



# Global epidemiology of cutaneous zygomycosis

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**Abstract** The large majority of cases reported worldwide as zygomycosis are infections caused by fungi belonging to the order Mucorales. These infections are invasive, often lethal, and they primarily affect immunocompromised patients.

Cutaneous zygomycosis is the third most common clinical presentation, after sinusitis and pulmonary disease. Most patients with cutaneous zygomycosis have underlying diseases, such as hematological malignancies and diabetes mellitus, or have received solid organ transplantation, but a large proportion of these patients are immunocompetent. Trauma is an important mode of acquiring the disease. The disease can be very invasive locally and penetrate from the cutaneous and subcutaneous tissues into the adjacent fat, muscle, fascia, and bone. The diagnosis of cutaneous zygomycosis is often difficult because of the nonspecific findings of the infection. The clinician must have a high degree of suspicion and use all available diagnostic tools, because early diagnosis leads to an improved outcome. The treatment of zygomycosis is multimodal and consists of surgical debridement, use of antifungal drugs, and reversal of underlying risk factors, when possible. The main antifungal drug used in the treatment of zygomycosis is amphotericin B. Posaconazole is sometimes used for salvage treatment, as continuation of treatment after initial administration of amphotericin B, or in combination. The mortality of cutaneous zygomycosis is lower in comparison with other forms of the disease, but it is still significant. When the disease is localized, mortality still ranges from 4% to 10%.

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## Introduction

Zygomycosis is an invasive fungal infection caused by fungi of the class Zygomycetes, which is divided into 2 orders, Mucorales and Entomophthorales. Species of the latter order are responsible for the chronic subcutaneous disease, named entomophthoramyosis, observed in immu-

nocompetent patients in tropical and subtropical regions.<sup>1</sup> The large majority of cases reported worldwide as zygomycosis or mucormycosis are caused by fungi belonging to the order Mucorales. Mucormycosis is an invasive fungal infection, often lethal, mainly affecting immunocompromised patients. Cutaneous zygomycosis is one of the most common clinical presentations of the disease. In the review, which included cases published from 1940 to 2004, cutaneous zygomycosis was the third most common presentation after sinusitis and pulmonary zygomycosis, and it consisted of 176 cases (19%).<sup>2</sup>

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In 2009, we reviewed the literature for reports of cutaneous zygomycosis published from 2005 to 2008 and found 78 cases.<sup>3</sup> In the present article, we studied the case reports published from January 2009 to December 2010. We searched Medline using the keywords “cutaneous,” “zygomycosis,” or “mucormycosis,” and included contributions that were written in English, during the specified period, and where the diagnosis was confirmed by histology and/or culture. In this way, we identified 39 cases.<sup>4-26</sup>

## Epidemiology

It is not possible to estimate the exact rates of incidence of zygomycosis, because most data are from case reports or case series.<sup>2,27,28</sup> There are, however, some data, mainly from hematological patients, which indicate that the incidence of zygomycosis has increased in recent years.<sup>29-31</sup> For cutaneous zygomycosis in particular, it should be noted that although 176 cases were included in the review from 1940 to 2004,<sup>2</sup> the cases reported from 2005 to 2008<sup>3</sup> and from 2009 to 2010 (present review) were 78 and 39 respectively. Zygomycosis affects patients from around the world. In this review, 19 (50%) cases were from India, China, and Qatar. The ages of infected patients also had a wide variation, ranging from 3 months to 83 years, and there was no predilection for either sex. Most patients with cutaneous zygomycosis have underlying diseases, such as hematological malignancies or diabetes mellitus, or solid organ transplantation, but a large proportion of them are immunocompetent. In an older review,<sup>31</sup> diabetes was present in only 26% of cutaneous cases and leukemia and/or neutropenia in 16%. In the 2005 review,<sup>2</sup> of the 176 patients with cutaneous infection, 50% had no underlying conditions. The distribution of the various underlying diseases in patients with cutaneous zygomycosis, according to published case reports, is shown in Table 1.

