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Epidemiology of filamentous fungal infections in burned patients: A French retrospective study

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ABSTRACT

Introduction: Filamentous fungal infections (FFI) seem to become more frequent in burn patients, in whom they are usually accepted to cause severe. However published data regarding their incidence and consequences in that context remain scarce. The aim of this study was to evaluate the incidence of mould infections in our burn centre, and to review characteristics and outcomes of patients with such infections.

Methods: This retrospective single-centre study reviews all patients admitted in our centre with acute burns (2000–2011) and positive culture for moulds. Wound infections were defined as follows: fungal wound colonisations (FWC) for positive mycological cultures without signs of wound infection; fungal wound infections (FWI) for positive mycological cultures with local signs of wound infection; disseminated infection (DI) for FWI with a positive blood culture or a positive galactomannan (for aspergillosis) or severe sepsis or secondary organ localisation(s).

Results: Among 1849 patients, 31 patients presented a FFI. For 29 patients (93%), positive fungal samples were cutaneous: 20 Aspergillosis ASP (5 FWC, 8 FWI and 7 DI), 9 mucormycosis MMC (3 FWC and 6 FWI) and 3 fusariosis FUS (3 FWI). Two patients presented a catheter colonisation or a pulmonary colonisation (*Aspergillus fumigatus*). Incidence of FFI was 1.7%. Total body surface area burned, full-thickness burn surface area, Unit Burn Standard, Tobiasen score and SAPS2 (respectively 55% [40–73], 45% [30–63], 180 [129–259], 11 [8–12] and 50 [40–62]) were markedly higher than in burned patients without FFI hospitalised during the same time period. 30% of the patients with burn wound ASP (6/22) died. Mean length of stay was 111 ± 67 days.

Conclusion: FFI are essentially cutaneous, infrequent and occur in the most severe burned patients. ASP seems to be more serious than other FFI.

1. Introduction

Early surgical excision with extensive debridement of necrotic tissue and skin grafting of cover with skin substitutes have decreased mortality rates associated with extensive burns. Advances in patient care also include use of broad-spectrum antibiotics, surgical techniques for skin coverage, enteral and parenteral nutrition, and critical care support for organ dysfunctions [1,2]. Moreover, host defences of burned patients

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are severely impaired, with a high decrease in both innate and adaptive immune system responses [3,4]. As a result, burned patients are at high risk of developing life-threatening opportunistic infections during their stay in a burn unit. In patients with severe burns, almost 70% of all deaths are currently related to sepsis from local and systemic infections. Bacterial infections remain the main causes of sepsis in the burn units [4–6].

Incidence of fungal infections in burned patients has increased since the implementation of topical antimicrobial agents used to control bacterial colonisation [7]. *Candida* species remain the predominant cause of invasive fungal infections of burn wounds. *Candida* infections have been well described in burned patients. They represent a serious problem and are associated with increased mortality, morbidity, length of hospital stay and costs [8].

Filamentous fungi (also known as moulds) are not common, but are known to cause severe diseases and invasive wound infections in patients with extensive burns [4,9,10]. Filamentous fungi are made up of fine threads called hyphae. Hyphae grow at the tip and divide repeatedly along their length creating long and branching chains [11]. Hyphae keep growing until they form a network of threads called a mycelium. Some of the hyphal branches form a specialised structure called thallus that can produce spores or conidia. Spores enable the fungus to reproduce. Wind, rain, insects, ventilation systems or hand carriage can spread spores. They eventually land in new habitats to grow and produce new hyphae if conditions are right, and burn wounds provide such conditions. Diagnosis and treatment of invasive mould infections are a challenge because filamentous fungi have a much greater invasive potential than yeasts [12]. However data are scarce in the literature about incidence and consequences of filamentous infection in burns. The main objective of this study was to evaluate the incidence of filamentous infections in our burn centre. Secondary objectives were to review characteristics, treatments and outcomes of patients with such infections.

2. Patients and methods

2.1. Study design and setting

In this retrospective single centre study, medical records and charts of patients from the burn centre at Percy military teaching hospital were systematically reviewed. This department is the main French military burn centre. It features 16 acute care beds (10 ICU and 6 step down beds), two dedicated operating rooms, and two initial resuscitation rooms. The full time staff consists of physicians specialised in critical care and anaesthesiology and trained in burn care, assisted by dedicated nurses and nurse assistants. Surgeons from the plastic surgery department also perform surgical procedures.

2.2. Patients

All patients with burns admitted to our centre between January 1st 2000 and October 31st 2011 and with a microbiological sample with a positive filamentous culture (confirmed by a second isolate) were included. Non-burned patients such as dermatological disorders (Lyell syndrome, purpura fulminans, traumatic wound, graft-versus-host disease, Morel-Lavallée syndrome, or frostbites) were excluded.

2.3. Definition of fungal infections

The 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria are usually used to define fungal infections [13]. However, these criteria are not applicable for diagnosis of cutaneous, wound or burn infections. In our unit, these infections have been classified according to microbiological and clinical criteria. First, fungal wound colonisations (FWC) are defined by positive cultures (for moulds) on one single full thickness skin or wound biopsy, or on at least 2 wound swabs (Table 1). Second, fungal wound infections (FWI) are defined by similar microbiological results yet associated with local signs of wound infection (Table 1). Third, a disseminated infection (DI) is a FWI associated with positive blood culture or presence of galactomannan (for disseminated aspergillosis) or secondary organ localisation (including other cutaneous localisation).

2.4. Microbiological methods

Wound swabs were regularly performed in order to detect the presence of microorganisms as part of our standard of care. In cases of clinically suspected wound infection, culture of full thickness skin biopsy was performed either directly on full thickness burns before excision, or after a swab culture positive for moulds on other sites.

