MAJOR ARTICLE

Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases

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Background. Zygomycosis is an increasingly emerging life-threatening infection. There is no single comprehensive literature review that describes the epidemiology and outcome of this disease.

Methods. We reviewed reports of zygomycosis in the English-language literature since 1885 and analyzed 929 eligible cases. We included in the database only those cases for which the underlying condition, the pattern of infection, the surgical and antifungal treatments, and survival were described.

Results. The mean age of patients was 38.8 years; 65% were male. The prevalence and overall mortality were 36% and 44%, respectively, for diabetes; 19% and 35%, respectively, for no underlying condition; and 17% and 66%, respectively, for malignancy. The most common types of infection were sinus (39%), pulmonary (24%), and cutaneous (19%). Dissemination developed in 23% of cases. Mortality varied with the site of infection: 96% of patients with disseminated disease died, 85% with gastrointestinal infection died, and 76% with pulmonary infection died. The majority of patients with malignancy (92 [60%] of 154) had pulmonary disease, whereas the majority of patients with diabetes (222 [66%] of 337) had sinus disease. Rhinocerebral disease was seen more frequently in patients with diabetes (145 [33%] of 337), compared with patients with malignancy (6 [4%] of 154). Hematogenous dissemination to skin was rare; however, 78 (44%) of 176 cutaneous infections were complicated by deep extension or dissemination. Survival was 3% (8 of 241 patients) for cases that were not treated, 61% (324 of 532) for cases treated with amphotericin B deoxycholate, 57% (51 of 90) for cases treated with surgery alone, and 70% (328 of 470) for cases treated with antifungal therapy and surgery. By multivariate analysis, infection due to *Cunninghamella* species and disseminated disease were independently associated with increased rates of death (odds ratios, 2.78 and 11.2, respectively).

Conclusions. Outcome from zygomycosis varies as a function of the underlying condition, site of infection, and use of antifungal therapy.

Zygomycosis has emerged as an increasingly important pathogen during the past decade [1–5]. This increase has been particularly evident in hematopoietic stem cell transplant recipients and patients with hematological malignancies [6–12]. Unlike other filamentous fungi that are largely opportunistic in patients with cancer, transplant recipients, and patients with inherited immunodeficiencies, zygomycosis also can be a frequently lethal infection in hosts with greater immunocompetency, such as those with diabetes mellitus [13–23], those receiving deferoxamine therapy [24–32], injection drug users (IDUs) [33–39], and those with no apparent immune impairment [40–46].

To date, there has been no definitive, comprehensive review of the literature on zygomycosis to guide our understanding of the epidemiology and outcome of zygomycosis in the general population. We therefore reviewed the English-language literature for all cases of zygomycosis, from the original case report in 1885 to the present. In this review, we sought to understand the distribution of infection within the general population and to ascertain whether the patterns of infection are associated with specific host factors and outcomes.

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METHODS

Literature search

We initiated our search by reviewing all references from the chapters of major books written on the subject of zygomycosis. We then carefully scrutinized the references for single case reports or case series. We then expanded this initial review by a MEDLINE search using the following key words: zygomycosis, mucormycosis, phycomycosis, *Rhizopus, Mucor, Rhizomucor, Cunninghamella, Absidia, Apophysomyces, Syncephalastrum, Saksenaea, Cokeromyces, Entomophthora, Conidiobolus,* and *Basidiobolus.* After this initial series of reports was reviewed, the individual references listed in each publication were again reviewed for ascertainment of additional case reports.

Criteria for inclusion of zygomycosis case reports

Only those case reports that included data on the following 6 variables were included in our review.

Documentation of infection. The zygomycete infection had to be confirmed either histologically or by culture. Information about whether the infection was documented premortem or postmortem also was required.

Anatomical location of infection. Documentation of the primary site of infection at the time of diagnosis and whether the infection remained localized or disseminated was required. Disseminated infection was defined as infection at ⩾2 noncontiguous sites. Patients with disseminated infection at the time of diagnosis for which the primary site of infection was impossible to identify were classified as having generalized disseminated infection. Patients with cutaneous infection were subcategorized into 3 groups. Patients in whom the infection was confined to the cutaneous or subcutaneous tissue were defined as having localized disease. Patients with invasion into muscle, tendon, or bone were classified as having deep extension of infection. Patients with cutaneous disease involving

Table 1. Demographic and clinical characteristics of 929 patients with zygomycosis, 504 of whom died.

Characteristic	All patients	Proportion (%) of patients who died[a]
Age, years		
Mean	38.8	…
Median (range)	40.0 (0.005–80)	…
Sex		
Male	605/929 (65)	330/605 (55)
Female	324/929 (35)	174/324 (54)
No underlying condition at time of infection, cause of infection		
Overall	176/929 (19)	61/176 (35)
Penetrating trauma	44/176 (25)	10/44 (23)
Surgery	32/176 (18)	12/32 (38)
Burns	11/176 (6)	7/11 (64)
Other	89/176 (51)	32/89 (36)
Underlying condition at time of infection		
Diabetes	337/929 (36)	147/337 (44)
Malignancy	154/929 (17)	101/154 (66)
Solid organ transplantation	61/929 (7)	29/61 (48)
Deferoxamine therapy	53/929 (6)	44/53 (83)
Injection drug use	45/929 (5)	23/45 (51)
Bone marrow transplantation	44/929 (5)	31/44 (91)
Renal failure	36/929 (4)	32/36 (89)
Low birth weight infant	27/929 (3)	20/27 (74)
Diarrhea and malnutrition	25/929 (3)	22/25 (88)
HIV infection	17/929 (2)	7/17 (41)
Systemic lupus erythematosus	9/929 (1)	8/9 (89)
Other[b]	43/929 (5)	27/43 (63)

NOTE. Data are proportion (%) of patients, unless otherwise specified.

