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The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus

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Zygomycosis is an emerging infection worldwide. A study was conducted to understand its spectrum in the Indian scenario. All patients diagnosed for invasive zygomycosis at a tertiary care center in north India from 2000–2004, were retrospectively analyzed. A total of 178 cases (mean average of 35.6 cases/year) of zygomycosis were diagnosed. Rhino-orbito-cerebral type (54.5%) was the commonest presentation followed by cutaneous (14.6%), disseminated (9.0%), and gastrointestinal (8.4%) zygomycosis. Renal and pulmonary zygomycosis were seen in 6.7% patients each. Uncontrolled diabetes mellitus (in 73.6% of cases) was the significant risk factor in all types (Odds Ratio 1.5–8.0) except renal zygomycosis. Breach of skin was the risk factor in 46.2% patients with cutaneous zygomycosis. However, no risk factor could be detected in 11.8% patients. Antemortem diagnosis was possible in 83.7% cases. The commonest (61.5%) isolate was *Rhizopus oryzae* followed by *Apophysomyces elegans* in 27% patients. Combination of debridement surgery and amphotericin B therapy was significantly better in survival of the patients ($P < 0.005$) than amphotericin B alone (79.6% vs. 51.7% survival). Thus, a rising trend of invasive zygomycosis was observed in patients with uncontrolled diabetes mellitus in India. Consistent diagnosis of renal zygomycosis in apparently healthy hosts and the emergence of *A. elegans* in India demand further study.

Keywords zygomycosis, diagnosis, diabetes mellitus management, *Apophysomyces elegans*

Introduction

Zygomycosis, a polymorphic disease, is caused by fungi belonging to various genera of class *Zygomycetes* – order *Mucorales* and *Entomophthorales*. The disease caused by organisms under *Mucorales* can be categorized as rhino-orbito-cerebral (ROC), pulmonary, gastrointestinal, cutaneous, or disseminated. The disease usually occurs in predisposed individuals, with the belief that the different clinical forms are often associated with particular underlying conditions, e.g., rhino-orbito-cerebral type in individuals with diabetic keto-acidosis, pulmonary and disseminated infection in patients with hematological malignancies and bone marrow transplantation, gastrointestinal in patients with malnutrition and cutaneous lesions following trauma/burns [1–4].

The incidence of zygomycosis has increased in the last decade [2,3]. However, a large number of cases are identified at autopsy, as the disease is difficult to diagnose antemortem unless a high index of clinical suspicion is maintained [2–4]. The disease is still considered to have low prevalence in the majority of centers. In our earlier series, we reported the largest series of 129 cases over 10 years from a single centre [3].

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The present study was carried out to further understand the clinical behavior, natural history and to document any change in incidence, epidemiology, clinical course and outcome of the disease. The results were also compared with the large review by Roden *et al*. [4].

Materials and methods

A retrospective case analysis of all patients with zygomycosis (due to *Mucorales* fungi) diagnosed over the period of 2000–2004 at Nehru Hospital, attached to the Postgraduate Institute of Medical Education and Research, Chandigarh, India was made. Nehru Hospital is a 1200 bed tertiary care centre that provides service to patients from the northern part of India. The cases of invasive zygomycosis were identified consecutively from the mycology laboratory record as well as the histopathology antemortem tissue and postmortem records. The patients with clinical suspicion of zygomycosis but without mycology or histopathology laboratory confirmation were not included in the study.

The diagnosis of zygomycosis was made either antemortem or postmortem. In antemortem cases, the disease was suspected on the basis of clinical and/or radiological evidence. The diagnosis was confirmed on the basis of histopathological demonstration of broad, aseptate, ribbon-like hyphae with right-angled branching in the tissue specimens obtained from the suspected organs, with or without culture isolation of the agents under *Zygomycetes*. In the absence of histopathology, microscopic evidence of similar hyphae in the aseptically aspirated material from deep sites with or without positive culture isolation was also considered diagnostic of the disease. Positive culture alone unaccompanied by microscopic evidence of the agent in the sample was disregarded for diagnosis due to saprophytic nature of these organisms. In autopsy cases, demonstration of similar hyphae on histopathology of tissue was also considered diagnostic for zygomycosis.

