The Epidemiological Features of Invasive Mycotic Infections in the San Francisco Bay Area, 1992–1993: Results of Population-Based Laboratory Active Surveillance

Judy R. Rees, Robert W. Pinner, Rana A. Hajjeh, Mary E. Brandt, and Arthur L. Reingold

Population-based active laboratory surveillance for invasive mycotic infections was conducted during 1992 and 1993 in three California counties: Alameda, Contra Costa, and San Francisco (population, 2.94 million). The cumulative incidence of invasive mycotic infections was 178.3 per million per year. Invasive mycoses were most commonly caused by Candida (72.8 per million per year), Cryptococcus (65.5), Coccidioides (15.3), Aspergillus (12.4), and Histoplasma (7.1). The clinical significance of other, less common fungi was determined by detailed chart review. The cumulative incidence was determined for zygomycosis (1.7 per million per year), hyalohyphomycosis (1.2), and phaeohyphomycosis (1.0). The most common underlying conditions were human immunodeficiency virus infection (47.4%), nonhematologic malignancy (14.7%), diabetes mellitus (9.9%), and chronic lung disease (9.3%). This represents the first population-based epidemiological assessment of invasive mycoses in the United States.

Many indications suggest that the epidemiological features of fungal infections in the United States are changing and that this group of infections is becoming an increasing problem. Because invasive mycotic infections tend to occur in those with impaired immunity, the growing population of immunocompromised individuals is a principal explanation for this phenomenon. The HIV disease epidemic has been shown to be responsible for dramatic increases in cryptococcal infections and esophageal candidiasis, and it has contributed to increases in cases of severe histoplasmosis and coccidioidomycosis [1–5]. Organ transplantation, immunosuppressive chemotherapy, and increasing use of invasive intravascular devices have all contributed to the growing numbers of patients susceptible to invasive mycotic diseases.

See editorial response by Pfaffer on pages 1148–50.

Despite this general sense that mycotic diseases are becoming increasingly important, our understanding of the epidemiological features of these diseases is incomplete. Some studies have evaluated selected mycoses in specific settings [6–8]. Many have focused on specific groups of patients such as transplant recipients [9, 10], patients with malignancies [11, 12] or human immunodeficiency virus infection [13, 14], children [15], and neonates [16]. Others have described mycoses through single hospital series [17–21], and some have focused on autopsy surveys [22–24]. Other studies have used large databases of hospital discharge diagnoses from the Commission on Hospital and Professional Activities (CPHA) to examine the epidemiological features of fungal diseases [25–27].

However, each of these approaches has important limitations. Reports describing individual mycoses fail to capture the impact of mycotic infections as a whole. Hospital case series usually reflect unique circumstances that cannot be generalized. Analyses of discharge data are limited both by the uncertainty of documented diagnoses and by concerns about the representativeness of participating hospitals.

Beck-Sague et al. used the National Nosocomial Infections Surveillance (NNIS) system to quantify the increasing morbidity and mortality associated with nosocomial fungal pathogens [28]. While their data described the increasing importance of the mycoses, nosocomial infections constitute only a proportion of fungal infections. The study also relied on the NNIS system, a sentinel surveillance system of self-selecting hospitals [29] that may not be a representative sample of all hospitals [30].

In 1992, in view of the lack of accurate surveillance data, Halde et al. called for a universal mycoses reporting system to evaluate and monitor the emerging threat from invasive fungal infections [31]. Reporting of mycotic infections varies considerably among states [31]. Only 29 states require reporting of one or more mycotic infections [32]. However, even in these states, the reported data may be subject to numerous inaccuracies [33]. Passive reporting may underestimate incidence rates [34–39], and the extent of under-reporting varies for different infectious diseases [40]. In addition, by differential reporting of patients in various risk groups, passive reporting may also lead to inaccurate descriptions of the epidemiological features of infectious diseases [41].

Received 17 December 1997; revised 11 June 1998.
Reprints or correspondence: Dr. Judy Rees, California Emerging Infections Program, 2140 Shattuck Avenue #406, Berkeley, California 94704.
Clinical Infectious Diseases 1998;27:1138–47
© 1998 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/98/2705–0005$03.00
The limitations of all these approaches emphasize the difficulties of conducting epidemiological studies of mycotic infections. For many of these infections, diagnosis rests on clinical judgment. Epidemiological studies that rely on convenient sources of data, such as hospital discharge diagnoses, are less likely to identify cases accurately than intensive, clinical-based case-finding efforts. However, while the former may provide less-accurate data, the latter may be too limited (e.g., hospital series) to permit general conclusions or too costly to conduct on a large scale.

