Journal of Infection 84 (2022) 701–709

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Invasive mould infections in patients from floodwater-damaged areas after hurricane Harvey – a closer look at an immunocompromised cancer patient population

Sebastian Wurster[a], Timotheos Paraskevopoulos[a], Mitsuru Toda[b], Ying Jiang[a], Jeffrey J. Tarrand[c], Samantha Williams[b], Tom M. Chiller[b], Brendan R. Jackson[b], Dimitrios P. Kontoyiannis[a,*]

[a] Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States
[b] Centers for Disease Control and Prevention, Mycotic Diseases Branch, Atlanta, GA, United States
[c] Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States

ARTICLE INFO

Article history:
Accepted 8 March 2022
Available online 12 March 2022

Keywords:
Mould exposure
Floodwater damage
Invasive mould infections
Aspergillosis
Mucormycosis
Disease surveillance
Mortality

SUMMARY

Objectives: Extensive floodwater damage following hurricane Harvey raised concerns of increase in invasive mould infections (IMIs), especially in immunocompromised patients. To more comprehensively characterize the IMI landscape pre- and post-Harvey, we used a modified, less restrictive clinical IMI (mcIMI) definition by incorporating therapeutic-intent antifungal drug prescriptions combined with an expanded list of host and clinical features.

Methods: We reviewed 103 patients at MD Anderson Cancer Center (Houston, Texas), who lived in Harvey-affected counties and had mould-positive cultures within 12 months pre-/post-Harvey (36 and 67 patients, respectively). Cases were classified as proven or probable IMI (EORTC/MSG criteria), mcIMI, or colonization/contamination. We also compared in-hospital mortality and 42- day survival outcomes of patients with mcIMI pre-/post-Harvey.

Results: The number of patients with mould- positive cultures from Harvey-affected counties almost doubled from 36 pre- Harvey to 67 post- Harvey ($p < 0.01$). In contrast, no significant changes in (mc)IMI incidence post-Harvey nor changes in the aetiological mould genera were noted. However, patients with mcIMIs from flood affected areas had significantly higher in-hospital mortality ($p = 0.01$).

Conclusions: We observed increased colonization but no excess cases of (mc)IMIs in immunosuppressed cancer patients from affected areas following a large flooding event such as hurricane Harvey.

Introduction

In August 2017, hurricane Harvey and historic scale of flooding devastated the Houston metropolitan area and adjacent counties. A survey amongst immunocompromised Houston area residents revealed that almost half of them engaged in home clean-up and mould remediation activities, often with no or suboptimal personal protective equipment.[1] Although this observation raised the concern of extensive mould exposure of patients at risk for invasive mould infections (IMIs), prior research by our group at the University of Texas MD Anderson Cancer Center (MDACC) found no institution-wide increase in culture-documented IMIs after the hurricane.[2] As an increased use of voriconazole and amphotericin B was seen at MDACC in the 12 month- period following the hurricane,[2] there might have been a lower threshold for initiation of mould-active antifungal treatment or prophylaxis in high-risk patients and/or an increased incidence of infection events not meeting the conventional IMI definitions.

In order to provide a more comprehensive characterization of hurricane Harvey's impact on the IMI landscape, the U.S. Centers for Disease Control and Prevention (CDC) developed a modified clinical IMI (mcIMI) case definition based on an expanded set of host and clinical features combined with therapeutic-intent antifungal drug prescription. We herein applied this less-restrictive mcIMI case definition specifically to MDACC patients residing in Harvey-affected Texas counties.

* Corresponding author.
E-mail addresses: dkontoyi@mdanderson.org, sysaxton@mdanderson.org (D.P. Kontoyiannis).

https://doi.org/10.1016/j.jinf.2022.03.009
0163-4453/

Table 1
Host and clinical criteria applied for case adjudication.

Category	Criteria
EORTC/MSG host Factors	• Recent history of neutropenia (ANC < 500/μL for >10 d) temporally related to the onset of invasive fungal disease • Active hematologic malignancy • Receipt of an allogeneic stem cell transplant • Receipt of a solid organ transplant • Prolonged use of corticosteroids at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 d • Treatment with other recognized T-cell immunosuppressants (e.g., calcineurin inhibitors or immunosuppressive nucleoside analogues) during the past 90 d • Treatment with recognized B-cell immunosuppressants (e.g., ibrutinib) • Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT3 deficiency, or severe combined immunodeficiency) • Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
Non-EORTC/MSG Host Factors	• Other immunosuppressive or chemotherapeutic medications in the 90 d before DOI • Total body irradiation in the 90 d before DOI • Lymphopenia (≤1000/μL) in the 90 d before DOI • Acquired immunodeficiency syndrome ($CD4^+$ T-helper cells <200/μL) • B cell lymphoma • New cancer diagnosis in the 90 d before DOI, with or without therapy • Active cancer: cancer patient on chemotherapy at time of DOI, or diagnosed in the past 6 months, or cancer noted to be recurrent, metastatic or inoperable • Autologous stem cell transplant • Temporal arteritis or scleroderma • Chronic obstructive pulmonary disease • Hepatitis C, cirrhosis, and/or alcoholism • X-linked adrenoleukodystrophy • Uncontrolled diabetes mellitus (HbA1c >8%) • End stage renal disease • Burn • Recent eye surgery
EORTC/MSG clinical Factors	• Pulmonary aspergillosis: The presence of 1 of the following 4 patterns on CT: a) Dense, well-circumscribed lesions(s) with or without a halo sign, b) air crescent sign, c) cavity, d) wedge-shaped and segmental or lobar consolidation • Other pulmonary mould infections: Same criteria as for pulmonary aspergillosis but also including a reverse halo sign • Tracheobronchitis: Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen in bronchoscopy • Sino-nasal diseases: Acute localized pain (including pain radiating to the eye), nasal ulcer with black eschar, or lesions extending from the paranasal sinus across bony barriers (e.g., into the orbit) • Central nervous system infection: 1 of the following 2 signs: a) Focal lesions on imaging, b) Meningeal enhancement on magnetic resonance imaging or CT
Non-EORTC/MSG clinical factors	• Lower respiratory tract: Cavity on X-ray; focal opacity, tree-in-bud micronodularity/opacity, ground glass opacity, nodular opacity, patchy opacity, consolidation, nodule, mass lesions, pleural effusions, or other abnormal pulmonary CT findings not specifically included in the MSG definition; pneumothorax (lung collapse); clinical signs of pneumonia • Sinonasal infection: Manifestations not meeting MSG definition or including other signs, e.g., orbital cellulitis • Wound infections: Burns, open fracture, necrotic tissue, and/or ulcers

