Invasive fungal disease in patients with severe COVID-19 infection at a midwestern academic medical center

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Background

- Invasive fungal diseases (IFD) have been described in patients with severe coronavirus disease 2019 (COVID), albeit with substantial geographic variability in rates
- Rates of IFD are not well characterized in the United States, and most data are from early pandemic months
- A recent pilot study in our institution noted rates of CAPA at 1%
- As CAPA awareness raised and standard of care evolved, we sought to reassess the occurrence of COVID-19 associated IFD in our institution as the pandemic progressed

Methods

- This is a retrospective observational study of rates of IFD and risk factors for IFD within 30 days of admission to intensive care unit (ICU) for severe COVID between 5/11/2020 and 2/7/2021 at University of Michigan Hospital in Ann Arbor, MI, a 1100-bed tertiary medical center
- Severe COVID was defined as requiring advanced respiratory support with heated high flow nasal cannula of 40%/40L or more, noninvasive ventilation, or invasive mechanical ventilation, or shock requiring vasopressor support
- ECMM/ISHAM criteria were used for COVID-associated pulmonary aspergillosis (CAPA) and EORTC/MSGERC were criteria used for other IFD
- Groups were separated into patients who developed IFD (IFD Group) within 30d of ICU start date, and patients who did not develop IFD within 30d of ICU start date (No IFD Group)
- Groups were compared using Fisher's exact test or two-tailed t-test
- Outcomes included overall mortality at 30 and 90 days after diagnosis of COVID-19, and 84 days after diagnosis of IFD

Results

218 pts were included; median age was 62 (19 – 91) & 63% were men

Underlying conditions included:

- cirrhosis (2; 1.0%)
- end-stage renal disease (6; 2.8%)
- solid organ transplant (Tx) (16; 7%)
- allogenic stem cell Tx (3; 1%)
- malignancy (21; 10%)
- exposure to either high-dose steroids (HDS) within 90 d prior to COVID dx (11; 5%)
- exposure or T- or B-cell suppressants within 90 d prior to COVID dx (29; 13%)

COVID with IFD vs COVID without IFD:

- There were no significant differences between groups with regards to age, gender or underlying conditions, however **B**MI was significantly higher among patients who developed IFD vs those who did not develop IFD (BMI > 30; 11 (91.7%) vs. 104 (50.4%) (p = 0.0059).

- Patients who developed IFI had significantly longer mean ICU durations (37.5d +/- 31.2) than those without IFI (17.3 +/- 19.4) (p = 0.00922) and had a longer delay between COVID diagnosis and ICU admission (11.6 +/- 6.6 and 5.5 +/- 6.3 respectively, p = 0.001455)

Results

Table 1: Demographics and details on patients who developed invasive mold infections within 30d of ICU admission.

Sex	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age / Sex	66 F	48 F	63 M	70 M	83 F	60 M	35 M
Relevant Comorbidities	BMI >30, chronic obstructive pulmonary disease	BMI >30, diabetes mellitus	BMI >30, rheumatoid arthritis on low-dose (10mg) prednisone, ulcerative colitis, primary biliary cholangitis	BMI >30	Microscopic polyangiitis on low-dose (5mg) prednisone	BMI >30	BMI >30, diabetes mellitus
IFD	CAPA	CAPA	CAPA	CAPA	CAPA	CAPA	*Paecilomyces spp.* pneumonia
Days from COVID dx to IFD dx	11d	23d	40d	10d	-1d***	18d	22d
Mechanical ventilation	Yes, 17d	Yes, 14d	No	Yes, 36d	No	Yes, 9d	Yes, 33d
ECMO	No	No	No	No	No	No	No
Acute RRT	Yes	No	No	No	No	Yes	Yes
COVID Therapies	RDV, CTS, CP	RDV, CTS, CP	RDV, CTS	RDV, CTS	RDV, CTS	RDV, CTS, CP	RDV, CTS
Classic host factors for IFD*	None	None	Prolonged corticosteroids^	None	None	None	Prolonged corticosteroids^
Mycological findings	Tracheal aspirate: *A. fumigatus*; Tracheal GM 6.6	Tracheal aspirate: *A. fumigatus*	Sputum: *A. fumigatus*	Tracheal aspirate: *A. fumigatus*	BAL: *A. fumigatus*	Tracheal aspirate: *A. fumigatus,* serum GM 3.3	Tracheal aspirate: *Paecilomyces* spp.
Radiological findings	CT confluent and peripheral nodular opacities	CXR: Diffuse interstitial and airspace opacities	CXR: Diffuse interstitial infiltrates	CT: Confluent consolidations and ground glass opacities	CT: Ground glass opacities with peri-bronchial consolidation and small nodule	CXR: Interstitial opacities	CT: Multiple cavitary lesions
IFD Classification**	Possible	Possible	Possible	Possible	Probable	Probable	Probable
Antifungal therapy (duration)	VCZ (13d)	VCZ (28d)	VCZ (6 months)	VCZ (27d)	VCZ (4d)	VCZ (4d)	VCZ (21d), L-AMB (6d), PSZ x 7d, ITZ (16.5 weeks)
84d outcome	Deceased	Alive	Alive	Deceased	Deceased	Deceased	Alive

