. Aspergillus was isolated from endobronchial biopsy specimens from all three patients with endobronchial disease and from the endotracheal specimen from the fourth patient with endotracheal disease. The BAL specimen was positive for two colonies of Aspergillus for patient 1 and for only one colony for patient 2. Aspergillus fumigatus was isolated in three cases, but identification by species was not performed in the remaining case. Cultures of BAL fluid were also positive for Candida albicans and CMV for patient 2.

Cytological examination of BAL fluid from patients 3 and 4 revealed moderately increased numbers of inflammatory cells and hyphal elements, but no hyphal elements were visualized in patients 1 and 2.

**Autopsy Findings**

Examination of sections through the right middle lobe of patient 1 revealed a 2-mm focus of necrosis around a bronchiole. Numerous septate branching hyphae consistent with Aspergillus species were visualized in the necrotic material. The remainder of the lungs appeared congested, with focally necrotic, hemorrhagic areas of consolidation and prominent intranuclear inclusion bodies consistent with CMV infection. The remainder of the studies, including microscopic examination of the brain, showed no evidence of aspergillosis.

Postmortem examination of patient 2 revealed multiple, well-circumscribed tan ulcers averaging 5 mm in diameter involving the main-stem bronchial mucosa (figure 1). There was histological evidence of necrosis extending to the sub-
Figure 1. Postmortem examination of patient 2 revealed multiple well-circumscribed tan-colored ulcers averaging 5 mm in diameter involving the mainstem and segmental bronchi. One such ulcer near the main stem bronchus, shown above, extended to the submucosa of the bronchus.

mucosa of the bronchus with multiple fungal hyphae consistent with Aspergillus species. Perichondral invasion by fungal hyphae was present, but the cartilage itself was intact. Full-thickness involvement or impending perforation of the bronchial wall was not seen. There was, in addition, histological evidence of invasive aspergillosis involving the brain, lungs, liver, adrenal glands, and thyroid.

Review of Aspergillus Tracheobronchitis

At least 60 cases of aspergillus tracheobronchitis, 38 of them recently reviewed [21], have been reported in the literature since 1962. However, 22 additional cases relevant to this discussion have since been described [5, 6, 22-29], including three cases in HIV-infected patients [5-7]. Several additional cases of upper-airway disease involving the nares, larynx, and epiglottis described elsewhere, including a case of epiglottitis in an HIV-infected patient, will not be considered here [11, 30-33]. Four of these 60 cases lack a clear description by which to judge the presence or absence of mucosal invasion, but two are believed to represent invasive disease [6, 23] and two are not [21, 23]. One case described by Clarke et al. [21] may be better classified as mucoid impaction syndrome or what has recently been described as "obstructing bronchial aspergillosis" [5]. This entity was recently described in three individuals with HIV infection; one of these cases progressed to invasive bronchial disease and dissemination despite therapy [5]. Two French authors have described three patients with a similar entity, "bronchique obstructive aspergillosis" [6, 23], but the distinction between invasive disease and noninvasive disease in these cases is not clear. One of these three patients developed widely disseminated disease despite antifungal therapy, and one remained free of disease following antifungal therapy [23]. The third patient, a young man with HIV infection, presented with dyspnea, mucous plugging, superficial mucosal ulcerations, and hyphal invasion [6]. Despite having received only corticosteroids, he reportedly remains free of disease more than 6 years later (Dr. V. LeGros, personal communication).

The information provided in these case reports is summarized in table 3. Reportedly, only 16 of the 58 cases were diagnosed before death; 34 were diagnosed post-mortem or presented as part of an autopsy series. Several of these latter case reports lack information necessary for a complete assessment of factors pertinent to the diagnosis of invasive fungal disease. The median age of affected patients was 44 years, with a range of 2.5-87 years. Approximately 73% of the patients so described were immunoincompetent, including six