Abbreviations: ANC = absolute neutrophil count, CD = cluster of differentiation, CT = computed tomography, *d* = days, DOI = date of incidence, EORTC/MSG = European Organization for Research and Treatment of Cancer & Mycosis Study Group, STAT3 = signal transducer and activator of transcription 3.

Methods

Ethics statement

This study was approved by the MDACC institutional review board. Patient consent was waived for anonymized chart review.

Identification of mould- positive cultures

We used the Cerner Millennium Microbiology module of MDACC's laboratory information system to identify mould-positive cultures, including dimorphic fungi, within a 12-month period before and after hurricane Harvey. Multiple mould-positive cultures from the same patient within a 60-day period were considered a single case.

Data filtering and chart review

The postal codes of the patients' place of residence were compared against the Federal Emergency Management Agency (FEMA) Texas Hurricane Harvey map DR-4332-TX.[3] Counties designated "public assistance areas" at a minimum were considered "affected counties". Records of patients living outside these areas were excluded and the remaining cases proceeded to an in-depth chart review, which included the following items: Demographic data (age, gender), place of residence (postal code, county, state), evidence of possible mould infection (mould-positive cultures, pathology specimens consistent with an IMI, positive serum galactomannan or beta-glucan tests, other non-culture biomarkers, IMI-related ICD-10 codes), clinical and radiological evidence of an IMI (clinical criteria specified in Table 1), cytopenia (neutropenia < 500/μL, lymphopenia < 1000/μL), cancer diagnosis, transplant history (solid organ transplant or hematopoietic stem cell transplant, including presence of graft-versus-host disease [GvHD]), other predisposing conditions (diabetes mellitus, autoimmune diseases, alcoholism and liver cirrhosis, hemochromatosis, cytomegalovirus infection, total parental nutrition), recent surgeries or injuries, use of corticosteroids or other immunosuppressive or cytotoxic medications, use of mould-active antifungals, hospitalization, ICU admission, and in-hospital mortality. Data were entered into an electronic case report form (RedCap platform) provided by the CDC, Mycotic Diseases Branch. In addition, 42-day mortality outcomes were recorded by the investigators.

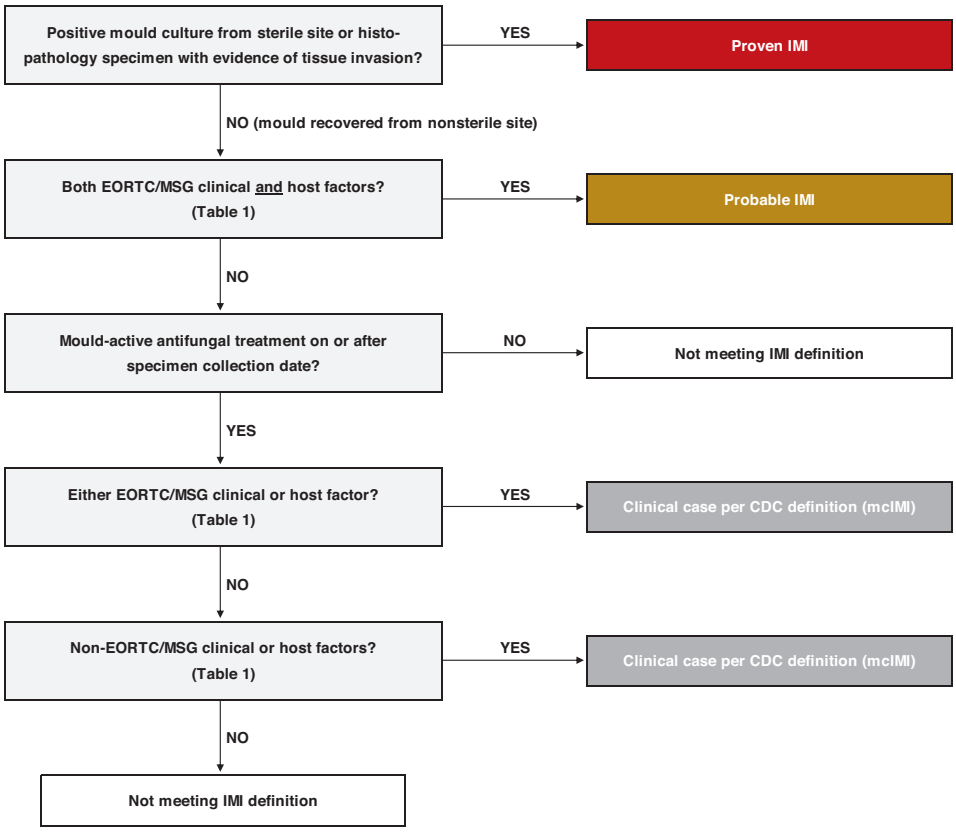

Fig. 1. Flow chart for case adjudication.

Determination of the date of incidence (DOI)

The DOI was defined as the earliest date of possible evidence of an IMI event, considering cultures and non-culture biomarkers, histopathological evidence, therapeutic-intent antifungal drug prescription, and ICD-10 billing codes indicating an IMI event. Cases with a DOI before September 1, 2017, were considered "pre-Harvey" and cases with a DOI on or after September 1, 2017 were considered "post-Harvey", respectively. Of note, no patient had a DOI between the landfall of hurricane Harvey in Texas (August 26, 2017) and the second week of September 2017.