[a] Data are no. of patients with the characteristic who died/total no. with the characteristic (%).

[b] Includes hepatic disease, hematologic disorders, metabolic acidosis, tuberculosis, and pulmonary mycoses.

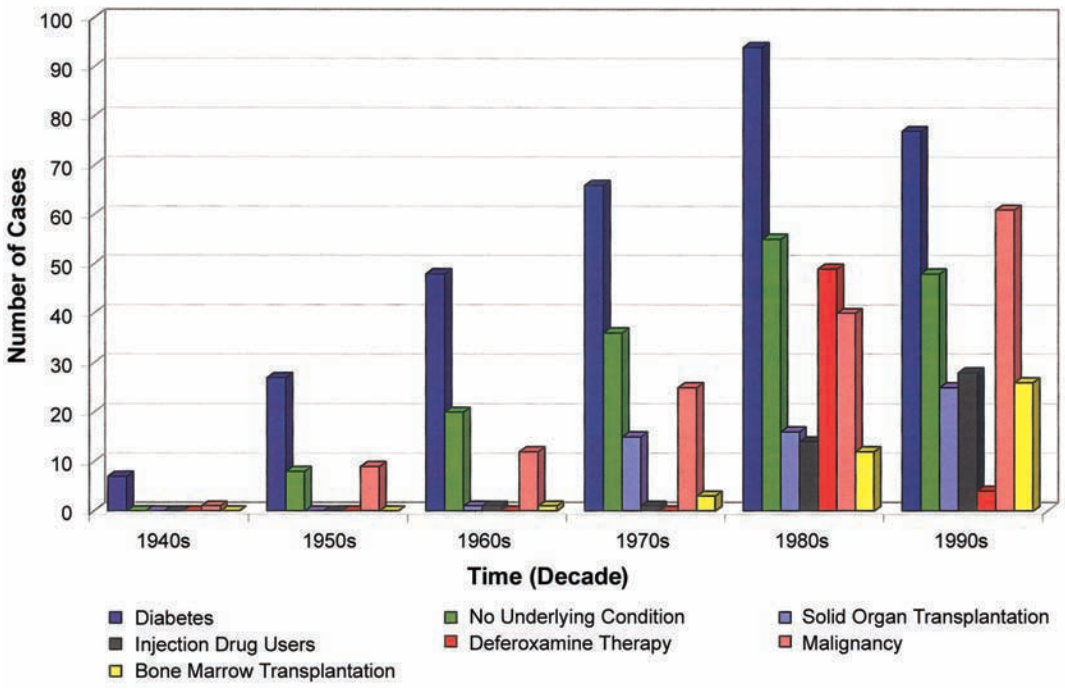

Figure 1. Incidences of zygomycosis over 6 decades (1940–1999), by host population

another noncontiguous site were defined as having disseminated infection. Patients with pulmonary infection were subcategorized in a similar manner, as follows: those with disease confined to the lungs were classified as having localized infection; those with disease that extended to the chest wall, pulmonary artery, aorta, or heart were defined as having deep extension of infection; and those with demonstrated involvement of a noncontiguous site were defined as having disseminated infection.

We were especially careful to subcategorize patients with sinus involvement, because we found "rhinocerebral" to be an overused term for this infection. Consequently, we distinguished patients with true cerebral involvement from those with localized sinus disease. We also separately categorized patients on the basis of sino-orbital involvement and sinopulmonary disease. Patients with disease confined to the paranasal sinuses were defined as having sinusitis; those with disease in the paranasal sinuses and infiltrating the orbit were defined as having sino-orbital infection; those with disease in the paranasal sinuses and the brain were categorized as having rhinocerebral infection, with cerebral involvement defined as tissue invasion demonstrated histologically or by culture during life or at autopsy, radiological evidence of disease by either CT or MRI, or severe neurological impairment; and those with disease in the paranasal sinuses and lungs were defined as having sinopulmonary infection.

Primary condition. Documentation of the primary underlying condition or of immunosuppression was required for each reported case, unless the patient was described as having no underlying condition.

Therapeutic intervention. Only those cases that specified the presence or absence of both surgery and antifungal therapy were included.

Documentation of antifungal therapy. Only those patients with a documented absence or specific presence of antifungal therapy were included in the review. When not specified, we estimated the approximate duration of amphotericin B therapy for adult patients by dividing the total dose by 70 kg and assuming a dosage of 1 mg/kg per day.

Outcome. Mortality was assessed as all-cause mortality during the course of zygomycosis.