Clinical forms of zygomycosis were defined on the basis of the site of involvement. The term rhino-orbito-cerebral (ROC) zygomycosis was described when the lesion originated in nasal sinuses and extended contiguously to orbit, palate, face, or brain. Pulmonary, gastrointestinal zygomycosis were termed when the disease was restricted to respective organs, while the involvement of skin and subcutaneous tissue was defined as cutaneous zygomycosis. The term disseminated was used when more than one non-continuous organ was involved, except in those with renal involvement where the patients primarily presented with fever, flank pain, pyuria/anuria with evidence of enlarged, infracted kidney on computed tomography. These cases were termed as renal zygomycosis because of the above-defined clinical presentation although in some cases additional organs were involved. The term uncontrolled diabetes was used when the fasting blood sugar was $\geq$ 140 mg/dl in a patient (without any dextrose infusion) with or without anti-diabetic therapy. The patient was further qualified for diabetic ketoacidosis when blood glucose was >200 mg/dl with low bicarbonate (<10 mmol/l), low serum pH (pH ≤ 7.2) and ketones were present in urine and serum. Recovery in patients with zygomycosis was considered when the patient was symptom free and/or radiologically improved at the time of discharge.

The case histories of the patients with zygomycosis were analyzed regarding incidence, sites of involvement, underlying diseases, mode of diagnosis, agents isolated and outcome of the disease. Chi-square test and Odds Ratio were applied wherever required. The results of the present series were compared with our previous series [3] and the review of Roden *et al*. [4].

Results

A total of 178 cases (35.6 cases/year) of zygomycosis were diagnosed during the 5-year period (2000–2004) compared to 129 cases (12.9 cases/year) over the 10-year period (1990–1999) from the same center [3] (Fig. 1). Males were the most common sufferers (male to female ratio 2.2:1). Ninety-three (52.3%) of these cases occurred after the 4th decade of life and five (2.8%) patients were less than 10 years old (Table 1).

Clinical presentation could be categorized as rhino-orbito-cerebral (ROC) zygomycosis in 97 (54.5%), cutaneous zygomycosis in 26 (14.6%), disseminated zygomycosis in 16 (9.0%) and gastrointestinal zygomycosis in 15 (8.4%). Renal and pulmonary zygomycosis were seen in 12 (6.7%) patients each (Table 2). Uncontrolled diabetes was the commonest predisposing factor ($n=131$, 73.6%) in all types except renal zygomycosis. The association was significant in all those cases (Odds Ratio 1.5–8.0). Of those 131 patients, diabetes was diagnosed for the first time in 56 patients while investigating for invasive zygomycosis. In the remaining 75 known diabetics, 10 patients had Type I diabetes. Among patients with rhino-orbito-cerebral type zygomycosis, all the parameters to diagnose ketoacidosis were evaluated in 22 patients and six (27.3%) patients were confirmed for ketoacidosis. Three of those six patients responded to therapy. In cutaneous type, the association of uncontrolled diabetes and breach of skin as predisposing factor were seen in equal percentage (46.2%) of patients. One