## Pathogenesis, mode of transmission

The Mucorales are ubiquitous in nature; they are thermotolerant and are usually found in decaying organic matter. Spores can be found in wood, cotton, bread, fruits,

**Table 1** Underlying diseases in patients with cutaneous zygomycosis

Underlying diseases	No. of cases published (%)		
	1885-2004	2005-2008	2009-2010
None (immunocompetent)	88 (50)	33 (43)	26 (67)
Malignancy	18 (12)	18 (23)	5 (13)
Diabetes mellitus	34 (10)	10 (13)	6 (15)
Solid organ transplant	10 (16)	5 (6)	2 (5)

**Table 2** Mode of transmission in patients with cutaneous zygomycosis

Mode of transmission	No. of cases published (%)		
	1940-2004	2005-2008	2009-2010
Penetrating trauma	60 (34)	31(40) <sup>a</sup>	9 (23) <sup>b</sup>
Dressings	26 (15)	6 (8)	3 (8)
Surgery	26 (15)	6 (8)	4 (10)
Burns	11 (6)	7 (9)	2 (5)
Motor vehicle accident	5 (3)	8 (10)	3 (8)
Other trauma	5 (3)	2 (2)	9 (23)
Not well described	42 (24)	18 (23)	3 (8) <sup>c</sup>

<sup>a</sup> Of the 31 cases of penetrating trauma, 17 (55%) were nosocomial, related to intravenous, arterial, or other catheters or needles.

<sup>b</sup> Of the 9 cases of penetrating trauma, 6 (67%) were nosocomial. The other 3 were attributable to animal or insect bites (dog, spider, and scorpion).

<sup>c</sup> In the remaining 6 cases, no known trauma or other mode of transmission was identified.

vegetables, soil, compost piles, and animal excreta. In cutaneous zygomycosis, the most common mode of acquiring the fungus is by direct inoculation, in contrast to the other forms of the disease, where inhalation or ingestion play the major role. Intact mucosal and endothelial barriers serve as structural defenses against tissue invasion and angioinvasion by zygomycetes. These barriers can be disrupted by trauma, prior infection, or cytotoxic chemotherapy, allowing high loads of sporangiospores to invade the dermis. The disease can be very invasive locally and penetrate from the cutaneous and subcutaneous tissues into the adjacent fat, muscle, fascia, and bone. The extensive angioinvasion results in infarctions and tissue necrosis.<sup>32,33</sup> Depending on the immune status of the host, the infection can remain localized or disseminate to noncontiguous organs. Although dissemination from skin to other organs is relatively common, the reverse, ie, dissemination to the skin, is rare.<sup>33</sup> In the review of 176 cases of cutaneous zygomycosis, only 3% had this reverse dissemination.<sup>2</sup> In the literature after 2004, there was only 1 such case, in which the authors reported fungemia with *Mucor circinelloides* preceding cutaneous zygomycosis by the same fungus.<sup>8</sup>

As shown in Table 2, there are various ways by which the fungal spores can enter the skin, but trauma is the most common. In another review, where in 25 cases of cutaneous mucormycosis some local risk factors were identified, such as surgery (17%), burns (16%), motor vehicle-related trauma (12%), the use of needles (13%), knife wounds (3%), insect or spider bites (3%), and other types of trauma (23%).<sup>31</sup> In the present review, as in the older reviews, trauma ranged from minimal, such as a scorpion sting,<sup>11</sup> to massive, owing to crush injury<sup>4</sup> or car accidents,<sup>23</sup> where there is traumatic implantation of soil. Zygomycosis has also been reported to occur as a result of injury in a natural disaster, such as the tsunami that struck Southeast Asia in 2004<sup>34</sup> or the volcano eruption that wiped out the town of Armero, Colombia, in 1985.<sup>35</sup>