Database development

Filemaker Pro software, version 5.5 (Filemaker), was used to develop a database of categorical and continuous variables. The categorical variables included sex, underlying diagnosis, diabetes (type and presence of ketoacidosis), neutropenic status, infecting organism, diagnostic method used for recovery of infecting organism, premortem or postmortem diagnosis, infection site (focal or disseminated disease), surgery, hyperbaric oxygen therapy, immunomodulation, and outcome. The continuous variables included year of diagnosis, year of case publication, age of patient, and dose and/or duration of antifungal

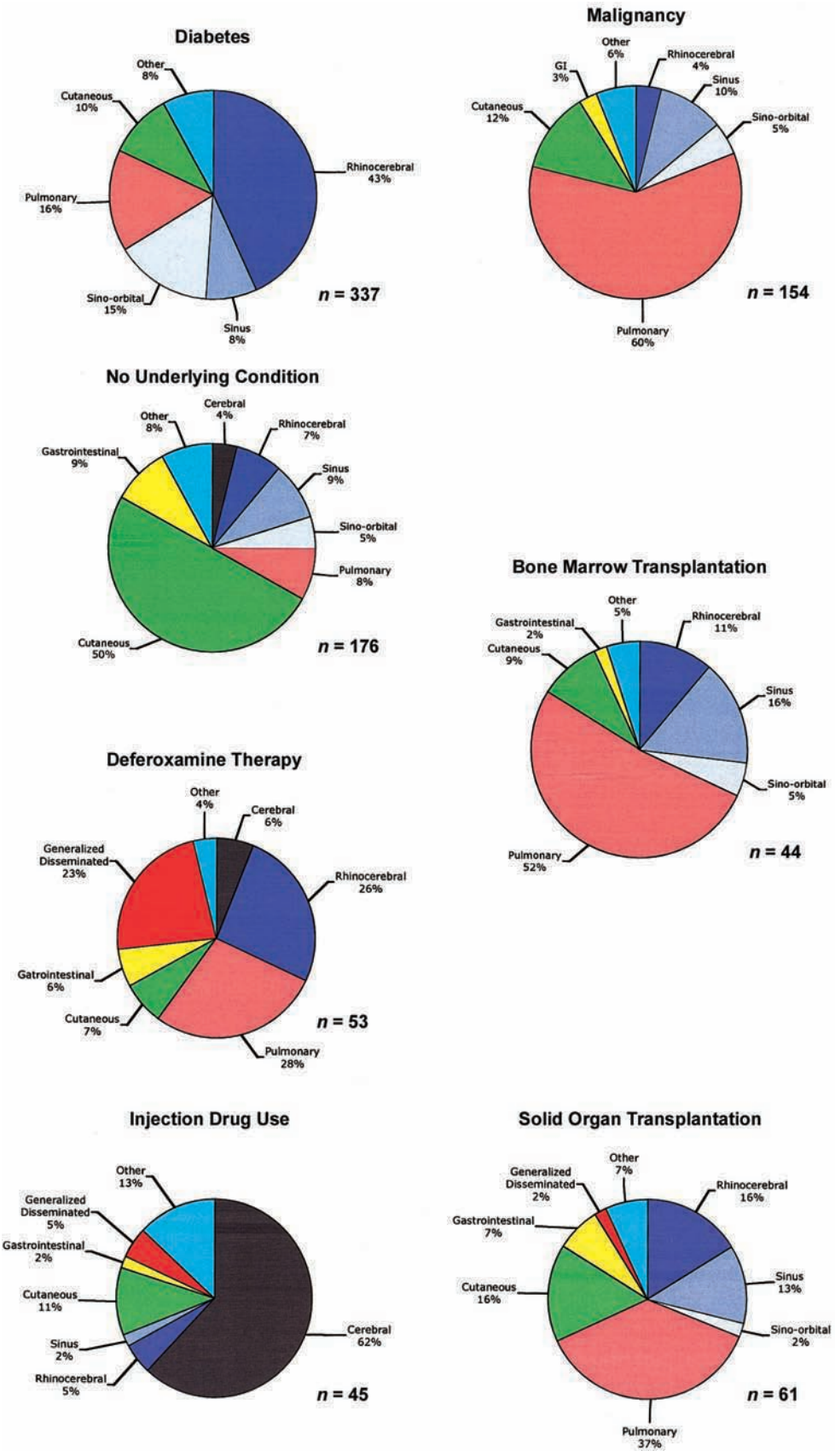

Figure 2. Patterns of zygomycosis, by host population

Table 2. Infection patterns among 929 patients with zygomycosis, 504 of whom died.