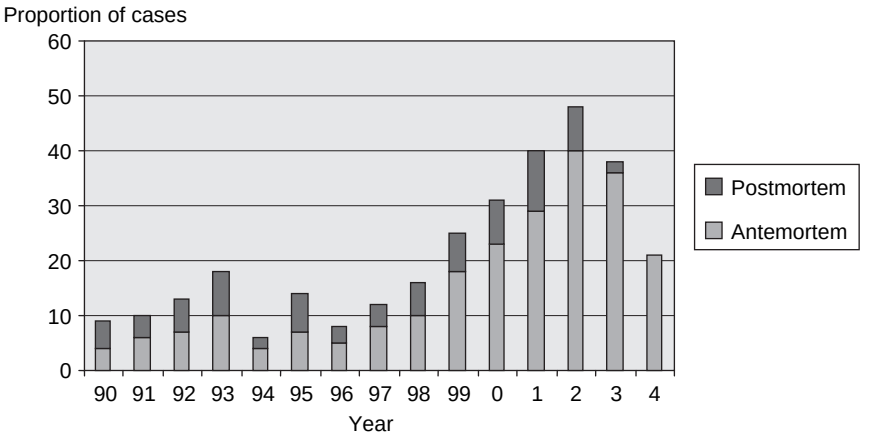

Fig. 1 Proportion of cases diagnosed antemortem and postmortem over 15 years including the results of Chakrabarti *et al*. [3].

patient with cutaneous type was HIV positive. Chronic alcoholism was seen in five patients. Hematological malignancies and renal transplantation were predisposing diseases in two and one patient respectively. History of drug abuse was not found in any patient. No predisposing factor could be detected in 11.8% patients including all patients with renal zygomycosis.

Zygomycosis was diagnosed antemortem in 149 (83.7%) cases and 29 (16.3%) additional patients were diagnosed at autopsy (Fig. 1 and Table 3). Most patients (58.1%) with pulmonary, gastrointestinal and disseminated types were diagnosed postmortem. A total of 78 samples from equal number of patients were submitted for culture, out of which 63 (80.8%) were culture positive (Table 4). Seventy-one (42.7%) samples were deposited in formol saline in the histopathology laboratory and could not be cultured. The commonest (61.5%) isolate was *Rhizopus oryzae*. *Apophysomyces elegans* was isolated from 27.0% of culture positive cases. Besides cutaneous zygomycosis, *A. elegans* was isolated from three cases with renal zygomycosis and one each from rhino-orbito-cerebral and disseminated types.

Outcome of therapy was evaluated in 125 (83.9%) antemortem cases where amphotericin B at least 1 g total dose was injected and/or radical surgery was performed (Table 5). Of the other 24 antemortem cases, 11 patients had incomplete case records, seven died before institution of therapy, five died before infusion of 1 g of amphotericin B and one left against medical advice during amphotericin B therapy. Outcome was best (82.4% recovery) in cutaneous zygomycosis. Due to early diagnosis and early management, two patients with gastrointestinal and three patients with disseminated zygomycosis could be saved. Overall, combination of radical surgery and amphotericin B therapy was significantly better ($P < 0.005$) than amphotericin B alone (79.6% vs. 51.7% patient survival). In none of our patients was lipid formulation of amphotericin B given.

Comparison regarding predisposing factors, fungi isolated and response to therapy between the present series and our earlier series [3] and the review of Roden *et al*. [4] are presented in Tables 6–8.

Table 1 Age distribution of zygomycosis cases

Age (years)	Number of cases (%)
<10	5 (3)
11–20	21 (11.8)
21–30	30 (17)
31–40	29 (16.3)
41–50	42 (24)
>50	51 (29)
Total	178

Discussion

During the last two decades, there has been a dramatic increase in the occurrence of invasive fungal infections observed worldwide largely as a result of the increase in the size of the population at risk. While most of those serious fungal infections are caused by species under the Genus *Candida* and *Aspergillus*, *Zygomycetes* are emerging as the third most important pathogen among immunocompromised patients [3–6]. We earlier reported the largest series of 129 cases of invasive zygomycosis over a decade (12.9 cases/year) from a single center [3]. In the present series, the number increased to 178 over a 5-year period (35.6 cases/year) from the same center without any significant change in sex and age group distribution comparing earlier series [3]. This age and sex group distribution corroborates the largest review [4], where median age was 40.0 years and 65% males suffered among 929 cases. The reason

