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Clearing the Air: Acute Invasive Fungal Rhinosinusitis in Hematologic Cancer Patients

Ezra Pak-Harvey, BA; Daniel Lubin, MD; Amy Chen, MD, MPH, FACS; Elizabeth Willingham, MD

Objectives: Air quality has been shown to impact the rates of fungal infection of the airway, causing diseases such as acute invasive fungal rhinosinusitis (AIFRS), particularly in immunocompromised patients. We theorize that patients with hematologic malignancies in units with aging air handling units (AHUs) have a higher attack rate of AIFRS.

Methods: Retrospective chart review identified patients with hematologic malignancy and AIFRS in two distinct and equal time periods between 2013 and 2022, representing the presence of aging AHUs and new AHUs, respectively. Cubic feet per minute (CFM) air flows, AIFRS attack rates, and clinical data were compared between the two groups and statistical analyses performed.

Results: The older AHUs produce air flow of 27,610 CFM and the newer AHUs produce air flow of 80,000 CFM. There were 18 patients with air supplied by older AHUs and 7 patients with air supplied by new AHUs who developed AIFRS. There was a significantly higher AIFRS attack rate for patients supplied by the older AHUs compared with patients supplied by newer AHUs ($p = 0.033$). The patients supplied by the older AHUs tended to be younger. The white blood cell counts, absolute neutrophil counts, and the mean time to diagnosis did not differ between the two groups.

Conclusions: To our knowledge, this is the first study to examine AIFRS in immunocompromised patients' inpatient environment. Further research should explore whether higher CFM AHUs can decrease this disease among our most vulnerable patients.

Key Words: AIFRS, air flow, hematologic cancer, HVAC, invasive fungal sinusitis, risk factors.

Level of Evidence: 3

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INTRODUCTION

Fungal rhinosinusitis (FRS) encompasses a broad spectrum of diseases and is broadly split into two categories: invasive and noninvasive, based on the presence or absence of fungal invasion into sinonasal mucosa.[1] Although noninvasive FRS is a serious disease requiring careful medical and surgical management, invasive FRS has a more aggressive course and has been reported to have a mortality rate of up to 80%.[1,2] Invasive FRS can be further subdivided into three types: acute invasive FRS (AIFRS), chronic invasive FRS, and chronic granulomatous invasive FRS.[3] Of these three, AIFRS is the most common.[4]

AIFRS has been defined as 'the presence of fungal hyphae within the sinonasal mucosa, submucosa, vasculature, or bone, in the setting of one month or less of sinusitis symptoms'.[5] This disease is most often seen in two primary subsets of patients: immunosuppressed patients, such as those with hematologic malignancies, or undergoing bone marrow transplantation, and diabetics. The two most common causative organisms of AIFRS are *Aspergillus* and the Zygomycetes order, including *Mucor* and *Rhizopus*. Diabetic patients with AIFRS will often have *Mucor* or *Rhizopus* isolated from biopsy and cultures, while immunosuppressed patients often have *Aspergillus* isolated.[3] The etiology of AIFRS is poorly understood. However, it is theorized that inhalation of omnipresent fungal elements in the air leads to colonization and eventual invasion of sinonasal mucosa. Importantly, AIFRS is exceedingly rare in immunocompetent patients, whereas those with diabetes, using corticosteroids, undergoing chemotherapy, or with any form of immunosuppression are at higher risk.[6] Diagnosis for AIFRS is confirmed by tissue biopsy and is aided by imaging, showing mucosal thickening and invasion outside of the sinuses. Once a diagnosis is made, management is comprised of surgical resection, anti-fungal therapy, and treatment of underlying disease. Despite aggressive management, the prognosis for patients with AIFRS remains poor.

Given the severity of AIFRS, emphasis should be placed on its prevention through careful identification and minimization of environmental risk factors. In this study, we hypothesized that older air-handling units may contribute to an increased attack rate of AIFRS in hematologic cancer patients. Specifically, this study analyzed

From the Department of Otolaryngology-Head and Neck Surgery (E.P.-H., A.C., E.W.), Emory University School of Medicine, Atlanta, Georgia, U.S.A.; Department of Pathology and Laboratory Medicine (D.L.), Emory University School of Medicine, Atlanta, Georgia, U.S.A.