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients described (%)</th>
<th>No. of patients for whom information is provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (76)</td>
<td>38</td>
</tr>
<tr>
<td>Female</td>
<td>9 (24)</td>
<td>38</td>
</tr>
<tr>
<td>Time of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antemortem</td>
<td>16 (32)</td>
<td>50</td>
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<tr>
<td>Postmortem</td>
<td>34 (78)</td>
<td>50</td>
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<tr>
<td>Immunoincompetent host</td>
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<tr>
<td>Heart/lung transplant</td>
<td>7 (17.5)</td>
<td>31</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>6 (15.0)</td>
<td>31</td>
</tr>
<tr>
<td>Bone-marrow transplant</td>
<td>5 (12.5)</td>
<td>31</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>5 (12.5)</td>
<td>31</td>
</tr>
<tr>
<td>HIV infection</td>
<td>3 (7.5)</td>
<td>31</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2 (5.0)</td>
<td>31</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1 (2.5)</td>
<td>31</td>
</tr>
<tr>
<td>Antibacterial therapy</td>
<td>24 (77)</td>
<td>31</td>
</tr>
<tr>
<td>Chemotherapy/radiation therapy</td>
<td>23 (61)</td>
<td>38</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>23 (61)</td>
<td>38</td>
</tr>
<tr>
<td>Absolute neutrophil count,</td>
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<td>&lt;1,000/mm³</td>
<td>21 (55)</td>
<td>38</td>
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<tr>
<td>Underlying pulmonary disease</td>
<td>14 (45)</td>
<td>31</td>
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<tr>
<td>Histological evidence of parenchymal lung involvement</td>
<td>27 (47)</td>
<td>58</td>
</tr>
<tr>
<td>Antemortem culture confirmation of Aspergillus species</td>
<td>17 (61)</td>
<td>28</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
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<tr>
<td>&quot;Cure&quot;</td>
<td>6 (21)</td>
<td>28</td>
</tr>
<tr>
<td>Death due to aspergillosis</td>
<td>12 (43)</td>
<td>28</td>
</tr>
<tr>
<td>Death possibly contributed to aspergillosis</td>
<td>7 (25)</td>
<td>28</td>
</tr>
<tr>
<td>Death not due to aspergillosis</td>
<td>3 (11)</td>
<td>28</td>
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</table>

NOTE. Includes one patient each from larger series described by Denning et al. [5] and Baud et al. [23] with invasive bronchial disease and one patient described by LeGros et al. [6] with mucosal invasion that was confirmed through personal communication with C.A.K.

CID 1993:17 (September) Kemper et al.
patients who had solid tumors (three lung, one breast, one rectum, and one kidney) and one patient who had pancto-
penia secondary to gold therapy. Neutropenia was an under-
lying factor in 55% of patients; cytotoxic chemotherapy (or 
radiation therapy) had been administered to 61% and cortico-
steroids, to 61%. Five patients, however, were reported to 
have none of these well-described risk factors for invasive 
fungal disease, including a patient with diabetes, one who 
had lung cancer, a former alcoholic, and an HIV-infected 
patient [34–36]. At least 45% had underlying pulmonary dis-
ease, including seven patients with histological evidence of 
lung rejection [26, 29]. Twenty-six (81%) of 32 patients were 
described as symptomatic. The most frequent complaints, in 
descending order of frequency, were cough (in 12), fever (in 
11), dyspnea (in 11), chest pain (in 3), and hemoptysis (in 
2). Nineteen patients had abnormal chest roentgenograms, 
four of which were possibly attributable to other causes, but 
chest roentgenograms were normal for at least 9 (32%) of 28 
patients described [6, 7, 26, 27, 37, 38].

All of the affected patients demonstrated some degree of 
histological invasion, but at least 10 had invasion of the carti-
lage [22, 26–28, 37, 39]. One case resulted in tracheoesoph-
ageal fistulization [37] and one in fatal fistula formation to 
the right pulmonary artery [39]. At least 13 (26%) of 50 cases 
were described as “pseudomembranous,” but the degree of 
pseudomembrane formation varied from focal areas of fibrin 
deposition on histopathological examination to a thick, ob-
structing carpet of necrotic debris visualized throughout the 
bronchial tree [5, 7, 21, 26–28, 40]. Fourteen (35%) of 40 
cases resulted in airway obstruction due to pseudomembrane 
formation or mucoid impaction [3, 5, 21, 23, 25, 29, 37, 39]; 
only three (7.5%) of these cases resulted in acute respiratory 
compromise and death. While dissemination of infection 
was not identified in any patient at the time of initial diagno-
sis, five patients, including one patient with HIV infection, 
subsequently had extrathoracic spread of disease despite the 
initiation of antifungal therapy [5, 23, 26, 28]. Clinical out-
come was described in 28 patients; despite therapy in 22 
patients, only 6 (21%) were described as “cured” of their 
disease.