Table 2 Predisposing factors in respective categories of zygomycosis

Risk factors	Rhino-orbito-cerebral (%)	Cutaneous (%)	Pulmonary (%)	Gastrointestinal (%)	Renal (%)	Disseminated (%)	Total (%)
Uncontrolled diabetes	81 (83.5) [OR, 8.0; $P<0.001$]	12 (46.2) [OR, 1.5; $P=0.023$]	9 (75.0) [OR, 6.9; $P<0.0025$]	14 (93.3) [OR, 1.5; $P<0.001$]	–	15(93.8) [OR, 1.6; $P<0.001$]	131 (73.6)
Chronic alcoholism	4 (4.1)	1 (3.8)	–	–	–	–	5 (2.8)
Renal transplant			1 (8.3)				1 (0.6)
Hematological malignancies	2 (2.1)	–	–	–	–	–	2 (1.1)
Steroid therapy	2 (2.1)	–	1 (8.3)	–	–	–	3 (1.7)
Breach of skin (trauma, postoperative, injection, burn)	–	12 (46.2) [OR, 1.4; $P<0.001$]	–	1 (6.7)	–	–	13 (7.3)
HIV	–	1 (3.8)	–	–	–	–	1 (0.6)
Tuberculosis	–	–	1 (8.3)	–	–	–	1 (0.6)
No predisposing factor	8.2	–	–	–	12 (100)	1 (6.3)	21 (11.8)
Total	97 (54.5)	26 (14.6)	12 (6.7)	15 (8.4)	12 (6.7)	16 (9.0)	178

for higher prevalence of zygomycosis among males is unclear.

The rise in the number of patients with zygomycosis in developed countries has been particularly evident in hematopoietic stem cell transplant recipients and patients with hematological malignancies [4,7–10]. However, in our series from developing and tropical countries, an alarmingly higher (73.6%) association of uncontrolled diabetes mellitus with invasive zygomycosis was noted compared to 36% patients with diabetes in the review of Roden *et al*. [4]. This was the most common predisposing factor in all categories of zygomycosis in our series except patients with renal zygomycosis. The association of uncontrolled diabetes was also significant in all those categories (Odds Ratio 1.5–8.0). The rise in number of patients with invasive zygomycosis may be correlated with an increase in the population of diabetics in developing and tropical countries. The global population of diabetics increased to 171 million in 2000 from 135 million in 1985. Presently, it is estimated that more than 177 million people have diabetes in the world. India, China, USA and Indonesia are the countries harboring the maximum number of cases. In India alone, possibly more than 30 million diabetics reside [11,12]. Large numbers of these cases remain undiagnosed and uncontrolled due to deficiency in health care facilities in developing countries like India. *Zygomycetes* get an opportunity to flourish on such patients with uncontrolled diabetes. Thus, it becomes imperative that in all cases with uncontrolled diabetes in the tropics reporting to any health care facility with possible infection at any site, the patients should be investigated for zygomycosis.

Table 3 Diagnostic modalities of zygomycosis cases

Category	Antemortem	Postmortem	Total
Rhino-orbito-cerebral (%)	95 (97.9)	2 (2.1)	97
Cutaneous (%)	26 (100)	–	26
Pulmonary (%)	6 (50)	6 (50)	12
Gastrointestinal (%)	7 (46.7)	8 (53.3)	15
Renal (%)	10 (83.3)	2 (16.7)	12
Disseminated (%)	5 (31.3)	11 (68.7)	16
Total (%)	149 (83.7)	29 (16.3)	178

In uncontrolled diabetes, ketoacidosis is considered the key factor for predisposition to *Zygomycetes* infection, as low serum pH diminishes the phagocytic effect of macrophages, chemotactic and oxidative burst of neutrophils. Macrophages and neutrophils are the main host defenses against invasion of *Zygomycetes*. Moreover, other serum components like the transferrin system is less active at acidic pH, allowing unbound iron to circulate in blood and the free iron is then utilized by *Zygomycetes* [2,13,14]. In a review of 179 cases of paranasal sinus zygomycosis, 70% patients had diabetic ketoacidosis [14]. In the review of Roden *et al*. [4], 34% of patients with type II diabetes had ketoacidosis. In comparison, ketoacidosis could be confirmed only in 27.3% patients with rhino-orbito-cerebral type of zygomycosis in the present series. However, we considered ketoacidosis only when pH was less than <7.2, which indicates severe ketoacidosis. A higher