Tissue biopsy and other relevant samples were processed by standard microbiological procedures using direct microscopy

Table 1 – Clinical description of filamentous burn wound infection.

Localisation	Clinical description
Unexcised burn wound	• Moderate to severe changes in appearance of burn wound (>48th hour) • Unexplained conversion of partial-thickness to full-thickness lesions • Haemorrhagic or necrotic discoloration of subeschar tissues • Unexpectedly fast separation of eschar
Excised burn wound	• Formation of neoeschar or focal necrosis on wound surface (or both) • Failure to heal
Grafted wound	• Partial or total lysis of graft areas • Haemorrhagic or necrotic discoloration of tissues under the graft • Failure to heal
Donor site	• Formation of neoeschar or focal necrosis • Failure to heal
Healed burn	• Lysis of healed burn
All sites	• Changes at wound surface suspicious for mould colonies • Wound colour change: focal dark red, brown, or black eschar discoloration • Necrotic lesions

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and culture. Culture of the tissue biopsy was interpreted as per Loebl et al. using quantitative method $>10^3$ CFU g^{-1} (colony-forming units per gram) of tissue [14]. Samples were inoculated in the clinical mycology laboratory on various mycological media (Sabouraud's dextrose agar with and without chloramphenicol and blood agar) in duplicate tubes and were incubated at 30 °C and 37 °C for up to 6 weeks, before reporting a negative culture report. Genus and species were identified using colony characteristics and conidiophore, conidia or spores morphology at 48 h [11].

In order to confirm phenotypic observation, sequence-based species identification of isolates or tissue samples was performed (Protein Chain Reaction PCR) either in the microbiology laboratory of our hospital or at the National Reference Centre for Mycoses and Antifungal agents (Institut Pasteur, Paris, France). PCR was not systematically performed in our unit in case of mould isolate.

Upon the initial isolation of *Aspergillus sp*, determination of galactomannan was requested and performed by Platelia (BioRad, Hercules, USA). The cut-off is 0.5 ng/ml in our hospital.

2.5. Collected data

The following data were recovered from charts and patient records. Demographic data extracted from the medical records included age, gender, weight, body mass index (BMI), and usual risk factors of filamentous fungal infection such as neutropenia (defined as neutrophil count <1000/mm^3), haematological malignancy, bone marrow transplantation, prolonged treatment with corticosteroids before admission, solid organ cancer, HIV infection, systemic diseases or immunosuppressive therapy, solid organ transplant recipients, diabetes mellitus, chronic obstructive pulmonary disease, liver cirrhosis, injection drug use, deferoxamin therapy and chronic renal failure [15].

Characteristics of burns included total body surface area burned, expressed as a percentage (%TBSA) and evaluated according to the Lund and Browder charts, full-thickness (or 3rd degree) burn surface area (FTBSA) expressed in % TBSA, presence of inhalation injury, circumstances and mechanisms of burn.

The following burn severity scores were calculated: Baux score [16], Unit Burn Standard (UBS) [17], Abbreviated Burn Severity Index (ABSI) [18]. SAPS2 [19] and the ODIN model [20] were used to describe overall patient severity and organ dysfunctions (Table 2).

General outcomes recorded included hospital mortality, and length of stay at the burn centre. Other clinical parameters recorded were number of surgical procedures, mechanical ventilation, renal replacement therapy, vasopressor or inotrope support and grafting with cultured epithelial autografts. All bacterial or non-filamentous fungal (with *Candida sp.*) cutaneous infectious episodes as defined in current recommendations of the American Burn Association were also recorded [21].

Microbiological data for mould isolates included sampling date and site, isolate species (or at least genus when species unknown), Galactomannan (GM), identification by PCR and histological examination. Anti-fungal systemic and local treatments were recorded.

Table 2 – Definitions of organ dysfunctions according to the ODIN model [20].

Organ failure	Definitions
Respiratory	• $PaO_2 < 60$ mmHg with $FiO_2 = 0.21$ • Need for ventilatory support
Cardiovascular	• Systolic arterial pressure <90 mmHg with signs of peripheral hypoperfusion • Continuous infusion of vasopressor or inotropic agents to maintain systolic arterial pressure >90 mmHg
Renal	• Serum creatinine >300 μmol/L • Urine output <500 ml/24 h or <180 ml/8 h • Need for hemodialysis or peritoneal dialysis
Neurologic	• Glasgow coma scale ≤6 (in the absence of sedation) • Sudden onset of confusion or psychosis
Hepatic	• Serum bilirubin >100 μmol/L • Alkaline phosphatase >3 × normal
Hematologic	• Haematocrit ≤20% • White blood cell count <2000/mm^3 • Platelet count <40,000/mm^3

2.6. Statistical analysis

Statistical calculations were performed with XLSTAT® (Addinsoft, XLSTAT-Medical, Paris, France). Quantitative data were expressed as mean ± standard deviation or median [interquartile range] as appropriate. Considering the small number of patients included, we mainly used univariate methods of analysis. Univariate associations were tested by Mann–Whitney or Kruskal–Wallis tests as appropriate. Categorical data were reported as counts and percentages, and compared using Fisher's exact test. A p-value <0.05 was considered significant.

3. Results

3.1. Incidence

1849 burned patients were admitted to Percy military burn centre between January 2000 and October 2011. Among these admissions, 31 burned patients had grown a filamentous fungal isolate at any site (Fig. 1). Among all the burned patients admitted in our centre for the study period, the incidence of mould infection was 1.7%: 1.2% for aspergillosis (ASP), 0.5% for mucormycosis (MMC) and 0.2% for fusariosis (FUS).

3.2. Baseline patients and burns characteristics

Table 3 gives an overview of baseline characteristics of all 31 cases according to type of fungal infection.

Nineteen patients (61%) were secondarily transferred from other facilities (11 transfers from remote French regions, 8 international transfers), leaving only 12 direct admissions (39%).

