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REVIEW

Mould Infections of Traumatic Wounds: A Brief Narrative Review

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ABSTRACT

Mould infections may follow traumatic injuries, with direct fungal inoculum in the site of injury and subsequent angioinvasion, possibly resulting in tissue necrosis and systemic dissemination. The pathogenesis of mould infections following trauma injuries presents unique features compared with classical mould infections occurring in neutropenic or diabetic patients, because a large fraction of post-traumatic mould infections is observed in previously healthy individuals. Most of the published clinical experience and research on mould infections following traumatic injuries regards soldiers and infections after natural disasters. However, following trauma and soil contamination (e.g., agricultural or automotive injuries) other immunocompetent individuals may develop mould infections. In these cases, delays in correct diagnosis and treatment may occur if pertinent signs such as necrosis and absent or reduced response to antibacterial therapy are not promptly recognized. Awareness of mould infections in at-risk populations is needed to rapidly start adequate laboratory workflow and early antifungal therapy in rapidly evolving cases to improve treatment success and reduce mortality.

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Keywords: *Aspergillus*; *Fusarium*; Injury; Mucorales; *Scedosporium*; Trauma; Wound

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Key Summary Points

The pathogenesis of mould infections following trauma injuries presents unique features.

Delays in correct diagnosis and treatment may occur if pertinent signs such as necrosis and absent or reduced response to antibacterial therapy are not promptly recognized.

Most of the published clinical experience and research on mould infections following traumatic injuries involve military and natural disasters.

More research is needed to further optimize diagnostic and therapeutic algorithms outside classical categories at risk.

INTRODUCTION

Invasive fungal diseases caused by moulds are associated with high mortality [1]. They may develop, with different spectra of prevalence, involved organisms, and clinical presentations, in patients with congenital/acquired immune defects and in patients with uncontrolled diabetes mellitus or other chronic/acute comorbid conditions (e.g., mucormycosis in patients with uncontrolled diabetes mellitus or invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease or in patients with severe influenza) [2, 3].

Mould infections may also follow traumatic injuries, with direct fungal inoculum in the site of injury and subsequent angioinvasion, possibly resulting in vessel thrombosis and tissue necrosis [4, 5]. In this regard, penetrating traumas are a well-known risk factor for mucormycosis, especially amongst soldiers during campaigns war, although mould infections may also be observed in civilians experiencing severe trauma [6–8].

Owing to the ubiquitous nature of moulds, there are a variety of settings where traumatic injuries can result in mould infections, such as agricultural traumas, motor vehicles crashes, blast traumas, and natural disasters [9, 10]. In such settings, contamination of open wounds with organic/environmental material and moulds can be followed by severe, necrotizing mould infections that, according to some published series, may need for surgical debridement or amputations in more than half of patients [11–13]. In similar situations, a high clinical suspicion and a timely diagnosis are pivotal to decrease mortality and avoid sequelae [13]. In addition, in some cases moulds can also disseminate through the bloodstream, leading to fungal meningitis, ophthalmitis, sinusitis, or osteomyelitis [1, 9, 14].

The aim of this review is to give a brief overview of the epidemiology, diagnosis, and treatment of wound mould infections following traumatic injuries. This article is based on previously conducted studies and does not contain any studies with human or animal subjects performed by either of the authors.

METHODS

In June 2019 we performed a MEDLINE/PubMed search, employing various combinations of the following key words: mold*; mould*; traum*, human. The search period was from January 1990 to June 2019. Of the 1024 papers identified, 806 were excluded by title and abstract screening. The full texts of the remaining 218 papers and of pertinent references were then retrieved and discussed. The final decision on their inclusion in the present narrative review was based upon the subjective impression of the authors. The final draft was structured in the following paragraphs: (1) epidemiology and risk factors; (2) pathogenesis; (3) diagnosis; (4) treatment.

