

COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Appendix

Additional References

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Appendix Table 1. Data sources describing patients with coronavirus disease–associated pulmonary aspergillosis, March–August 2020

Location and reference
Argentina
N.B. Fernández, et al. (26)
Australia
A. Sharma, et al. (27)
Austria
J. Prattes, et al. (28)
Belgium
L. Rutsaert, et al. (29)
C. Sarrazyn, et al. (30)
Brazil
D.R.Q. Lemos, et al. (31)
Denmark
M. Helleberg, et al. (32)
France
A. Alanio, et al. (33)
M. Blaize, et al. (34)
D. Dupont, et al. (35)*
J.P. Gangneux, et al. (36)
T. Ghelfenstein-Ferreira, et al. (37)
F.X. Lescure, et al. (38)
F. Schein, et al. (39)†
Germany
P. Koehler, et al. (40)
T. Lahmer, et al. (41)
Ireland
A. Mohamed, et al. (42)
Italy
S. Antinori S, et al. (43)
M. Bartoletti, et al. (44)
G. Bruno, et al. (45)
Netherlands
E.F.J. Meijer, et al. (46)
A.L.E. van Arkel, et al. (47)
S. Van Biesen, et al. (48)
Pakistan
N. Nasir, et al. (49)
Qatar
S. Abdalla, et al. (50)
Spain
I. Falces-Romero I, et al. (Appendix Reference 51)†
M. Machado, et al. (Appendix Reference 52)*
K.A. Marr KA, et al. (Appendix Reference 53)*‡
Switzerland
F. Lamothe, et al. (Appendix Reference 54)
United Kingdom
P.L. White, et al. (Appendix Reference 55)

*The patients described in references 35, Appendix Reference 52, and Appendix Reference 53 were also documented in the FungiScope registry during the preparation of the current work.

†References 39 and Appendix Reference 51 describe patients that were not previously admitted to intensive care units.

‡Appendix Reference 53 includes cases from the United States.

Appendix Table 2. Data collection tool used in study on CAPA, March–August 2020*
Case published in the literature? (*If yes, please provide the DOI number*):

Sex:

Age:

Country:

Year of infection:

Baseline conditions:

COVID-19:

- Length of treatment, *in days*:

- Treatment sequence:

ICU stay, (*yes/no*):

- Length from ICU admission to CAPA, *in days*:

- ARDS, (*yes/no*):

- Mechanical ventilation, (*yes/no*):

o Start of ventilation before CAPA, *in days*:

Other relevant underlying conditions, (*please provide details*):

Diagnostics:

Microbiological evidence:

- Tests:

o Culture, *origin*:

o Microscopy, *origin*:

o Histology, *origin*:

o PCR, *origin*:

o Galactomannan, *origin and ODI*:

- Pathogen:

- Coinfection (*bacterial, fungal, viral*):

Image abnormalities, (*yes/no*):

- CT scan, (*please provide details*):

-x-ray, (*please provide details*):

Site(s) of CAPA involvement:

Antifungal susceptibility test:

Method:

MIC value per antifungal:

Antifungal treatment:

Length of treatment, *in days*:

Treatment sequence:

Outcome (*alive/dead*):

Observation days from CAPA diagnosis, *in days*:

Day of death:

Autopsy, (*yes/no*):

Death attributable to, (*please provide details*):

*ARDS, acute respiratory distress syndrome; CAPA, COVID-19–associated pulmonary aspergillosis; COVID-19, coronavirus disease; CT, computed tomography scan; DOI, digital object identifier; ICU, intensive care unit; MIC, minimum inhibitory concentration; ODI, optical density index.

Appendix Table 3. Coronavirus disease treatment in patients with aspergillosis, March–August 2020