Case adjudication

The probability of an IMI event was independently determined by two investigators. European Organization for Research and Treatment of Cancer & Mycosis Study Group (EORTC/MSG) consensus definitions[4] were used to identify patients with proven or probable IMIs. In addition, we applied the CDC's expanded case definition to classify the remaining patients as either mcIMI cases or "patients not meeting IMI criteria" (colonization/contamination). Patients were classified as mcIMI cases if they received mould-active antifungal therapy after collection of a mould-positive specimen and additionally met at least one EORTC/MSG or non-EORTC/MSG clinical or host criterion (Table 1). One discordant adjudication was resolved by a joint review of the investigators.

Hospital census

The following denominators were used to calculate incidence rates within a 12-month period pre- and post-Harvey, respectively: Number of inpatient hospital admissions, 28,793 pre-Harvey and 29,118 post-Harvey; number of inpatient days, 202,411 pre-Harvey and 207,071 post-Harvey.

Statistical analyses

Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were compared using Kruskal-Wallis and Wilcoxon rank-sum tests for 3- and 2-group comparisons, respectively. If a significant result ($p < 0.05$) was detected for a 3-group comparison, pairwise comparisons were performed with α levels adjusted using Holm's sequential Bonferroni method. Poisson distribution and chi-square test were used to compare incidence rates of mould infections. Survival curves were estimated using the Kaplan-Meier method and compared with the Mantel-Cox log-rank test. All tests were 2-sided with a significance level of 0.05 except for pairwise comparisons with α adjustment. Statistical analyses and data visualization were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC), GraphPad Prism version 8 (GraphPad Software Inc., San Diego, USA), and Microsoft Excel.

Results

Four-hundred-and-four MDACC patients with mould-positive cultures between September 2016 (12 months pre-Harvey) and August 2018 (12 months post-Harvey) were identified using the institutional microbiology laboratory information system (Supplementary Data Set). A single mould genus was isolated from a single material in 329 out of these 404 patients. *Aspergillus* was the most commonly identified genus ($n = 153$, including 10 patients

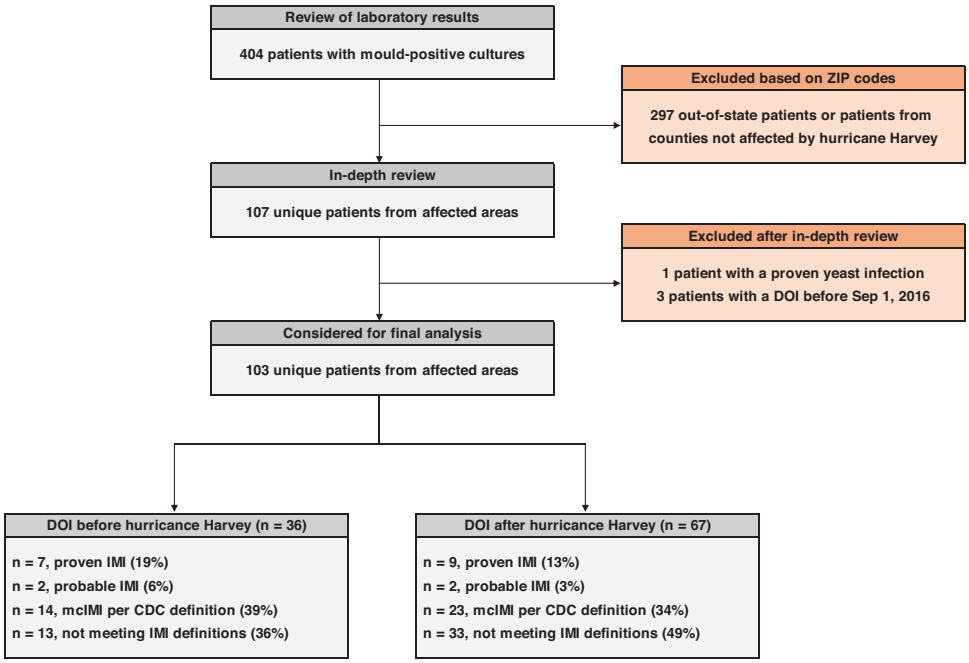

Fig. 2. Numbers of cases identified by classification and date of incidence (DOI).

with multiple *Aspergillus* species). Nineteen patients had a single genus isolated from multiple respiratory samples and 8 patients had the same mould/genus isolated from multiple sites or materials. Thirty-one patients had two or more genera isolated from a single site or material. A total of 17 patients had multiple mould genera recovered from multiple respiratory samples or multiple sampling sites (Supplementary Data Set).

One-hundred-and-seven out of the 404 unique cases represented patients living in Harvey-affected areas (Fig. 2). Four out of these 107 patients were excluded from further analysis after chart review. Three patients had a mould-positive culture within the study period, but their finally determined DOI was more than 12 months prior to hurricane Harvey. In addition, one case of "sterile hyphae" recovered from a skin lesion was later identified as a proven yeast infection with no evidence of an IMI event and was excluded from analysis (Fig. 2). After exclusions, 103 cases remained in the final analysis.

Notably, these 103 cases were not distributed evenly between the pre- and post-Harvey period. Instead, the number of patients with mould-positive cultures from Harvey-affected counties almost doubled from 36 pre-Harvey to 67 post-Harvey (Fig. 2), resulting in a significantly increased incidence of positive cultures after the hurricane (Fig. 3A, $p < 0.01$). Thirty-four out of the 67 patients with mould-positive cultures post-Harvey (51%) were adjudicated as having probable/proven IMIs ($n = 11$) or mcIMI ($n = 23$), compared to 23 (mc)IMI cases pre-Harvey (9 probable/proven IMIs and 14 mcIMI cases). The difference in incidence rates of probable/proven IMIs or mcIMI cases pre- and post-Harvey did not reach significance (Fig. 3B, $p = 0.15$- 0.18), whereas the incidence rate of patients with mould-positive cultures not meeting the IMI criteria significantly increased post-Harvey (Fig. 3C, $p < 0.01$). Of note, 76% of mould-positive cultures in patients not meeting the IMI criteria were obtained from respiratory samples, suggesting increased asymptomatic colonization of respiratory epithelia.