Medical history was as follows. Two patients had chronic obstructive pulmonary disease, 1 patient was a drug user (injection), and one patient had prolonged treatment with corticosteroids (for multiple sclerosis). There was no patient with neutropenia (before and during hospitalisation), haematological malignancy, bone marrow transplantation, solid organ cancer, HIV infection, immunosuppressive therapy,

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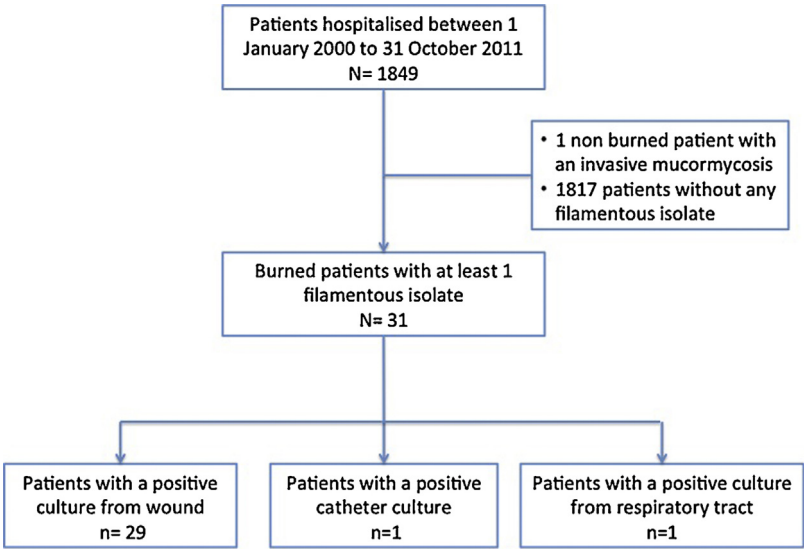

Fig. 1 – Flow chart.

solid organ transplant recipients, diabetes mellitus, liver cirrhosis, deferoxamin therapy or chronic renal failure.

The characteristics and circumstances of occurrence of sustained burns are summarised in Table 3. Burns were thermal in 29 patients (by flame or by radiated heat) and electrical in 2 patients (1 ASP/FWI and 1 MMC/FWC). There was neither chemical burn, nor burns by adherent product (oil, tar, wax, ...) or hot liquid, nor radiation-induced burn. Main burn causes were residential fire (32%), traffic accident (23%), self-burning (13%), domestic fire incident (19%), combat-related burns (7%), and aggression (3.5%).

3.3. *Fungal infections*

34 moulds were recovered, including several species of *Aspergillus*, *Fusarium* and Mucorales (Fig. 2). For 3 patients, 2 moulds were identified from wounds. For example, case 20 developed *Rhizomucor variabilis* from a back wound, and then developed *A. fumigatus* 5 weeks later from the same wound.

For all patients, fungal identifications were based on phenotypic observations from cultured wound biopsy: 23 species were identified and genus only was identified for 6 fungi. For 13 species, PCR was implemented and confirmed identifications (8 *Aspergillus* sp, 3 Mucorales, 2 *Fusarium* sp). Among patients with ASP, GM was positive for 7 patients. Histopathological analyses were carried out on only 3 patients, and showed invasion of viable tissue.

For 29 patients (93%), positive fungal samples were cutaneous (biopsies or superficial swabs): 20 patients for *Aspergillus* (5 FWC, 8 FWI and 7 DI), 9 for Mucorales (3 FWC and 6 FWI), 3 for *Fusarium* (3 FWI). Among the 7 patients with an ASP/DI, 1 patient showed 2 episodes of distinct DI by same germ (*Aspergillus terreus*) during his hospitalisation. Disseminate characteristics have been defined in those 7 patients by positive GM.

We also included two other patients with an *Aspergillus fumigatus* catheter colonisation (10^3 UFC/ml culture) and one *A. fumigatus* pulmonary colonisation (culture of the 10^3 UFC/ml bronco-alveolar cleaning and negative aspergillar antigenemy).

ASP, MMC and FUS respectively occurred 5 [3–8], 4 [3–5] and 4 [3–6] weeks after burn.

3.4. *Severity criteria*

Severity criteria are detailed in Table 3. TBSA, FTBSA, UBS scores, BAUX score, ABSI, and inhalation were consistently higher in patients of the series than in other burned patients hospitalised in the unit during the same time period (Table 4). For patients with cutaneous ASP, there was no significant difference between mean TBSA, FTBSA, Baux score and ABSI according to the different types of fungal infections (FWC, FWI, DI; Kruskal–Wallis test).

3.5. *Outcomes*

One third of the patients with burn wound ASP (6/20) died and all of them showed DI criteria. Thus among 7 patients with ASP/DI, 6 died. Two patients with MMC died. Those two patients also had an ASP and belonged to the 6 dead ASP/DI group. No patient with FUS died.

Mean length of stay was high (111 ± 67 days). All patients showed a respiratory or haemodynamic failure. Renal, neurologic, hepatic and hematologic failure was identified in respectively 12 (38.7%), 9 (29%), 9 (29%) and 21 (67.7%) patients.

Patients had a mean 3.5 ± 1.0 organ failures. Six patients (19%), 8 patients (26%), 12 patients (39%) and 5 patients (16%) had respectively 2, 3, 4 and 5 organ failures.

All patients of this series underwent invasive mechanical ventilation. 71% of patients received vasopressor and/or inotrope support. Renal replacement therapy (continuous hemodiafiltration or intermittent hemodialysis) was used in 11 patients out of 31 (36%). Finally, 7 patients (23%) received cultured epithelial autografts (CEA).