Treatment	No. (%)
Hydroxy-/chloroquine	110 (59.1)
Hydroxychloroquine	98 (52.7)
Chloroquine	12 (6.5)
Antiviral treatment	67 (36.0)
Lopinavir/ritonavir	56 (30.1)
Remdesivir	3 (1.6)
Lopinavir/ritonavir + remdesivir	2 (1.1)
Atazanavir	1 (0.5)
Darunavir + cobicistat	1 (0.5)
Lopinavir/ritonavir + darunavir	1 (0.5)
Lopinavir/ritonavir + oseltamivir	1 (0.5)
Lopinavir/ritonavir + ribavirin	1 (0.5)
Oseltamivir	1 (0.5)
Corticosteroids	69 (37.1)
Methylprednisolone	27 (14.5)
Hydrocortisone	9 (4.8)
Dexamethasone	9 (4.8)
Hydrocortisone + methylprednisolone	4 (2.2)
Dexamethasone + hydrocortisone + methylprednisolone	1 (0.5)
Dexamethasone + hydrocortisone + prednisolone	1 (0.5)
Dexamethasone + methylprednisolone	1 (0.5)
Methotrexate	1 (0.5)
Methylprednisolone + prednisone	1 (0.5)
Prednisolone	1 (0.5)
Prednisone	1 (0.5)
Nonspecified corticosteroids	13 (7.0)
Tocilizumab	51 (27.4)
Total	134 (72.0)

Appendix Table 4. Minimum inhibitory concentration values for *Aspergillus fumigatus* from 32 patients with coronavirus disease, March–August 2020

Antimicrobial drug, no. samples*	Antifungal susceptibility testing, no. (IQR)†		
	EUCAST n = 20	CLSI n = 1	E-test n = 11
Amphotericin B, 30	0.25 (0.25–0.5)	0.5 (0.5–0.5)	0.25 (0.125–0.38)
Anidulafungin, 5	0.008 (0.008–0.008)	0.008 (0.008–0.008)	
Caspofungin, 10	0.125 (0.125–0.125)		0.125 (0.125–0.25)
Micafungin, 1		0.008 (0.008–0.008)	
Isavuconazole, 22	0.5 (0.5–1)		0.06 (0.03–0.125)
Itraconazole, 25	0.5 (0.25–0.5)	16 (16–16)	0.38 (0.25–0.38)
Posaconazole, 24	0.064 (0.032–0.064)	0.5 (0.5–0.5)	0.125 (0.06–0.25)
Voriconazole, 31	0.5 (0.125–0.5)	2 (2–2)	0.094 (0.094–0.125)

*No. samples tested for susceptibility to each antifungal drug. One sample per patient.

†CLSI, Clinical and Laboratory Standards Institute (Reference 59 in Appendix); EUCAST, European Committee on Antimicrobial Susceptibility Testing (Reference 58 in Appendix).

Appendix Table 5. Antifungal treatments for aspergillosis in patients with coronavirus disease, March–August 2020

Treatment	no. (%)
VRZ	65 (34.9)
Isavuconazole	9 (4.8)
Liposomal AMB	8 (4.3)
VRZ + AMB + nebulized AMB, VRZ	7 (3.8)
Caspofungin	5 (2.7)
VRZ, isavuconazole	4 (2.2)
Posaconazole	3 (1.6)
VRZ, liposomal AMB	3 (0.6)
Anidulafungin	2 (1.1)
Caspofungin + VRZ, VRZ	2 (1.1)
Caspofungin, VRZ	2 (1.1)
Deoxycholate AMB	2 (1.1)
VRZ + AMB + nebulized AMB	2 (1.1)
Anidulafungin, anidulafungin + liposomal AMB, liposomal AMB	1 (0.5)
Anidulafungin, anidulafungin + liposomal AMB, liposomal AMB, anidulafungin + isavuconazole	1 (0.5)
Caspofungin + VRZ, VRZ, liposomal AMB	1 (0.5)
Caspofungin, isavuconazole	1 (0.5)
FLZ, VRZ	1 (0.5)
Isavuconazole + anidulafungin, anidulafungin	1 (0.5)
Isavuconazole + anidulafungin, isavuconazole	1 (0.5)
Isavuconazole, isavuconazole + nebulized AMB	1 (0.5)
isavuconazole, AMB lipid complex	1 (0.5)
liposomal AMB + anidulafungin	1 (0.5)
liposomal AMB, isavuconazole	1 (0.5)
liposomal AMB, isavuconazole, liposomal AMB	1 (0.5)
liposomal AMB, VRZ	1 (0.5)
liposomal AMB, VRZ, VRZ + caspofungin	1 (0.5)
AMB lipid complex	1 (0.5)
Micafungin, VRZ, isavuconazole, liposomal AMB	1 (0.5)
VRZ + anidulafungin	1 (0.5)
VRZ, ibrexafungerp*	1 (0.5)
VRZ, liposomal AMB + anidulafungin	1 (0.5)
VRZ, liposomal AMB, isavuconazole	1 (0.5)
VRZ, posaconazole	1 (0.5)
VRZ, VRZ + anidulafungin, liposomal AMB+ anidulafungin	1 (0.5)
VRZ, VRZ + caspofungin, VRZ	1 (0.5)
No antifungal treatment	49 (26.3)
Total	186 (100.0)

