Although it has hitherto been considered a rare type of infection, the incidence of zygomycosis (also known as mucormycosis) appears to be increasing. Zygomycosis is almost always lethal if not aggressively treated, and often lethal even with appropriate medical management. Zygomycetes are generally opportunistic organisms, although infection can occur in a normal host. Aerosolization of spores occurs easily, and the portals of entry include the respiratory tract, a disrupted integument, and ingestion of contaminated food. Zygomycetes are often angioinvasive and can manifest as sinusitis, pneumonia, skin infection, and sometimes gastrointestinal infections or necrosis. Patterns of infection vary by the host’s underlying condition. Histopathologically, one sees wide, thin-walled, “ribbony,” aseptate hyphae. Some reports suggest that an increase in zygomycotic infections may be because of increasing voriconazole use. Because Zygomycetes are not susceptible to voriconazole, their emergence in the presence of this drug is not unexpected. The optimal treatment for zygomycosis should include a combination of surgical debriement, medical antifungal therapy, and efforts to improve host defenses. Amphotericin B is the first-line choice for zygomycosis treatment. Posaconazole has shown some efficacy for zygomycosis, but it is not currently approved for its treatment; it is only available for compassionate use.

Although it has hitherto been considered a rare type of infection, zygomycosis (also known as mucormycosis) appears to be increasingly prevalent. The class Zygomycetes includes 2 orders: Mucorales and Entomophthorales. Some use the term mucormycosis, but the important point to note is that most of zygomycoses are caused by Rhizopus species (47%), and only 13% are the result of infection by Mucor spp. Environmental exposure to Zygomycetes is widespread; these organisms are present in soil, decaying vegetation, manure, and foodstuffs (eg, bread, fruit, and cheese).

EPIDEMIOLOGY

Increasing attention is being paid to zygomycosis by the infectious diseases community. Although candidiasis and aspergillosis remain the most common invasive fungal infections, the incidence of zygomycosis is increasing measurably. Although it remains a relatively infrequent infection, zygomycosis is almost always lethal if not aggressively treated, and often lethal even with appropriate medical management.

Much of the increased attention to zygomycosis is
based on 2 published reports. Marr et al show a doubling in the number of *Zygomycetes* infections in the Bone Marrow Transplant Program of the Fred Hutchinson Cancer Research Center over a 15-year period (1985–1999), as shown in Figure 1. However, the percentage of bone marrow transplant patients who develop these infections is not stated, so that while the total number of cases has gone up, it is not clear whether the prevalence has increased.

Kontoyiannis et al, in a case-control observational study of 27 cases of zygomycosis at the MD Anderson Cancer Center, note an apparent increase in zygomycosis incidence from 2000 to 2003 (Figure 2) and suggest that “zygomycosis should be considered in immunosuppressed patients who develop sinusitis while receiving voriconazole prophylaxis, especially those with diabetes and malnutrition.” However, closer examination of the data reveals that even at the highest incidence of zygomycosis, the incidence is much lower than that of invasive aspergillosis (comparing the right-hand y axis to the left-hand y axis).

Another way to track the increased attention to zygomycosis is to consider the number of publications on this topic. A survey of PubMed shows the dramatic increase in the number of reports discussing zygomycosis (Figure 3). However, this measure does not reflect the true dearth of data on zygomycosis infection rates in at-risk patients. In fact, the only published estimate is from 1998, in which the annual infection rate in the San Francisco Bay Area was 4.7 cases per million population compared to 72.8 cases per million of *Candida* and 12.4 cases per million of *Aspergillus*.

**PRESENTATION**

*Zygomycetes* are generally opportunistic organisms; healthy individuals have a strong natural immunity to them, but they can occasionally be pathogenic in normal hosts. Angioinvasive disease is common in patients with type 2 diabetes, hematologic or solid-organ malignancies, transplantation, neutropenia, steroid therapy, and other immunocompromising conditions. Aerosolization of spores occurs rather easily; in fact, 2 studies (presented at the 2005 annual Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC]) reported the rates of *Mucorales* in air samples. In one study, 20% to 39% of outdoor air samples in Madrid, Spain, were positive...
for *Mucorales*. The percentages varied by season, and drinking water was not a source.\(^{10}\)

In the second study, hospital air sampling over a 6-year period revealed that 3.2% of the samples were positive for *Mucorales*, with 1.6% positive in the operating rooms, 2.2% in protected areas with HEPA (high-efficiency particulate air) filters, and 9.5% in unprotected areas.\(^{11}\) Therefore, not surprisingly, the portals of entry for *Mucorales* are nasal passages and the respiratory tract in many patients, particularly those with diabetes or cancer. Other portals include a disrupted integument, particularly in trauma victims and illicit intravenous drug users. It can also be ingested through contaminated food, which is problematic for neonates and those who are malnourished.

**Clinical Manifestations**

Depending on its portal of entry, zygomycoses can manifest as sinusitis, pneumonia, skin infection, and sometimes gastrointestinal infections. (Although the organism circulates in the bloodstream in disseminated infections, a blood culture is not reliable for diagnosis.) Thus, the clinical manifestations can be myriad. Orbital infections are probably the most common presentation, seen as conjunctival infection, scleral hemorrhage and exudate, and proptosis. A computed tomography scan of the orbit will reveal tissue invasion and orbital bony destruction. In the lungs, peripheral, nodular infiltrates occur. Histopathologically, one sees wide, ribbony, aseptate hyphae, in contrast to *Aspergillus*. Frequently, there is tissue necrosis and, as mentioned earlier in this article, infections are angioinvasive.