Epidemiology and Risk Factors

The reported incidence of post-traumatic mould infections among the general population is frequently unseparated from that of other types of

mould infections, e.g., approximately 0.43–1.7 cases per million persons have been reported for mucormycosis [4, 15–17]. Nonetheless, two important factors should be necessarily considered when interpreting these epidemiological data: (1) owing to the difficulties of diagnosing mould infections outside specific contexts, there could be an underestimation of incidence in the general population [18]; (2) incidence and prevalence of post-traumatic mould infections are undoubtedly higher in specific populations at risk (e.g., soldiers) [4, 10]. It is also worth mentioning that an important factor hampering the comparison of incidence and/or prevalence data across different studies, even when conducted in similar populations, is the frequent use of different denominators (e.g., person-time, number of patients, number of patient at risk, number of patients with wound infection) [18]. Nonetheless, while keeping in mind these important limitations, two general features of the epidemiology of post-traumatic mould infections can be extrapolated from the available data.

The first is that, from the clinician's perspective, mould infections should always be suspected in patients presenting with infected wound and belonging to specific at-risk populations or in particular environmental conditions. For example, fungal infections were observed in 15% (9/60) of corn-picker hand injuries in a single-center study [19]. In another retrospective study of 1133 soldiers with injuries, fungal elements on histopathology and/or fungal growth from wounds was detected in 8.5% of cases (96/1133) [20]. Prevalence of mould infections following combat-related injuries peaked at 3.5% in another observational study among US military personnel [10]. Up to 11.7% prevalence of post-traumatic mould infections was observed in injured soldiers admitted to intensive care units [21]. Of note, combat-related injuries, by their nature, involve young people without any other comorbidity and/or immunosuppression and are thus one of the best example of how traumatisms are a key predisposing factor for mould infections (by altering not only mechanical defences, but possibly also by prompting a local/systemic immunosuppressed status) [4, 22, 23]. Other factors, besides the occurrence of trauma itself, are also likely to increase the risk of wound mould infections in soldiers with injuries. In geographical areas of military operations, temperate climate, dismounted status, blast injuries, above-knee amputations, massive blood transfusion, and use of broad-spectrum antibiotics have all been identified as possible risk factors for the development of mould infections in military personnel [4, 9, 24, 25].

With regard to predisposing environmental conditions, people affected by natural disasters are at increased risk of both injuries and wound contamination [26, 27]. After the eruption of the Armero volcano in Colombia in 1985, mucormycosis was diagnosed in 21% of patients with necrotizing lesions (8/38) [28]. Thirteen cases of necrotizing cutaneous mucormycosis were also reported after the Joplin tornado in Missouri (USA) in 2011 [9], and several other cases of post-traumatic mould infections following natural disasters have been described [29–33]. Of note, local health structures unable to guarantee sterile irrigation of wounds and rapid care for patients with injuries may be another predisposing factor to post-traumatic mould infections during natural disasters [26, 27]. Finally, patients with burn injuries are also at increased risk of developing post-traumatic mould infections [6, 34, 35]. Overall, the general picture stemming from these epidemiological data is that wound mould infections can be observed in previously healthy people who are affected by severe trauma [12, 33, 36]. Therefore, this possibility should be considered, especially in those patients not responding to antibacterial therapy.

The second general epidemiological feature regards the aetiology of post-traumatic mould infections. Among US soldiers in Afghanistan, the most frequent moulds isolated from post-traumatic infections were Mucorales, followed by *Aspergillus* spp. and *Fusarium* spp. [4, 20, 24, 33]. Reports of post-traumatic mould infections due to Mucorales are also predominant after burn-related trauma and natural disasters, although infections due to other moulds (e.g., *Aspergillus* spp., *Scedosporium* spp.) have also been reported [26, 31, 32, 37]. Of note, contaminated bandages have been identified as the possible source for an outbreak of *Absidia*

corymbifera wound infections in burn patients [38].

Following natural disasters and flooding, near-drowning-related respiratory mould infections may also be observed, which represent a particular type of post-traumatic mould infection not addressed in this review [26].