We used active, population-based laboratory surveillance to examine the epidemiological features of mycotic infections in the San Francisco Bay Area. While this approach has been used previously to study a variety of bacterial diseases [42–48], it has not been employed to study mycotic diseases. We applied standardized laboratory-based case definitions in a defined population so that case ascertainment was uniform throughout the surveillance area and incidence rates could be determined.

Methods

Data Collection

The data were collected for calendar years 1992 and 1993 as part of a hospital laboratory–based active surveillance program covering 45 laboratories in three counties in northern California (Alameda, Contra Costa, and San Francisco). The laboratory-based active surveillance system used a combination of methods to maximize reporting. Laboratory staff were requested to return notification slips for each positive culture and to send subcultures to the Centers for Disease Control and Prevention (CDC) for future study. In some laboratories, staff were also telephoned at weekly intervals for verbal reports of recently diagnosed cases.

For verification, some laboratories provided monthly computer printouts showing all relevant test results. Others allowed surveillance staff to examine laboratory work cards at frequent intervals. This system was supplemented by a comprehensive audit of laboratory records at the end of the surveillance period to ensure the identification of all isolates defined in the protocol.

Each laboratory received a list defining the organisms, anatomical test sites, and test types of interest. One aim of this list was to exclude superficial infections such as oral, esophageal, and genital candidiasis and to minimize the inclusion of contaminants as cases. Sterile sites were defined as amniotic fluid; biopsy material from bone marrow, brain, kidney, liver, lymph node, or spleen; blood; CSF; joint aspirate; pleural fluid; pericardial fluid; peritoneal fluid; peritoneal dialysate; and vascular catheter specimens. Nonsterile sites were defined as bronchoalveolar lavage (BAL) fluid; tracheal aspirate; sputum; gastric washings; and stool. Intermediate sites were defined as urine and biopsy material from colon, lung, sinus, skin, small intestine, and trachea.

Candida species isolates were documented only when recovered from blood and CSF. Acremonium, Penicillium, and Saccharomyces species isolates were documented when recovered from sterile and intermediate sites. Aspergillus species were documented from sterile and intermediate sites and from BAL fluid, unless the laboratory slip suggested that the isolate was likely to be a contaminant.

All other fungi were documented when isolated from any body site, with the exception of Pneumocystis carinii and dermatophytes such as Trichophyton species, which were excluded from surveillance altogether. Pathogenic Trichosporon species were erroneously excluded in many laboratories. Surveillance for this organism must therefore be regarded as incomplete. In addition to the inclusion of the defined mycotic agents, cases were also documented in which the bacteria Nocardia and Actinomyces were identified from any body site. These were analyzed separately and excluded from incidence calculations.

Two kinds of medical record review were performed, according to the organism of interest: one short and the other more detailed. A short review was attempted for all organisms, to obtain basic demographic and clinical data, along with outcome (defined as survival or death during that hospital admission or episode). Underlying clinical conditions were documented to the extent that they were apparent in the patient’s chart. For patients with long-term hospital stays, the end of the acute episode was defined as either discharge from the hospital or 30 days after the last positive culture, whichever occurred sooner. A fatal outcome was defined as death during the acute episode.

For all organisms, a prevalent case was defined as one in which the original diagnosis was known to have been made either before 1 January 1992 or before the first acute episode identified through active surveillance. An incident case was defined by detection of the first episode of infection through this active surveillance system during 1992 and 1993.

In evaluating the proportions of patients with specific underlying conditions, the denominator was taken as the number of patients fulfilling the case definition for whom adequate information was available from medical records to determine whether or not the underlying condition was present. For all underlying illnesses described, with the exception of previous abdominal or cardiac surgery, this information was available for ~96% of the medical records reviewed. Only 67.5% of patients had adequate information in their medical records to confirm whether or not abdominal or cardiac surgery had occurred within the 2 months before the culture date.

A more detailed medical record review was performed by a physician (J.R.R.) to investigate the clinical significance and epidemiological features of infections caused by the less common fungi. This group of “other mycoses” was defined as infections due to fungi other than Aspergillus, Candida, Coccioidoides, Cryptococcus, and Histoplasma. These detailed medical record reviews were attempted for 137 residents and 24 nonresidents of the Bay Area who had one of these organisms...
isolated from a sterile/intermediate site. Detailed chart reviews were not performed for patients whose isolate had been obtained only from respiratory secretions or other nonsterile sites (n = 91).

In many instances the clinical records documented that the organism identified was regarded as an insignificant colonizing organism or contaminant. In none of these cases was sufficient evidence found during chart review to overrule this opinion. In other cases, no mention was made of the culture result in the clinical notes, often because of delay in identification of the organism. In these cases, clinical significance was evaluated with use of the criteria described.