Table 4 Species of Zygomycetes isolated from different categories of zygomycosis

	Rhino-orbito-cerebral (%)	Cutaneous (%)	Pulmonary (%)	Gastrointestinal (%)	Renal (%)	Disseminated (%)	Total (%)
R. oryzae	36 (87.8)	1 (7.1)	1 (100)	1 (100)	1 (25)	1 (50)	41 (65.1)
A. elegans	1 (2.4)	12 (85.7)	–	–	3 (75)	1 (50)	17 (27.0)
R. rhizopodoformis	2 (4.9)	–	–	–	–	–	2 (3.2)
R. microsporus	–	1 (7.1)	–	–	–	–	1 (1.6)
R. pusillus	1 (2.4)	–	–	–	–	–	1 (1.6)
S. vasiformis	1 (2.4)	–	–	–	–	–	1 (1.6)
Total	41	14	1	1	4	2	63

frequency of cases would have been revealed if a more liberal definition of diabetic ketoacidosis was followed.

It was believed that particular underlying diseases are often associated with specific clinical types of zygomycosis like rhino-orbito-cerebral type in diabetic ketoacidosis; pulmonary and disseminated infection in patients with acute leukemia, lymphoma, or a history of desferoxamine therapy; gastrointestinal type in patients with malnutrition and cutaneous lesions in the site having trauma/burns [1–5]. Intravenous drug abuse has been a pre-existing condition in patients with central nervous system infection of *Zygomycetes* [2,16,17]. The association of trauma/burns with cutaneous involvement and between intravenous drug abuse and central nervous system infection seems to be logical. However, the association of hematological malignancies and bone marrow transplantation and pulmonary disease and the relationship between diabetes and rhino-orbito-cerebral is more complicated [4]. These interesting associations with the particular category of zygomycosis were emphasized by several workers [1,2,4,15]. However, we did not find such category association in the present series except in uncontrolled diabetes. In our earlier series, we reported that uncontrolled diabetes was the significant risk factor in rhino-orbito-cerebral type and breach of skin in cutaneous zygomycosis [3]. In the present series, breach of skin and uncontrolled diabetes as predisposing factors were observed in equal (46.2%) numbers of patients with cutaneous zygomycosis. This overwhelming association of uncontrolled diabetes in all types of zygomycosis other than renal zygomycosis in Indian scenario is intriguing and requires further study. Patients with diabetes have more micro-vascular disease and in the opportune moment the *Zygomycetes* invade the injured blood vessels and directly damage the endothelial cells. This leads to tissue necrosis, the hallmark of the pathology of zygomycosis [18].

Acquired Immune Deficiency Syndrome (AIDS) does not appear to be a significant risk factor in zygomycosis as only a few infections associated with AIDS have been reported to date [2]. HIV infection produces a defect in T helper cells and this T cell depletion alone is not a major determinant in development of zygomycosis. Several studies have documented impairment in neutrophil function as well in AIDS patients, but this defect may not be significantly profound to predispose for zygomycosis [19]. In our series, only one patient was positive for HIV infection.

The importance of zygomycosis is further stressed as the disease can occur in apparently healthy hosts in contrast to other invasive fungal infections. In the review of 929 cases, the second largest population consisted of persons who had no primary underlying

Table 5 Treatment and outcome of zygomycosis cases (125 patients)

	Outcome	Rhino-orbito-cerebral ($n=87$)	Cutaneous ($n=17$)	Pulmonary ($n=4$)	Gastrointestinal ($n=3$)	Renal ($n=4$)	Disseminated ($n=10$)	Total
Amphotericin B alone* ($n=29$)	Survived	9	4	2	–	–	–	15 (51.7%)
	Died	8	1	1	–	2	2	14 (48.3%)
Surgery only ($n=3$)	Survived	1	–	–	–	–	–	1 (33.3)
	Died	–	1	–	–	–	1	2 (66.6)
Surgery and amphotericin B* ($n=93$)	Survived	58	10	–	2	1	3	74 (79.6%)
	Died	11	1	1	1	1	4	19 (20.4%)

*P value <0.005 – between amphotericin B alone and surgery along with amphotericin B.