Pathogenesis

Although still to be fully elucidated, the pathogenesis of mould infections following trauma injuries presents unique features compared with classical mould infections occurring in immunocompromised or diabetic patients, because a large fraction of post-traumatic mould infections is observed in previously healthy individuals [33]. In this regard, it has been observed that trauma injuries can affect the immune system, impairing both innate and adaptive immune responses [39, 40]. In addition, severe trauma may impair phagocyte function through rhabdomyolysis-induced acidosis, which also causes a release of free iron (potentially favouring Mucorales infection) [41].

A prerequisite for post-traumatic mould infection is wound colonization by moulds [29]. After colonization exploiting the breakdown in the integrity of the cutaneous barrier, spores are able to germinate and then, in the presence of impaired phagocytosis and oxidative killing, hyphal elements can proliferate [42]. Broad-spectrum antibiotics may also create favourable conditions for the development of fungal infection [42, 43]. In addition, patients suffering from blast trauma can experience stress-induced hyperglycaemia and glycosuria, which may increase the risk for developing post-traumatic mucormycosis [42, 44–46].

The growth of moulds in the wound is able to elicit an acute inflammatory response with possible abscess formation, tissue swelling, and ultimately necrosis that often progress to form black eschars [42, 47]. If the necrotic tissue falls off, it produces large ulcers. Local invasion with cutaneous, subcutaneous tissue, adipose tissue, and muscular involvement can be observed [42, 47]. Necrotizing fasciitis may be secondary to cutaneous or subcutaneous mould infection [29, 48, 49]. Through the bloodstream, dissemination to non-contiguous sites may occur.

Diagnosis

The clinical presentation of post-traumatic mould infections represents a challenge for physicians, ranging from minimal oedema associated with erythematous skin to necrotizing lesions with concomitant septic shock [4, 6, 8]. Absence of response to antibacterial therapy (or partial response in view of the non-negligible prevalence of mixed bacterial-fungal infections) may help recognizing the possibility of mould infection, although, at least in at-risk categories of patients with severe traumatic injuries (e.g., soldiers, natural disasters), mould infections should already be suspected before waiting for response to antibacterials, owing to the possible rapid progression to necrosis and septic shock [8, 50, 51].

The classical laboratory diagnostic approach to post-traumatic mould infections consists of microscopy, culture, and histopathology of infected tissues. Presumptive identification and differentiation of Mucorales from other moulds can be obtained through microscopy of wound specimens with fluorescent brighteners, although with possible suboptimal sensitivity (for both identification and differentiation) and with no identification at the genus and species level, which is achievable with culture [18, 52, 53]. Nonetheless, also cultures may be hampered by suboptimal/variable sensitivity [4, 53]. On specimens obtained from post-traumatic wounds, cultures showed variable sensitivity in different studies, with false-negative results being observed in 17–56% of cases with positive histopathology [13, 36, 54, 55]. On the other hand, up to 11% of histopathology specimens from wounds with positive cultures may not show evidence of mould infection [13, 36, 54, 55]. The characteristics of classical laboratory techniques for the diagnosis of post-traumatic mould infections are summarized in Fig. 1.