Type of infection, by site	Proportion (%) of all patients	No. of patients with the infection who died/total no. with the infection (%)
Sinus		
Overall	359/929 (39)	165/359 (46)
Rhinocerebral[a]	196/929 (21)	122/196 (62)
Sino-orbital	74/929 (8)	18/74 (24)
Sinusitis	74/929 (8)	12/74 (16)
Sinopulmonary	15/929 (2)	13/15 (87)
Pulmonary		
Overall	224/929 (24)	170/224 (76)
Localized	121/224 (54)	73/121 (60)
Deep extension	15/224 (7)	13/15 (87)
Disseminated	88/224 (39)	84/88 (95)
Cutaneous		
Overall	176/929 (19)	54/176 (31)
Localized	98/176 (56)	10/98 (10)
Deep extension	43/176 (24)	11/43 (26)
Disseminated	35/176 (20)	33/35 (94)
Cerebral		
Overall	87/929 (9)	69/87 (79)
Localized[a]	45/87 (52)	28/45 (62)
CNS dissemination	42/87 (48)	41/42 (98)
Gastrointestinal	66/929 (7)	56/66 (85)
Generalized disseminated	25/929 (3)	25/25 (100)
Kidney	22/929 (2)	9/22 (41)
Other solid organ	15/929 (2)	9/15 (60)
Other[b]	14/929 (2)	4/14 (29)

NOTE. Patient counts in each column total to more than the *n* values because patients with infection at >1 site are counted more than once. Thus, 988 sites are reported for all patients, and 561 sites are reported for patients who died.

[a] Patients with rhinocerebral infection and those with localized cerebral infection together constituted 283 patients (30%).

[b] Includes peritoneum, mastoid, oral mucosa, bone, and bladder.

therapy. When available, additional information regarding serum ferritin, transferrin, and transferrin saturation levels, as well as glucose and bicarbonate levels, were recorded.

Statistical analysis

Univariate analyses were conducted to determine the association between potential risk factors and death. Categorical variables were compared by χ^2 analysis or Fisher's exact test, whereas continuous variables were compared by the Wilcoxon rank-sum test. All variables with a *P* value of <.20 on univariate analysis were considered for inclusion in a multivariate model, as were those variables noted to be confounders on stratified analysis. Multivariate analysis was performed using logistic regression methods. Survey estimation was applied to the logistic regression models, to adjust for the modest degree of case clustering among the reporting sites. Clustering was evident from estimates of statistically significant but modest interclass correlation (by site). The analyses used standard algorithms as described by Korn and Graubard [47] to determine variance estimates for this correlation. Construction of the multivariate model began with inclusion of certain variables (i.e., disseminated disease and therapy) considered to be important on the basis of a priori hypotheses. Reported CIs are therefore somewhat more conservative (wider) and *P* values are somewhat larger than would be estimated by conventional logistic regression methods. A 2-tailed *P* value of <.05 was considered to be statistically significant. All statistical calculations were performed using standard programs in Stata, version 7.0 (Stata).

RESULTS

The first case of zygomycosis reported in the literature was by Paultauf in 1885 [48]. This case, however, did not meet the predefined eligibility criteria and, consequently, was not included in our database. The first case to be included was reported in 1940. A total of 1049 individual cases of zygomycosis from 1940 through 2003 were identified. Of these, 120 cases were excluded from the database because they did not meet the stringent predefined inclusion criteria. The total database thus consisted of 929 cases (in 1 patient each) reported in 459 published reports [14–476].

Demographic characteristics. The underlying conditions and their associated all cause mortality are summarized in table 1. The mean age was 38.8 years, and the median age was 40.0 years (range, 0.005–80 years). A total of 65% of all Zygomycetes infections occurred in males. The overall mortality in the total population was 54% (504 of 929 patients).

Diabetes was the most common underlying condition. Only 68 patients (20%) with diabetes had type I diabetes, and of these, 33 (48%) had documented ketoacidosis. Conversely, most patients with diabetes in this review had type II diabetes ($n = 187$), with 64 (34%) having documented ketoacidosis. In 54 (16%) of 337 patients with diabetes, zygomycosis presented as the diabetes-defining illness. The second largest patient population consisted of persons who had no primary underlying disease at the time of infection. Among 154 patients with malignancy, 147 (95%) had a hematological malignancy. There were only 7 cases of zygomycosis reported in patients with a nonhematological malignancy.

Secular trends in reported hosts. There was an increase in the reporting of zygomycosis in all underlying host populations during the study period (figure 1). Diabetes was the most commonly reported underlying condition in each decade. However, an increasing proportion of other host populations, including those with malignancy, recipients of bone marrow transplants,

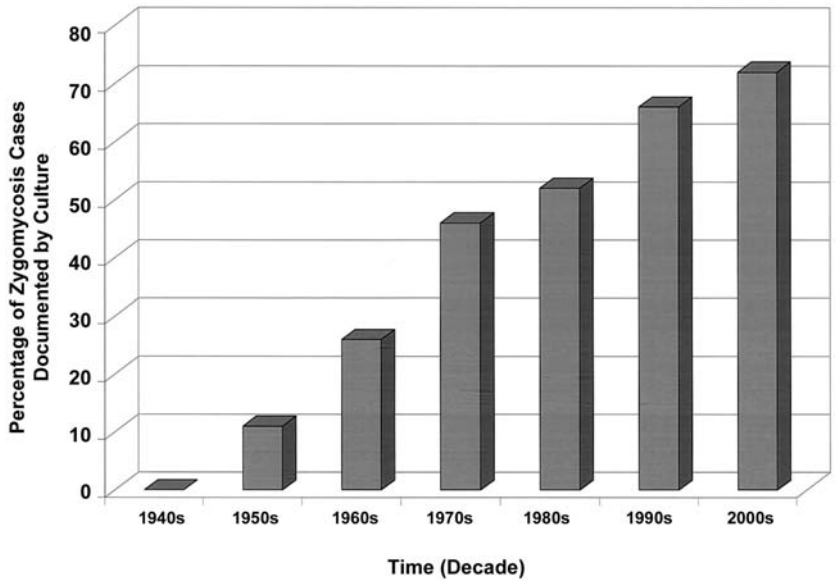

Figure 3. Percentages of zygomycosis cases documented by culture since the 1940s, by decade