Table 6 Comparison of predisposing factors of the present series with the earlier series [3] and the review of Roden *et al*. [4]

Predisposing factors	Present series	Earlier series [3]	Roden *et al*. [4]
Diabetes	73.6*	24	36
Chronic alcoholism	2.8	–	–
Solid organ transplant	0.6	4.2	7
Bone marrow transplant	–	–	5
Malignancy	1.1	7.3	17
Breach of skin (trauma, postoperative, injection, burn)	7.3	14.6	54
HIV positive	0.6	–	2
Tuberculosis	0.6	–	–
Steroid therapy	1.7	3.1	–
Desferoxamine therapy	–	–	6
Others	–	24.0	16
No predisposing factor	11.8	22.9	19

All figures are percentages.

disease at the time of infection [4]. In our earlier series, we reported 22.9% patients had no underlying disease [3]. However, in the present series the number decreased to 11.8% patients possibly due to the overwhelming number of cases with uncontrolled diabetes. Interestingly all patients with renal zygomycosis were found to be apparently healthy before acquisition of the disease.

The increase in the number of cases of zygomycosis in our center may be additionally due to an increased awareness amongst the clinicians as there was a significant improvement in the number of cases with antemortem diagnosis. In the present series, 83.7% patients were diagnosed antemortem compared to 65.1% patients in the earlier series [3] and the difference is statistically significant ($P < 0.025$). In most of the centers the diagnosis of zygomycosis is rarely suspected and antemortem diagnosis is made in only 23–50% cases [20,21]. The higher rate (83.7%) of antemortem diagnosis in our center may be due to increased awareness and also because most of our cases ($n = 123$, 69.1%) presented either rhino-orbito-cerebral type or cutaneous zygomycosis, which may be more easily diagnosed. In other clinical forms of zygomycosis (pulmonary, gastrointestinal, renal and disseminated), 50.9% patients were diagnosed antemortem. For antemortem diagnosis of these forms of zygomycosis, there was also a significant improvement ($P < 0.001$) observed in the present study compared to our earlier series (12 of 52 patients, 19.4%) [3]. As clinical signs and symptoms of invasive fungal diseases are nonspecific, awareness amongst clinicians is the key factor for antemortem early diagnosis. Regular medical autopsies and clinico-pathological meetings in our center have helped considerably in the awareness campaign. Still there is scope for improvement as 29 (16.3%) patients were diagnosed postmortem.

The present series did not show any difference in prevalence of different categories of zygomycosis as compared to the earlier study, as rhino-orbito-cerebral and cutaneous zygomycosis were the commonest two types. However, cases of renal zygomycosis have been consistently reported from this center [3,22–24]. Renal involvement in disseminated zygomycosis is reported frequently in patients with intravenous drug abuse or conrticosteroids therapy, but isolated renal disease has been documented rarely from other centers [25,26]. In contrast, isolated renal zygomycosis is a common occurrence in India as nearly 50 cases were reported in the last two decades from this center [3,22–24]. These patients usually present with fever, flank pain, haematuria, pyuria or anuria with infarction in the kidney unilaterally or bilaterally but without any predisposing factor. None of the 12 patients in the present series had any underlying illness. Earlier, most of the patients were diagnosed on autopsy [3,22–24]. Due to increased awareness most (83.3%) of the cases of renal zygomycosis in the present series were diagnosed antemortem. The interesting observation of renal zygomycosis demands further study on the epidemiology and pathogenesis of this entity.