A large proportion of penetrating trauma is nosocomially acquired, although the use of needles and intravenous catheters have been implicated.<sup>6,16,20</sup> Other sources of nosocomially acquired zygomycosis are caused by various adhesive tapes,<sup>9</sup> elastoplasts,<sup>26</sup> and even plaster casts.<sup>6</sup> “Surgical wound zygomycosis or infections after occlusive plaster highlights the requirement of improvement of hospital care practices,” especially in developing countries.<sup>36</sup> Burn injury is another well-described cause of cutaneous zygomycosis.<sup>15,24</sup> In addition to disrupting the skin barriers, burns confer significant immunosuppression of variable duration.<sup>37</sup>

## Clinical manifestations

Classic clinical presentations of zygomycosis include rhinocerebral, pulmonary, gastrointestinal, disseminated, and cutaneous forms. The typical clinical presentation of zygomycosis is the necrotic eschar; however, this may be absent in the first stages of the disease, and there seems to be a wide variation of signs and symptoms. The disease may be of gradual onset and slowly progressive or it may be fulminant, leading to gangrene and hematogenous dissemination. In the initial phase, zygomycosis may be localized to a small area of the skin. Patients with invasion into muscle, tendon, or bone are classified as having deep extension of infection, and patients with cutaneous disease involving another noncontiguous site are defined as having disseminated infection. In one analysis, 96 (56%) infections were localized, 43 (24%) were accompanied by deep extension, and 35 (20%) were disseminated.<sup>2</sup> In the present review, 19 (49%) had localized zygomycosis, 14 (36%) had deep extension, and the remaining 5 (13%) had disseminated disease. In 1 case, the presentation was not well described, so it was not included in the analysis.

The arms and legs are the most common sites of zygomycosis, but any area of the skin can be affected. In the present review, 12 (31%) cases involved the legs, 6 (15%) the arms, 7 (18%) the abdominal wall, 5 (13%) the face, and 2 each involved the face, chest, back, gluteal region, and scalp.

Clinical presentations of cutaneous zygomycosis include dark yellow, nodular lesions<sup>4</sup>; black discoloration with surrounding edema<sup>6</sup>; superficial lesions having only slightly elevated circinate and squamous borders resembling tinea corporis<sup>37</sup>; targetoid plaques with outer erythematous rim<sup>38,39</sup>; and a “fuzzy discharge” at the borders of a wound, resembling bread mold.<sup>7</sup> In a recent case report, the investigators described a man with acute myelogenous leukemia who presented with disseminated zygomycosis heralded by a clinically nonspecific erythematous macule that showed nonspecific, mild, inflammatory changes on histological examination.<sup>10</sup> Another clinical presentation of cutaneous zygomycosis has emerged from various case reports from China.<sup>19,22</sup>

The authors in 1 case describe a swollen plaque on the root of the nose, 3.5 × 2.5 cm in diameter, with dry scales on

the surface,<sup>22</sup> whereas in another they report a confluent, infiltrated, light-red plaque (18 × 10 cm) with a clear boundary involving the nose, cheeks, eyelids, and glabella, accompanied by punctiform blood crust formation and slight desquamation.<sup>19</sup> In most cases, the lesions affect the face, they are noninvasive, and they progress very slowly, in the range of 7 months to 18 years. The patients are usually immunocompetent and there is no clear history of trauma. They are all caused by *Rhizomucor variabilis*. Interestingly, a similar case, attributable to the same species, was recently reported from Japan.<sup>25</sup>

At the other end of the spectrum of clinical manifestations of cutaneous zygomycosis are necrotizing fasciitis and gangrene. The infection may initially have the form of an induration, blisters, pustules, or necrotic ulcerations and rapidly progress, forming cutaneous abscesses and necrosis of the deep subcutaneous tissues.<sup>21,23,24</sup> The lesions may mimic pyoderma gangrenosum,<sup>40</sup> bacterial synergistic gangrene, or other infections.<sup>3</sup> When the disease is disseminated, the patient may have general signs and symptoms of sepsis.