Case Definitions

Common mycoses. For infections due to Aspergillus, Candida, Coccidioides, and Cryptococcus species, a case was defined by (1) documentation that the patient’s residence was within the three-county area and (2) diagnosis and documentation of clinical infection by the clinician, as determined by medical record review, and (3) isolation of the organism from a defined site. For Aspergillus, at least two BAL isolates, or one sterile/intermediate site isolate was required to fulfill part 3 of the case definition. For Coccidioides, Cryptococcus, and Histoplasma, part 3 of the case definition could be fulfilled by a positive culture or serological test.

Other mycoses. For all other fungi, a case was defined by (1) documentation that the patient’s place of residence was within the three-county area; (2) the presence of clinical symptoms compatible with mycotic infection; and (3) one of the following circumstances: histologic confirmation of invasive infection, isolation of the same species on more than one occasion from the same or different sites, or failure to identify another etiologic agent and documentation by the physician of a likely etiologic role for the fungal species isolated. A case was excluded if laboratory or clinical records documented a strong suspicion that the species was a contaminant. Response to antifungal therapy was also evaluated but was not incorporated into the case definition.

Surveillance Population

Active surveillance was performed in 45 laboratories serving three counties in the San Francisco Bay Area: Alameda, Contra Costa, and San Francisco. The total population of these three counties on 1 January 1993 was 2.94 million (Alameda, 1,338,000; Contra Costa, 854,000; and San Francisco, 747,000) [49]. The racial distribution of the three counties is diverse: white non-Hispanic, 53.8%; Asian/Pacific Islander, 16.4%; Hispanic, 14.3%; black non-Hispanic, 13.3%; and other, 2.4%. The estimated prevalences of HIV infection and AIDS were 1.28% and 0.16%, respectively [50–53]. The estimated prevalence of diagnosed diabetes mellitus was ~3% [54]. The population is largely urban, although parts of Alameda and Contra Costa counties are suburban and rural. Histoplasmosis and coccidioidomycosis are not endemic in the surveillance area, but coccidioidomycosis is endemic in neighboring areas.

Statistical Methods

The data were analyzed with use of Epi-Info, version 6.01 (CDC). Cumulative incidence rates were calculated on the basis of population sizes at the midpoint of the study [49]. Proportions of cases reported as having underlying illnesses were calculated from those for whom the data were available in medical records. A χ² test was used to compare proportions of patients with diabetes mellitus.

Results

During the study period, 1992–1993, 1,619 patients with one or more fungal isolates were identified. In calculating the overall incidence rate for invasive fungal infection, prevalent cases were excluded (table 1). A total of 1,048 patients fulfilled the definition for incident cases. Table 2 shows the incidence estimates from our surveillance data, alongside previous estimates from CPHA analyses. For the less common fungal organisms (isolated from 136 patients), 30 cases of invasive mycotic infection were identified in the surveillance area.

Overall, the annual cumulative incidence of invasive mycotic infection was 178.3 per million. The mean age for these patients was 45.5 years, with a male:female ratio of 2.8:1, which decreased to 1.3:1 after HIV-infected patients were excluded. Age-specific incidence rates are shown in figures 1 and 2. The incidence was 274 per million per year among blacks, 170 per million per year among whites, 141 per million per year among Hispanics, and 103 per million per year among Asians.

Among the patients whose records contained adequate information, a diagnosis of HIV infection was recorded for 47.4% of the patients with an invasive mycotic infection. Other common predisposing illnesses were nonhematologic malignancy (including Kaposi’s sarcoma), 14.7%; diabetes mellitus, 9.9%; and chronic lung disease, 9.3%. Ninety-one patients (8.5%) had no documented history of any serious medical conditions prior to the episode of mycotic infection; 48 (52.7%) of these were in the group identified as having coccidioidomycosis. Overall, the case-fatality ratio for episodes known to be first invasive mycotic infections was 22.4%.

