Investigations of an increased incidence of non-Aspergillus invasive mould infections in an onco-haematology unit

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Summary

AIMS OF THE STUDY: Invasive mould infections are life-threatening complications in patients with haematologic cancer and chemotherapy-induced neutropenia. While invasive aspergillosis represents the main cause of invasive mould infections, non-*Aspergillus* mould infections, such as mucormycosis, are increasingly reported. Consequently, their local epidemiology should be closely monitored. The aim of this study was to investigate the causes of an increased incidence of non-*Aspergillus* mould infections in the onco-haematology unit of a Swiss tertiary care hospital.

METHODS: All cases of proven and probable invasive mould infections were retrospectively identified via a local registry for the period 2007–2021 and their incidence was calculated per 10,000 patient-days per year. The relative proportion of invasive aspergillosis and non-*Aspergillus* mould infections was assessed. Factors that may affect invasive mould infections' incidence, such as antifungal drug consumption, environmental contamination and changes in diagnostic approaches, were investigated.

RESULTS: A significant increase of the incidence of non-*Aspergillus* mould infections (mainly mucormycosis) was observed from 2017 onwards (Mann and Kendall test p = 0.0053), peaking in 2020 (8.62 episodes per 10,000 patient-days). The incidence of invasive aspergillosis remained stable across the period of observation. The proportion of non-*Aspergillus* mould infections increased significantly from 2017 (33% vs 16.8% for the periods 2017–2021 and 2007–2016, respectively, p = 0.02). Building projects on the hospital site were identified as possible contributors of this increase in non-*Aspergillus* mould infections. However, novel diagnostic procedures may have improved their detection.

CONCLUSIONS: We report a significant increase in non-*Aspergillus* mould infections, and mainly in mucormycosis infections, since 2017. There seems to be a multifactorial origin to this increase. Epidemiological trends of invasive mould infections should be carefully monitored in onco-haematology units in order to implement potential corrective measures.

Introduction

Invasive mould infections (IMI) affect between 5% and 10% of patients with haematologic malignancies and chemotherapy-induced neutropenia. *Aspergillus* spp. accounts for the majority of cases [1, 2]. Albeit less frequent, non-*Aspergillus* moulds, and particularly the Mucorales, are often refractory to standard antifungal therapies and associated with high mortality rates (40–50%) [3, 4]. A selection of recent reports suggest that their incidence and relative proportion are increasing [5–8]. This epidemiological shift might be explained by various factors, such as the development of novel anti-cancer therapies, or the selective pressure of antifungal agents. Environmental changes, including the contamination of hospital rooms by airborne spores, may also play a role [9]. Moreover, the development of diagnostic tools with increased sensitivity, such as PCR, may lead to a better recognition of these fungi that are fastidious to grow in cultures [3].

We observed an increased incidence of non-*Aspergillus* invasive mould infections (NAIMI) in a single Swiss tertiary care hospital between 2017-2021. The aim of this study was to investigate the potential causes of this epidemiological shift.

Materials and methods

Patients and setting

The Lausanne University Hospital is a 1500-bed hospital in which there is an 18-bed isolation unit both for patients undergoing chemotherapy for acute leukaemia and for those receiving autologous haematopoietic stem cell transplantation for other haematologic malignancies. In 2019, the isolation unit had been moved from a satellite building

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to a renovated unit in the main hospital building. This unit had positive-pressure rooms as well as the high efficiency particulate air (HEPA) filtration system. Also in 2019, important renovation works have been undertaken close to the main hospital building in the form of ground excavation for the construction of a new hospital building.

Patients undergoing myeloablative chemotherapies with an expected duration of neutropenia >10 days receive fluconazole prophylaxis and are monitored twice weekly for galactomannan and $(1{\to}3)$-β-d-glucan in serum. Fluconazole may be substituted by posaconazole for individual cases who are considered at higher risk or for patients included in a study protocol requiring posaconazole prophylaxis. Patients with persisting or recurrent neutropenic fever undergo a chest CT-scan and, in case of lung CT abnormality, a bronchoscopy. In addition to standard fungal cultures, the microbiology laboratory provides an *Aspergillus fumigatus*-specific PCR and a panfungal PCR, as previously described [10]. Moreover, a pan-Mucorales PCR has been implemented in 2018, as previously described [11].