Patients of the series had as a mean 3 ± 1 separate bacterial infections: 26 patients (84%) had a pneumonia, 26 (84%) an

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Table 3 – Characteristics and gravity scores of burned patients. The total of *Aspergillus* positive isolates outnumbers the fungal wound colonisation, the fungal wound infections and the disseminated infections by 2, due to the inclusion of 1 case of catheter colonisation and 1 case of pulmonary colonisation. Results are expressed as median [interquartile range] or mean ± standard deviation as appropriate.

Parameters	ASP				MMC			FUS	All $n = 31$
	FWC $n = 5$	FWI $n = 8$	DI $n = 7$	All $n = 22$	FWC $n = 3$	FWI $n = 6$	All $n = 9$	FWI $n = 3$	
Age, years	40 ± 20	40 ± 14	40 ± 12	40 ± 14	48 ± 11	37 ± 15	41 ± 14	28 ± 25	39 ± 16
Male	4/5	5/8	6/7	17/22	3/3	5/6	8/9	2/3	24/31
Weight (kg)	74 ± 8	75 ± 18	104 ± 48	85 ± 31	77 ± 2	83 ± 13	81 ± 11	60 ± 38	82 ± 29
BMI	24 ± 4	25 ± 4	34 ± 15	28 ± 10	25 ± 1	28 ± 5	27 ± 5	26 ± 8	28 ± 9
TBSA (%)	45 [40–75]	75 [59–86]	70 [56–77]	65 [46–83]	50 [50–60]	43 [40–57]	50 [40–61]	50 [40–52]	55 [40–73]
FBSA (%)	30 [25–70]	48 [35–60]	65 [49–74]	50 [30–70]	30 [30–46]	40 [31–50]	35 [30–52]	37 [33–44]	45 [30–63]
Inhalation injury	3/5	5/8	7/7	17/22	2/3	4/6	6/9	0/3	21/31
Number of surgery	6 ± 4	10 ± 5	12 ± 2	8 ± 5	5 ± 3	6 ± 3	6 ± 3	8 ± 3	8 ± 5
UBS	130 [115–300]	212 [151–259]	265 [199–299]	215 [129–294]	140 [140–196]	163 [134–208]	145 [140–217]	159 [137–185]	180 [129–259]
BAUX	84 [81–112]	117 [109–127]	119 [97–134]	112 [89–125]	99 [93–109]	78 [73–122]	87 [75–118]	86 [60–93]	99 [83–119]
ABSI	8 [7–12]	12 [9–13]	11 [10–14]	11 [8–13]	11 [11,12]	9 [8–13]	11 [8–13]	9 [7–10]	11 [8–12]
IGS2	29 [26–32]	47 [36–48]	52 [50–64]	48 [47–52]	50 [40–60]	52 [50–74]	61 [51–73]	25 [22–42]	50 [40–62]
Organ Failure	2 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 2	4 ± 1		

Table 4 – Comparison of severity scores between patients burned with or without mould infection. Mann Whitney test.

Parameters	Patients burned without mould infection	Patients burned with mould infection	*p*
TBSA (%)	15 [10–30]	55 [40–73]	<0.001
FTBSA (%)	5 [0–15]	45 [30–63]	
UBS	30 [11–75]	180 [129–259]	
BAUX	59 [42–80]	99 [83–119]	
ABSI	6 [4–8]	11 [8–12]	
IGS2	22 [16–42]	50 [40–62]	

invasive cutaneous infection, 12 (39%) a urinary tract infection, 11 (35%) a blood strain infection, 6 (20%) a catheter related infection and 4 (13%) another infection (1 Fournier gangrene, 2 sinusites et 1 angiocholitis).

Candida sp. were isolated in 19 patients (61%) during they stay in the department. Eight of them (42%) had only colonisations and the remaining 11 had infections receiving a systemic treatment (58%). Finally, 4 patients (13%) had a documented viral infection (three cutaneous *Herpes simplex virus* infections and 1 pulmonary *Cytomegalovirus* infection).

3.6. *Treatments*

All patients with ASP/DI, 7/8 patients with ASP/FWI and 5/6 patients with MMC/FWI received initial anti-fungal treatment. Definitive treatment was administered according to medical staff decision after species identification.

For the ASP (DI + FWI), initial treatments were voriconazole (5 patients), lipid formulations of amphotericin B (6 patients), itraconazole (2 patients) and posaconazole (1 patients). Flucytosine was used in one patient, in association with amphotericin B (lipid formulations).

For the MMC, initial treatments were lipid formulations of amphotericin B (4 patients), and amphotericin B deoxycholate (1 patient).

Two patients with FUS/FWI out of three were treated with voriconazole. Three patients with FWI (1 ASP, 1 MMC and 1 FUS) did not receive systemic anti-fungal treatment, but only local anti-fungal treatment.

Ten patients (34%) were bathed in a 0.55% sodium hypochlorite solution (0.55% sodium hypochlorite/sterile water). A local anti-fungal treatment was administered in 25 patients (86%), among whom all patients with an ASP/DI. Two separate ways of administration were use. For most patients, dressings were soaked 3 times a day with an amphotericin B (0.1 mg/ml) solution until clinical improvement of the cutaneous condition. For patients with CEA, their dressing was changed daily, using gauzes impregnated with amphotericin B along with vancomycin and colistin, according to our standard protocol [Cirodde 2011]. Three patients with ASP/FWC received neither a systemic treatment, nor a local treatment, and their condition improved spontaneously.

For the patient with catheter colonisation, the unique treatment consisted with catheter ablation. For the patient with respiratory colonisation, treatment consisted with aerosols of amphotericin B during 14 days.