The use of conventional methods (which remain mandatory) may be coupled with the

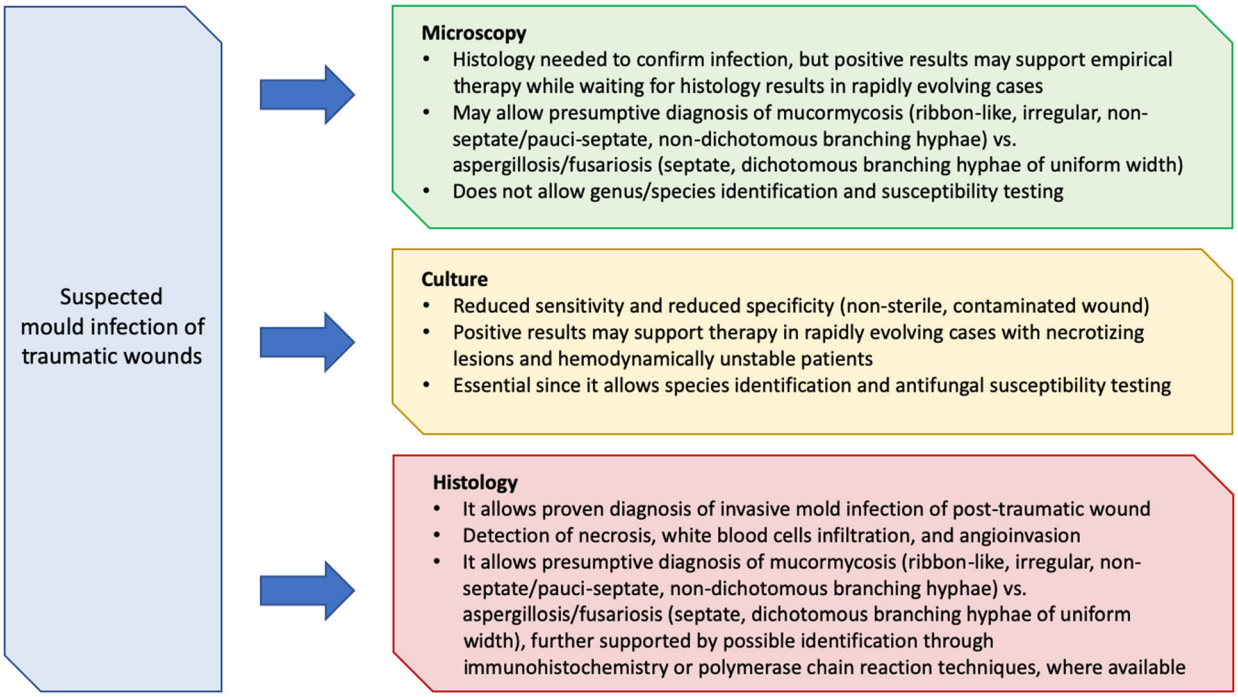

Fig. 1 Classical laboratory techniques for the diagnosis of post-traumatic mould infections. Diagnostic criteria for invasive fungal diseases in war wounds are: (1) traumatic wound; (2) recurrent necrosis after at least two consecutive debridements; (3) positive laboratory results (i.e., positivity of mould culture and/or histological evidence of tissue invasion) [21, 64]

use of rapid assays for the detection of fungal antigen detection in serum and with that of polymerase chain reaction (PCR)-based tests. In the former case, negativity of both serum galactomannan and (1,3)-beta-D-glucan, especially in patients with systemic dissemination, may support the diagnosis of mucormycosis, while their positivity may conversely support the involvement of other moulds (e.g., *Aspergillus* spp., *Fusarium* spp.) [56]. PCR-based tests also represent a very useful complementary test, since they may allow earlier identification (e.g., up to 9–11 days before conventional diagnostics for mucormycosis) [57, 58]. Nonetheless, as anticipated above, they still cannot be employed as a standalone test in view of heterogeneous performances and possible suboptimal sensitivity according to some series [57, 59].

Of note, some other laboratory techniques have been proposed but their discussion is beyond the scope of the present article. For interested readers, a comprehensive review of novel techniques for the diagnosis of mould infections has been recently published [60].

Treatment

Most data regarding the treatment of post-traumatic mould infections come from experiences in wounded soldiers, in whom timely and aggressive surgical debridement is coupled with early and effective antifungal therapy [4, 21]. A key challenge is the need for repeated debridement of necrotic material [25]. In a military series of post-traumatic mould infections, a median of 17 debridements was required to achieve cure [25]. In addition, amputations were necessary in 19% of patients following scarce control with debridement and antifungal treatment [25].