Candida Species

Candida species were identified more frequently than any other fungal species: they were recovered from the blood or CSF of 428 patients during the 2-year period, for a cumulative incidence of 72.8 per million per year and a case-fatality ratio of 33.9%. The majority of Candida isolates were C. albicans (50.9%), followed by C. parapsilosis (22.2%), C. glabrata (11.7%), and C. tropicalis (7.9%). Case-fatality ratios were
Table 1. Period prevalence, incidence, and case-fatality ratios for selected invasive fungal and other infections, San Francisco Bay Area counties, 1992–1993.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. of cases per million per year (n)</th>
<th>No. of patients with &gt;1 isolate</th>
<th>Period prevalence</th>
<th>Incidence*</th>
<th>Case-fatality ratio (%) for first episode*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candida species</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>218</td>
<td></td>
<td>37.1 (218)</td>
<td>37.1 (218)</td>
<td>38.1 (83/218)</td>
</tr>
<tr>
<td><em>Non-albicans</em></td>
<td>210</td>
<td></td>
<td>35.7 (210)</td>
<td>35.7 (210)</td>
<td>29.5 (62/210)</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>495</td>
<td></td>
<td>84.2 (495)</td>
<td>65.5 (385)</td>
<td>12.7 (49/385)</td>
</tr>
<tr>
<td>Coccidioides</td>
<td>116</td>
<td></td>
<td>19.7 (116)</td>
<td>15.3 (90)</td>
<td>11.1 (10/90)</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>87</td>
<td></td>
<td>14.8 (87)</td>
<td>12.4 (73)</td>
<td>23.3 (17/73)</td>
</tr>
<tr>
<td>Histoplasma</td>
<td>51</td>
<td></td>
<td>8.7 (51)</td>
<td>7.1 (42)</td>
<td>21.4 (9/42)</td>
</tr>
<tr>
<td>Agents of Zygomycosis</td>
<td>42</td>
<td></td>
<td>. . .</td>
<td>1.7° (10)</td>
<td>30.0 (3/10)</td>
</tr>
<tr>
<td>Agents of Hyalohyphomycosis</td>
<td>93</td>
<td></td>
<td>. . .</td>
<td>1.2° (7)</td>
<td>14.3 (1/7)</td>
</tr>
<tr>
<td>Agents of Phaeohyphomycosis</td>
<td>40</td>
<td></td>
<td>. . .</td>
<td>1.0° (6)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td>7</td>
<td></td>
<td>&lt;1° (5)</td>
<td></td>
<td>20.0 (1/5)</td>
</tr>
<tr>
<td>Saccharomyces</td>
<td>7</td>
<td></td>
<td>&lt;1° (1)</td>
<td></td>
<td>50.0 (0/1)</td>
</tr>
<tr>
<td>Malassezia furfur</td>
<td>1</td>
<td></td>
<td>&lt;1° (1)</td>
<td></td>
<td>0 (0/1)</td>
</tr>
<tr>
<td>Other fungi</td>
<td>37</td>
<td></td>
<td>. . .</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Total</td>
<td>1,617</td>
<td></td>
<td>. . .</td>
<td>178.3 (1,048)</td>
<td>22.4 (235/1,048)</td>
</tr>
</tbody>
</table>

* Based on cases in which infection was known to be patient's first episode.

1 Incidence based on cases confirmed by review of charts for patients with sterile and intermediate site isolates.

2 Agents of hyalohyphomycosis not otherwise specified.

highest for *C. tropicalis* (44.1%), *C. albicans* (38.1%), *C. glabrata* (34.7%), and *C. parapsilosis* (16.8%).

The major underlying conditions among all patients with invasive candidal infections were nonhematologic malignancies (18.2%; n = 78), HIV infection (15.3%; n = 61), diabetes (13.6%; n = 58), and chronic lung disease (13.6%; n = 56) (table 3). Abdominal or cardiac surgery had been performed within the preceding 2 months on 17.9% of patients with invasive candidiasis for whom information was available in the medical records (n = 284). Recent surgery was known to be a factor for 9 of 34 patients with *C. tropicalis* infection and 10 of 49 patients infected with *C. glabrata*. Leukemia was a common predisposing illness among patients with invasive *C. tropicalis* infection (17.6%; n = 6), but overall only 3.5% (n = 15) of the patients with invasive candidiasis had leukemia.

For two *Candida* species, *C. albicans* and *C. parapsilosis*, the race-specific cumulative incidence rates among blacks were more than twice those among other racial groups. In all racial groups, *C. parapsilosis* was the most frequently isolated invasive fungal pathogen in children aged <10 years, with a cumulative incidence of 33.3 per million per year, followed by *C. albicans* (29.6 per million per year). The cumulative incidences among black children in this age group (66.0 per million per year for *C. parapsilosis*; 73.4 per million per year for

Table 2. Cumulative incidences of selected invasive mycoses.

<table>
<thead>
<tr>
<th>Mycosis</th>
<th>Incidence per million per year (source)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td>19.7</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>10.3</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>1.9</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1.3</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>1.8</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>0.9</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>0.6</td>
</tr>
</tbody>
</table>

NOTE. CPHA = Commission on Hospital and Professional Activities; PR = present report.
The episode during which the diagnosis was first made was 11.1% (table 1). Forty-eight cases of coccidioidomycosis (55.8%) occurred in previously healthy people, and 20 (41.7%) of these patients had extrapulmonary disease. Diabetes was present in 10.5% of cases, HIV infection in 9.6%, and malignancy or chronic lung disease in 8.1% each (table 3). Eight of the 10 patients who died had a history of serious predisposing illness(es).