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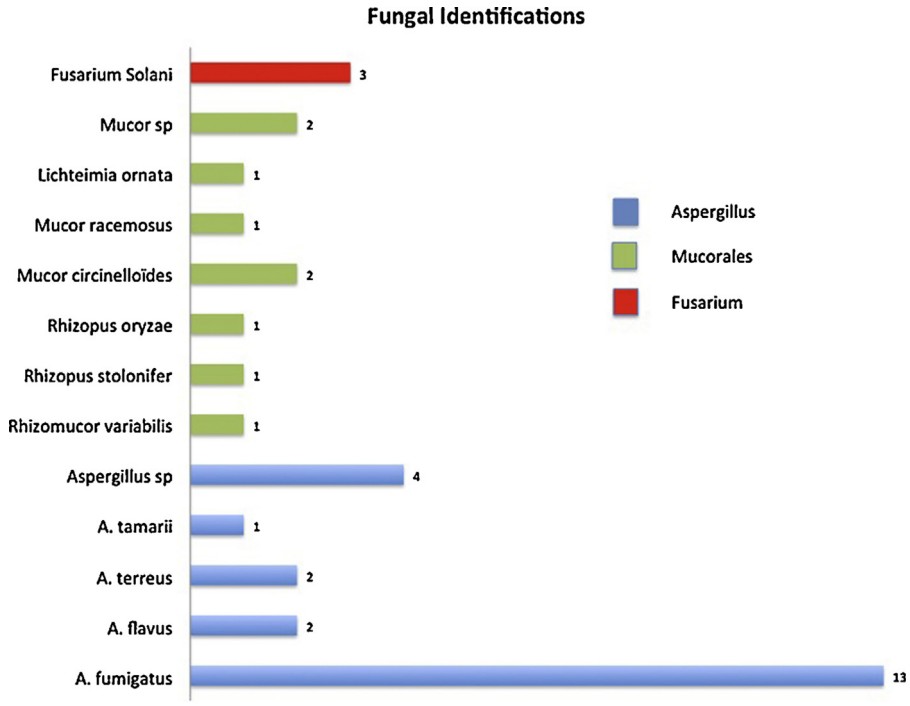

Fig. 2 – Filamentous fungal organisms isolated from patients admitted to Percy Burn Centre. *Aspergillus* is the most frequent pathogen.

4. Discussion

4.1. *Incidence, ecology*

In this 12 year-long retrospective single centre study in burned patients, most filamentous fungal infections were cutaneous. The fungal ecology of our department involved *Aspergillus*, *Fusarium* genus among the hyalohyphomycetes and the Mucorales. ASP was more frequent than in studies by Schofield et al. (0.85%, 13 out of 1515 patients), Ballard et al. (0.87%, 60 out of 6918 patients), or Katz et al. (0.2%, 7 out of 3300 patients) [22–24]. Conversely, our incidence was low compared to those of the Indian study by Capoor et al. (2.8%, 2 out of 71 patients) [25]. In this last report, both cases involved *Aspergillus niger*. *A. fumigatus* was the most frequently isolated species in our series. These results differ from the American study by Schofield et al. [22] in which 6 *A. terreus*, 4 *A. fumigatus*, 2 *A. flavus* and 1 *A. nidulans* were isolated.

The four main groups of Mucoraceae were represented: *Absidia sp.* (*or Lichteimia sp*), *Mucor sp.*, *Rhizomucor sp.* and *Rhizopus sp.* The species found were very heterogeneous. Contrary to our series, Mucorales were very rare in the Schofield et al. series (2/6918 patients) [22]. Incidence of FUS was comparable to that in this last study (6/68) [22]. However those results differ from those from Bransly et al., in which *Fusarium* was the most often isolated filamentous fungus (30% of the isolated fungi) [10].

No other type of filamentous fungus was found in our patients. Differences in fungal ecology between theses studies cannot be explained by geography, because these species of filamentous fungi have a worldwide distribution [11].

4.2. *Mortality*

Mortality was high in patients with ASP (6/22) in our series. Mortality associated with MMC can hardly be interpreted, since both patients who died with a diagnosis of MMC/FWI had a simultaneous ASP/DI, most likely to explain death per se. No patient with FUS died, but the small sample size precludes interpretation. Our results do not match the high mortality rates in the study by Schofield et al. where 90% of patients with *Fusarium* died, 100% of patients with MMC, 100% of patients with invasive cutaneous aspergillosis, and 38% of patients with aspergillar cutaneous colonisation [22]. Other American studies also report important mortality rates, with variations according to fungi species, type of infection, and definition of the fungal infection [12,23,26,27].

Literature is rather limited about the incidence of filamentous fungi infections, and above all about their impact on patient outcomes. Whether these infections are essentially a supplementary marker of patient fragility or immunodepression, or they directly contribute to worsened outcomes cannot be inferred from our results, due to the limited sample size despite a 12-year long study period. A multivariate analysis theoretically might have helped answering this question, but it could not be implemented because of our limited sample size.

4.3. *Factors associated with filamentous fungal infections in burned patients*

Baseline characteristics of patients in our series and their burn history basically reflect national epidemiology of hospitalised burned patients in France [28].

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Conversely, filamentous fungi seemed to be isolated in critical, severely burned patients, with high severity criteria and undergoing a long stay in burn ICU and aggressive supportive therapy, as shown by results about organ dysfunctions. Their high number of surgical procedures reflected the extent of deep burns undergoing surgery. Such an extent of burns always received many dressing changes, high fluid intakes, deep sedations and a permanent thermal balance [1]. Intravascular catheter accesses, invasive ventilation, and often renal replacement therapy were necessary. Besides burn extent, smoke inhalation is known to induce direct respiratory lesions and increased susceptibility to respiratory infections, both leading to higher morbidity and mortality: this condition was observed in 23 patients in our series (74%). Most included patients also developed bacterial and fungal *Candida* infections, conditions known to increase morbi-mortality in burned patients [8,29].

No burned surface or severity score (BAUX and ABSI scores) difference was observed between types of aspergillar infection, but our study may lack the power to show such differences due to its limited sample size. In the larger study by Schofield et al., the total body surface area burned was indeed significantly lower in colonised than in infected patients (39% vs. 63%) [22].