recipients of deferoxamine, IDUs, and patients with no underlying condition becomes apparent in the 1980s and 1990s.

Sites and patterns of infection. The primary site of infection at the time of initial diagnosis varied as a function of the host population (figure 2). Sinus involvement consisting of rhinocerebral, sinus, and sino-orbital infections constituted the majority of infections (222 [66%] of 337) in patients with diabetes. This differs from the pattern of infection in persons with no underlying condition, in which cutaneous zygomycosis constituted one-half of all cases. By further comparison, pulmonary zygomycosis constituted more than one-half of all sites of infection in patients with malignancy and recipients of bone marrow transplants. Sinus involvement was the second most common pattern of infection in this patient population. Patients undergoing solid organ transplantation had another distinctive pattern, with relatively similar frequencies of pulmonary and sinus infections. On the other hand, patients receiving deferoxamine therapy presented more frequently with generalized disseminated zygomycosis, compared with other host categories. Finally, cerebral zygomycosis was the most common presenting pattern of infection in IDUs. The pattern of cerebral zygomycosis in IDUs was hematogenous and was seldom associated with rhinocerebral infection.

The patterns of infection and their associated all-cause mortality are detailed in table 2. The paranasal sinuses were the most common site of infection, presenting in 39% of cases. Rhinocerebral infection was the most commonly reported pattern of sinus zygomycosis. Independent predictors for sinus zygomycosis were diabetes type 1 (OR, 4.04; 95% CI, 2.36–6.90), diabetes type 2 (OR, 6.35; 95% CI, 3.89–10.36), and injection drug use (OR, 0.15; 95% CI, 0.04–0.51). Pulmonary disease was the second most common presenting pattern. Approximately one-half of all cases were restricted to the lung, whereas the remaining cases were either disseminated or complicated by deep extension into the chest wall, pulmonary artery, or heart. Independent risk factors for pulmonary zygomycosis were infection with *Cunninghamella* species (compared with infection with *Rhizopus* species) (OR, 7.75; 95% CI, 2.44–24.58), neutropenia (OR, 2.28; 95% CI, 1.26–4.11), and receipt of a solid organ transplant (OR, 3.41; 95% CI, 1.41–8.20).

Cutaneous involvement was the presenting pattern in 176 (19%) of 929 patients. Penetrating trauma was reported for 60 (34%) of these patients, dressings were reported for 26 (15%), surgery was reported for 26 (15%), burns were reported for 11 (6%), motor vehicle accident was reported for 5 (3%), and falls were reported for 5 (3%). The histories for the remaining 42 patients (24%) were not well described. Most cases were localized to the integument. However, deep extension to bone, tendon, or muscle occurred in 42 (24%) of 176 cases, and hematogenous dissemination from skin to other noncontiguous organs occurred in 35 (20%). Hematogenous dissemination from other organs to skin occurred rarely, in only 6 cases (3%). The majority of patients with cutaneous infection were either nonneutropenic or had no underlying condition. Independent risk factors for localized cutaneous infection were female sex (OR, 2.27; 95% CI, 1.46–3.55), no underlying condition (OR, 2.60; 95% CI, 1.32–5.14), prior surgery (OR, 5.40; 95% CI, 1.84–15.86), and HIV infection (OR, 2.62; 95% CI, 1.01–6.79).

There were 283 patients with CNS infection, of which 69% had rhinocerebral infection, 16% had localized cerebral infection, and 15% had hematogenous dissemination of infection from other organs to the brain. Both rhinocerebral infection

Table 3. Microbiological findings for 465 patients with zygomycosis, 219 of whom died.

Organism isolated	No. (%) of all patients	No. of patients who died/total no. with the organism (%)
Rhizopus species	218 (47)	105/218 (48)
Not speciated	125 (27)	61/125 (49)
R. oryzae	55 (12)	26/55 (47)
R. rhizopodiformis	20 (4)	9/20 (45)
R. microsporus	11 (2)	7/11 (64)
R. nigricans	7 (2)	1/7 (17)
R. stolonifer	1 (1)	1/1 (100)
Mucor species	85 (18)	44/85 (52)
Cunninghamella bertholletiae	34 (7)	26/34 (76)
Apophysomyces elegans	27 (6)	6/27 (22)
Absidia species	25 (5)	8/25 (32)
Saksenaea species	21 (5)	9/21 (43)
Rhizomucor pusillus	19 (4)	10/19 (53)
Entomophthora species	13 (3)	2/13 (15)
Conidiobolus species	10 (2.2)	5/10 (50)
Basidiobolus species	9 (2)	3/9 (33)
Cokeromyces species	3 (0.6)	1/3 (33)
Syncephalastrum species	1 (0.2)	0/1 (0)

NOTE. Interspecies differences in mortality may be due to other codependent variables, including species-related host factors and patterns of infection.

and localized cerebral infection were associated with a mortality of 62%. Of patients with localized cerebral infection, most were IDUs who were independently associated with the development of primary CNS disease (OR, 80.25; 95% CI, 26.69–241.28). There were no patients with diabetes who had hematogenous dissemination to the brain. Instead, all CNS infections in patients with diabetes occurred in those with rhinocerebral infection.

