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LETTER TO THE EDITOR

# COVID-Associated Pulmonary Aspergillosis in the United States: Is It Rare or Have We Missed the Diagnosis?

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While the incidence of coronavirus disease (COVID)-associated pulmonary aspergillosis (CAPA) in COVID-19 patients admitted to the intensive care unit (ICU) in Europe is widely published (incidence up to 30%) (1), data on CAPA from the United States is lacking or has not been well described (2, 3). During the first surge of COVID-19 (March to August 2020), members of the Fungal Diagnostic Laboratories Consortium (FDLC) were formally asked if they had recovered *Aspergillus* species in respiratory specimens from patients with confirmed COVID-19 after ICU admission (4). Only 8 of the 23 FDLC member laboratory sites (35%) responded in the affirmative. Cumulatively, data from 33 patients who were admitted to the ICU and/or intubated in the ICU setting were identified at four academic medical centers (among a total of 1,633 ICU patients) and were collected and summarized (Table 1). The overall incidence was 2%. Based on the most recent CAPA case definition (3, 5), 17 cases were considered to be possible CAPA, and 16 cases were determined to be probable CAPA.

The mean age was 63.2 (range, 38 to 85), 55% were male, 42% were white, and 58% had hypertension. Only 9 (27%) patients were immunosuppressed at the time of COVID-19 diagnosis, but 16 (48%) patients received immunosuppression therapy during COVID-19 treatment. Overall, 20 cases (61%) were treated with antifungals (75% in probable CAPA, 47% in possible CAPA). Mortality was 67% overall (75% in probable CAPA cases; 59% in possible CAPA cases).

The median time of first isolation of *Aspergillus* spp. from respiratory tract specimens was 13 days after ICU admission (range, 0 to 35 days). *A. fumigatus* was the most common species (79%), followed by *A. niger* (15%), *A. flavus* (3%), and *A. parasiticus* (3%). These *Aspergillus* spp. were initially recovered from the following sources: endotracheal tube aspirate (61%), tracheal aspirate (12%), sputum (21%), and bronchoalveolar lavage (BAL) fluid (21%).

Testing for serum galactomannan (GM) (Platelia EIA, Bio-Rad) was performed in 23 cases (70%). Only four cases (17%) tested positive, yielding a positive rate of 28.6% (4/14) for probable CAPA. This is consistent with other published reports (6, 7). Only 7 cases (21%) had BAL samples collected, of which BAL GM was not even ordered in 4 cases (57%), and of the 3 cases that underwent BAL GM testing, two were positive (GM index 6.16, 3.52). Serum 1,3-beta-D-glucan (BDG) (Fungitell, Associated of Cape Cod, Inc.) testing was available for 23 cases (70%); 8 (35%) were positive, yielding a positive rate of 50% (7/14) for probable CAPA cases.

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**TABLE 1** COVID-19 patients who were admitted to the ICU, intubated, and had positive *Aspergillus* culture[a]