Acute invasive filamentous fungal infections occur as opportunistic infections. Host-risk factors classically include neutropenia, immunosuppressive therapy, high dose of corticosteroids, haematological malignancy, solid organ transplantation, and hematopoietic stem cell transplantation [15]. For MMC, uncontrolled diabetes mellitus, chelation therapy and severe malnutrition are known specific risk factors. Data about MMC in burn patients are scarce and were mostly obtained from reviews of case reports or small series [30–32]. Breakdown of cutaneous barrier (such as wounds, penetrating trauma or burns) also seems to play an important role. Filamentous species have a propensity to invade blood vessels and can result in tissue necrosis and invasive infection.

Besides their burns, few patients in this series had immunosuppression conditions classically associated with an increased risk of filamentous fungal infections in other critical care or haematology series. Conversely, a burn extent over 30% TBSA was present in almost all patients in our series. Burn severity criteria (surface, depth, and inhalation) could thus be proposed as risk factors of filamentous fungus infection, with likely thresholds still to be determined.

4.4. *Diagnosis strategy*

In our unit, wound swabs for superficial microbiological sampling are performed at least weekly on burned skin, and more frequently in case of clinical signs suggesting wound infection: presence of pus, increased exudation, leathery appearance, change in wound colour, inflammation, or graft lysis [4,6,21]. This large utilisation of swabs during dressing changes in our unit allows for a real-time microbiological cartography of wounds in order to monitor the microbiological ecology of patients, to perform our epidemiological surveillance, and to guide our treatment approach regarding anti-infective peri-operative prophylaxis or preemptive antimicrobial treatments in cases of severe septic complications from suspected cutaneous origin. Swabs indeed allow for qualitative screening with identification of pathogens and determination of their susceptibility.

Wound biopsies with microbiologic examination and quantitative culture are performed at the discretion of attending physicians when a skin infection is clinically suspected, as described above. Wound biopsies are the gold standard to classify infected burn wound as colonised or infected when pathogens are bacteria. In quantitative culture, isolation of bacteria at a density of 10^5 CFU/g of tissue or greater is considered as a documented burn wound infection [21]. But for fungal burn infections, there is no established correlation between quantitative culture results and histological lesions, and a relevant threshold therefore remains to be determined [22]. That is why we do not exclusively rely on quantitative skin biopsy cultures for the diagnosis of FWI, but rather on the association of clinical signs of infection with positive cultures, whatever the sample type but with the supplementary demand of duplicate positive results when only wound swabs are used, in order to improve specificity. However, in our FWI series, quantitative biopsies were systematically performed in order to identify concomitant bacterial wound infection, and all patients proved to have a positive wound biopsy culture. Therefore, whether our current working definition of FWI should be made more restrictive and include only positive wound biopsy cultures remains an open question, which cannot be addressed by the present study.

Despite the wide use of wound swabs in our unit, no sampling strategy is ever exhaustive. A specific limitation of our approach is that specific mycological cultures cannot be performed on all samples for obvious logistical considerations. They are thus performed upon agreement between the attending physician and the microbiologist. Colonisations might therefore have gone unnoticed in study patients, leading to a possible underestimation of the presence of filamentous fungi in our department.

Strain identification by PCR was also not systematic, but it has been more frequently performed in the last years.

EORTC/MSG criteria are not adapted to the diagnosis of invasive skin infections, especially for burns [13]. Indeed, according to these criteria, fungal infection is ''proven'' only with histopathological examination, or with a positive culture of a normally sterile tissue or fluid sample. However, skin is usually not a sterile area, whether healthy or burned. Similarly, a fungal infection is rated ''probable'' based on the association of three elements: risks factors, clinical criteria and mycological criteria. However, burns are not listed among risk factors, clinical criteria do not deal with skin infection, and mycological criteria are defined for respiratory tract or sinus sample cultures, and not for skin sample cultures (biopsies). This is not surprising, since these criteria were mainly developed for haematology patients.

The reference examination to establish invasiveness of a cutaneous infection is histological examination of cutaneous biopsies [27,33]. Described in the burned patient, histological analysis is the only technique able to assess the degree of cutaneous invasion and to formally differentiate colonisation from invasive infection. However, due to local limitations, only 3 histopathological analyses were performed in the study patients, showing tissue invasion by hyphae. Our proposed

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classification has the advantage of relying on clinical (general and local) signs and the presence of a positive culture on a wound sample to identify a fungal cutaneous infection. A formal cross-validation against gold standard histopathological examinations would be useful to establish bioclinical correlations.

Validated in neutropenic haematology patients, galactomannan can contribute to the diagnosis of invasive ASP, but its interpretation in non-neutropenic patients is probably more complex [34]. Using this test in other populations than haematology patients, particularly burned patients, would ideally require a specific evaluation to determine its discriminating ability and appropriate GM thresholds in that context. The repartition between FWI and DI could be altered in case of poor GM sensitivity in our non-neutropenic patients.

4.5. *Treatment*

Antifungal treatments administered were in line with current international recommendations [35–37]. FWI and DI were managed by systemic antifungal treatments. The two molecules generally used for ASP were either amphotericin B (lipid formulations), or voriconazole. In case of MMC, the molecule generally used was amphotericin B. In case of FUS, voriconazole was preferred. Lipid formulations of amphotericin B are currently the preferred initial treatment in our department when hyphae are identified in a sample, due to its broad spectrum. This is indeed the treatment of choice for MMC and FUS [38]. That molecule also remains one of the reference treatments for invasive ASP. Once the fungal identification and the antifungigram obtained, the treatment is adapted.