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Amy Chen and Elizabeth Willingham Co-Senior Authors.

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Send correspondence to Elizabeth Willingham, Department of Otolaryngology, Head and Neck Surgery, Emory University, 550 Peachtree St, MOT Suite 1135, Atlanta, GA 30308. Email: elizabeth.willingham@emory.edu

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the functional capabilities of AHUs and AIFRS in hematologic cancer patients at a large tertiary care center in Atlanta, GA. With this study, we hope to establish a relationship between the attack rate of AIFRS and the age and functional capabilities of air-conditioning units.

MATERIALS AND METHODS

This retrospective study analyzed the attack rates of acute invasive fungal rhinosinusitis in patients with hematologic malignancies in two locations and two time periods in Emory University Hospital. The first period examined was from 2/28/13 to 11/1/17, with 11/1/17 being the date of opening of a new hospital floor supplied by new AHUs. The second period was from 11/1/17 to 7/5/22, with 7/5/22 being the date of conception of the study. The start date of the first period was chosen because it creates an equal number of days for the first and second time periods. In the first period, patients were housed in a portion of the hospital supplied by older, less effective AHUs. In the second period, patients were housed in a new hospital floor supplied by newer and more effective AHUs. None of the patients who developed AIFRS on the new hospital floor had been previously housed on the older floor during their admission.

The Emory University Institutional Review Board approved the study (STUDY00004486). Documented cases of AIFRS with a concurrent hematologic cancer diagnosis from 2/28/13 to 7/5/22 were identified and the medical records were reviewed. Patients who were referred from other care centers, patients with pre-existing diagnoses of AIFRS, and patients without a hematologic cancer diagnosis were excluded. Patient location, age, race/ethnicity, gender, length of time from admission to diagnosis, white blood cell count at time of surgery, mortality secondary to AIFRS, antifungal prophylaxis, automated absolute neutrophil count, and comorbid conditions at time of admission were collected.

Statistical analysis was conducted using Microsoft Excel as well as a comparison of two rates calculator.[7] The attack rates of AIFRS in EUH from 2/28/13 to 11/1/17 (1707 days) and from 11/1/17 to 7/5/22 (1707 days) were calculated. For our analysis, we estimated the attack rates of cases using the number of total beds in the old and new floors as our denominator for patients at risk (62 and 92, respectively). Census data and length of stay for the study time period were unavailable for analysis due to a recent transition in the electronic medical record utilized at our institution. In the setting of this limitation, the incidence of AIFRS could not be calculated. The authors instead used a proportion calculation where the number of beds in the old and new hospital units served as the constant denominator (62 and 92 respectively), assuming all beds were consistently full and that all patients were at risk of AIFRS. The number of cases of AIFRS/person at risk gives the "attack rate" of 18 of 62 and 7 of 92 respectively. It is noteworthy that the number of cases in the new unit is lower despite a larger denominator (number of beds).

The attack rate difference was determined with 95% confidence intervals. The *P*-value for attack rate difference was obtained using a Chi-square method. Additionally, one sided t-tests were used to compare average values for age, length of time from admission to surgical intervention, white blood cell count, and absolute neutrophil count. *P*-values below 0.05 were considered statistically significant.

RESULTS

From 2013 to 2017, there were 18 hematologic cancer patients with a pathology-confirmed diagnosis of AIFRS who had air supplied by older AHUs. From 2017 to 2022, there were seven hematologic cancer patients diagnosed with AIFRS who had air supplied by the newer AHUs (Table I). Patients diagnosed with AIFRS had varying hematologic/oncologic diseases at the time of diagnosis, with the most common being acute myeloid leukemia (AML) (Table II). Species isolated from surgical samples included *Fusarium*, *Curvularia*, *Trichoderma*, *Rhizopus*, *Aspergillus*, *Candida*, and *Bipolaris*; however, not every patient had speciation following surgery. There was a statistically significant difference in AIFRS attack rates for patients with air supplied by the older AHUs than those with air supplied by the newer AHUs (95% CI: 0.0129–0.3178, $p = 0.033$). Additionally, patients diagnosed with AIFRS who had air supplied by the older AHUs tended to be younger ($p = 0.02081$). There was no significant difference in absolute neutrophil count, mean white blood cell counts, or mean time to diagnosis between the two groups (Table I).

