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Concise Communication

Association between negative-pressure room utilization and hospital-acquired *Aspergillus* rates in patients with coronavirus disease 2019 (COVID-19) in two academic hospitals

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Abstract

Hospital-acquired *Aspergillus* rates among coronavirus disease 2019 (COVID-19) patients were initially higher at a hospital with high negative-pressure room utilization compared to a similar hospital with low utilization but with otherwise identical infection control policies. After the index hospital decreased negative-pressure utilization, hospital-acquired *Aspergillus* case rates at the 2 hospitals converged.

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Invasive aspergillosis is a common complication in patients with severe coronavirus disease 2019 (COVID-19).[1,2] Predisposing factors include severe acute respiratory coronavirus virus 2 (SARS-CoV-2)–induced epithelial lung damage, lymphopenia, and cellular immune dysfunction as well as broad-spectrum antibiotics, corticosteroids, and other immunosuppressants.[3] Early in the pandemic, many hospitals converted standard-pressure rooms to negative pressure to mitigate airborne transmission of SARS-CoV-2. Negative-pressure rooms, however, may increase airborne fungal spore levels and, in one small case series, were associated with a high rate of *Aspergillus* clinical infections in patients with SARS-CoV-2.[4,5] In light of this possible risk, we evaluated the impact of caring for COVID-19 patients in negative-pressure versus standard-pressure rooms on hospital-acquired *Aspergillus* in 2 hospitals with different negative-pressure room utilization rates but otherwise similar infection control policies.

Mass General Brigham (MGB) includes 2 major academic hospitals, Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) in Boston, Massachusetts. Both hospitals have high case-mix indices and provide comprehensive medical and surgical services; BWH also serves as an inpatient hospital for Dana Farber Cancer Institute and therefore cares for a large oncology population. MGH has a fixed, limited number of designated airborne infection isolation rooms (AIIRs) that were prioritized for COVID-19 patients undergoing aerosol-generating procedures (AGPs); BWH, by contrast, converted all rooms across multiple wards to modified AIIRs to care for nearly all COVID-19 patients early in the pandemic (regardless of AGPs). Between March and August 2020, 96% of COVID-19 patient days at BWH occurred in negative pressure versus 22% at MGH.[6] In March 2021, however, BWH shifted to using only a small and fixed number of designated AIIRs, similar to MGH. Infection control policies for both hospitals were otherwise shared and identical.

We evaluated the association between negative pressure use and pulmonary *Aspergillus* rates in COVID-19 patients by comparing the average incidence rates between the 2 hospitals before and after the shift from high to low negative-pressure utilization at BWH. We used MGH as a control hospital to account for changes in climate, season, vaccination, COVID-19 disease severity, and treatment patterns over time.

Methods

This retrospective study of patients hospitalized at MGH and BWH with COVID-19 was conducted between March 2020 and February 2022. SARS-CoV-2 PCR–positive patients were flagged for COVID-19 in the electronic health record. We excluded patients with COVID-19 flags for ≤3 days, an indication that the infection control team deemed PCR results to be false positives or residual RNA from resolved infections.[7] Among patients with COVID-19, we defined hospital-acquired *Aspergillus* as a positive respiratory culture for *Aspergillus* spp, or a serum or bronchoalveolar lavage galactomannan ≥0.5, first detected ≥7 days after admission. We did not attempt to distinguish invasive infections from colonization because infection control programs strive to prevent all instances of hospital-acquired *Aspergillus,* given that colonization is a potential precursor to invasive infection.

For each hospital, we determined the number of hospital-acquired *Aspergillus* cases per month, and the total number of hospitalization days for all COVID-19 patients admitted each

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Table 1. Characteristics and Outcomes of COVID-19 Patients With and Without Hospital-Acquired *Aspergillus* Colonization or Infections at Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH)