Incidence of invasive mould infections

All episodes of proven or probable invasive mould infections, according to the European Organisation for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium (EORTC-MSGERC) [12], were extracted from the ward registry for the period 2007–2021. Incidence of proven or probable invasive aspergillosis, invasive mucormycosis and other NAIMI were expressed for each year in the number of cases per 10,000 patient-days with expression of the 95% confidence interval (CI).

Room air analyses

The contamination of room air with mould was investigated by passive air sampling using open Sabouraud agar plates that were dispatched at different locations within each room (3 per room) for 4 h. The plates were then closed and incubated for 5 days at 20 °C.

Antifungal drug consumption

Consumption of antifungals was extrapolated from the hospital pharmacy's delivery data for posaconazole and other antifungal agents. The total mass of compounds (in grams) was converted into defined daily dose (DDD) according to the Anatomical Therapeutic Chemical (ATC) code / DDD index (https://www.whocc.no/atc_ddd_index/ last accessed June 19th 2023). An adjustment was made for the posaconazole suspension formulation (used before 2015) with a DDD defined at 0.6 g (0.2 g three times daily) instead of 0.3 g for the tablet formulation (0.3 g once daily).

Statistical analyses

Two time periods (2007–2016 and 2017–2021) were compared. The Fisher exact test was used to compare proportions of NAIMI. Temporal variations of the incidence rates of invasive aspergillosis and NAIMI have been investigated. The Mann and Kendall test was used to assess the significance of the trend in incidence. The significance level was set at p ≤0.05. Analyses were performed on Microsoft Excel with XLSTAT program (Microsoft Corporation, Redmont WA)

Ethical statement

The patients included in this study have signed informed consent for inclusion in a previous cohort study of epidemiological survey during febrile neutropenia, which was approved by the local ethics committee (CER-VD, protocol number 2017-01975). No protocol has been publicly deposited for the present study, which was part of the routine investigations of the infection control unit within our institution.

Results

Incidence of non-Aspergillus mould infections over years

From 2007 to 2021, a total of 103 episodes of proven or probable invasive mould infections occurred in the isolation unit. This includes 79 invasive aspergillosis and 24 NAIMI (including 18 invasive mucormycosis). The incidence of invasive mould infections, invasive aspergillosis and NAIMI over years is shown in figure 1. A significant increase of the incidence of NAIMI was observed from 2017 onwards (Mann and Kendall test, p = 0.0053), while the incidence of invasive aspergillosis remained stable (p = 0.77). While NAIMI represented 16.8% of invasive mould infection cases for the period 2007–2016, their proportion was 33% for the period 2017–2021 (p = 0.02), with the peak observed in 2020 (8.62 episodes per 10,000 patient-days, 95% CI: 3.74–18.64, 45% of all invasive mould infections). The increased incidence was significant for mucormycosis (p = 0.003), which represented the majority of NAIMI. All NAIMI other than mucormycosis, except one, occurred in the later period (2017–2021).

Investigations of potential causes of non-Aspergillus mould infections outbreak

Analyses of antifungal drug consumption did not reveal a significant increase in the use of posaconazole (median 661.3 DDD/year for the period 2017–2021, *vs* 934.9 DDD/year for the period 2007–2016, p = 0.13) or other anti-mould active antifungal drugs (data not shown).

In 2020, a passive air sample was taken from all 18 rooms of the isolation unit. No Mucorales were recovered by this method; only *Cladosporium* spp. grew on 2 out of 54 of the plates.