| Case no. | Age, sex, race | Underlying | Prior IS/COVID IS | *Aspergillus* culture | | Serum GM index (day)[b] | BAL GM index (day)[b] | Serum BDG (pg/ml) (day)[b] | Chest CT or CXR (lung) | Antifungals | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Species (day)[b] | Source | | | | | | |
| Prob-CAPA[c] | | | | | | | | | | | |
| 1 | 64, M, W | Cirrhosis, MDS, HTN, COPD, OSA | No/tocilizumab | *Aspergillus* sp (D11) | TA | 0.08 (D9) | ND | <31 (D1) | CT: GGO, consolidation, **pulmonary nodules**, small air-filled cystic lesions, pleural effusions | Caspofungin | Deceased |
| 2 | 54, M, W | HTN, HLD, obesity | No/sarilumab | *A. niger* (D13, D21) | BAL | 0.17 (D4) | **6.16** (D5) | **303** (D8), **286** (D33) | CT: GGO, bronchiectasis, multiple cystic foci within the areas of consolidation | Voriconazole, amphotericin B | Deceased |
| 3 | 68, M, W | COPD, HTN, GERD, HLD, stroke, SZD | No/no | *A. fumigatus* (D1)<br>*A. fumigatus* (D8) | BAL<br>Sputum | **1.51** (D4) | **3.52** (D1) | ND | CXR: patchy airspace opacities, emphysema | Amphotericin B | Deceased |
| 4 | 57, F, W | Asthma, fatty liver, OSA, HTN, GERD, DM | No/no | *A. fumigatus* (D1)<br>*A. fumigatus* (D20) | TA<br>BAL | 0.1 (D6) | ND | 66 (D6) | CXR: patchy and nodular opacities, air bronchograms | Voriconazole | Deceased |
| 5 | 69, M, UK | DM, HTN, PUD | No/MPS, anakinra, tocilizumab | *A. fumigatus* (D13) | ETA | ND | ND | **97** (D17) | CT: more widespread GGO at the time of growth of *Aspergillus*, consolidation | Voriconazole, amphotericin B | Deceased |
| 6 | 66, M, H | Asthma, HTN | Yes/no | *A. fumigatus* (D30) | ETA | 0.16 (D23) | ND | **391** (D23) | CXR: infiltrative opacities, crescent-shaped lucency | None | Alive |
| 7 | 72, F, H | CHF, CAD, DM, HLD, HTN, RA | Yes (steroids)/no | *A. fumigatus* (D21) | BAL | ND | ND | ND | CXR: opacities | None | Deceased |
| 8 | 71, M, W | HLD, HTN, long-time smoking | No/tocilizumab, corticosteroids | *A. niger* (D5) | ETA | 0.08 (D7), **0.61** (D10) | ND | 52 (D6), **>500** (D10) | CT: pulmonary parenchymal opacities, pleural effusion | None | Deceased |
| 9 | 81, M, A | DM, HTN, BPH | No/no | *A. flavus*, *A. fumigatus* (D18) | ETA | 0.17 (D0), 0.05 (D21) | ND | **209** (D21) | CT: GGO, airspace opacities | Voriconazole | Alive |
| 10 | 65, M, UK | ANCA vasculitis with AKI and lung involvement; pre-DM | Yes/corticosteroid, possible leronlimab (RCT) | *A. fumigatus* (D23) | BAL | 0.03 (D0), 0.12 (D12), 0.21 (D20) | ND | 45 (D0), 75 (D12), **125** (D20) | CT: cavity lesion, GGO, pneumomediatsinum | None | Deceased |
| 11[d] | 69, M, H | Obesity | No/MPS | *A. niger* (D19) | BAL | 0.08 (D6), 0.16 (D18), 0.06 (D35) | 0.05 (D19) | <31 (D6), <31 (D18), <31 (D35) | CT: consolidation, GGO, bronchiectasis | Voriconazole | Deceased |
| 12[d] | 45, F, UK | Obesity, asthma, multiple sclerosis | Ocrelizumab/ dexamethasone | *A. niger* (D13) | BAL | 0.10 (D10), 0.09 (D11) | ND | <31 (D10), 76 (D11) | CT: GGO, consolidative lesions, interlobular septal thickening, bronchiectasis | Voriconazole | Alive |
| 13[d] | 85, F, W | HTN, DM, ESRD | No/no | *A. fumigatus* (D7, D40)<br>*A. fumigatus* (D15) | ETA<br>Exp sputum | **2.38** (D8), 0.23 (D17), 0.08 (D40), 0.07 (D52), 0.11 (D63), 0.06 (D81), 0.07 (D83) | ND | **>500** (D8), **>500** (D17), **>500** (D40), **270** (D52), **256** (D63), **308** (D81), **161** (D83) | CT: pleural effusions, GGO, scattered **pulmonary nodules**, **cavitary lesions**, consolidations | Voriconazole, micafungin | Alive |

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**TABLE 1** (Continued)