A history of travel to an area of endemicity was not uniformly available from medical records, but exposure in an area of endemicity was noted in the records of 26 patients (28.9%). Extrapulmonary disease was present in 36 (40%) of the incident cases identified by this surveillance system, most commonly in Asians (n = 13) and blacks (n = 10). Twenty-six of the 116 cases detected by surveillance had been previously diagnosed at the time the infection was identified through active surveillance, although the date of the initial diagnosis was usually not documented. These patients were excluded from incidence calculations.

**Cryptococcus Species**

During the 2-year surveillance period, 495 patients with either positive cryptococcal cultures or elevated cryptococcal antigen levels were identified. The diagnoses of 385 of these patients were known to have been made during the study interval, for a cumulative incidence of 65.5 per million per year and a case-fatality ratio of 12.7%. Of the 378 patients for whom the information could be determined, 339 (89.7%) were infected with HIV. Thirty-three of the remainder had other significant underlying illnesses (table 3). Only 10 (2.7%) of the patients for whom records were adequate had no identifiable significant predisposing conditions.

Among the 385 newly diagnosed cases, at least one positive culture was obtained from any site in 306 cases (79.5%): 202 (52.5%) were diagnosed by at least one positive CSF culture; 158 (41.0%) had at least one positive blood culture; and 92 (23.9%) had both.

**Coccidioides immitis**

Active surveillance identified 90 new cases of infection caused by Coccidioides immitis, for a cumulative incidence of 15.3 cases per million per year. The case-fatality ratio for the

---

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Age-specific cumulative incidence rates (per million per year) of invasive infection with Candida (○), Cryptococcus (●), and Aspergillus species (▲), by 10-year age group, in the San Francisco Bay Area, 1992–1993.

C. albicans) greatly exceeded those in the racial group with the next highest incidences (whites, 27.8 per million per year for C. parapsilosis; Hispanics, 43.6 per million per year for C. albicans).

The majority of infections with C. parapsilosis and C. albicans in children <10 years old occurred in those aged <1 year (36 of 58). In contrast, no cases of invasive C. glabrata infection occurred in patients below the age of 20 years.

**Aspergillus Species**

Of the 87 patients with Aspergillus isolates who fulfilled the case definition, 73 had no history of aspergillosis documented in the medical records, yielding a cumulative incidence of 12.4 per million per year and a case-fatality ratio of 23.3%. Among patients known to have been admitted to the hospital (n = 55), the case-fatality ratio was 32.7%. The most common underlying illnesses for these patients were HIV infection (34.8%), chronic lung disease (18.3%), and nonhematologic malignancy (18.1%).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Age-specific cumulative incidence rates (per million per year) of invasive infection with Coccidioides (●) and Histoplasma (□) species, by 10-year age group, in the San Francisco Bay Area, 1992–1993.

<table>
<thead>
<tr>
<th>Organism (no. of patients infected)</th>
<th>HIV infection</th>
<th>Nonhematologic malignancy</th>
<th>Diabetes mellitus</th>
<th>Chronic lung disease</th>
<th>Abdominal or cardiac surgery</th>
<th>Lymphoma</th>
<th>Leukemia</th>
<th>Dialysis</th>
<th>Organ transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus (73)</td>
<td>34.8</td>
<td>18.1</td>
<td>5.6</td>
<td>18.3</td>
<td>6.8</td>
<td>5.6</td>
<td>11.1</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Candida albicans (218)</td>
<td>15.3</td>
<td>17.9</td>
<td>15.6</td>
<td>12.8</td>
<td>16.9</td>
<td>3.8</td>
<td>1.4</td>
<td>7.6</td>
<td>1.9</td>
</tr>
<tr>
<td>C. non-albicans (210)</td>
<td>15.4</td>
<td>19.8</td>
<td>12.4</td>
<td>14.4</td>
<td>18.8</td>
<td>5.0</td>
<td>5.9</td>
<td>4.5</td>
<td>2.0</td>
</tr>
<tr>
<td>C. parapsilosis (95)</td>
<td>10.3</td>
<td>13.2</td>
<td>7.7</td>
<td>13.2</td>
<td>5.8</td>
<td>5.5</td>
<td>3.3</td>
<td>4.4</td>
<td>0</td>
</tr>
<tr>
<td>C. glabrata (49)</td>
<td>22.9</td>
<td>25.0</td>
<td>20.4</td>
<td>8.2</td>
<td>27.0</td>
<td>4.1</td>
<td>0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>C. tropicalis (34)</td>
<td>6.2</td>
<td>32.4</td>
<td>18.2</td>
<td>23.5</td>
<td>4.6</td>
<td>5.9</td>
<td>17.6</td>
<td>8.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Coccioides (90)</td>
<td>9.6</td>
<td>8.1</td>
<td>10.5</td>
<td>8.1</td>
<td>1.4</td>
<td>0</td>
<td>1.2</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>Cryptococcus (385)</td>
<td>89.7</td>
<td>12.3</td>
<td>4.8</td>
<td>3.7</td>
<td>0</td>
<td>4.0</td>
<td>1.1</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Histoplasma (42)</td>
<td>90.0</td>
<td>7.3</td>
<td>2.4</td>
<td>2.5</td>
<td>0</td>
<td>4.9</td>
<td>0</td>
<td>4.9</td>
<td>0</td>
</tr>
<tr>
<td>Other fungi (30)</td>
<td>14.3</td>
<td>10.0</td>
<td>33.3</td>
<td>10.0</td>
<td>4.8</td>
<td>6.6</td>
<td>10.0</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Total (1,048)</td>
<td>47.4</td>
<td>14.7</td>
<td>9.9</td>
<td>9.3</td>
<td>7.6</td>
<td>4.0</td>
<td>3.0</td>
<td>3.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