We also assessed the impact of the novel Mucorales PCR, which may have resulted in increased recognition of proven or probable mucormycosis among cases that would otherwise have been classified only as possible invasive mould infections, according to EORTC-MSGERC criteria. Since its introduction in 2018, the Mucorales PCR was performed in 9 out of 10 cases of mucormycosis. There were positive results in 8 (89%) cases and one negative result (one invasive mould infections due to *Cunninghamella*, not included in the PCR panel) (table 1). In 3 out of 10 cases (30%), the diagnosis of mucormycosis was obtained via a positive result of the Mucorales PCR only (i.e. negative histopathology, culture and panfungal PCR).

Characteristics of patients and non-Aspergillus invasive mould infections episodes

The demographic characteristics of the 24 patients with a documented NAIMI are described in table 1. Most patients (n = 21, 87.5%) had chemotherapy-induced prolonged neutropenia. Eight (33%) patients were receiving antifungal prophylaxis that was considered to be mould-active (posaconazole n = 5, voriconazole n = 2, isavuconazole n = 1) for ≥7 days when they developed breakthrough NAIMI (table 2). The characteristics of all 24 NAIMI episodes are shown in table 2. Most cases (n = 20, 83%) were proven invasive fungal infections. The lungs were the primary site of infection in most cases (n = 22, 92%) and disseminated disease (≥2 affected organs) was observed in 8 (33%) patients. Extra-pulmonary sites of in-fection were intra-abdominal abscesses (liver or spleen, n = 5, 21% of patients), skin or soft tissue lesions (n = 5, 21%) and brain lesions (n = 2, 8%). Among episodes of mucormycosis (n = 18), the most frequent pathogen was *Rhizomucor* spp. (n = 7, 39%) followed by *Lichtheimia* spp. (n = 5, 28%), *Mucor* or *Rhizopus* spp. (n = 4, 22%) and *Cunninghamella* (n = 1, 6%). In one case, the diagnosis of mucormycosis relied on histopathological documentation only (no genus or species identification occured). Other NAIMI were attributed to *Hormographiella aspergillata* (n = 3), *Alternaria* spp. (n = 2) and *Conidiobolus* spp. (n = 1). First-line antifungal therapy of mucormycosis consisted of liposomal amphotericin B alone (n = 8) or combined with an echinocandin (n = 6) or isavuconazole (n = 1), posaconazole (n = 2) and isavuconazole (n = 1). A triazole was used as second-line, or "maintenance", therapy in 12 cases (isavuconazole, n = 7, and posaconazole, n

Figure 1: Incidence and proportions of different invasive mould infections in the isolation unit of onco-haematology. Incidences are represented in the number of cases per 10,000 patient-days for invasive aspergillosis (green), invasive mucormycosis (violet) and other invasive mould in-fections (red) for each year. Bars represent the 95% confidence interval. The black arrows and grey boxes indicate the different events with a potential impact on invasive mould infections incidence. "Construction works": construction of a new hospital building near the main building; "Mucorales PCR": introduction of a new PCR for detection of Mucorales; "Moving unit": re-localization of the isolation unit in another hospital building.
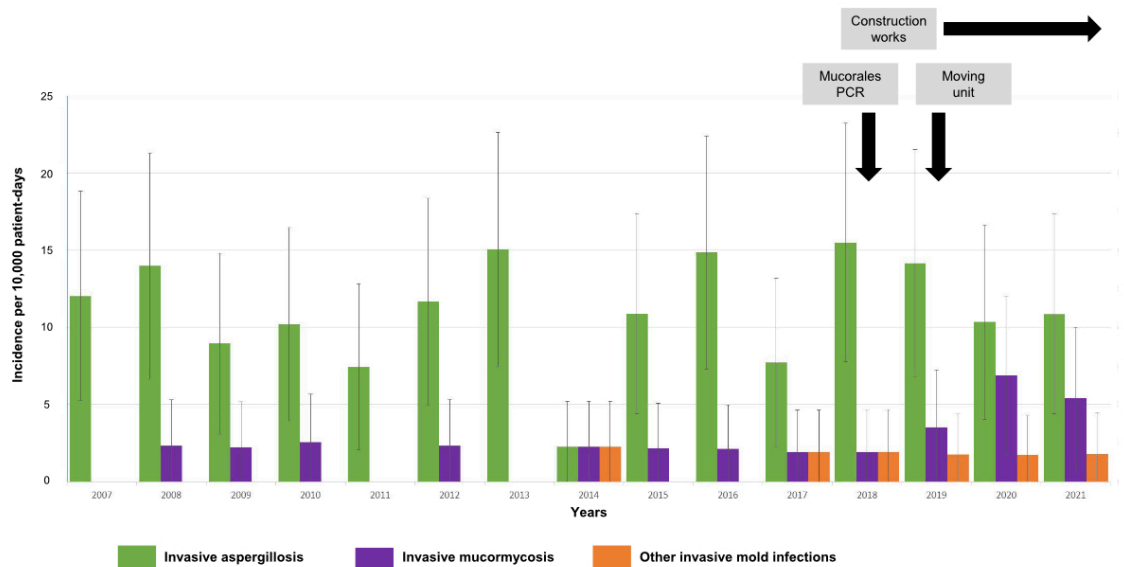
Table 1:

Characteristics of patients with non-*Aspergillus* invasive mould infections. Numbers are total number (percentage) for proportions and median (range) for continuous variables.

N total		24
Demographic characteristics	Female / Male	8 (33%) / 16 (67%)
	Age (years)	55 (19–72)
Underlying haematologic disease	Acute myeloid leukaemia	16 (67%)
	Other haematologic cancer*	8 (33%)
Predisposing conditions**	Neutropenia***	22 (92%)
	Recent chemotherapy	21 (87.5%)
	Induction	9 (43%)
	Re-induction / consolidation	5 (24%)
	Salvage / maintenance	7 (33%)
	Allogeneic haematopoietic cell transplantation	6 (25%)
	Graft versus host disease	5 (83%)

* Other haematologic cancer: ambiguous acute leukaemia (n = 3), myelodysplastic syndrome (n = 2), acute lymphoblastic leukaemia (n = 1), lymphoma (n = 1), chronic myeloid leukaemia (n = 1)

** More than one possible

*** Neutropenia: neutrophil count <500/mm^3 for at least 10 days temporally related to the onset of non-*Aspergillus* mould infection

= 5). Different drugs were used for the treatment of other NAIMI (liposomal amphotericin B, posaconazole, isavuconzole, voriconazole). Overall, surgical interventions for therapeutic purposes were performed in 18 out of 24 (75%) cases. Response to therapy was assessed at week 12 according to recommended criteria [13]. Success (complete or partial response) was observed in 15 out of 24 (63%) cases. The overall mortality rate at week 12 was 2 out of 24 (8%). Two patients subsequently died between week 12 and 24. The mortality rate for mucormycosis was 11% and 22% at week 12 and 24, respectively. All patients with other NAIMI were alive at week 24.

Discussion

We have documented a significant burden of NAIMI over the last 5 years in our onco-haematology unit. These epidemiological changes appear to result from diverse factors. We hypothesize that the relocation of the unit (2019) and occurrence of building work nearby the hospital (from 2019 to present) may have been a major factor. The timing of events is strongly suggestive of a cause-effect association, as these events corresponded to the peaks of NAIMI

Table 2:

Characteristics of episodes of non-*Aspergillus* invasive mould infections.