In comparing the AHUs, the newer AHUs installed in 2017 were found to have 80,000 cubic feet per minute (CFM) of air flow, whereas the older AHUs installed in 1987 were found to have 27,610 CFM (Table I). Differences in the filtration systems of the AHUs were also noted. Filters are rated based on their minimum efficiency reporting value (MERV), which reports a filter's ability to capture particles between 0.3 and 10 microns

TABLE I.
AIFRS Patient Clinical Data and Results of Statistical Testing.

	Older AHUs	Newer AHUs	*p* value
AIFRS Cases	18	7	$p = 0.033$
Mean Age	40.3 ± 18.5 years	56.4 ± 10.3 years	$p = 0.02$
Mean ANC (cells/uL)	976 ± 2562	55 ± 62	$p = 0.18$
Mean WBC Count	0.96 ± 1.95	0.53 ± 0.57	$p = 0.29$
Mean time to Diagnosis	24.2 ± 13.9 days	17.7 ± 6.9 days	$p = 0.12$
AHU Air Flow (CFM)	27,610	80,000	
Patients on Antifungal Prophylaxis	18	5	
Mortality Due to AIFRS	1	1	

AHU = air handling unit; AIFRS = acute invasive fungal rhinosinusitis; ANC = absolute neutrophil count; CFM = cubic feet per minute; WBC = white blood cell.

TABLE II.
AIFRS Patient Hematologic/Oncologic Diagnosis at Time of Infection.

Cancer Type	Older AHUs	Newer AHUs
Acute Myeloid Leukemia	8	2
Acute Lymphocytic Leukemia	2	1
Chronic Myeloid Leukemia	0	1
Chronic Lymphocytic Leukemia	0	1
Myelodysplastic Syndrome	1	1
Burkitt's Lymphoma	2	0
Angioimmunoblastic T-Cell Lymphoma	1	0
Marginal Zone Lymphoma	0	1
Other*	4	0
Total	18	7

AHU, air handling unit; AIFRS, acute invasive fungal rhinosinusitis.
*Including hemophagocytic syndrome (1), aplastic anemia (2), and plasmacytoid dendritic cell neoplasm (1).

with a percentage of particles expected to be removed from the air.[8] The older AHUs used MERV 11 filters, MERV 14 filters, and a high-efficiency particulate air (HEPA) filter (a total of three filters). The newer AHUs used MERV 13 filters and a HEPA filter (a total of two filters). Please see Table III for the technical data on filtration systems. Furthermore, patients diagnosed with AIFRS who had air supplied by the older AHUs were all prescribed antifungal prophylaxis with drugs including fluconazole, micafungin, voriconazole, posaconazole, and isavuconazonium. Of the seven patients diagnosed with AIFRS with air supplied by the newer AHUs, two of them were not prescribed any antifungal prophylaxis, while the other five patients received either micafungin or fluconazole. One patient from each of the two time periods measured expired due to AIFRS (Table I).

For each patient diagnosed with AIFRS, comorbid conditions present on admission were recorded. There were no significant differences in the percentage of patients with comorbidities between the two cohorts (Table IV). The most common comorbidities in both cohorts were hypertension and type 2 diabetes mellitus.

TABLE III.
Minimum Efficiency Reporting Value (MERV) Filter Specifications and Frequency of Change.

Filter Type (MERV)	Average Particle Size Efficiency in Microns	Frequency of Filter Change
MERV 11	1–3 microns in size at 65% efficiency	Once per year
MERV 13	1–3 microns in size at 85% efficiency	Once every 18 months
MERV 14	1–3 microns in size at 90% efficiency	Once every 2 years
HEPA	Particles larger or smaller than 0.3 microns at 99.97% efficiency	Once every 5 years

HEPA = high-efficiency particulate air; MERV = minimum efficiency reporting value.