In three patients, FWI was managed with a local antifungal treatment only, because of a non-severe local condition and a favourable evolution under this local treatment. This point could be explained by an incorrect classification. These three FWI could actually be FWC, revealing a limit of our classification based on clinical wound examination. As described before, histological examination would have been the only mean to sort out such uncorrectly labelled cases, but was not routinely performed. However, these three patients presented clinical signs of local infections and were successfully treated with local antifungals. No antibiotics were administered during this period.

No study ever addressed the effect of local antifungal treatment of colonisations on mortality or on the occurrence of cutaneous infections. However, considering the likely high lethality of fungal invasive or disseminated infections, local treatment of wound colonisations is standard of care in our department, in order to reduce the likelihood of worsening from colonisation towards infection. A systemic antifungal treatment is added upon identification of cutaneous hyphae associated with general signs of infection.

Surgical management, although essential in case of extensive, necrotic or destructive infections [4,26,30], was not systematically analysed in this study due to its heterogeneity and lack of standardisation. Depending on cases and evolution stage, it involved simple cleaning, debridement of necrotic tissues, selective or extended excisions, amputations, and regrafting. Depending on their complexity and estimated level of emergency, those procedures were performed either by the surgical team in the operating room, or by the critical care team at bedside during dressing change. Our strategy is in line with Katz et al. who suggest early extensive debridement and appropriate antifungal treatment in order to decrease mortality in burned patients with mould infection [24].

4.6. *Prevention strategy*

Chemoprophylaxis was never proved effective to prevent nosocomial fungal infection in burned patients. Thus, surveillance and prevention of filamentous contamination is necessary, especially in units housing immunocompromised patients [39]. Based on extrapolation from literature about non-burned patients, prevention strategies are most likely necessary in burn units, to prevent contamination from various sources of spore or conidia transmission: water, air, food, hand carriage, contact with contaminated devices.

In our unit, environmental prevention is achieved mainly through air control strategy, using high rates of air renewal, overpressure in patient rooms and theatres, effective air filtration devices (high efficiency particulate air filtration) and laminar air flow facilities for theatres. Infection control includes a strict aseptic technique, the use of sterile gloves and dressing materials, and the wearing of masks, gowns and caps for dressing changes. Structural measures are also used in our unit such as different access locks (for patient admission, for family access, for service staff, and for delivery entrance), individual rooms, doors and windows closed, and spatial separation of patients from external contact. Further preventive measures based on the confinement of the working area are recommended during construction or renovation works. In our facility, the last heavy renovation was achieved in 1996 and thus predated the study period of the present work.

Incidence of fungal infections was low in our unit during the study period, hopefully thanks to aforementioned prevention measures, yet still noticeable despite of them. Besides intrinsic limitations of this prevention strategy, other factors of contamination could be considered such as distortions of prevention measures, lack of maintenance of prevention devices, or minor repairs into the units. Moreover, isolation of patients could have been interrupted during in-hospital transport (to the medical imaging department or to the theatre for example) [40].

4.7. *Limits of the study*

The main limit of our study is its retrospective design, mainly leading to missing data. Six species diagnoses out of 34 were missing. Antifungigrams were available in a minority of patient records, ad the same was true for PCR identification. The precise location of the initial accident (closed or open space, rural or urban area) was not mentioned in most records, which could have helped explaining a contamination mode in some patients. There is also a high likelihood of evolution in standards of care over the study period.

Finally, despite rewieving as long as 12 years of filamentous fungal colonisations or infections in burned patients, we observed a low incidence of theses events, which limited the possibilities of statistical analysis. The impact of iterative

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antibiotics on cutaneous microbial ecology and the role of burn related immune disorders in the development of fungal infections still need to be studied in burned patients.

5. Conclusion: opportunities for improvements

Although fungal infections remain infrequent in burned patients, their increasing incidence, high expenses related to their treatment with recent antifungal molecules, and their consequences in terms of morbi-mortality underline the importance of getting better knowledge of these infections and their epidemiology in the burned patients. The present series is the first one in Europe to describe burned patients with filamentous fungi infection or colonisation. The occurrence of a filamentous fungi infection, and especially ASP, is a rare but feared complication in burned patients. Most often, it is initially cutaneous, then becomes invasive with local and general signs. Involved patients are different from those in other medico-surgical intensive care units, as they usually do not present the classic immunosuppression risk factors. However, they are among the most severely burned patients, with extensive burns and often inhalation injury, and they receive intensive surgical treatment and heavy supportive critical care.

This study reveals several important points. Our epidemiology is quite different from those in India or in North America with essentially some ASP and few MMC. FUS are very rare. This epidemiology commands a specific policy for first line antifungal treatments. Lipid formulations of amphotericin B are our first line empirical treatment in case of suspected FWI because of the significant presence of Mucorales. Antifungigram with minimum inhibitory concentrations and dosage of antifungals should be systematically performed to avoid inadequate or underdosed treatments. Moreover, when a mould is identified on wound samples, we now systematically perform a local treatment such as amphotericin B, or sodium hypochlorite in cases of bacterial co-infection. This strategy relies on the assumption that reducing colonisation might decrease the risk of developing infection, which remains to be studied.

Diagnosis of filamentous wound infections remains difficult with several gaps in knowledge, especially in signification of quantitative cultures and dosage of galactomannan. In the absence of histological examination, we propose our classification based on clinical signs and microbiological identification to help clinicians choosing therapeutic strategies.

Prognostics of filamentous infections are quite different in our unit from that in others such as haematology, particularly for MMC that are known to be rapidly devastating and fatal.

Finally, improvement of prevention strategies is also crucial, beginning with an attempt at documenting their level of efficacy in burned patients.

Other studies with a larger number of patients would be necessary to formally identify risk factors associated with fungal infection in burned patients, possibly with discrimination between fungal species involved. Considering the limited incidence of these infections, it would be difficult to formally prove the benefit of surveillance aimed at detecting colonisation earlier. However, considering their high apparent lethality, such a surveillance associated with early local treatment measures to prevent evolution towards invasive or disseminated infection make sense and would match the strategy used to fight bacterial infections in the same patients.