Gastrointestinal infection occurred in 65 patients (7%). The rate of dissemination to other noncontiguous organs was 38% (25 of 65 patients). Mortality was high, primarily because of bowel perforation. The infection occurred predominantly in low birth weight infants, patients with diarrhea and malnutrition, and patients receiving peritoneal dialysis.

The risk for development of disseminated zygomycosis from any site varied as a function of host characteristics. Independent risk predictors were burns (OR, 6.26; 95% CI, 1.16–33.81), prematurity (OR, 2.85; 95% CI, 1.26–6.43), deferoxamine use (OR, 2.76; 95% CI, 1.66–4.59), diabetes (OR, 0.29; 95% CI, 0.17–0.50), no underlying condition (OR, 0.47; 95% CI, 0.25–0.91), and HIV infection (OR, 0.15; 95% CI, 0.03–0.63).

Microbiologic and histopathologic findings. All patients had infection documented either histologically or by culture. A positive culture result was obtained in 50% of cases (table 3). There was a clear increase in culture positivity over time, with 71% of all cases since 2000 diagnosed on the basis of culture results (figure 3). Among the 465 cases with a culture positive for a Zygomycetes organism, *Rhizopus* species were the most commonly recovered organisms, with *Rhizopus oryzae* the most frequently recovered species.

Sex and zygomycosis. Zygomycosis occurred primarily in males (605 [65%] of 929 cases). The following genera were clearly associated with infection in males, constituting >78% of infections in this group: *Basidiobolus, Cunninghamella, Absidia,* and *Apophysomyces* (table 4).

Entomophthorales organisms caused 7.2% of all zygomycoses in this review. The order Entomophthorales differed from the order Mucorales in overall survival (69% vs. 52%) and in the frequency of persons with no underlying condition (69% vs. 50%). Of infections due to *Conidiobolus* species, 5 (50%) of 10 were cutaneous. Of infections due to *Basidiobolus* species, 7 (78%) of 9 were gastrointestinal.

Treatment. Of the 929 cases reviewed, 596 (64%) were treated with some form of antifungal chemotherapy (table 5). Survival in this group was 62% (369 of 596 patients). Of these 596 patients, 532 (89%) received amphotericin B deoxycholate, with an overall survival of 61%. Survival was 57% (51 of 90 patients) for those treated with surgery alone; survival increased to 70% (328 of 470 patients) for those treated with a combination of surgery and antifungal chemotherapy. A total of 241 patients (26%) received no treatment for their infection. Within this subgroup, the survival rate was 3% (8 of 241 patients).

Outcome. Analysis of survival by decade revealed that overall mortality improved from 84% in the 1950s to 47% in the 1990s (figure 4). However, mortality due to zygomycosis has remained essentially unchanged since the 1960s, when amphotericin B deoxycholate was widely introduced (figure 5).

Table 6 summarizes results of the multivariate regression analysis of risk factors for mortality among all patients. Significant risk factors for mortality included disseminated disease,

Table 4. Relationship between microbiologic findings and male sex in 465 cases of culture-confirmed zygomycosis.

Organism	No. of cases in males/ total no. of cases (%)
Rhizopus species	139/233 (65)
Mucor species	51/85 (60)
Cunninghamella bertholletiae	27/34 (79)
Apophysomyces elegans	23/27 (85)
Absidia species	20/25 (80)
Saksenaea species	4/6 (67)
Rhizomucor pusillus	12/19 (63)
Entomophthora species	7/13 (54)
Conidiobolus species	7/10 (70)
Basidiobolus species	7/9 (78)
Cokeromyces species	2/3 (67)
Syncephalastrum species	1/1 (100)

Table 5. Treatment administered to 929 patients with zygomycosis, 425 of whom survived.

Treatment	No. (%) of all patients	No. of patients who survived/total no. who received the treatment (%)
Amphotericin B formulation		
Deoxycholate	532 (57)	324/532 (61)
Lipid	116 (12)	80/116 (69)
Itraconazole, ketoconazole, or posaconazole	15 (2)	10/15 (67)
No antifungal therapy	333 (36)	59/333 (18)
Surgery alone	90 (10)	51/90 (57)
Surgery and antifungal chemotherapy	470 (51)	328/470 (70)
Hyperbaric oxygen	44 (5)	28/44 (64)
Granulocyte colony-stimulating factor	18 (2)	15/18 (83)
Granulocyte transfusion	7 (1)	2/7 (29)
None	241 (26)	8/241 (3)

renal failure, and infection with *Cunninghamella* species. Conversely, type I diabetes and no underlying condition were independently associated with a reduced risk of death. Compared with no receipt of antifungal therapy, all forms of antifungal therapy were also significantly associated with a reduced risk of mortality. Patients who underwent surgery as primary therapy were also significantly more likely to survive. Pulmonary, rhinocerebral, kidney, and gastrointestinal infection were associated with the highest risks of mortality.