Discussion

Aspergillus airway disease encompasses a variety of pro-
cesses including saprophytic colonization, allergic broncho-
pulmonary aspergillosis, bronchocentric aspergillosis, mu-
coid impaction, obstructing bronchial aspergillosis, and 
tracheobronchitis. These clinical syndromes are seldom dis-
tinct, and features of each may overlap, as elegantly illus-
trated by Katzenstein et al. [41], or may occur in a progres-
sive fashion. For example, allergic bronchopulmonary 
aspergillosis is described as noninvasive, but cases with lim-
ited tissue invasion have been described [42, 43]. “Broncho-
centric mycosis,” with features resembling bronchocentric 
granulomatosis, has recently been described in two trans-
plant recipients; however, both had invasive disease and one 
had inspissated secretions [44]. Mucoid impaction, a local-
ized form of aspergillosis characterized by bronchial casts of 
mucus and mycelia, is associated with allergic broncho-pul-
monary aspergillosis [41]. Although ordinarily considered 
noninvasive, superficial erosion with subsequent ulceration 
and invasion may ensue. In addition, mucoid impaction may 
be a prominent (and occasionally fatal) feature in cases of 
invasive tracheobronchitis, particularly in patients with un-
derlying airway disease such as that due to rejection of a 
transplanted lung [3, 21, 39]. Mucoid impaction also pre-
ceded the development of invasive disease in one of three 
recently described cases of obstructing bronchial aspergillo-
sis in HIV disease [5].

Although it is apparent that the pathogenesis of these 
forms of aspergillosis is dependent on host factors, the immu-
nologic mechanisms underlying these processes have not 
been substantially illuminated. It may be helpful to consider 
their evolution as manifestations of different types of host 
responses, with varying degrees of allergic response, mucus 
formation, inability to clear secretions, and tissue invasion. 
Anatomic location may also be important in the pathogene-
sis of these responses. A classification of tracheobronchitis 
recently was proposed to differentiate among diffuse bron-
chitis/tracheitis, ulcerative bronchitis/tracheitis, and pseudo-
membranous bronchitis/tracheitis [26]. A classification sys-

tem for aspergillus airway disease that provides clinically 
meaningful information based on pathophysiological mech-
anisms, anatomic and histological features, and potential for 
invasion, which is correlated to clinical outcome, is needed.

The clinical and histological features of our four patients 
with AIDS and ulcerative tracheobronchitis are similar to 
those of the patients without AIDS reviewed. All four of our 
patients were severely immunocompromised. One had re-
ceived corticosteroids, one was neutropenic at presentation, 
and one had both of these well-defined risk factors for inva-
sive aspergillosis. One patient, who did not have histological 
evidence of invasive disease, had neither of these well-de-
defined risk factors at presentation, although he had a history of 
neutropenia. This patient had a preexisting tracheal ulcer 
that probably was secondarily infected with Aspergillus. PCP 
preceded the diagnosis of aspergillosis in the other three pa-
tients. Aspergillus infection of the lung has occurred in pa-
tients with preexistent cavitary disease caused by PCP [45]. 
A possible association between invasion by Aspergillus and 
CMV, which was responsible for clinically invasive retinal 
disease in two of these patients and identified in BAL fluid in 
one of them, has also been raised [5, 26].

All four of the patients had symptoms referable to the air-
ways or lungs, but only two had abnormal chest roentgeno-
grams. Pulmonary parenchymal involvement and dissemina-
tion were documented at presentation in only one case. 
Although transbronchial biopsy specimens and cultures were
negative for *Aspergillus* for a second patient, parenchymal lung involvement probably occurred concurrently with PCP at presentation and was subsequently documented at autopsy. Both the incidence of parenchymal lung involvement (50%) and the incidence of dissemination (25%) are similar to those found in the review of other cases.