Regarding antifungal therapy, although not sufficient alone due to the limited tissue penetration in the presence of vessel thrombosis and/or tissue necrosis, it remains an essential

Table 1 Characteristics of antifungal agents for the treatment of wound mould infections following traumatic injuries

Antifungal agent	Dosage	Comments
Liposomal amphotericin B	*Intravenous* 5–10 mg/kg/die	Used as first-line therapy in most reported cases of post-traumatic mould infection of war wounds, alone or in combination with an azole agent [10, 64] Active against Mucorales, most *Aspergillus* spp., and *Fusarium* spp. Inactive against *Scedosporium apiospermum*, *Lomentospora prolificans*, and *Aspergillus terreus* Possible infusion-related and renal toxicity
Voriconazole	*Intravenous* 6 mg/kg mg 2 times daily on day 1, then 4 mg/kg 2 times daily *Oral* 400 mg mg 2 times daily on day 1, then 200 mg 2 times daily	In soldiers with mould infection of war wounds it has been used in combination with liposomal amphotericin B as empiric regimen until aetiological diagnosis [10, 64] Active against *Aspergillus* spp. (including *Aspergillus terreus*), *Fusarium* spp., and *Scedosporium apiospermum* Inactive against Mucorales High minimum inhibitory concentrations against *Lomentospora prolificans* have been reported
Posaconazole	*Intravenous* 300 mg 2 times daily on day 1, then 300 mg/die *Oral* 200 mg 4 times daily (oral suspension formulation); 300 mg 2 times daily on day 1, then 300 mg/die (delayed release tablets)	In soldiers with mould infection of war wounds it has been used in combination with liposomal amphotericin B as empiric regimen until aetiological diagnosis [10, 64] Active against Mucorales, *Aspergillus* spp. (including *Aspergillus terreus*), *Fusarium* spp., and *Scedosporium apiospermum* High minimum inhibitory concentrations against *Lomentospora prolificans* have been reported In the recently released global guidelines for the treatment of mucormycosis, recommended as possible salvage therapy (intravenous or delayed release tablets) after progression of disease or toxicity following initial polyene treatment, or as possible first-line therapy (intravenous) in patients with pre-existing renal failure, in setting where all classical antifungal classes are available [18]

Table 1 continued

Antifungal agent	Dosage	Comments
Isavuconazole	*Intravenous* 200 mg 3 times daily on days 1 and 2, then 200 mg/die (from 12-24 h after the last loading dose) *Oral* 200 mg 3 times daily on days 1 and 2, then 200 mg/die (from 12-24 h after the last loading dose)	Limited experience in the treatment of post-traumatic mould infections Active against Mucorales, *Aspergillus* spp. (including *Aspergillus terreus*), *Fusarium* spp., and *Scedosporium apiospermum* High minimum inhibitory concentrations against *Lomentospora prolificans* have been reported In the recently released global guidelines for the treatment of mucormycosis, recommended as possible salvage therapy (intravenous) after progression of disease or toxicity following initial polyene treatment, or as possible first-line therapy (intravenous) in patients with pre-existing renal failure, in setting where all classical antifungal classes are available [18]

component of the therapeutic approach to post-traumatic mould infections. The usual drug of choice for empirical antifungal treatment, for its broad-spectrum of activity against moulds, its efficacy against Mucorales, most *Aspergillus* spp., and *Fusarium* spp, and its bactericidal activity, is liposomal amphotericin B (L-AmB) [12]. A combination of L-AmB with voriconazole (which is inactive against Mucorales but retain activity against *Aspergillus terreus* and *Scedosporium apiospermum*, which are resistant to L-AmB) was the most frequent empirical regimen employed (71%, 55/77) in a series of soldiers with post-traumatic mould infections and recurrent necrosis, followed by a maintenance regimen with liposomal amphotericin B after proven diagnosis of mucormycosis [20]. The possible role of isavuconazole in the setting of post-traumatic mucormycosis still needs to be fully elucidated.

Owing to the above-mentioned concern about poor tissue penetration of antifungal treatment in the presence of angio-necrosis and tissue necrosis, local therapies may be considered [25]. Sodium hypochlorite (Dakin's solution at 0.025%), combined with the use of vacuum-assisted closure (VAC) therapy, surgical debridement, and systemic antifungal therapy, is used for the local treatment of mould infections following war wounds [61]. Topical L-AmB and nystatin have also been used in some settings, although no randomized controlled trials have been conducted [25, 62].