Conflict of interest

None.

Appendix

Details of 31 patients reviewed with a filamentous fungal isolate.

Pt	Age	TBSA/ FTBSA (%)	Species (week to isolate)	Sites	Diagnostic examination	Classification	Anti-fungal treatment	Local treatment
1	59	67/53	*A. fumigatus* (17)	Wound	Culture (BWB)	FWI	AmBlip	AmB
2	57	30/20	*A. fumigatus* (2)	Pulmonary	Culture (bronchoalveolar lavage fluid: 10^3 UFC/ml)	Respiratory colonisation	–	Aerosolised AmB
3	37	92/85	*A. fumigatus* (8)	Wound, Grafted wound, Donor site	Culture (BWB)	FWI	Itraconazole	AmB NaClO
4	30	40/30	*Aspergillus* sp. (5)	Wound	Culture (BWB)	FWC	–	–
5	32	40/35	*Mucor* sp. (5)	Grafted Wound	Culture (BWB) Histopathology: tissue invasion	FWI	AmB	AmB NaClO
6	49	50/30	*Mucor* sp. (5)	Wound	Culture (BWB)	FWC	–	AmB NaClO
7	46	75/70	*A. fumigatus* (3)	Wound	Culture (BWB)	FWC	–	AmB
8	40	90/80	*A. fumigatus* (5)	Wound	Culture (BWB)	FWI	AmBcl + Flucytosine	AmB NaClO
9	27	85/50	*Aspergillus* sp. (8)	Wound	Culture (BWB)	FWI	–	AmB

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(Continued)

Pt	Age	TBSA/ FTBSA (%)	Species (week to isolate)	Sites	Diagnostic examination	Classification	Anti-fungal treatment	Local treatment
10	36	83/15	*A. fumigatus* (7)	Wound	Culture (BWB)	FWI	Itraconazole	AmB NaClO
11[b]	49	82/80	*A. fumigatus* (20)	Wound, donor site	Culture (BWB) GM+	DI	Voriconazole	AmB
12	37	50/30	*Rhizopus stolonifer* (7)	Wound	Culture (BWB)	FWC	–	AmB
13[b]	55	45/45	*A. flavus* (9)	Wound	Culture (BWB and oesophageal biopsy) PCR GM+	DI	AmBcl	AmB
14	69	13/13	*A. fumigatus* (1)	Wound	Culture (BWB)	FWC	–	–
15	24	63/50	*Aspergillus* sp. (11)	Central Venous Catheter	Culture (1 Blood culture: 10^3 UFC/ml)	Catheter colonisation	–	–
16	15	97/95	*Aspergillus* sp. (15)	Wound	Culture (BWB)	FWC	–	AmB
17[b]	42	96/96	*Rhizomucor variabilis* (3)	Wound	Culture (BWB) PCR Histopathology: tissue invasion	FWI	Voriconazole [a]AmBlip	AmB
			A. fumigatus (8)	Wound	Culture (BWB) PCR GM+	DI	AmBlip	AmB
18	22	45/45	*Rhizopus ozyzae* (2)	Wound	Culture (BWB)	FWI	Voriconazole [a]AmBlip	AmB
19[b]	42	70/65	*A. terreus* (3)	Wound	Culture (BWB) GM+	DI	Posaconazole [a]Voriconazole	AmB NaClO
			A. terreus (20)	Grafted wound	Culture (BWB) GM+	DI	AmBlip	AmB
20	64	14/4	*Mucor racemosus* (3)	Grafted Wound	Culture (BWB)	FWI	AmBlip	AmB
21	44	40/25	*A. fumigatus* (4)	Wound	Culture (BWB)	FWC	–	AmB
22	52	50/37	*A. fumigatus* (4) *Fusarium solani* (4)	Wound	Culture (BWB) PCR (the both) Histopathology: tissue invasion	FWI	Voriconazole	AmB
23	53	62/45	*A. tamarii* (3)	Wound, grafted wound,	Culture (BWB) PCR	FWI	Voriconazole	AmB NaClO
24	19	30/30	*A. flavus* (4)	Wound	Culture (BWB) PCR	FWI	Voriconazole	–
25[b]	29	61/52	*A. terreus* (2)	Wound, Donor site, Skin	Culture (BWB) PCR GM+	DI	Voriconazole [a]AmBlip	AmB
			Mucor circinelloïdes (2,5)	Wound	Culture (BWB) PCR	FWI		
26	58	69/61	*Lichteimia ornata* (8)	Wound	Culture (BWB)	FWC	–	AmB NaClO
27	33	40/30	*Mucor circinelloïdes* (4)	Wound	Culture (BWB)	FWI	–	AmB
28	19	71/68	*A. fumigatus* (17)	Wound	Culture (BWB and Blood Culture) PCR GM+	DI	AmBlip	AmB
29[b]	43	50/25	*A. fumigatus* (4)	Wound	Culture (BWB) PCR GM+	DI	AmBlip [a]Voriconazole	AmB NaClO
30	2	30/28	*Fusarium solani* (7)	Wound	Culture (BWB) PCR	FWI	–	AmB
31	31	54/50	*Fusarium solani* (3)	Wound	Culture (BWB) PCR	FWI	Voriconazole	NaClO

Note. TBSA/FTBSA (%): percent total body surface area and percent full thickness burn surface area; GM: galactomannan; BWB: Burn wound biopsy; NaClO: sodium hypochlorite (bath); AmB: amphotericin B deoxycholate; AmBlip: liposomal amphotericin B; AmBcl: amphotericin B lipid complex.

[a] Change of antifungal treatments.

[b] Dead.

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