DISCUSSION

Given the severe and life-threatening nature of AIFRS, it is imperative that environmental risk factors for the disease be minimized, especially in immunocompromised patients where the underlying immune deficiency is not readily correctable. This study found that there was a higher attack rate of AIFRS for hematologic cancer patients located in hospital units supplied by older, less effective AHUs. Although there have been no studies specifically analyzing the functional capabilities of AHUs and AIFRS rates, our results are consistent with prior literature demonstrating relationships between poor air flow, air quality, filtration, and rates of fungal infections. Studies have shown that airborne fungal concentrations fluctuate based on the seasons, and that increasing temperature is associated with increased airborne *Aspergillus* spore concentrations.[9,10] One study found that there was a greater incidence of AIFRS during the summer when there were significantly greater mean and max temperatures.[11] There are also data showing significant relationships between exposure to dust, surface area of rooms, and poor air-conditioning with rates of noninvasive FRS.[12] Furthermore, both high-efficiency particulate air (HEPA) filters and laminar flow rooms have been shown to decrease aspergillus in air samples from patient rooms and prevent outbreaks of pulmonary aspergillosis in hematologic oncology patients.[13,14] Proposed etiologies for aspergillosis outbreaks in immunosuppressed patients include nearby areas of construction causing increased airborne fungal burden as well as fungal contamination of air ventilation systems.[13,15] Interventions targeted toward decreasing fungal burden in the air have been proposed to decrease rates of sinusitis and include removal of potted plants and flowers, regular cleaning of air ducts, and even avoidance of ground pepper as a seasoning.[16] Our results suggest that the use of AHUs with higher air flows could help mitigate fungal burden and decrease the rates of AIFRS. Interestingly, it was found that the older AHUs have a greater number of filters that perform at or above the level of the filters of the newer AHUs (Tables I and III), suggesting equivalent air filtration. Due to the difference in CFM between the old and new AHU, however, there is less air being cleansed of particulates by the older units and thus a theoretical risk of higher fungal burden.

In analyzing other variables such as age, white blood cell (WBC) count, automated absolute neutrophil count (ANC), and time from hospitalization to diagnosis, our results show that the patients with air supplied by the older AHUs had a statistically significant lower mean age than those with air supplied by the newer AHUs. Although all patients in this study were immunosuppressed due to hematologic malignancy, this age difference between the two groups is noteworthy. It is known that immunosuppressive activity increases with aging, with a decrease in the number and efficacy of T-cells.[17] It is possible that this difference in age could stem from older AHUs providing poorer air flow and thus leading to AIFRS infection at an earlier age. Furthermore, although there were no statistically significant

TABLE IV.
Number of Comorbidities in AIFRS Patients With Air Supplied by Older and Newer AHUs and Respective Percentage of Each Patient Population.

	Patients with Air Supplied by Older AHUs	Patients with Air Supplied by Newer AHUs	Percentage of Patients (Older AHUs)	Percentage of Patients (Newer AHUs)
Zero Comorbidities	8	3	44.4%	42.9%
1 Comorbidity	4	0	22.2%	0%
2 Comorbidities	2	1	11.1%	14.3%
3 Comorbidities	3	1	16.7%	14.3%
4+ Comorbidities	1	2	5.6%	28.6%

Comorbidities include diabetes, hypertension, hypothyroidism, hyperlipidemia, panhypopituitarism, rheumatoid arthritis, gastroesophageal reflux disease, obstructive sleep apnea, osteoarthritis, herpes simplex virus, history of COVID-19 infection, chronic kidney disease, anxiety, autoimmune immunodeficiency, steroid-induced avascular necrosis, human immunodeficiency virus, coronary artery disease, deep venous thrombosis, pulmonary embolism, end-stage renal disease, and breast cancer.

AHU = air handling unit; AIFRS = acute invasive fungal rhinosinusitis.

differences in WBC count and ANC, it is also notable that the mean ANC for patients with air supplied by older AHUs was 976/uL, whereas the mean ANC for patients supplied by newer AHUs was 55/uL. Neutrophils are vitally important cells for defense against fungal infections including invasive candida and aspergillosis.[18] Additionally, prolonged neutrophil counts <500/uL have been shown to be a significant risk factor for AIFRS.[19] Given the mean ANC values of 976/uL for the patients supplied by older AHUs, it is again suggested that the poorer airflow may have contributed to more invasive fungal infections despite higher ANCs.