Patient	Period [1]	EORTC-MS-GERC criteria	Site(s) of infection	Fungal species	Method of identification	Prior antifungal [2]	Anti-fungal therapy [3]	Outcome at week 12 (response) [4]
Cases of mucormycosis								
1	1	Proven	Lung	*Lichtheimia corymbifera*	Histology / Panfungal PCR	CAS	L-AMB, then POS / Surgery	Alive (Complete)
2	1	Proven	Lung	*Rhizopus microsporus*	Histology / Panfungal PCR	No	POS / Surgery	Alive (Partial)
3	1	Proven	Lung, liver, spleen	Not identified	Histology	No	L-AMB[5]	Deceased
4	1	Proven	Lung	*Rhizopus* spp.	Histology / Panfungal PCR	No	L-AMB / Surgery	Alive (Complete)
5	1	Proven	Lung, soft tissue	*Lichtheimia* spp.	Histology / Panfungal PCR	No	L-AMB, then POS / Surgery	Alive (Complete)
6	1	Proven	Lung, liver, spleen, soft tissues	*Rhizomucor miehei / pusillus*	Histology / Panfungal PCR	FLU	L-AMB / Surgery	Alive (Progression)
7	1	Proven	Lung	*Lichtheimia corymbifera*	Histology / Panfungal PCR	FLU	L-AMB, then POS / Surgery	Alive (Partial)
8	2	Proven	Lung	*Rhizomucor pusillus / microsporus*	Histology / Culture	FLU	L-AMB, then POS / Surgery	Alive (Progression)
9	2	Proven	Lung	*Rhizomucor* spp.	Histology / Mucorales PCR	VOR	L-AMB, then ISA / Surgery	Alive (Partial)
10	2	Proven	Lung, liver	*Rhizomucor* spp.	Histology / Panfungal PCR	FLU	ISA, then POS / Surgery	Alive (Stable)
11	2	Probable	Lung	*Lichteimia* spp.	Mucorales PCR	POS	POS	Alive (Complete)
12	2	Probable	Lung	*Mucor / Rhizopus* spp.	Mucorales PCR	ISA	L-AMB and ISA, then ISA	Alive (Stable)
13	2	Probable	Lung	*Mucor / Rhizopus* spp.	Mucorales PCR	ANI	L-AMB and CAS, then ISA / Surgery	Alive (Progression)
14	2	Proven	Lung	*Cunninghamella* spp.	Histology / Panfungal PCR	FLU	L-AMB and CAS, then ISA / Surgery	Alive (Progression)
15	2	Proven	Lung, brain	*Rhizomucor* spp.	Histology / Panfungal PCR / Mucorales PCR	POS	L-AMB and CAS, then L-AMB and ISA, then ISA / Surgery	Alive (Complete)
16	2	Proven	Lung	*Rhizomucor* spp.	Histology / Panfungal PCR / Mucorales PCR	FLU	L-AMB and CAS, then ISA / Surgery	Alive (Complete)
17	2	Proven	Lung, liver, intestine	*Rhizomucor* spp.	Histology / Panfungal PCR / Mucorales PCR	AND	L-AMB and ANI, then ISA	Alive (Progression)
18	2	Probable	Lung, brain, spleen	*Lichtheimia corymbifera*	Panfungal PCR / Mucorales PCR	POS	L-AMB and CAS	Deceased
Cases of other non-mould infections								
19	1	Proven	Skin	*Alternaria alternata*	Histology / Culture / Panfungal PCR	FLU	POS / Surgery	Alive (Complete)
20	2	Proven	Lung	*Hormographiella aspergillata*	Histology / Panfungal PCR	POS	L-AMB, then VOR / Surgery	Alive (Complete)
21	2	Proven	Skin	*Alternaria* spp.	Culture / Panfungal PCR	VOR	L-AMB, then VOR	Alive (Complete)
22	2	Proven	Lung	*Conidiobolus pachyzygosporus*	Histology / Panfungal PCR	FLU	L-AMB, then ISA / Surgery	Alive (Partial)
23	2	Proven	Lung, soft tissue	*Hormographiella aspergillata*	Histology / Culture / Panfungal PCR	FLU	POS, then VOR / Surgery	Alive (Complete)
24	2	Proven	Lung	*Hormographiella aspergillata*	Histology / Panfungal PCR	POS	L-AMB, then ISA, then VOR / Surgery	Alive (Partial)

EORTC-MSGERC: European Organisation for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium; PCR: polymerase chain reaction; CAS: caspofungin; FLU: fluconazole; VOR: voriconazole; ISA: isavuconazole; POS: posaconazole; ANI: anidulafungin; L-AMB: liposomal amphotericin B.

[1] Period 1: 2007–2016, period 2: 2017–2021.