*Patient enrolled in the FURI Study (NCT 03059992; EuDra-CT 2017–000381–29). AMB, amphotericin B; FLZ, fluconazole; VRZ, voriconazole. + indicates drugs used in combination.

Appendix Table 6. Additional pathogens isolated from 186 patients with coronavirus disease–associated pulmonary aspergillosis, March–August 2020*

Sample	Pathogens	no. (%)
Blood	<i>Clostridium perfringens</i>	1 (0.5)
	Coagulase-negative Staphylococci	1 (0.5)
	<i>Enterococcus</i> spp.	1 (0.5)
	<i>Enterococcus faecium</i>	1 (0.5)
	<i>Pseudomonas aeruginosa</i>	2 (1.1)
	<i>Staphylococcus aureus</i>	1 (0.5)
	<i>Staphylococcus epidermidis</i>	3 (1.6)
	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus haemolyticus</i>	1 (0.5)
	<i>Stenotrophomonas maltophilia</i>	1 (0.5)
	Unknown bacteria	1 (0.5)
Blood + catheter tip	Coagulase-negative Staphylococci, blood; <i>Klebsiella pneumoniae</i> , catheter tip	1 (0.5)
Blood + lung	<i>Enterobacter cloacae</i> , blood; <i>Pseudomonas aeruginosa</i> , NBL	1 (0.5)
	<i>Enterococcus faecalis</i> , blood and tracheal aspirate; <i>Staphylococcus capitis</i> , blood	1 (0.5)
	<i>Enterococcus</i> spp., blood; <i>Serratia</i> spp., NBL	1 (0.5)
	<i>Pseudomonas aeruginosa</i> , bronchial aspirate	1 (0.5)
	<i>Staphylococcus aureus</i> , blood + <i>Klebsiella</i> spp., NBL + <i>Haemophilus</i> spp., NBL	1 (0.5)
Blood + lung + deep soft tissue	<i>Enterococcus faecium</i> ; <i>Elizabethkingia miciirola</i> , bronchial aspirate	1 (0.5)
Blood + urine	<i>Facklamia hominis</i> , blood; <i>Escherichia coli</i> , urine	1 (0.5)
Central nervous system	Herpes simplex virus	1 (0.5)
Lung	<i>Acinetobacter baumannii</i> , tracheal aspirate	1 (0.5)
	<i>Acinetobacter</i> spp., tracheal aspirate (n = 1) and sputum (n = 1)	2 (1.1)
	<i>Candida albicans</i> , low-respiratory tract NOS	2 (1.1)
	<i>Candida</i> spp., sputum	1 (0.5)
	<i>Citrobacter</i> spp., <i>Pseudomonas aeruginosa</i> , and <i>Herpes simplex virus</i> , bronchial aspirate	1 (0.5)
	<i>Corynebacterium striatum</i> ; <i>Bordetella bronchiseptica</i> , bronchial aspirate	1 (0.5)
	<i>Klebsiella pneumoniae</i> ; <i>Staphylococcus aureus</i> , tracheal aspirate	1 (0.5)
	<i>Klebsiella</i> spp., NBL	1 (0.5)
	<i>Klebsiella varicola</i> ; <i>Candida albicans</i> , tracheal aspirate	1 (0.5)
	<i>Pseudomonas aeruginosa</i> , tracheal aspirate	2 (1.1)
	<i>Stenotrophomonas maltophilia</i> , tracheal aspirate (n = 1) and sputum (n = 1)	2 (1.1)
Unspecified yeasts, bronchial aspirate	1 (0.5)	
Urinary tract	<i>Citrobacter amalonaticus</i>	1 (0.5)
	<i>Enterococcus faecium</i>	1 (0.5)
Total		40 (21.5)

*NBL, nondirected bronchial lavage; NOS, not otherwise specified

Appendix Table 7. Other conditions and exposures of 186 patients with coronavirus disease–associated pulmonary aspergillosis, March–August 2020