* Percentage of patients for whom the information was known.

Isolates from 61 of the 73 incident cases were evaluated further by local laboratories, and 36 (59.0%) were identified as Aspergillus fumigatus. A further 11 isolates (18.0%) were identified as Aspergillus niger. For the majority of patients, the case definition was fulfilled by recovery of a single isolate from a sterile site. Only 17 patients (23.3%) had Aspergillus isolates recovered from more than one site or on more than one occasion.

**Histoplasma capsulatum**

Forty-two patients were found to be infected with Histoplasma capsulatum, for a cumulative incidence of 7.1 per million per year and a case-fatality ratio of 21.4% (n = 9). All the patients who died had serious predisposing illnesses. The underlying medical conditions of the patients with histoplasmosis resembled those of the patients with cryptococcal disease (table 3). Ninety percent of the 41 patients whose HIV status was known were infected with HIV. Only two patients had no documented predisposing illnesses.

Patients with histoplasmosis comprised the youngest group, with a mean age of 39.1 years. The highest incidence was found among the Hispanic population (15.5 per million per year). Most cases (93%; n = 39) were identified through positive cultures, most commonly of blood (52%; n = 22), bone marrow (28.6%; n = 12), and respiratory secretions (11.9%; n = 5). Only three patients (7.1%) were identified through serological methods alone. Extrapulmonary disease was diagnosed in 38 patients (90.5%).

**Other Mycooses**

Active surveillance identified 226 other fungal isolates. Detailed chart review was not performed for patients whose fungal isolates were only from respiratory secretions or other nonsterile sites (n = 91). An attempt was made to review the remaining 135 charts for patients with unusual fungal isolates from sterile/intermediate sites. Thirteen charts either were unavailable or contained insufficient data.

Of the 122 remaining patients, significant clinical disease caused by one of the fungi was identified in 30. The diagnosis was stated either in the discharge summary or the medical notes of 26 of these 30 (86.7%). Of those cases without medical-record confirmation of the organism’s clinical significance, in two cases cultures were reported positive after the patient was discharged from the hospital. In one case confirmed by histopathologic examination of sinus tissue and another with multiple positive cultures, the patients were treated surgically, and no mention of the result could be found in the physicians’ notes. Seventeen of the cases found to be clinically significant were confirmed histopathologically; in 20 cases the organism was isolated either from more than one site or on more than one occasion. In 27 of the 30 cases, no other organisms were identified that could have accounted for the patients’ symptoms.

Isolates from 19 of the patients in this category with clinically significant isolates were sent to the CDC in order to confirm their identification. Of these, 16 were viable and their identities were confirmed. Two isolates initially identified as Mucor in Bay Area laboratories were identified by the CDC as Absidia corymbifera and Rhizopus arrhizus. An additional isolate originally identified as Saccharomycyes was identified at the CDC as C. glabrata. This case is therefore included in the Candida figures. The remaining 13 were confirmed as having the correct identity.

The main fungal infections in this category, among Bay Area residents, were the zygomycoses (n = 10), hyalohyphomycoses (n = 7), phaeohyphomycoses (n = 6), and sporotrichosis (n = 5) (table 1). The most common predisposing illness,
occurring in 11 (36.7%) of the 30 patients with invasive fungal infections, was diabetes mellitus, found in 50% of patients with zygomycosis (5 of 10) and phaeohyphomycosis (3 of 6), and in 3 (21.4%) of the 14 patients with other invasive infections in this category.