Most of zygomycotic infections occur in patients with underlying diseases, as shown in Figure 4.\(^{12}\) In a recent review of 929 zygomycosis cases, approximately 20% occurred in healthy individuals, but the most common reported cases were in those with diabetes, followed by cancer and bone marrow transplant.\(^{12}\) The clinical manifestations differ according to the host group at risk. In normal, nonimmunocompromised patients, approximately 50% of all zygomycosis infections are cutaneous (Figure 5), presumably resulting from inoculation of traumatic breaks in the integument.\(^{12}\) In contrast, in patients with diabetes, particularly those with ketoacidosis, sinus/orbit/rhinocerebral involvement accounts for roughly 66% of all presentations. Pulmonary manifestations predominate in patients with cancer and bone marrow transplant, and cerebral and disseminated infections are the predominant manifestations in patients who are intravenous drug abusers and in patients receiving deferoxamine.\(^{12}\)

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**Figure 3. The Number of Reports on Zygomycosis in PubMed Over Time**

![Graph showing the number of reports discussing zygomycosis over time.](image)

*I performed a literature survey using PubMed to track the number of reports discussing zygomycosis.*

**Figure 4. Underlying Conditions in 929 Reported Cases of Zygomycosis**

![Pie chart showing the proportion of patients with underlying conditions.](image)

Data are the proportion of patients with the characteristic. Deferoxamine is an iron chelator, and studies have shown that this agent can actually act as a siderophore (to supply previously unavailable iron to the fungus), facilitating its growth.

BMT = bone marrow transplantation; IV = intravenous.

Data from Roden et al.\(^{12}\)
ROLE OF VORICONAZOLE USE

In recent years, reports have suggested that the apparent increase in zygomycosis infections is a result of increasing voriconazole use in high-risk patients. In one center, voriconazole use was associated with a nearly 8-fold increase in the risk of pulmonary zygomycosis (odds ratio [OR], 7.76; 95% confidence interval, 1.32–45.53; \( P = .023 \)). However, it is important to remember that voriconazole use was not systematic in most centers. Clinicians are presumably most likely to administer voriconazole to those patients at highest risk for a mould infection, in an effort to suppress Aspergillus. Because Zygomycetes are not susceptible to voriconazole, their emergence in its presence is not surprising. A large survey of 25 transplant centers may provide a more realistic picture of the prevalence of zygomycosis. The TRANSNET database compiles information from more than 1000 cases of invasive fungal infections. The results to date indicate that the rates of aspergillosis and zygomycosis varied over different time periods during 2001 to 2004. There is no clear-cut trend for Zygomycetes, Aspergillus, or Fusarium (J. Baggely, personal communication). The prospective, randomized trial of voriconazole versus fluconazole in patients with bone marrow transplant (www.bmtctn.net) will most likely clarify whether voriconazole use contributes to zygomycoses.

MANAGEMENT STRATEGIES

The optimal treatment for zygomycosis should include a combination of surgical debridement, medical antifungal therapy, and efforts to improve host defenses. The series of 929 cases described earlier by Roden et al show that survival is clearly related to treatment, and combination therapy improves survival compared to surgery alone, as shown in the Table. The risk of treatment failure varies depending on the underlying host group, as is seen with other organisms. Bone marrow transplant recipients are at greater risk for dying compared to patients with cancer not requiring transplantation, patients with diabetes, or those with intact immunity.

A multivariate analysis showed that the risk factors for death include disseminated infection (OR, 11.21; \( P < .001 \)), renal failure (OR, 7.16; \( P < .001 \)), and infection with \textit{Cunninghamella} species (OR, 2.78; \( P = .029 \)). By contrast, factors associated with an increased chance of survival include diabetes (OR for mortality, 0.31; \( P = .001 \)), no underlying disease (OR, 0.38; \( P = .001 \)), all forms of treatment (OR, 0.09–0.21; \( P < .001 \)), and surgery when performed early in the treatment course (OR, 0.24; \( P < .001 \)).

EMERGING THERAPIES

Amphotericin B is the first-line choice for zygomycosis treatment, at the highest tolerated doses and in lipid formulation, if possible. Posaconazole has shown some efficacy for zygomycosis but is not currently

<table>
<thead>
<tr>
<th>Type</th>
<th>Patients Who Survived/ Total Patients Who Received the Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antifungal treatment</td>
<td>663 (71) / 414/663 (62)</td>
</tr>
<tr>
<td>No antifungal treatment</td>
<td>333 (36) / 59/333 (18)</td>
</tr>
<tr>
<td>No treatment</td>
<td>241 (26) / 8/241 (3)</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>90 (10) / 51/90 (57)</td>
</tr>
<tr>
<td>Surgery + antifungal therapy</td>
<td>470 (51) / 328/470 (70)</td>
</tr>
</tbody>
</table>

Note that not all of the patients and treatments are represented in this table. Adapted with permission from Roden et al. \textit{Clin Infect Dis.} 2005;41:634-653.
approved for its treatment; it is only available for compassionate use. Kontoyiannis et al have shown, in an abstract from the 2005 ICAAC annual meeting, that posaconazole is highly effective as a second-line agent for zygomycosis, in a series of 91 patients.\textsuperscript{16,17} The overall success rate at 12 weeks was 60\% (14\% complete response, 46\% partial response). Seventy percent had adjunctive surgical debridement along with the antifungal therapy.\textsuperscript{16,17} Other emerging therapies include combination of a polyene plus echinocandin and adjuvant immunotherapies (eg, interferon and granulocytes).

**CONCLUSIONS**

Zygomycosis (or mucormycosis) appears to be increasing in incidence, but more data are needed to confirm this suggested trend. If the rates of infection are increasing, the reasons are multifactorial. Optimal management should combine drug and surgical treatment. However, there is a paucity of data regarding this hitherto uncommon infection, and there is a clear need for better diagnostic tools and safer, more effective therapies.

**REFERENCES**