| Case no. | Age, sex, race | Underlying | Prior IS/COVID IS | *Aspergillus* culture | | Serum GM index (day)[b] | BAL GM index (day)[b] | Serum BDG (pg/ml) (day)[b] | Chest CT or CXR (lung) | Antifungals | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Species (day)[b] | Source | | | | | | |
| 14 | 70, F, W | Obesity, HTN | No/no | *A. fumigatus* (D8) | ETA | **0.67** (D9) | ND | **152** (D9) | CXR: air space opacities, air bronchogram | Voriconazole, micafungin | Deceased |
| 15[d] | 50, F, B | COPD, CKD/ESRD, asthma, HTN | No/tocilizumab | *A. fumigatus* (D23) | Exp sputum | 0.27 (D25), 0.14 (D26) | ND | **312**, **293** (D26), **304** (D34) | CT: persistent bilateral infiltrates | Voriconazole, micafungin, amphotericin B | Deceased |
| 16[d] | 71, F, B | DM, obesity, COPD, HTN, emphysema, tobacco use, CKD/ESRD, vascular dementia | No/no | *A. fumigatus* (D9)<br>*A. fumigatus* (D13) | ETA<br>Exp sputum | 0.06 (D11) | ND | **129** (D11), 36 (D41), **233** (D57) | CT: GGO, consolidations, possible cavitation | Isavuconazole | Deceased |
| Pos-CAPA[c] | | | | | | | | | | | |
| 1 | 51, M, W | Kidney and pancreas TX, HLD, HTN, depression, GERD, Charcot arthropathy foot | Cyclosporine/ tocilizumab | *A. fumigatus* (D17) | TA | ND | ND | ND | CXR: opacifications, pleural effusions | None | Deceased |
| 2 | 64, M, W | COPD, CAD | No/no | *A. fumigatus* (D13, D21) | TA | ND | ND | ND | CXR: emphysema, patchy bibasilar airspace, diffuse interstitial change | Voriconazole | Deceased |
| 3 | 85, F, H | DM, CAD, HLD, osteoporosis, CHF | No/MPS, possible sarilumab (RCT) | *A. fumigatus* (D7) | ETA | ND | ND | ND | CT: pleural effusion, atelectasis | None | Deceased |
| 4 | 53, F, H | HTN, COPD, HCV | No/MPS, anakinra | *A. fumigatus* (D5) | ETA | ND | ND | ND | CT: multifocal GGO | Voiconazole | Deceased |
| 5 | 68, M, UK | HTN | No/MPS, hydrocortisone, anakinra | *A. fumigatus* (D12) | ETA | ND | ND | ND | CT: GGO, atelectasis, pleural effusion with coarse pleural and internal calcification | Isavuconazole | Deceased |
| 6 | 45, M, UK | DM | No/MPS, possible sarilumab (RCT) | *A. fumigatus* (D6) | ETA | ND | ND | ND | CT: diffuse patchy GGO, bronchiectasis | Voriconazole | Deceased |
| 7 | 65, M, UK | ESRD, HTN, COPD | No/MPS, tocilizumab | *A. fumigatus* (D13) | ETA | ND | ND | ND | CT: emphysema, crazy paving pattern | None | Deceased |
| 8 | 82, F, W | Asthma, hypothyroidism | Yes/no | *A. fumigatus* (D15) | ETA | 0.18 (D14) | ND | <31 (D14) | CXR: opacifications, pleural effusions, increased airspace opacity | None | Deceased |
| 9 | 49, F, W | SLE, antiphospholipid syndrome, stoke | Yes/no | *A. fumigatus* (D14) | ETA | 0.28 (D25) | ND | 44 (D25) | CT: GGO, consolidation | None | Alive |
| 10 | 72, F, W | DM, COPD, HTN, HLD, AFib, osteoporosis, lung cancer/lobectomy | Yes/fluticasone, albuterol inhalers | *A. fumigatus* (D15) | ETA | 0.18 (D12) | ND | 37 (D12) | CT: patchy parenchyma opacifications | None | Alive |
| 11 | 70, M, H | DM, obesity | No/dexamethasone | *A. parasiticus* (D13, D26) | ETA | 0.14 (D16), 0.20 (D24) | 0.05 (D26) | **>500** (D16), **263** (D27)[e] | CT: pleural effusions, diffuse pulmonary infiltrates | Voriconazole, micafungin | Alive |

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**TABLE 1** (Continued)