Characteristic	COVID-19 Patients at BWH without *Aspergillus* (n=3,188), No. (%)[a]	COVID-19 Patients at MGH without *Aspergillus* (n=6,001), No. (%)[a]	COVID-19 Patients with *Aspergillus* at BWH and MGH (n=55), No. (%)[a]
Age, median y (IQR)	60 (43–72)	59 (41–73)	66 (56-75)
Sex, male	1,511 (47)	3,351 (56)	36 (65)
Race, white	1,663 (52)	3,435 (57)	37 (67)
Elixhauser mortality score, median (IQR)	2.0 (−1.0 to 18.5)	0.0 (−3.0 to 13.0)	13 (0.5–25.0)
Cancer	522 (16)	512 (9)	12 (22)
Cardiovascular disease	376 (12)	688 (11)	10 (18)
Diabetes	964 (30)	1858 (31)	29 (53)
Kidney disease	579 (18)	1059 (18)	21 (38)
Chronic lung disease	670 (21)	1255 (21)	21 (38)
Congestive heart failure	511 (16)	930 (15)	15 (27)
Hypertension	1713 (54)	3171 (53)	40 (73)
Liver disease	224 (7)	567 (9)	6 (11)
Obesity	630 (20)	1346 (22)	17 (31)
Dexamethasone receipt during hospitalization	887 (28)	1,845 (31)	36 (65)
Required ICU admission	962 (30)	1,282 (21)	47 (85)
Underwent galactomannan testing	400 (13)	216 (4)	48 (87)
Positive aspergillus marker (day ≥7)	N/A	N/A	
Respiratory culture			41 (75)
Serum galactomannan			12 (22)
BAL galactomannan			12 (22)
Median days from admission to first positive marker (IQR)			12 (7–21)
Hospital length of stay, median d (IQR)	6 (3–12)	5 (3–11)	26 (17–48)
In-hospital death	249 (8)	462 (8)	30 (55)

Note. IQR, interquartile range; ICU, intensive care unit.
[a]Units unless otherwise specified.

month during the period they were flagged as COVID-19 ("COVID-19 patient days," corresponding to the period where they would be potentially eligible for negative-pressure rooms). We calculated monthly rates of hospital-acquired *Aspergillus* per COVID-19 patient days.

We used Poisson regression to compare the average incidence rates between hospital-acquired *Aspergillus* rates at MGH versus BWH before and after March 1, 2021, when BWH transitioned from high to low utilization of negative-pressure rooms. The study was approved by the MGB Institutional Review Board with a waiver of informed consent.

Results

Between March 2020 and February 2022, 3,219 patients were hospitalized with COVID-19 at BWH for 23,016 COVID-19 patient days, of whom 31 developed hospital-acquired *Aspergillus*. At MGH, 6,025 COVID-19 patients were hospitalized for 44,524 COVID-19 patient days, of whom 24 developed hospital-acquired *Aspergillus*. Compared with MGH, COVID-19 patients at BWH more often required ICU care and had a greater burden of cancer. Compared with COVID-19 patients without hospital-acquired *Aspergillus*, those with *Aspergillus* were generally older with more comorbidities, longer hospital stays, and had higher rates of ICU admission, dexamethasone receipt, and in-hospital mortality (Table 1). Hospital-acquired *Aspergillus* rates were significantly higher at BWH versus MGH during the period of high negative-pressure utilization at BWH (1.8 vs 0.4 cases per 1,000 patient days; $P = .0007$), but following the transition to low negative-pressure utilization in March 2021 there was no significant difference between the 2 hospitals (1.3 vs 0.9 cases per 1,000 patient days; $P = .55$) (Fig. 1).

Discussion

We compared hospital-acquired pulmonary *Aspergillus* rates among patients hospitalized with COVID-19 at 2 academic hospitals with identical infection control policies but different negative-pressure utilization rates early in the pandemic. The hospital with high negative-pressure utilization initially had significantly higher hospital-acquired *Aspergillus* rates, but this

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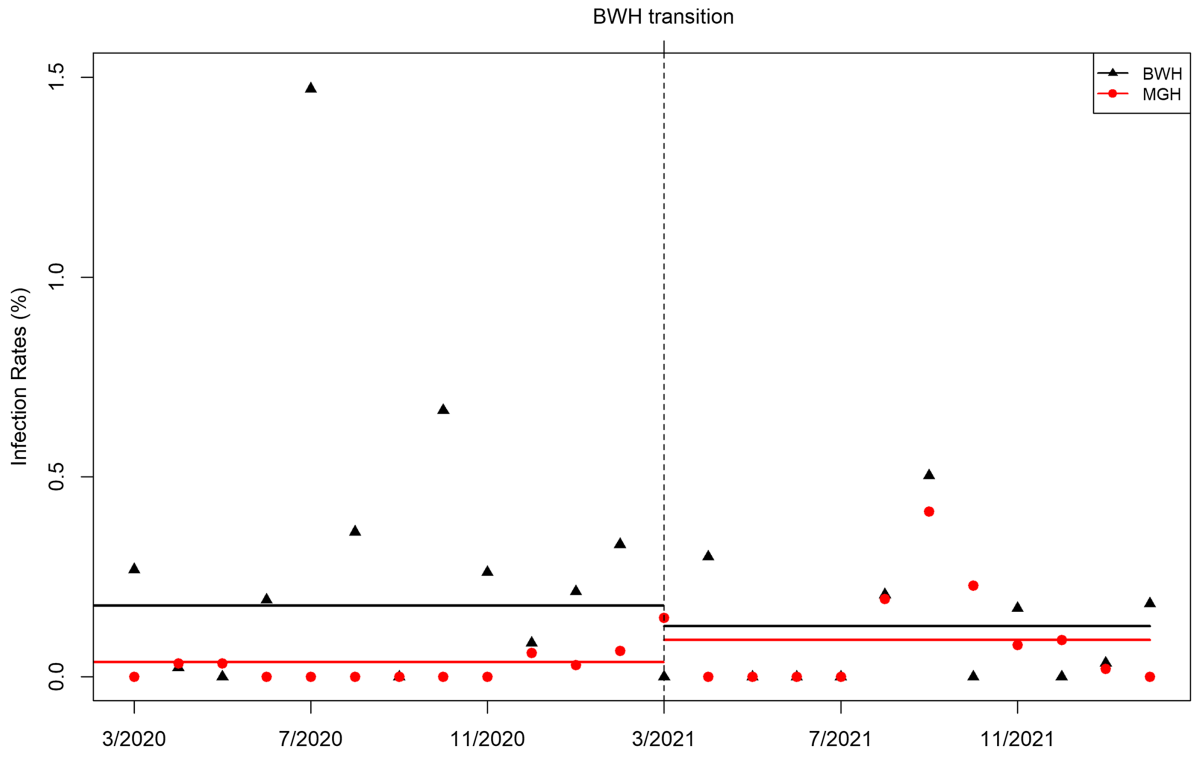