Patients with probable/proven IMIs were more likely to have active leukaemia/myelodysplastic syndrome ($p < 0.001$) and/or severe neutropenia $< 500/\mu L$ ($p < 0.001$) and to receive corticosteroids ($p < 0.01$) or other immunosuppressive therapies ($p < 0.001$) compared with mcIMI cases and patients not meeting the IMI definitions (Table 2). Patients with proven/probable IMIs had higher rates of extrapulmonary or disseminated mycoses and had a higher proportion of Mucorales or *Fusarium* spp. recovered as the causative agent than patients with mcIMIs (Table 2). Compared to patients not meeting the IMI definitions, a higher proportion of patients with probable/proven IMIs or mcIMIs received systemic antifungal therapy, such as liposomal amphotericin B or broad-spectrum triazoles ($p < 0.001$) (Table 2). Similarly, patients meeting at least the mcIMI definition more often required hospitalization ($p < 0.001$) or ICU admission ($p = 0.03$) and had higher in-hospital mortality ($p = 0.05$) than patients with mould-positive cultures but no clinical correlate (Table 2).

Comparing all patients from Harvey-affected counties with mould-positive cultures before and after the hurricane, no significant differences in demographics, predisposing factors, and outcomes were seen, except for a higher percentage of patients with a history of lymphopenia in the post-Harvey cohort (Table S1, $p < 0.01$). Restricting the comparison to patients with IMI or mcIMI events, no significant differences in baseline characteristics and predisposing factors were found between the pre- and post-Harvey cohorts (Table 3). Nonetheless, the percentage of hospitalized patients requiring ICU admission in the course of their (mc)IMI treatment increased from 30% pre-Harvey to 56% post-Harvey (Table 3, $p = 0.06$). Likewise, the percentage of patients with (mc)IMI dying in-hospital rose from 17% pre- Harvey to 50% ($p = 0.01$), whereas 42-day mortality (30% pre-Harvey versus 45% post-Harvey, $p = 0.26$) and survival curves (log-rank test, $p = 0.18$) did not significantly differ depending on the DOI (Fig. 4).

Discussion

Considering all patients regardless of their place of residence, our previous study, using the conventional and rather restrictive EORTC/MSG diagnostic criteria, revealed no significant changes to the institutional mould infection landscape after hurricane Harvey.[2] However, institution-wide data, including patients from non-affected areas, may "dilute" the trends and lack the granularity to identify subtle changes in IMI epidemiology in patient from areas impacted by floodwater damage. Therefore, the present study