(IFD: invasive fungal disease, CAPA: covid-associated aspergillosis, dx: diagnosis, RDV: Remdesivir, CTS: corticosteroids, CP: convalescent plasma, CT: thoracic computed tomography, CXR: chest x-ray, ECMO: extracorporeal membrane oxygenation, RRT: renal replacement therapy, PSZ: posaconazole, L-AMB: liposomal amphotericin B, VCZ: voriconazole, ITZ: itraconazole, MFG: micafungin, FLU: fluconazole, 5-FC: flucytosine, BAL: bronchoalveolar lavage, GM: galactomannan)
* Classic host factors defined as per EORTC/MSGERC criteria
** CAPA classification as per ECMM/ISHAM consensus criteria, other mold criteria as per EORTC/MSGERC criteria
*** Patient was admitted with respiratory failure of initially unclear etiology, later determined to be COVID-19 on repeat testing with initially negative testing, underwent bronchoscopy prior to diagnosis of COVID-19.
^ Defined as 3 or more weeks of 0.3mg/kg of prednisone-equivalent steroids prior to IFD diagnosis

Table 2: Demographics and details on patients who developed candidemia within 30d of ICU admission.

Sex	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age / Sex	55 M	61 M	58 M	67 M	77 F
Relevant Comorbidities	Obesity, diabetes mellitus	Obesity	Obesity	Diabetes mellitus, asthma	Obesity, diabetes mellitus
IFD	Candidemia	Candidemia	Candidemia	Candidemia	Candidemia
Days from COVID dx to IFD dx	39d	37d	14d	35d	19d
Mechanical ventilation	Yes	Yes	Yes	Yes	No
ECMO	No	No	No	No	No
Acute RRT	Yes	Yes	Yes	No	Yes
COVID Therapies	RDV, CTS, CP	RDV, CTS, CP	RDV, CTS	RDV, CTS, CP	RDV, CTS
Classic host factors for IFID	Prolonged corticosteroids^	Prolonged corticosteroids^	None	Prolonged corticosteroids^	None
Candida species	*C. albicans*	*C. parapsilosis*	*C. glabrata*	*C. krusei*	*C. albicans*
Mycological	Positive blood culture	Positive blood culture	Positive blood culture	Positive blood culture	Positive blood culture
Central line 14 day prior to *Candida* infection	Yes	Yes	Yes	Yes	Yes
Antifungal Therapy	MFG (3d), FLU (12d)	MFG (3d), FLU (5d), MFG + FLU (10d), L-AMB + 5-FU (23d)	MFG (14d)	MFG (14d)	None, diagnosed postmortem
Central line disposition	2/2 CVC removed (9d, 16d after dx)	2/2 CVC removed (2d, 3d after dx); one replaced same day	2/2 CVC removed/replaced same day (1d, 2d after dx)	1/1 CVC removed (2d after dx)	Not applicable, diagnosed postmortem
84d outcome	Alive	Deceased	Alive	Deceased	Deceased

Table 3: Comparison of therapeutic interventions for COVID-19 in patients who did not develop IFD within 30d of ICU onset vs. those who did develop IFD within 30d of ICU admission.

Therapeutics	Overall, n (%)	No IFD, n (%)	IFD, n (%)	p-value
Organ support within 30 days of COVID-19 diagnosis				
Mechanical ventilation	127 (58.3%)	118 (57.3%)	9 (75%)	0.37
Days on mechanical ventilation; median [range]	13 [1 – 118]	12 (1 – 118)	36 (9 – 94)	
Days on mechanical ventilation; mean (SD)	22.4 (+/- 23.2)	20.6 (+/- 22)	42.9 (+/- 28.2)	**0.0052**
Extracorporeal membrane oxygenation	15 (6.9%)	15 (7.3%)	0 (0%)	1
Acute renal replacement therapy	32 (14.7%)	25 (12.1%)	7 (58.3%)	**0.0004**
COVID-19 Pharmacologic/Biologic Treatment				
Corticosteroids	205 (94.0%)	193 (93.6%)	12 (100%)	1
Remdesivir	202 (92.7%)	190 (92.2%)	12 (100%)	0.61
Tocilizumab	10 (4.6%)	10 (4.9%)	0 (0%)	1
Convalescent Plasma	68 (31.2%)	62 (30.1%)	6 (50%)	0.20

OUTCOMES:

- **30-day all cause mortality** overall was 26.1% (57 of 218), with no significant difference between patients developing IFD (4 of 12, 33.3%) and those not developing IFD (53 of 206, 25.7%) (p = 0.52)
- **90-day all cause mortality** overall was 37.6% (82 of 218), with no significant difference between patients developing IFD (7 of 12, 58.3%) and those not developing IFD (75 of 206, 36.4%)(p = 0.14)
- **84-day mortality** from time of IFD diagnosis was 58.3% (7 of 12)

Conclusions

- Rates of IFD associated with severe COVID at our institution remained low as the COVID pandemic progressed.
- Except for patients who received prolonged high-dose steroids for COVID treatment, patients who developed COVID-associated IFD had no "classic" risk factors.
- Patients with COVID-associated IFD were more likely to have had a BMI >30, required longer ICU stays, spent longer time on mechanical ventilation, and required acute renal replacement therapy during their clinical course, when compared to those patients with severe COVID who did not develop IFD.
- Most post-COVID IFD cases included CAPA and catheter-associated candidemia. No mucormycosis was observed.
- Overall mortality of patients with severe COVID was similar among patients who developed IFD and those who did not.