DISCUSSION

Zygomycosis was first reported as a cause of human disease in 1885 [48]. Unlike other filamentous fungal pathogens that target immunocompromised hosts, Zygomycetes organisms infect a broader and more heterogeneous population. In this review, persons with no underlying condition and patients with diabetes represented >50% of all infected patients. In the past 20 years, there also has been an emergence of this infection in the more classically defined immunocompromised risk groups, such as patients with hematological malignancy, recipients of a bone marrow transplant, and recipients of a solid organ transplant [6–12].

Zygomycetes organisms are unique among filamentous fungi because of their disproportionately high capacity to cause devastating disease in persons with no underlying condition. Among persons with no underlying condition who had a his-

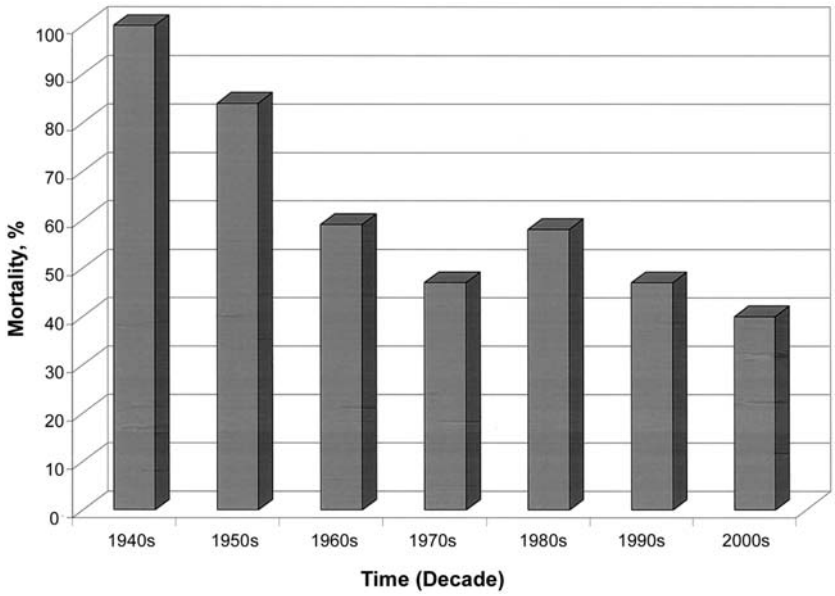

Figure 4. Mortality due to zygomycosis since the 1940s, by decade

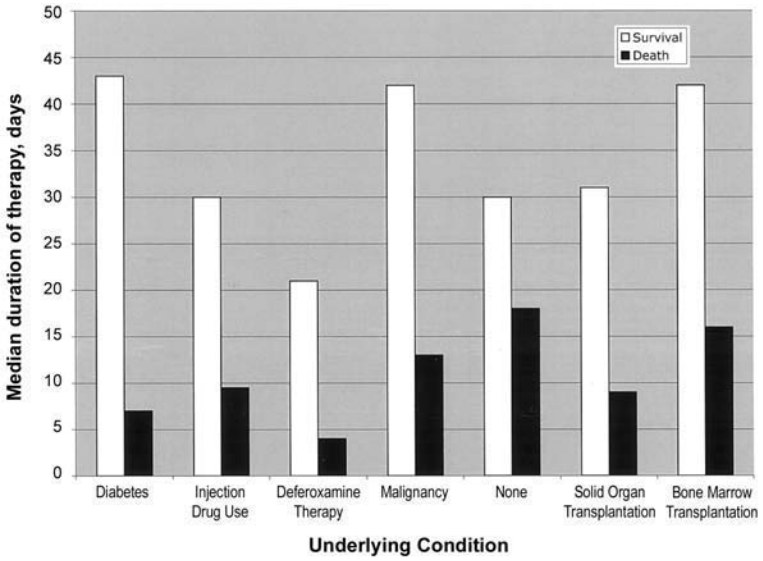

Figure 5. Median duration of polyene therapy for patients with zygomycosis who survived or who died, by host population

tory of burns, surgery, or trauma, the majority (63 [73%] of 87) presented with cutaneous disease. In the subgroup of persons with no underlying condition, only 25 (28%) of 89 presented with cutaneous disease. The remaining 64 patients (72%) presented with deeply invasive infection.

Cutaneous inoculation from a Zygomycetes organism may have underestimated consequences. Of all cutaneous infections in this review, 43 (24%) of 176 deeply extended to tendon, muscle, or bone. Moreover, an additional 35 (20%) of 176 patients with cutaneous disease developed hematogenous dissemination from the original cutaneous site to another organ, resulting in an overall mortality of 94% (33 of 35 patients) in this subgroup. Unlike other filamentous fungi that will hematogenously disseminate from another organ to skin, we found converse behavior in this review. There were 220 cases of hematogenously disseminated infection, yet only 6 had documented cutaneous involvement. Of the 4 cases in which culture was performed, 3 were due to *Rhizomucor pusillus*, which, overall, is a relatively uncommon pathogen [49–51].