Treatment of invasive zygomycosis requires several multimodality approaches: radical surgery in localized diseases, aggressive antifungal therapy and correction of the underlying conditions. Early medical and surgical treatment could prevent progression of the disease though overall mortality remains $>50\%$ [4,27]. The ischemic necrosis as a result of Zygomycetes-mediated angioinvasion is likely an important mechanism by which the fungus survives therapy [18]. In the present series, due to early diagnosis, therapy could be instituted in 83.9% patients and 72% patients survived. Importantly, two patients with gastrointestinal type and three patients with disseminated zygomycosis could be saved by early diagnosis and management. Combination of surgery and amphotericin B therapy was significantly better ($P < 0.005$) than amphotericin B alone (79.6% vs. 51.7% patient survival). However, the limitation of the present study is that the patients were followed up until their discharge only. The higher survival rate in the present study may be because most (69.1%) of the patients, included for outcome analysis, were in either the rhino-orbito-cerebral or cutaneous category, which were diagnosed easily and treated quickly. Still, the improvement in antemortem diagnosis due to increased awareness in our center cannot be ignored. In the review of 929 cases, multivariate analysis clearly demonstrated that antifungal

Table 7 Comparison of fungi isolated in the present series with the earlier series [3] and the review of Roden *et al*. [4].

	Present series $N=63$ (%)	Earlier series [3] $N=25$ (%)	Roden *et al*. [4] $N=465$ (%)
Rhizopus sp.	44 (70)	11 (44)	218 (47)
Mucor sp.	–	1 (4)	85 (18)
Cunninghamella bertholletiae	–	–	34 (7)
Apophysomyces elegans	17 (27)	8 (32)	27 (6)
Absidia sp.	–	2 (8)	25 (5)
Saksenaea sp.	1 (1.6)	2 (8)	21 (5)
Rhizomucor sp.	1 (1.6)	1 (4)	19 (4)
Entomophthora sp.	–	–	13 (3)
Conidiobolus sp.	–	–	10 (2.2)
Basidiobolus sp.	–	–	9 (2)
Cokeromyces sp.	–	–	3 (0.6)
Syncephalastrum sp.	–	–	1 (0.2)

therapy and surgery were independently associated with decrease risk of mortality [4].

Amongst the various *Zygomycetes* isolated, emergence of *A. elegans* in Indian scenario is an important phenomenon. The distribution of this fungus in tropical and subtropical countries is substantiated by the occurrence of most human cases in such climates [28]. In the present series, though *Rhizopus oryzae* was isolated from most (63.5%) patients, *A. elegans* was isolated from a considerable number (27.0%) of patients. In our earlier series also *A. elegans* was isolated in 32% patients [3]. *A. elegans* is known to cause cutaneous, subcutaneous and soft tissue infection following trauma, burns or invasive procedure in apparently healthy hosts. However, in the present series, besides the majority (85.7%) of cases of cutaneous or subcutaneous tissue involvement, three patients had renal involvement and one patient each had rhino-orbito-cerebral and disseminated type due to *A. elegans*. This further confirms the earlier study from our center [28].

Thus, the present study highlights the following important facts: (i) the number of patients with invasive zygomycosis are steadily increasing in India; (ii) the present series is the largest series of zygomycosis from a single center in the world; (iii) the rise is significantly associated with the rise in the number of patients with uncontrolled diabetes in tropical and developing countries; (iv) an improvement in the awareness of fungal diseases amongst clinicians is observed in our center; (v) renal zygomycosis is an interesting entity and demands further study; (vi) radical surgery and amphotericin B therapy help in improvement of prognosis; and (vii) *A. elegans* is an emerging fungus in the Indian scenario.

Table 8 Comparison of survival in the present series with the earlier series [3] and the review of Roden *et al*. [4].

	Present series $N=122$ (%)	Earlier series [3] $N=31$ (%)	Roden *et al*. [4] $N=1002$ (%)
Amphotericin B	15/29 (51.7)	7/15 (46.7)	324/532 (61)
Amphotericin B & surgery	74/93 (79.6)	13/16 (81.3)	328/470 (70)

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