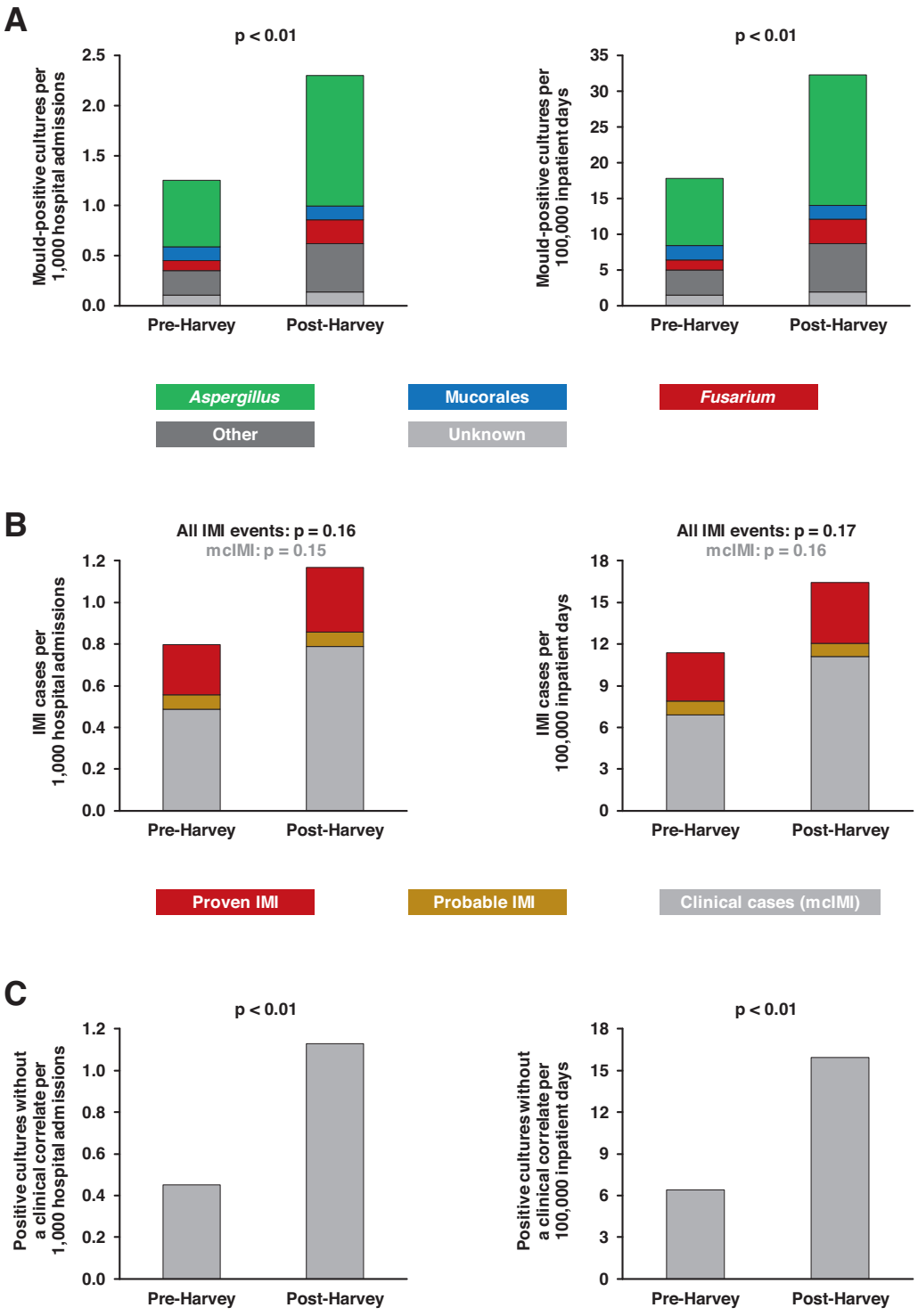

Fig. 3. Incidence rates of mould-positive cultures and IMI events pre- and post-Harvey. (A) Breakdown of incidence rates of mould positive cultures in patients from Harvey-affected areas per 1000 hospital admissions and per 100,000 inpatient days before (n = 36) and after (n = 67) hurricane Harvey by causative genus/order. (B) Comparison of IMI incidence rates before and after hurricane Harvey. (C) Incidence rates of mould-positive cultures without a clinical correlate, i.e. cases not meeting the IMI definitions, before and after hurricane Harvey. Chi-square test.

was uniquely restricted to patients from Harvey-affected counties, that is, counties qualifying for disaster assistance.[3] In this cohort, we indeed found a significantly increased number of mould-positive cultures in the year following the hurricane compared with pre-Harvey data. However, although the incidence rates of proven/probable IMIs and mcIMIs slightly increased after the hurricane, this trend did not reach statistical significance. Instead, 49% of the mould-positive cultures in patients from Harvey-affected counties were not associated with clinical correlates meeting either the conventional EORTC/MSG definition or the mcIMI definition. As most mould-positive cultures without a clinical correlate were obtained from respiratory materials (76%), we hypothesize that the increase in mould-positive cultures post-Harvey is primarily due to asymptomatic colonization of respiratory epithelia.

Table 2
Comparison of patient demographics, predisposing factors, treatment, and outcomes by final case determination. Unless specified otherwise in the "characteristics" column, numbers of patients and percentages (%) are provided. Significant p-values for 3-group comparisons are highlighted in bold. Significant p-values for pairwise post tests are indicated by the following symbols: # proven/probable IMI (EORTC/MSG definition) versus mcIMI, $ proven/probable IMI versus patients not meeting IMI criteria, § mcIMI versus patients not meeting IMI criteria.

Characteristics		Proven/probable IMI $N = 20$	mcIMI (CDC definition) $N = 37$	Not meeting IMI criteria $N = 46$	P-value	Pairwise comp.
Age	Median (range)	58 (23-84)	61 (33-89)	68 (26-90)	**< 0.01**	$
Gender	Male	14 (70)	23 (62)	24 (52)	0.36	
	Female	6 (30)	14 (38)	22 (48)		
Cancer diagnoses[a]	Active cancer within the last 2 years	20 (100)	37 (100)	44 (96)	0.68	
	Leukaemia/MDS	16 (80)	17 (46)	4 (9)	**< 0.001**	#, $, §
	Lymphoma/myeloma	2 (10)	11 (30)	7 (15)	0.12	
	Solid tumour	3 (15)	10 (27)	36 (78)	**< 0.001**	$, §
HSCT	Any HSCT	4 (20)	7 (19)	2 (4)	0.06	
	Allogenic	4/4 (100)	3/7 (43)	0/2 (0)		
	Autologous	0/4 (0)	4/7 (57)	2/2 (100)		
GvHD	(% amongst allo-HSCT recipients)	1/4 (25)	1/3 (33)	n/a		
Neutropenia	< 500/µL for >10 d within the last 30 d	3 (15)	1 (3)	0 (0)	**< 0.001**	#, $
	< 500/μL within the last 30 d	10 (50)	6 (16)	4 (9)		
	History of neutropenia	3 (15)	4 (11)	2 (4)		
	No neutropenia	4 (20)	26 (70)	40 (87)		
Lymphopenia	< 1000/µL within the last 30 d	10 (50)	18 (49)	11(24)	0.11	
	History of lymphopenia	4 (20)	8 (22)	11 (24)		
	No lymphopenia	6 (30)	11 (30)	24 (52)		
Diabetes mellitus	Any type	3 (15)	9 (24)	5 (11)	0.25	
	Type 1	0/3 (0)	2/9 (22)	0/5 (0)		
	Type 2	3/3 (100)	6/9 (67)	5/5 (100)		
	Other	0/3 (0)	1/9 (11)	0/5 (0)		
	HbA1c > 8%	1/3 (33)	2/9 (22)	1/5 (20)	> 0.99	
GCS	Systemic GCS within the last 90 d	16 (80)	24 (65)	19 (41)	**< 0.01**	$
	> 200 mg prednisolone eq. per day	13/16 (81)	19/24 (79)	14/19 (74)	0.85	
Other immunosuppressive or cytotoxic therapies (last 90 d)		8 (40)	17 (46)	4 (9)	**< 0.01**	$, §
Pathogen	*Aspergillus* spp.	4/19 (21)	24/32 (75)	29/45 (64)	**< 0.001**	#, $, §
	Fusarium spp.	8/19 (42)	1/32 (3)	1/45 (2)		
	Mucorales	5/19 (26)	3/32 (9)	0/45 (0)		
	Other	2/19 (11)	4/32 (13)	15/45 (33)		
	Unknown	1	5	1		
Site of infection	Lung	4 (20)	34 (92)	n/a	**< 0.001**	#
	Nasal/sinus	5 (25)	0 (0)	n/a		
	Skin/soft tissue/wound	8 (40)	1 (3)	n/a		
	Disseminated	3 (15)	2 (5)	n/a		
Mould-active antifungal therapy[b]	At least 1 antifungal drug	19 (95)[c]	37 (100)	12 (26)	**< 0.001**	$, §
	Liposomal amphotericin B	13 (65)	13 (35)	2 (4)	**< 0.001**	#, $, §
	Fluconazole[d]	3 (15)	2 (5)	2 (4)	0.26	
	Itraconazole	0 (0)	0 (0)	1 (2)	> 0.99	
	Posaconazole	15 (75)	23 (62)	2 (4)	**< 0.001**	$, §
	Voriconazole	6 (30)	26 (70)	4 (9)	**< 0.001**	#, §
	Isavuconazole	8 (40)	9 (24)	1 (2)	**< 0.001**	$, §
	Echinocandins	14 (70)	16 (43)	4 (9)	**< 0.001**	$, §
Outcomes	Hospitalization	20 (100)	32 (86)	25 (54)	**< 0.001**	$, §
	ICU admission	6 (30)	20 (54)	12 (26)	**0.03**	§
	Died in hospital	7 (35)	14 (38)	7 (15)	**0.05**	