In five of 11 of these diabetic patients, diabetes was the only serious underlying condition. Diabetic ketoacidosis was a presenting condition in three of the patients. The other illnesses found most frequently in these 30 patients were HIV disease (14.3%; n = 4), chronic lung disease (10.0%; n = 3), and leukemia (10.0%; n = 3). An additional 24 charts were reviewed for Bay Area nonresidents who had fungi identified from sterile/intermediate sites. A further 18 cases of invasive fungal infection were found, which were analyzed separately (table 4).

Other Organisms

In previous studies describing mycotic infections, bacteria such as Nocardia and Actinomyces have been included because of their tendency to behave like fungi. In this analysis, they were excluded from incidence calculations, but data were collected with use of the same case definition described for cryptococcosis. Forty-six new cases of nocardia infection were identified, and 13 of actinomycosis. For nocardia infections, the cumulative incidence was 7.8 per million per year, and the case-fatality ratio was 4.3%.

The most common underlying condition among patients developing nocardia infection was HIV infection (31.1%; n = 14). The majority of Nocardia isolates that were evaluated in the hospital laboratory were found to be N. asteroides (80.4%; n = 37), followed by N. brasiliensis (8.7%; n = 4). Most nocardia infections were diagnosed by culture of respiratory secretions (71.7%; n = 33); positive blood cultures were documented for only two patients. The highest race-specific cumulative incidence rate was found for Asians (13.5 per million per year; n = 13), compared with that for whites (7.3 per million per year), Hispanics (7.1), and blacks (2.6). None of the Asian patients were known to be infected with HIV.

**Discussion**

To our knowledge, these are the first population-based estimates of cumulative incidence rates for invasive mycotic infection. The

| Table 4. Significant clinical infections occurring with the lesser known mycoses. |
|---------------------------------|---------------------------------|---------------------------------|
| **Organism or mycosis**      | **Bay Area residents**         | **Nonresidents treated in Bay Area** |
| **Zygomycosis**               |                                 |                                 |
| Rhizopus                      | Rhinocerebral (1), sinusitis/orbital invasion (1), sinusitis (2), cutaneous (1), cavitary pneumonia (1) | Sinusitis/orbital invasion (2), sinusitis (1), cutaneous (1) |
| Absidia                       | Cutaneous (1)                  |                                 |
| Mucor                         | Sinusitis (2), gastric (1)      | Rhinocerebral (1)               |
| Unspecified                   |                                 |                                 |
| Hyalohyphomycosis*            |                                 |                                 |
| Fusarium                     | Cutaneous (2), line infection (1) | Disseminated (2)               |
| Pseudallescheria boydii†      | Sinusitis (2), pneumonia (1)    | Rhinocerebral (1), disseminated multiple septic emboli (1), multiple brain abscesses (1), cavitary pneumonia (1), pneumonia (1) |
| Paecilomyces                  | Endophthalmitis (1)            |                                 |
| Phaeohyphomycosis             |                                 |                                 |
| Exophiala                     | Cutaneous (3)                  |                                 |
| Alternaria                    | Cutaneous (1)                  |                                 |
| Bipolaris hawaiensis          | Sinusitis (1)                  |                                 |
| Exserohilum                   | Sinusitis (1)                  |                                 |
| Sporothrix                    | Cutaneous (4), disseminated (1) |                                 |
| Saccharomyces                 | Fungemia (1)                   | Fungemia/pneumonia (1)          |
| Malassezia furfur             | Line infection (1)             | Line infection (3)              |
| Rhodotorula                   |                                 | Line infection (1)              |
| **Mycetoma (unspecified)**    |                                 |                                 |
| **Total**                     | 30                              | 18                              |

* Agents of the hyalohyphomycosis not otherwise specified in table 1.
† Includes isolates of Scedosporium apiospermum.
San Francisco Bay Area population has a unique combination of characteristics, including substantial racial heterogeneity and a high prevalence of HIV infection. These surveillance data provide insight into the epidemiological features of mycotic infections in the San Francisco Bay Area population as a whole, rather than focusing on specific groups of individuals.

In 1992–1993 the cumulative incidence for invasive mycotic infections was 178 cases per million per year in the San Francisco Bay Area, with a case-fatality ratio of at least 22.4%. (Our methods may have underestimated case-fatality ratios by the exclusion of deaths occurring after the hospitalization during which the diagnosis was made.) Previous incidence estimates, based on CPHA data, are shown in table 2. Even allowing for methodological and population differences between the studies, our data show striking increases in the rates of candidiasis and cryptococcosis.