## Diagnosis

The diagnosis of cutaneous zygomycosis is often difficult owing to the nonspecific findings of the infection. The clinician must have a high degree of suspicion and use all available diagnostic tools, because early diagnosis leads to improved outcome. Indications of a possible zygomycosis include necrotic lesions on the skin of an immunocompromised patient or an immunocompetent patient who is a trauma or burn victim. If a wound does not heal properly, despite the correct use of antibiotics, or if a mold appears on its edges, zygomycosis should be suspected among other diagnoses. Biopsy of the lesions for histology and culture is necessary to establish the diagnosis. The biopsy specimen should be taken from the center of the lesion and include subcutaneous fat, because molds frequently invade blood vessels of the dermis and subcutis, resulting in an ischemic cone at the skin surface.<sup>41</sup> Impression smears from the wound edges may also help in the diagnosis. Zygomycetes hyphae are characterized by broad, mostly aseptate hyphae, with irregular branching that occasionally occurs at right angles. Identification of the zygomycetes at the genus and species levels requires culture studies; however, in a high proportion of cases, cultures do not yield a fungus. Cultures are negative in about 50% of cases of zygomycosis, including all sites of infection.<sup>2</sup> In the present review, cultures were positive in 32 (82%) cases. This may represent publication bias, because to classify a zygomycosis as definite, it is imperative to have positive results from both histology and culture. Species identification is aided by molecular techniques.<sup>42</sup> In addition, when there are no culture results, paraffin-embedded tissue can be used for examination by polymerase chain reaction.<sup>43</sup>

The most frequently isolated fungi from patients with zygomycosis are those belonging to the Mucoraceae

(*Lichtheimia corymbifera*, former names *Absidia* and *Mycocladus*, *Apophysomyces*, *Mucor*, *Rhizopus*, *Rhizomucor*), followed by *Cunninghamella bertholletiae*, *Apophysomyces elegans*, and *Saksenaea vasiformis*. In our review, 6 (19%) of 32 isolated strains were *Rhizopus oryzae* (arrhizus), 6 (19%) *L corymbifera*, 5 (16%) *A elegans*, 5 (16%) *Rhizomucor variabilis*, 4 (13%) *Mucor* sp, 4 (13%) *S vasiformis*, 1 (3%) *C bertholletiae*, and 1 unspecified Mucorales.

## Treatment

The treatment of zygomycosis is multimodal, and consists of surgical debridement, use of antifungal drugs, and reversal of underlying risk factors, if possible. Surgical debridement should be repeated as often as necessary. In a series of upper extremity zygomycoses, patients had an average of 10 surgical debridements (range 4-20).<sup>44</sup> In some cases, amputation must be performed to save the patient's life.<sup>4</sup> The main antifungal drug used in the treatment of zygomycosis is amphotericin B. Liposomal amphotericin B allows the administration of higher doses (5-7 mg/kg body weight),<sup>33</sup> but conventional amphotericin B is still in use in some countries because of the reduced cost.<sup>6</sup> Posaconazole is the only azole with good in vitro activity against the Mucorales. It is sometimes used as salvage treatment, as continuation of treatment after initial administration of amphotericin B, or in combination.<sup>20</sup>

The prognosis of cutaneous zygomycosis is better than that of the other forms of zygomycosis, but it is not negligible. In one analysis, mortality was 10% for localized infection, 26% for cutaneous zygomycosis with deep extension, and 94% for disseminated disease. In the review for 2005 to 2008, the respective rates were 4.0%, 29.0%, and 83.0%<sup>3</sup>, whereas in the present review they were 5.5%, 43.0% and 50.0% for localized infection, infection with deep extension, and disseminated disease, respectively. Overall mortality for cutaneous zygomycosis was 31%, 30%, and 25% in the 3 case series<sup>2,3</sup> and in our current work.

## Conclusions

A high index of suspicion and early and aggressive management, with the use of all available modalities, may improve the outcome of zygomycosis. Prompt therapy, together with normalization of predisposing factors, makes a substantial difference in the final therapeutic outcome.

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