Of note, the treatment of post-traumatic mould infections is further complicated by the fact that many wounds may grow different moulds [63]. For example, combinations of Mucorales, *Aspergillus* spp., and *Fusarium* spp. have been found in an observational cohort study of infectious complications among military personnel injured during war in Iraq and Afghanistan [64]. Furthermore, post-traumatic wounds can also be infected with bacteria; thus, an antibiotic treatment should also be promptly started empirically and revaluated according to the course of the disease and laboratory results [25].

Finally, the necessary length of antifungal treatment is still not completely clear and frequently individualized [33]. In general, continuation of treatment at least until full surgical repair of the wound is warranted. On the other hand, empiric antifungal therapy should be

Table 2 Isolated moulds, surgical treatment, and outcome of mould wound infections in case series and case reports published in the last decade

Author (year) [ref]	Type of trauma (isolated mould/s)	No. of patients	Reported surgical debridement and/or amputation in addition to antifungal therapy No. of patients (%)	Mortality No. (%)
Wilson et al. (2019) [65]	Traffic accident (*Rhizopus* spp.)	1	Multiple surgical debridements 1/1 (100)	0/1 (0)
Lelievre et al. (2014) [12]	Traffic accidents, farm working accidents, blast injuries * (*Rhizopus* spp., *Lichtheimia* spp., *Mucor* spp., *Saksenaea* spp., *Apophysomyces* spp.)	16	Multiple surgical debridements 6/16 (37.5) Amputation 2/16 (12.5)	2/16 (12.5)
Rodriguez et al. (2014) [20] **	Combat-related injuries (Mucorales, *Aspergillus* spp., other moulds)	96	Multiple surgical debridements 96/96 (100) High-level amputations (total hip disarticulation or hemipelvectomy) 16/96 (16.7)	6/96 (6.3)
Neblett Fanfair et al. (2012) [9]	Tornado-related trauma (*Apophysomyces* spp., *Aspergillus* spp., *Mucor* spp., *Fusarium* spp.)	13	Surgical debridement 13/13 (100)	5/13 (38.5)
Vitrat-Hincky et al. (2009) [13]	Traffic accidents, farm working accidents (Mucorales, *Aspergillus* spp., *Fusarium* spp.)	6	Amputation 5/6 (83.3) Large musculocutaneous excision 1/6 (16.7)	0/6 (0)
Tully et al. (2009) [7]	Combat-related injuries (*Actinomucor* spp.)	1	Surgical debridement 1/1 (100)	1/1 (100)
Arnaiz-Garcia et al. (2009) [55]	Various (*Mucor* spp, *Rhizomucor* spp., *Lichtheimia* spp.)	5	Surgical debridement 3/5 (60) Amputation 2/5 (40)	0/5 (0)
Corti et al. (2009) [66]	Traffic accident (*Lichtheimia* spp.)	1	Surgical debridement 1/1 (100) Amputation 1/1 (100)	0/1 (0)
Volkmer et al. (2009) [67]	Traffic accident (*Mucor* spp., *Aspergillus* spp., *Fusarium* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)