[2] Ongoing antifungal prophylaxis or therapy for ≥7 days prior to diagnosis (first signs of non-*Aspergillus* mould infections).

[3] First-line targeted antifungal therapy (after identification of the causal fungal pathogen).

[4] Outcome at week 12 after start of targeted antifungal therapy. Response to therapy assessed according to recommended criteria [13].

[5] Empirical therapy (diagnosis obtained at autopsy).

incidence between 2019 and 2021. Although we could not document airborne contamination by moulds in the rooms, the lack of sensitivity of the method does not rule out this hypothesis. Of note, we did not perform quantification of airborne fungal spores in the rooms by sampling via an air impactor during the study period. However, the presence of positive air pressure and HEPA filters makes mould contamination of the rooms unlikely. The patients may have been in contact with airborne spores when outside of their isolation rooms during transfers to examination rooms (e.g. radiology, bronchoscopy).

Several outbreaks of invasive mould infections have been associated with airborne contamination arising from building work occurring near hospitals, although the link could not always be clearly demonstrated [9, 14]. These outbreaks were mainly caused by *Aspergillus* spp. Recently, a cluster of mucormycosis has been reported in a French intensive care unit among patients with Coronavirus disease 2019 (COVID-19), which was also possibly linked to building works [15].

Our results also suggest that improved diagnostic procedures may have contributed to an apparent rise of NAIMI incidence and that the disease could have gone underdiagnosed in the past. Indeed, the newly implemented Mucorales-specific PCR has been estimated to increase the yield of mucormycosis' detection by about 30%. Although this possible artefact should be considered, it is not the unique explanation of this epidemiological shift, as we observed a near 2-fold increase of mucormycosis incidence rates from 2018 to 2019 and a 3.5-fold increase from 2018 to 2020 (figure 1).

Although about one third of these NAIMI corresponded to breakthrough infections in patients receiving mould-active prophylaxis, we did not observe a significant change in the consumption of posaconazole or other mould-active drugs over the study period.

Finally, whether other factors, such as the global warming, may have contributed to this burden of NAIMI is unknown. Similarly to other European countries, Switzerland has experienced a constant rise of mean temperatures over the last few years [16]. Interestingly, in addition to the increased incidence of mucormycosis, we also observed some NAIMI attributed to rare moulds (*Hormographiella aspergillata*) or supposed tropical moulds (*Conidiobolus* spp.) since 2017, which was not the case during the early period. The COVID-19 pandemic has been associated with a significant burden of mucormycosis in some parts of the world, notably in India [17]. However, we did not observe any case of COVID-19-associated mucormycosis in our institution during the study period. Other factors, such as novel anti-cancer chemotherapy protocols, may have played a role in NAIMI incidence, but have not yet been investigated.

The analysis of the characteristics of these NAIMI cases also provided interesting epidemiological data about these rare infections. Interestingly, we observed relatively low overall mortality rates (11% for mucormycosis and 0% for other NAIMI at week 12) when compared to previous cohorts reporting mortality rates of 40–50% [4, 18, 19]. While diagnostic and therapeutic approaches have improved over time with the introduction of the Mucorales PCR and the approval of novel antifungal therapies (e.g.

isavuconazole) [11, 20], we did not observe any trend in mortality rates between periods 1 and 2 of our study. Longer survey and larger datasets are needed to assess mortality trends of NAIMI. Importantly, other recent advances, such as the development of international guidelines and of the European QUALity (EQUAL) score for the management of mucormycosis, may also contribute to improved outcomes of this severe disease in the future [21, 22].

In conclusion, continuous monitoring of the incidence of invasive mould infections, in particular NAIMI, may be helpful to detect possibly emerging mould diseases and, consequently, to trigger further investigations and potential preventive measures.

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. FL declares research grants from Pfizer, MSD, Gilead and Novartis, and honoraria for conferences or advisory boards from Pfizer, MSD, Gilead and Mundipharma. All contracts were made with and fees paid to his institution (CHUV). No other potential conflict of interest related to the content of this manuscript was disclosed.

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