Cerebral infection was the most common presentation of zygomycosis in IDUs. This pattern occurred in the absence of sinusitis or rhinocerebral disease and appears to have developed hematogenously. Because Zygomycetes organisms are ubiquitous, contamination of injected illicit drugs seems to be likely. If some of the injected sporangiospores are not adequately filtered by the pulmonary capillary bed, they will enter the systemic arterial circulation, where ~25% of the cardiac output is distributed to the brain. Particulate material the size of sporangiospores tend to distribute either to the gray-white junction of the brain or to the basal ganglia via the striatal arteries. The vast majority of the infections we reviewed presented in the basal ganglia.

We found that patterns of infection differ as a function of host characteristics. The relationships between persons with no underlying condition and cutaneous involvement and between IDUs and cerebral involvement seems to be logical. However, the strong association between both malignancy and bone marrow transplantation and pulmonary disease and the relationship

Table 6. Multivariate model of risk factors for mortality among patients with zygomycosis.

Variable	OR (95% CI)	*P*
Extent of infection		
Localized	Reference	…
Disseminated	11.21 (5.79–21.73)	<.001
Infecting organism		
Rhizopus species	Reference	…
Cunninghamella species	2.78 (1.11–6.96)	.029
Diabetes		
None	Reference	…
Type I	0.31 (0.16–0.62)	.001
No underlying condition	0.38 (0.22–0.66)	.001
HIV infection	0.38 (0.15–0.94)	.037
Renal failure	7.16 (3.40–15.07)	<.001
Antifungal therapy		
None	Reference	…
Amphotericin B deoxycholate only	0.21 (0.13–0.35)	<.001
Lipid amphotericin only	0.10 (0.04–0.24)	<.001
Amphotericin formulation and azole	0.09 (0.03–0.29)	<.001
Other	0.14 (0.07–0.28)	<.001
Surgery as primary therapy	0.24 (0.15–0.37)	<.001

NOTE. Additional risk factors included within a similar model for analysis of site-specific infections are (with cutaneous infections as the reference): pulmonary infection (OR, 7.50; 95% CI, 2.84–19.80; $P = < .001$), rhinocerebral infection (OR, 6.39; 95% CI, 2.64–15.48; $P = < .001$), kidney infection (OR, 8.30; 95% CI, 2.54–27.16; $P = .001$), and gastrointestinal infection (OR, 22.51; 95% CI, 5.50–92.14; $P = < .001$).

between diabetes and sinus involvement is more complicated. Perhaps one sees a preponderance of pulmonary disease in the population with malignancies as the result of chemotherapy-related defects in innate pulmonary host defenses that are associated with neutropenia and with chemotherapy-induced mucociliary dysfunction. The factors contributing to sinus involvement in patients with diabetes may be more multifactorial. Patients with diabetes have more microvascular disease, and perhaps this, in concert with the delicate architecture of the sinuses, may result in more tissue destruction and local dissemination.

The patterns of infection due to deferoxamine demonstrated the highest level of generalized disseminated infection (23%), compared with any other pattern. This finding underscores the importance of iron in the virulence of Zygomycetes organisms. When circulating deferoxamine molecules bind to host iron, the deferoxamine serves as a sideophore to the Zygomycetes organism. This iron-enriched systemic milieu tips the host-parasite balance in favor of the pathogen.

This study documents that the capacity to recover these organisms by culture has significantly improved over time. This improvement may be due to better training among mycology technologists, a greater understanding of specimen processing in the laboratory, improved culture techniques, and increased access to sophisticated reference laboratories.

The reason for a higher prevalence of Zygomycetes infections among males is unclear. There is mycologic precedent for this predisposition, as observed in the protective role of estrogen in paracoccidioidomycosis [477]. The potential role of estrogen in Zygomycetes infection has not yet been explored.

There were 157 pediatric cases in this review. Underlying host factors differed between adults and children: 17% of pediatric infections occurred in low birth weight infants, and 26% were associated with diarrhea and malnutrition.

Most patients in this review who were treated with antifungal chemotherapy received amphotericin B or one of its lipid formulations. This is not surprising, because amphotericin B has been essentially the only agent active against most Zygomycetes species. There did appear to be some added benefit to receiving surgery for the management of these infections. However, one must exercise caution in extrapolating treatment choices on the basis of these data, because all of the data are retrospective and may be subject to a period effect (i.e., a change in the rate of a condition irrespective of age and birth date) and publication bias. Nevertheless, multivariate analysis clearly demonstrates that antifungal therapy and surgery are independently associated with a decreased risk of mortality, with ORs of 0.9–0.24. There has been little change in the overall mortality during the past 40 years, since the introduction of amphotericin B. As recognition of host groups and their risk factors for zygomycosis increases, earlier intervention with antifungal therapy may improve the outcome of this devastating infection.

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