Table 2 continued

Author (year) [ref]	Type of trauma (isolated mould/s)	No. of patients	Reported surgical debridement and/or amputation in addition to antifungal therapy No. of patients (%)	Mortality No. (%)
Stasiak et al. (2009) [68]	Traffic accident (*Mucor* spp.)	1	Surgical debridement 1/1 (100) Amputation 1/1 (100)	1/1 (100)
Ozer et al. (2009) [69]	Farm accident (*Aspergillus* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)
Stewardson et al. (2009) [70]	Swimming accident (*Saksenaea* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)
Blazquez et al. (2010) [71]	Traffic accident (*Lichtheimia* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)
Van Sickels et al. (2011) [72]	Gun shots wounds (*Rhizopus* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)
Hospenthal et al. (2011) [73]	Combat-related injuries (*Saksenaea* spp.)	1	Multiple surgical debridements 1/1 (100)	1/1 (100)
Rabie et al. (2012) [74]	Traffic accident (*Rhizopus* spp.)	1	Not described	NA
Paolino et al. (2012) [75]	Combat-related injuries (*Aspergillus* spp., *Fusarium* spp., Mucorales, others)	6	Multiple debridements 6/6 (100) Amputation 3/6 (50)	0/6 (0)
Mayayo et al. (2013 [76]	Traffic accident (*Saksenaea* spp.)	1	Surgical debridement 1/1 (100)	1/1 (100)
Pozo-Laderas et al. (2015) [77]	Traffic accident (*Rhizomucor* spp.)	1	Multiple surgical interventions (disseminated infection) 1/1 (100)	0/1 (0)
Tak et al. (2013) [78]	Traffic accident (*Aspergillus* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)
Poirier et al. (2013) [79]	Various (*Lichtheimia* spp. ***)	3	Surgical debridement 1/3 (33.3) Amputation 1/3 (33.3)	1/3 (33.3)

Table 2 continued

Author (year) [ref]	Type of trauma (isolated mould/s)	No. of patients	Reported surgical debridement and/or amputation in addition to antifungal therapy No. of patients (%)	Mortality No. (%)
Gómez-Camarasa et al. (2014) [80]	Farm accident (*Saksenaea* spp.)	1	Multiple debridements 1/1 (100)	1/1 (100)
Lundy et al. (2014) [81]	Combat-related injuries (Mucorales)	2	Surgical debridement and proctectomy 2/2 (100)	0/2 (0)
Tyll et al. (2016) [82]	Traffic accident (*Lichtheimia* spp.)	1	Amputation 1/1 (100)	0/1 (0)
Obradović-Tomasev et al. (2016) [19]	Corn-picker hand injuries (*Aspergillus* spp., *Mucor* spp.)	8	Multiple surgical debridements 8/8 (100)	0/8 (0)
Kyriopoulos et al. (2015) [83]	Traffic accident (*Rhizomucor* spp., *Rhizopus* spp.)	2	Surgical debridement 2/2 (100)	0/2 (0)
Kite et al. (2016) [84]	Garden rake injury (*Scedosporium* spp.)	1	Surgical debridement 1/1 (100)	0/1 (0)
Liu et al. (2017) [85]	Branch scratch (*Aspergillus* spp.)	1	None	0/1 (0)
Egge et al. (2018) [86]	Traffic accident (*Apophysomyces* spp.)	1	Multiple debridements 1/1 (100)	1/1 (100)
Sękowska et al. (2019) [87]	Traffic accident (*Mucor* spp.)	1	Amputation 1/1 (100)	0/1 (100)

NA, not available. Comprehensive summaries of management of post-traumatic mould wound injuries in previous decades and in burn patients are available elsewhere [13, 34]

*Some cases of burn or postoperative mould wound infections were also included (4/16)

**Cohort overlapping with that of other studies investigating different aspects of combat-related injuries [10, 21, 24, 50, 63]

***Possible cross-transmission

stopped as soon as mould infection is no longer suspected [25].

The characteristics of systemic antifungal agents for the treatment of mould wound infections after traumatic injuries are summarized in Table 1, whereas additional information on isolated moulds, surgical treatment and outcome of mould wound infections in some series published in the last decade is presented in Table 2.

CONCLUSIONS

Most of the published clinical experience and research regarding wound mould infections following traumatic injuries regards soldiers and natural disasters. However, these infections may also be observed in other immunocompetent individuals with trauma and soil contamination (e.g., agricultural or automotive injuries). In such cases, diagnosis and treatment could be delayed due to lack of awareness of mould infections during routine care. Clinical signs such as necrosis and reduced response to antibacterial therapy should be promptly identified to rapidly start an adequate laboratory workflow and empirical antifungal therapy in rapidly evolving cases.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed in the current study.

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