| Case no. | Age, sex, race | Underlying | Prior IS/COVID IS | *Aspergillus* culture | | Serum GM index (day)[b] | BAL GM index (day)[b] | Serum BDG (pg/ml) (day)[b] | Chest CT or CXR (lung) | Antifungals | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Species (day)[b] | Source | | | | | | |
| 12 | 56, M, B | Cerebro-vascular disease, HCV | No/no | *A. fumigatus* (D0) | Sputum | 0.13 (D3) | ND | 36 (D3) | CT: diffuse and consolidative GGO | Voriconazole | Alive |
| 13 | 58, F, W | DM, obesity, tobacco use | No/no | *A. fumigatus* (D4)<br>*A. fumigatus* (D10) | ETA<br>Exp sputum | 0.08 (D6), 0.07 (D11) | ND | <31 (D11) | CT: consolidative opacities, GGO | Voriconazole, fluconazole | Alive |
| 14 | 48, M, H | HTN | No/no | *A. fumigatus* (D35) | ETA | 0.16 (D14) | ND | <31 (D14) | CXR: diffuse bilateral patchy airspace opacities | None | Alive |
| 15[d] | 68, F, B | Emphysema, tobacco use, HTN; seizures, bipolar, depression, schizophrenia | No/no | *A. fumigatus* (D1) | Exp sputum | 0.05 (D3) | ND | <31 (D3) | CT: consolidations, GGO | None | Alive |
| 16[d] | 57, M, H | Follicular lymphoma, HBV | Rituximab/no | *A. fumigatus* (D5) | ETA | 0.34 (D7), 0.35 (D15) | ND | 54 (D7), 59 (D15) | CXR: patchy airspace opacities, bibasilar atelectasis, pleural effusion | Isavuconazole, voriconazole, micafungin | Deceased |
| 17 | 38, F, W | Polysubstance abuse, HCV, syphilis, asthma | No/no | *A. niger* (D1) | ETA | ND | ND | ND | CT: consolidations consistent with aspiration | None | Deceased |
| Total 33/1,633 Pts | 65 (Md), 63 (Me), 55% M, 42% W, 24% H, 12% B | 58% HTN; 36% DM; 24% COPD; 21% HLD; 21% obesity; 18% asthma; 12% ESRD | 27% prior IS; 48% COVID IS; 12% both prior IS and COVID IS | 79% *A. fumigatus*; 15% *A. niger*; 3% *A. flavus*; 3% *A. parasiticus* | 61% ETA; 21% BAL; 21% sputum; 12% TA | 70% cases with serum GM tested; 17% positive | 12% cases with BAL GM tested; 50% positive | 70% cases with serum BDG tested; 35% positive | 1 case with cavity lesion; 2 cases with nodules; others were not specific findings for COVID-19 | 61% of cases with antifungal treatment (75% in probable CPAP; 47% in possible CAPA) | 67% deceased (75% in probable CAPA; 59% in possible CAPA) |

[a]A, Asian; AFib, atrial fibrillation; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibodies; B, black; BAL, bronchoalveolar lavage; BDG, beta-D-glucan; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; CAPA, COVID-associated pulmonary aspergillosis; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computerized tomography scan; CXR, chest X-ray; D, day; DM, diabetic mellitus; ESRD, end-stage renal disease; ETA, endotracheal tube aspirate; Exp, expectorated; F, female; GM, galactomannan; GERD, gastroesophageal reflux disease; GGO, ground glass opacities; H, Hispanic; HBV, hepatitis B virus; HCV, hepatitis C virus; HLD, hyperlipidemia; HTN, hypertension; IS, immunosuppression; M, male; Md, median; MDS, myelodysplastic syndrome; Me, mean; MPS, methylprednisolone; ND, not done; OSA, obstructive sleep apnea; Pos-, possible; Prob-, probable; Pts, patients; PUD, peptic ulcer disease; RA, rheumatoid arthritis; RCT, randomized clinical trial; SLE, systemic lupus erythematosus; SZD, schizoaffective disorder; TA, tracheal aspirate; TX, transplantation; UK, unknown; W, white. Boldface type indicates positive findings.

[b]Days from ICU admission.

[c]Probable CAPA was defined as having one of the following: (i) *Aspergillus* from BAL, (ii) positive serum GM index of ≥0.5, (iii) positive BAL GM index of ≥1.0, (iv) *Aspergillus* from non-BAL respiratory sources plus positive serum BDG of >80 pg/ml without alternative explanation, or (v) presence of new nodule or cavitary lesion(s) on chest CT without an alternative explanation. Possible CAPA was defined as having one of the following: (i) positive BAL GM index of 0.5 to 1.0, (ii) positive BDG of >80 pg/ml without alternative explanation, or (iii) non-BAL respiratory culture with growth of *Aspergillus* species.

[d]Partial data from these cases were published in reference (6).

[e]The patient developed candidemia on D17 and was treated with micafungin.

Based on our data, the incidence of CAPA after ICU admission in the United States appears to be low. This finding is consistent with findings in a recent autopsy study demonstrating a low incidence of CAPA (8) as well as low incidence reported from other centers (1, 9, 10). However, the low incidence may be due to a suboptimal diagnostic workup that may be hindering the establishment of a diagnosis of CAPA: (i) reluctance to perform bronchoalveolar lavage in COVID-19 cases for fungal culture plus underutilization of BAL GM testing, (ii) infrequent fungal diagnostic workup, (iii) low sensitivity of serum GM, and (iv) lack of alternative diagnostic tools (e.g., *Aspergillus* PCR, GM testing in non-BAL respiratory samples). Given the high mortality associated with CAPA, a concerted effort is needed to develop a diagnostic strategy that is both safe and sensitive. Furthermore, it may also need to take into account that the process of sample collection and environmental hygiene in various hospital settings may contribute to false diagnosis of aspergillosis (11). Further studies will be needed to assess the true incidence and prevalence of CAPA.

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