Figure 1. Monthly hospital-acquired *Aspergillus* rates in COVID-19 patients at Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH). Each time point represents a month of data; COVID-19 patients were assigned to their month of admission. *Aspergillus* rates were defined by positive respiratory cultures or elevated serum or bronchoalveolar lavage galactomannan levels (≥0.5). The vertical dotted line in March 2021 indicates the period when BWH shifted from high to low negative-pressure room utilization using a targeted strategy as per MGH. The solid lines represent the estimated mean incidence rates before and after the BWH transition.

gap decreased and was no longer significant after shifting to low negative-pressure use. This supports the concern that negative pressure may increase the risk of *Aspergillus* infections in patients with COVID-19.

Outbreaks of environmental airborne fungal infections have been reported in highly immunocompromised patients, with corresponding reductions in infection rates after controlling environmental exposures.[8] Negative pressure has also been associated with higher fungal airborne concentrations in negative-pressure rooms versus standard- or positive-pressure rooms.[5] One case series in France reported that 6 (23%) of 26 critically ill COVID-19 patients developed invasive aspergillosis when managed in modified negative-pressure rooms, with air sampling confirming high *Aspergillus* levels. The hospital consequently shifted from negative-pressure to positive-pressure rooms for ICU patients with COVID-19 and noted a marked decrease in positive air samples and no *Aspergillus* infections in the ensuing 3 months.[4] This study, however, did not have a control group to account for possible temporal changes in environmental factors (eg, temperature, humidity, season) and the characteristics and treatments for COVID-19 patients.

Although our study benefits from a control hospital and a relatively long follow-up period, we acknowledge several limitations. First, we did not directly account for characteristics of patients cared for in negative versus standard rooms and their specific treatments, nor were we able to assess associations between negative pressure and *Aspergillus* risk on a room-by-room basis; rather, we conducted a population-based analysis at the hospital level. Second, we did not distinguish invasive *Aspergillus* infections versus colonization. However, we expect that increased environmental exposure would predispose patients to both. Third, the number of hospital-acquired *Aspergillus* cases was low at both hospitals, limiting our power to detect small changes. Fourth, fungal cultures and galactomannan levels were not measured in all patients so some hospital-acquired *Aspergillus* cases may have been missed.[9] Similarly, differences in galactomannan or fungal culture testing practices between the 2 hospitals could have affected *Aspergillus* rates. Fifth, we did not perform air sampling to correlate room pressures with *Aspergillus* spore levels. Lastly, we did not account for construction or other environmental changes that may have occurred at either hospital.

In conclusion, hospital-acquired *Aspergillus* rates among COVID-19 patients were initially high in a hospital with high negative-pressure utilization versus a similar hospital with low negative-pressure utilization but otherwise identical infection control policies. Hospital-acquired *Aspergillus* rates then decreased following a shift to low negative-pressure utilization and were similar to those of the comparison hospital. Further evaluation of the relative merits versus risks of negative- versus standard-pressure rooms for patients with COVID-19 and other airborne pathogens are warranted.

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Competing interests. Dr Klompas reports royalties from UpToDate, Inc, for authoring chapters related to hospital-acquired pneumonia prevention. Dr Rhee reports royalties from UpToDate, Inc, for authoring chapters related to procalcitonin use in respiratory infections. All other authors report no conflicts of interest relevant to this article.

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