Antifungal prophylaxis has remained an important part of hematologic cancer patients' hospital course and is driven by evidence showing decreased rates of invasive fungal disease for those receiving prophylaxis. Choice of antifungal prophylaxis has shifted in the last 15 years, but high-risk patients (e.g., AML, ALL, neutropenic patients) are recommended to receive antifungal prophylaxis with agents such as posaconazole, voriconazole, itraconazole, micafungin, liposomal amphotericin, and isavuconazole. Lower risk patients either receive fluconazole or no antifungal medications.[20,21] In our study, it was found that every patient diagnosed with AIFRS located in units supplied by the older AHUs was receiving some form of antifungal prophylaxis prior to diagnosis of AIFRS. However, of the seven patients diagnosed with AIFRS with air supplied by the newer AHUs, only five were receiving prophylaxis. These findings suggest that the patients supplied by older AHUs had higher rates of AIFRS despite proper use of antifungal prophylaxis, possibly due to poorer air flow and filtration.

The incidence of invasive fungal infections has been increasing nationally. The sinus and orbital regions represent the sole site of involvement in 2.2% of cases.[22] A study from Washington University School of Medicine found a progressive increase in the incidence of AIFRS from January 1989 to September 2019. There were an average of 1.9 cases per year before 2009 and 6.8 cases per year from 2009 to 2019.[23] A similar trend was identified in invasive fungal diseases of other sites, thought at least in part due to more advanced therapies for hematologic malignancies resulting in a higher proportion of immunosuppressed individuals in the population.[24] Our results show a higher number of cases of AIFRS from 2/28/13 to 11/1/17 as compared with 11/1/17–7/5/22. This decrease coincides with the introduction of the new AHUs and is not in keeping with the national upward trend of cases.

Overall, our results show that immunocompromised patients admitted to floors with older, less powerful AHUs may be prone to higher rates of AIFRS. However, our study does not control for certain confounding variables. For example, difference in severity of hematologic cancer, differences in rate of admissions for hematologic cancer between the two time periods, differences in patient demographics, and treatment differences could all influence AIFRS rates. However, we believe that our findings elucidate an interesting association between age and functional capabilities of AHUs and AIFRS in hematologic cancer patients. We hypothesize that this may be due to a combination of factors. First, the older units may have a higher fungal burden after more years of use, which could cause increased colonization and eventual invasion of patients' sinonasal mucosa with pathogenic fungi. Second, the lower air flow in the older units means that less air is being filtered by the AHU system, which could also cause an increase in fungal burden. Of note, both the older and newer AHU systems in the hospital studied have their filters replaced every nine months. However, our results may indicate that the older units require more frequent filter replacement to prevent fungal infections in immunocompromised patients.

This study had several limitations. First, the sample size of the study is small, with only 25 total patients. This may have reduced our sample's power and made it more difficult to detect differences between cohorts. Second, although the AHUs were compared by their air flow and filtration protocols, our study did not evaluate other metrics such as air quality, air temperature, and fungal burden. Variations in any of these variables may have affected the attack rate of AIFRS in both patient populations. Third, studies have shown that there are increased rates of fungal infections for hospitals with nearby construction work. For those patients supplied by the older AHUs with lower CFM of air flow, there was active construction occurring on a new branch of the hospital. This could have skewed the attack rate of AIFRS for that population. Fourth, an incidence rate could not be calculated because of the lack of data on total number of patients admitted to each unit during the time periods studied. Although an estimated attack rate calculation was used, an incidence rate would provide more valuable and concise data for the relationship between AHUs and AIFRS diagnoses. Finally, because of data constraints, it was not feasible to run a multivariate analysis to control for other potential confounding factors. As a result, no correlation can be made between AHU capabilities and AIFRS rates. However, it is our hope that this study reveals an interesting association that may warrant further research.

CONCLUSION

In our study, patients with air supplied by older AHUs had a statistically significantly higher attack rate of AIFRS. We hypothesize that the older AHUs contributed to the increased attack rate of AIFRS. However, confounding factors such as environmental differences, disease severity, and patient demographics limit a suggestion of correlation. Further investigation into quality of air handling and filtration and AIFRS rates with multivariate analysis could help elucidate a relationship between the two and provide valuable insights into immunocompromised patients' inpatient environment.

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