Tracheobronchial disease presented grossly on bronchoscopic examination in our four patients with varied degrees of erythema and edema of the airway mucosa, with one to multiple ulcerative lesions, and occasionally with exophytic nodules and plaque-like lesions. In contrast to the cases reviewed, which included several patients with HIV disease [5, 7], we found no clinically apparent pseudomembrane formation and mucoid impaction in any of our HIV-infected patients (table 4). Involvement of the cartilage was seen in the case of ulcerative trachitis. Only a few colonies of *Aspergillus* species grew from both lavage and biopsy specimens despite evidence of significant hyphal invasion. These data are in apparent contradiction to a recent report suggesting that higher colony counts may correlate with the severity of invasive bronchial disease in heart-lung transplant recipients [26]. The occurrence of isolated airway infection with *Aspergillus* without apparent disease in some patients with HIV infection suggests that such colonization has little potential for invasion in these individuals [15, 46]. In one retrospective analysis, *Aspergillus* was isolated from the respiratory secretions of 26 HIV-infected patients, but only four (15%) had evidence of invasive disease at autopsy [15].

All four of our patients received itraconazole. Patients 1 and 4 had focally invasive disease that remained localized for a prolonged period during therapy. One patient who had disseminated aspergillosis, including cerebral disease, at presentation died within 8 days of diagnosis. If serum concentrations of itraconazole correlate with efficacy in vivo [47], treatment failure may have been due in part to insufficient blood concentrations resulting from concomitant administration of phenytoin and carbamazepine [48]. Although the treatment of invasive aspergillosis remains problematic, itraconazole may be an effective therapeutic alternative to amphotericin B [47, 49].

A total of nine cases of aspergillus airway disease, including our four cases, have now been identified in patients with HIV infection. These cases demonstrate varied degrees of mucoid impaction, pseudomembrane formation, mucosal inflammation and ulceration, and tissue invasion (table 4). Our four patients had evidence of invasive tracheobronchitis but no evidence of mucoid impaction. One had evidence of ulcerative bronchitis and evidence of invasion [7], one had mucoid impaction and limited tissue invasion that resolved following the administration of corticosteroids [6], one had mucoid impaction that progressed to invasive disease despite antifungal therapy [5], and two had mucoid impaction but no evidence of invasion, which resolved following antifungal therapy [5]. These nine cases comprise ~10% of all reported cases of aspergillosis in patients with AIDS [5, 10–13, 16–19]. Denning et al. documented the occurrence of airway disease in 3 (23%) of 13 patients who had pulmonary disease [5]. Whether this apparent increased frequency of airway disease in patients with AIDS is a result of more vigilant and frequent examination of the tracheobronchial tree in this patient population is not known. It is probable that the initial disease in these patients is superficial, involving the mucosa, and may imply abnormalities in mucus production or ciliary function in HIV-infected patients. In some patients, this initial disease progresses to ulceration and then invasion.

Fungal tracheobronchitis has been described as a rare but relatively benign process, causing few symptoms with little potential for invasion, apparently identified as an incidental finding at postmortem examination in otherwise terminally ill individuals [40]. Nevertheless, our review demonstrates that invasive tracheobronchitis due to *Aspergillus* can be a rapidly progressive and fatal illness in ~40% of patients so affected. Death occurs as a result of direct intrathoracic invasion and subsequent dissemination or, less commonly, from

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<th>Case [reference]</th>
<th>Mucoid impaction</th>
<th>Pseudomembrane formation</th>
<th>Ulcerative mucosal disease</th>
<th>Bronchial mucosal invasion</th>
<th>Pulmonary parenchymal involvement or dissemination</th>
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airway obstruction due to mucoid impaction or pseudomembrane formation. Respiratory symptoms, such as persistent cough, are common, but chest roentgenograms may be normal. Even a single colony of Aspergillus in sputum may signal invasive disease in symptomatic patients with AIDS and necessitates prompt investigation of the tracheobronchial tree. Despite histological evidence of only limited bronchial mucosal invasion, tracheobronchitis may herald occult or incipient development of pulmonary parenchymal involvement and dissemination in the appropriate host setting.

References
4. Lapham ME. Aspergillosis of the lungs and its association with tuberculosis. JAMA 1926;87:1031–