Condition	no. (%)
Acute renal failure requiring dialysis	13 (7.0)
Sepsis	10 (5.4)
Acute liver failure	9 (4.8)
Lymphopenia	8 (4.3)
Hypothyroidism	7 (3.8)
Rheumatic or autoimmune disorder	7 (3.8)
Ex-smoker	6 (3.2)
Smoker	6 (3.2)
Thrombocytopenia	6 (3.2)
Septic shock	4 (2.2)
Benign prostatic hypertrophy	3 (1.6)
Chronic liver failure	3 (1.6)
Non-ST segment elevation myocardial infarction	3 (1.6)
Acute renal failure requiring renal substitution	2 (1.1)
Chronic renal failure requiring dialysis	2 (1.1)
Depression	2 (1.1)
Exposure to fungicides or manipulation of organic matter possibly containing triazole-resistant isolates of <i>Aspergillus fumigatus</i>	2 (1.1)
History of pulmonary tuberculosis	2 (1.1)
Multiorgan dysfunction syndrome	2 (1.1)
Liver failure not otherwise specified	2 (1.1)
Psychiatric disorder	2 (1.1)
Alcoholism	1 (0.5)
Aneurysm coiling right arteria vertebralis	1 (0.5)
Atrial myxoma	1 (0.5)
CD8+ T-cell lymphocytosis	1 (0.5)
Contact with a patient with coronavirus disease	1 (0.5)
Cured thyroid cancer	1 (0.5)
Dementia	1 (0.5)
Epilepsy	1 (0.5)
Flavectomy and nucleotomy	1 (0.5)
Gas gangrene	1 (0.5)
Glaucoma	1 (0.5)
Hospital-acquired pneumonia	1 (0.5)
Hypercholesterinemia	1 (0.5)
Hyperkalemia	1 (0.5)
Hyperparathyroidism secondary to chronic kidney disease	1 (0.5)
Hyperthyroidism	1 (0.5)
Hypercholesterolemia	1 (0.5)
Hyperlipidemia	1 (0.5)
Laparoscopic cholecystectomy for cholecystitis	1 (0.5)
Mastoiditis	1 (0.5)
Osteopenia	1 (0.5)
Polyneuropathy	1 (0.5)
Posterior reversible encephalopathy syndrome	1 (0.5)
Previous hepatitis B	1 (0.5)
Reactivation of cytomegalovirus	1 (0.5)
Recent stroke	1 (0.5)
Sinusitis	1 (0.5)
Sleep apnea syndrome	1 (0.5)
Stenosis of the left internal carotid artery	1 (0.5)
Suspected pulmonary fibrosis	1 (0.5)
Thyroidectomy	1 (0.5)
Umbilical hernia	1 (0.5)
Vertebral disc herniation left L4/5	1 (0.5)
Total	67 (36.0)

Appendix Table 8. Distribution of patients with coronavirus disease–associated pulmonary aspergillosis, March–August 2020

Country	Data source, no. (%)			Total, no. (%)
	FungiScope	FungiScope + Literature	Literature	
Argentina		1 (0.5)		1 (0.5)
Australia			1 (0.5)	1 (0.5)
Austria			1 (0.5)	1 (0.5)
Belgium	4 (2.2)		4 (2.2)	8 (4.3)
Brazil	2 (1.1)		1 (0.5)	3 (1.6)
Denmark			2 (1.1)	2 (1.1)
France	18 (9.7)	9 (4.8)	12 (6.5)	39 (21.0)
Germany	17 (9.1)	4 (2.2)	2 (1.1)	23 (12.4)
Ireland			1 (0.5)	1 (0.5)
Italy	4 (2.2)	30 (16.1)	2 (1.1)	36 (19.4)
Mexico	6 (3.2)			6 (3.2)
Netherlands	3 (1.6)		11 (5.9)	14 (7.5)
Pakistan			9 (4.8)	9 (4.8)
Qatar			2 (1.1)	2 (1.1)
Spain	3 (1.6)	23 (12.4)		26 (14.0)
Switzerland			3 (1.6)	3 (1.6)
United Kingdom			11 (5.9)	11 (5.9)
Total	57 (30.6)	67 (36.0)	62 (33.3)	186 (100.0)