Footnotes:.
[a]five patients had two cancer diagnoses.
[b]does not include drugs that were initiated prior to the date of incidence and were given in prophylactic intention.
[c] (proven) IMI of one patient not receiving antifungal therapy was established post-mortem based on autopsy findings.
[d]fluconazole alone was only considered "mould-active antifungal therapy" when given for putative dimorphic fungal infections.
Abbreviations: CDC = United States Centers for Disease Control and Prevention, comp. = comparison, *d* = days, eq = equivalent, GCS = glucocorticosteroids, GvHD = graft versus host disease, (allo-) HSCT = (allogenic) hematopoietic stem cell transplant, ICU = intensive care unit, IMI = invasive mould infection, mcIMI = modified clinical IMI definition, MDS = myelodysplastic syndrome, mg = milligrams.

Historic data providing a clear link between residential mould exposure in post-disaster settings, airway colonization, and IMI events are scarce. Despite high levels of mould infestation immediately following hurricanes Katrina and Rita in 2005,[5–6] there has been no evidence of elevated IMI incidence rates in exposed patient cohorts;[6–7] however, transient asymptomatic airway colonization with Mucorales was seen in some residents of floodwater-damaged buildings.[8] A related observation was made for *Aspergillus*- and Basidiomycetes-positive sputum cultures after a tsunami in East Japan.[9] In contrast, our breakdown of positive cultures did not reveal major shifts or a selective predominance of causative genera post-Harvey (Fig. 3A), which might be due to the much larger catchment area of our patients compared to the cited studies.

Of note, floodwater-damaged buildings can remain a source of increased exposure to pathogenic moulds even after mould remediation activities.[10] Therefore, long-term surveillance programs are warranted in Harvey-affected areas for both, IMIs in immunocompromised populations and non-infectious respiratory hypersensitivity syndromes (e. g., mould-associated asthma) that were seen after previous geo-meteorological disasters.[7] As discussed previously,[2] there might also be a risk for delayed emergence of unusual mould pathogens such as the dimorphic fungus *Coccidioides immitis* in flooded areas.[11]

Table 3
Demographics, predisposing factors, and treatment by date of incidence, considering patients meeting either the proven or probable IMI definition (EORTC/MSG) or the mcIMI definition (CDC). Unless specified otherwise in the "characteristics" column, numbers of patients and percentages (%) are provided. Significant p-values are highlighted in bold.

		Pre-Harvey $N = 23$	Post-Harvey $N = 34$	P-value
Age	Median (range)	60 (23–78)	61 (25–89)	0.78
Gender	Male	17 (74)	20 (59)	0.24
	Female	6 (26)	14 (41)	
Cancer diagnoses[a]	Active cancer within the last 2 years	23 (100)	34 (100)	
	Leukaemia/MDS	14 (61)	19 (56)	0.71
	Lymphoma/myeloma	3 (13)	10 (29)	0.15
	Solid tumour	6 (26)	7 (21)	0.63
HSCT	Any HSCTAllogenicAutologous	2 (9)	9 (26)	0.17
	Allogenic	2/2 (100)	5/9 (56)	
	Autologous	0/2 (0)	4/9 (44)	
GvHD	(% amongst allo-HSCT recipients)	1/2 (50)	1/5 (20)	
Neutropenia	<500/µL for > 10 d within the last 30 d	3 (13)	1 (3)	0.49
	<500/μL within the last 30 d	7 (30)	9 (26)	
	History of neutropenia	3 (13)	4 (12)	
	No neutropenia	10 (43)	20 (59)	
Lymphopenia	<1000/ µL within the last 30 d	13 (57)	15 (44)	0.17
	History of lymphopenia	2 (9)	10 (29)	
	No lymphopenia	8 (35)	9 (26)	
Diabetes mellitus	Any type	5 (22)	7 (21)	>0.99
	Type 1	1/5 (20)	1/7 (14)	
	Type 2	4/5 (80)	5/7 (71)	
	Other	0/5 (0)	1/7 (14)	
	HbA1c > 8%	2/5 (40)	1/7 (14)	0.52
GCS	Systemic GCS within the last 90 d	19 (83)	21 (62)	0.09
	>200 mg prednisolone eq. per day	17/19 (89)	15/21 (71)	0.24
Other immunosuppressive or cytotoxic therapies (last 90d)		11 (48)	14 (41)	0.62
Pathogen	*Aspergillus* spp.	11/21 (52)	17/30 (57)	0.85
	Fusarium spp.	3/21 (14)	6/30 (20)	
	Mucorales	4/21 (19)	4/30 (13)	
	Other	3/21 (14)	3/30 (10)	
	Unknown	2	4	
Site of infection	Lung	16 (70)	22 (65)	0.26
	Nasal/sinus	2 (9)	3 (9)	
	Skin/soft tissue/wound	5 (22)	4 (12)	
	Disseminated	0 (0)	5 (15)	
Mould-active antifungal therapy[b]	At least 1 antifungal drug	23 (100)	33 (97)	>0.99
	Liposomal amphotericin B	9 (39)	17 (50)	0.42
	Fluconazole[c]	1 (4)	4 (12)	0.64
	Posaconazole	16 (70)	22 (65)	0.70
	Voriconazole	13 (57)	19 (56)	0.96
	Echinocandins	11 (48)	19 (56)	0.55
Outcomes	Hospitalization	22 (96)	30 (88)	0.64
	ICU admission	7 (30)	19 (56)	0.06
	Died in hospital	4 (17)	17 (50)	**0.01**
	Died within 42 days	7 (30)	15/33 (45)[d]	0.26

Footnotes:.
[a]two patients had two cancer diagnoses.
[b]does not include drugs that were initiated prior to the date of incidence and were given in prophylactic intention.
[c]fluconazole alone was only considered "mould-active antifungal therapy" when given for putative dimorphic fungal infections.
[d]follow-up was lost for one patient before day 42.
Abbreviations: *d* = days, def = definition, eq = equivalent, GCS = glucocorticosteroids, GvHD = graft versus host disease, (allo-) HSCT = (allogenic) hematopoietic stem cell transplant, ICU = intensive care unit, IMI = invasive mould infection, MDS = myelodysplastic syndrome, mg = milligrams.

In addition to increased numbers of mould-positive cultures, we observed a signal of worse outcomes in patients from Harvey-affected counties developing (mc)IMIs after the hurricane. While 42-day all-cause mortality did not significantly differ depending on the DOI, patients developing (mc)IMIs post-Harvey had significantly higher in-hospital mortality and tended to have higher ICU admission rates than patients with IMIs pre-Harvey. Although univariate analyses ruled out a significant impact of many important confounders (e. g., causative pathogens, sites of infection, cytopenia, underlying cancer diagnoses, and immunosuppressive therapies), the power of these analyses was limited, and meaningful multivariate analysis was not feasible due to the small sample size. Nonetheless, the observed trend toward worse outcomes in patients developing IMIs after hurricane Harvey is intriguing and the many dynamic and interrelated factors that could contribute to this observation deserve further study. One the one hand, it would be conceivable that increased colonization driven by extensive exposures increases the risk for severe IMI manifestations due to the high fungal burden.[12] On the other hand, residential exposure to moulds commonly found after water intrusion can trigger alterations in mould-reactive immune responses, especially elevated type−2 T-helper cell responses[13–14] that are considered non-protective and might contribute to immune pathology.[15] Furthermore, floodwater-damaged housing can be a reservoir of moulds producing mycotoxins[10] that have immunosuppressive properties and were shown to modulate host responses to invasive infection;[16] however, the clinical significance of this hypothesis remains to be established.

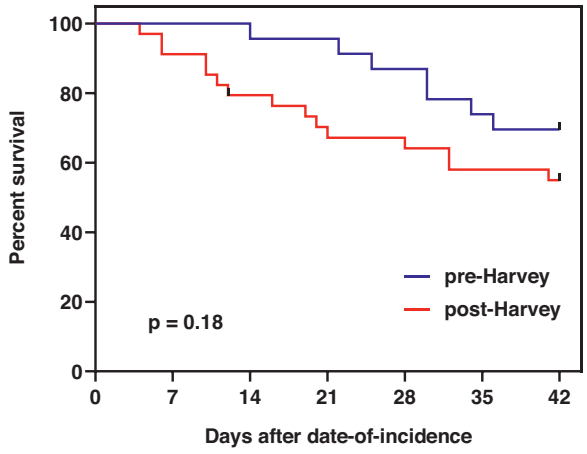

Fig. 4. 42-day Kaplan-Meier survival curves of patients with proven/probable IMI (EORTC/MSG definition) or mcIMI (CDC definition) before and after hurricane Harvey. Black ticks indicate censored data. Mantel-Cox log-rank test. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Our retrospective monocentric study has several limitations. While the FEMA assistance level[3] provides an at-large surrogate of a county's devastation by the hurricane and subsequent flooding, our study design did not facilitate correlation of the patients' individual risk for mould exposure (e.g., participation in mould remediation or home reconstruction activities) and the incidence of mould-positive cultures or IMIs. Furthermore, the denominators used for incidence density calculations (Fig. 2) were based on the institution-wide patient census since data restricted to patients living in Harvey-affected counties were not available. However, as there was no evidence for a significant shift in institutional patient catchment areas during the 2-year study period, this limitation likely has a minor impact on the validity of our analyses and conclusions. Similarly, the institutional laboratory information system did not facilitate a determination of the total number of mould cultures ordered from patients residing in Harvey-affected counties. We have previously reported that neither the number of mould cultures ordered institution-wide nor their positivity rate were significantly different before and after the hurricane.[2] However, in the absence of a culture census for patients from affected counties, our data do not allow us to determine whether the significantly higher post-Harvey incidence of positive cultures in patients from affected areas is driven by an increased number of cultures ordered, an increased culture positivity rate, or a combination of both. Furthermore, the relevance of individual pathogens as colonizers versus contaminants can be difficult to distinguish in the absence of a clinical correlate. For example, *Aspergillus niger* is known as a common colonizer of respiratory epithelia[17] and it is also a common contaminant at the MDACC Microbiology Laboratory. In addition, the uncommon saprophytic moulds are common colonizers and rarely true pathogens, even in high-risk cancer patients.[18] In order to examine these potential confounders in a sufficiently powered analysis and to evaluate the generalizability of our findings to other patient populations including patients with non-cancer-related predisposing factors for IMIs (e. g., patients with metabolic disorders such as diabetes mellitus), multi-centre data would be needed. Similarly, the mcIMI definition itself remains to be studied in multi-centre settings.

In summary, despite limitations, our unique study provides significant insights into the epidemiology of mould-positive cultures and IMI events after a devastating hurricane causing widespread flooding. Employing both, conventional EORTC/MSG definitions and a broader mcIMI case definition that considers therapeutic-intent antifungal drug prescription, our results corroborate the previously published observation that hurricane Harvey did not cause significant changes in IMI incidence and aetiological mould genera at MDACC.[2] The increased recovery of moulds from – predominantly respiratory – cultures in patients living in Harvey-affected counties likely reflects increased airway colonization and points to a need for long-term surveillance efforts, including non-infectious mould-associated diseases.[19] Lastly, we found that increased detection of moulds was a marker of poor outcomes of IMI events in patients from Harvey-affected counties. Altogether, these results emphasize the importance of risk awareness, enhanced mould prevention strategies,[20] and improved clinical management of IMIs in high-risk patients after geo-meteorological disasters.

Declaration of Competing Interest

DPK reports honoraria and research support from Gilead Sciences, received consultant fees from Astellas Pharma, Merck, and Gilead Sciences, and is a member of the Data Review Committee of Cidara Therapeutics, AbbVie, and the Mycoses Study Group. All other authors report no conflicts of interest.

Acknowledgment

This study was funded by the United States Centers for Disease Control and Prevention, Mycotic Diseases Branch (contract number 75D30119C05279). A part of this study was further supported by the Robert C. Hickey Chair in Clinical Care endowment to DPK.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.03.009.

References

1. Chow NA, Toda M, Pennington AF, Anassi E, Atmar RL, Cox-Ganser JM, et al. Hurricane-associated mold exposures among patients at risk for invasive mold infections after hurricane Harvey - Houston, Texas. *MMWR Morb Mortal Wkly Rep. 2019* 2017;**68**(21):469–73.
2. Kontoyiannis DP, Shah EC, Wurster S, Aitken SL, Graviss L, Raad II, et al. Culture-documented invasive mold infections at MD Anderson cancer center in Houston, Texas, pre- and post-hurricane Harvey. *Open Forum Infect Dis* 2019;**6**(4):ofz138.
3. https://gis.fema.gov/maps/dec_4332.pdf (last accessed on July 22, 2021)
4. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. *Clin Infect Dis* 2020;**71**(6):1367–76.
5. Chew GL, Wilson J, Rabito FA, Grimsley F, Iqbal S, Reponen T, Muilenberg ML, Thorne PS, Dearborn DG, Morley RL. Mold and endotoxin levels in the aftermath of Hurricane Katrina: a pilot project of homes in New Orleans undergoing renovation. *Environ Health Perspect* 2006;**114**(12):1883–9.
6. Benedict K, Park BJ. Invasive fungal infections after natural disasters. *Emerg Infect Dis* 2014;**20**(3):349–55.
7. Barbeau DN, Grimsley LF, White LE, El-Dahr JM, Lichtveld M. Mold exposure and health effects following hurricanes Katrina and Rita. *Annu Rev Public Health* 2010;**31**:165–78 1 p following 178.
8. Rao CY, Kurukularatne C, Garcia-Diaz JB, Kemmerly SA, Reed D, Fridkin SK, et al. Implications of detecting the mold Syncephalastrum in clinical specimens of New Orleans residents after Hurricanes Katrina and Rita. *J Occup Environ Med* 2007;**49**(4):411–16.
9. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Chronic cough in a tsunami-affected town. *Pulm Pharmacol Ther* 2012;**25**(1):11.
10. Jakšić D, Sertić M, Kocsubé S, Kovačević I, Kifer D, Mornar A, Nigović B, Šegvić Klarić M. Post-flood impacts on occurrence and distribution of mycotoxin-producing aspergilli from the sections Circumdati, Flavi, and Nigri in indoor environment. *J Fungi (Basel)* 2020;**6**(4):282.
11. Comrie AC. Climate factors influencing coccidioidomycosis seasonality and outbreaks. *Environ Health Perspect* 2005;**113**(6):688–92.
12. Gago S, Denning DW, Bowyer P. Pathophysiological aspects of Aspergillus colonization in disease. *Med Mycol* 2019;**57**(Supplement_2):S219–27.
13. Page L, Weis P, Müller T, Dittrich M, Lazariotou M, Dragan M, Waaga-Gasser AM, Helm J, Dandekar T, Einsele H, Löffler J, Ullmann AJ, Wurster S. Evaluation of Aspergillus and Mucorales specific T-cells and peripheral blood mononuclear cell

cytokine signatures as biomarkers of environmental mold exposure. *Int J Med Microbiol* 2018;**308**(8):1018–26.
14. Rosenblum Lichtenstein JH, Molina RM, Donaghey TC, Hsu YH, Mathews JA, Kasahara DI, Park JA, Bordini A, Godleski JJ, Gillis BS, Brain JD. Repeated mouse lung exposures to stachybotrys chartarum shift immune response from type 1 to type 2. *Am J Respir Cell Mol Biol* 2016;**55**(4):521–31.
15. McDermott AJ, Klein BS. Helper T-cell responses and pulmonary fungal infections. *Immunology* 2018;**155**(2):155–63.
16. Kamei K, Watanabe A. Aspergillus mycotoxins and their effect on the host. *Med Mycol* 2005;**43**(Suppl 1):S95–9.
17. Warris A, Verweij PE. Clinical implications of environmental sources for aspergillus. *Med Mycol* 2005;**43**(Suppl 1):S59–65.
18. Lionakis MS, Kontoyiannis DP. The significance of isolation of saprophytic molds from the lower respiratory tract in patients with cancer. *Cancer* 2004;**100**(1):165–72.
19. Saporta D, Hurst D. Increased sensitization to mold allergens measured by intradermal skin testing following hurricanes. *J Environ Public Health* 2017;**2017**:2793820.
20. Brandt M, Brown C, Burkhart J, Burton N, Cox-Ganser J, Damon S, et al. Mold prevention strategies and possible health effects in the aftermath of hurricanes and major floods. *MMWR Recomm Rep* 2006;**55**(RR–8):1–27.