A high male-to-female ratio was noted for most invasive mycotic infections. Most but not all of this difference was eliminated with the exclusion of individuals known to be infected with HIV. An excess of mycotic infections in males has been noted previously [26]. Race-specific incidence rates were highest among blacks, followed by whites, Hispanics, and Asians. Overall, age-specific incidence rates were highest for those aged >80 years (392 per million per year), primarily as a result of the high incidence of systemic candidiasis in this age group. Age-specific incidence rates showed considerable variation, according to the infecting organism (figures 1 and 2).

The cumulative incidence of invasive mycotic infection among individuals not known to be infected with HIV was 100 per million per year. The incidence among HIV-positive individuals was 50 times higher (five per thousand per year). It should be remembered that the prevalence of HIV infection in the San Francisco Bay Area is higher than in many other regions of the United States and that this had a significant impact on the incidence rates for invasive mycoses.

In our area, >47% of patients with an invasive mycotic infection were known to be infected with HIV, including ~90% of those with histoplasmosis or cryptococcosis (table 3). In contrast, the underlying conditions among patients with candidal infections were more varied, perhaps reflecting the iatrogenic etiologies of invasive candidiasis.

The incidence of any invasive mycotic infection among diabetics was 236 cases per million per year: diabetes mellitus was present in 9.9% of the cases identified, a proportion that significantly exceeds the prevalence of diabetes (7.2%) in the surveillance population ($\chi^2 = 10.68; P = .001$). Our surveillance also identified diabetes in 33% (10 of 30) of patients with “other mycoses” and in half (5 of 10) of those with zygomycosis, an association that has been noted previously [55]. A high proportion of patients with diabetes (17%) was also seen among those with “other and unspecified mycoses” in the CPHA data of 1980–1982 [27].

This surveillance system identified many cases of histoplasmosis and coccidioidomycosis, neither of which is endemic in the San Francisco Bay Area [56], although coccidioidomycosis is endemic in nearby counties. Presumably this reflects earlier exposure elsewhere and subsequent clinical presentation in the Bay Area. This may explain the high incidence of coccidioidomycosis seen among the Hispanic population, many of whom may have been exposed in South American countries. The high proportion of patients with histoplasmosis who were found to have disseminated infection suggests that our surveillance may have preferentially identified patients with severe disease.

Population-based active laboratory surveillance has certain advantages over previous methods used to describe the epidemiological features of invasive mycoses. The exclusion of nonresidents of the three counties eliminates the selection bias inherent in studies conducted in large tertiary-care hospitals, as table 4 illustrates. In addition, 17% of new cases in our study were initially identified among outpatients; many of these would have been missed by hospital-based surveillance such as the NNIS system. However, our approach required confirmation of the patient’s residence and other data, through a brief review of medical records.

This proved very labor-intensive and led to the use of restrictions in surveillance criteria (e.g., limiting Candida isolates to those cultured from blood and CSF) and, hence, the inevitable exclusion of an unknown number of cases of invasive disease. In addition, detailed medical record reviews could not be performed for 91 patients who had less common fungal isolates, obtained only from nonsterile sites. However, only about one-quarter of sterile/intermediate site isolates were found to reflect clinically significant illness, and it seems unlikely that nonsterile-site isolates would have yielded many additional cases.

Identical surveillance methods were used in the same three counties in 1992–1993 to identify invasive bacterial infections such as with Neisseria meningitidis. In comparison with the cumulative incidence of 65.5 per million per year for the primarily HIV-related cryptococcal disease, rates for meningococcal disease were only 10.2 per million per year. Laboratory-based surveillance is easiest when isolation of an organism from a sterile site is a specific indicator of clinical infection (e.g., with N. meningitidis, C. neoformans, Coccidioides, and Histoplasma). However, for many other fungi, positive cultures were found to be poor predictors of mycotic disease. For the less common mycoses, medical record review revealed invasive disease in only 24.6% (30 of 122) of patients with sterile-site or intermediate-site isolates.

It seems likely that the isolation of Aspergillus from a clinical specimen would also be a poor predictor of invasive disease [56]. Numerous Aspergillus isolates were identified from sterile sites and BAL specimens, but their clinical significance was often difficult to determine during the medical record review performed by surveillance staff. For this reason, our case definition for aspergillosis was based primarily on criteria relating to the site of specimen collection, which may have affected the characteristics of patients identified as having aspergillosis.
In this study, a surprising 35% of patients fulfilling the case definition for aspergillosis were infected with HIV. This may have resulted from our case-finding methods, combined with the high prevalence of HIV infection in the Bay Area. High-quality surveillance for invasive aspergillosis would require clinical and microbiological confirmation of invasive disease, with use of a detailed medical record review.

The preferential identification of specific groups of patients may be a more general problem of our surveillance system. Immunocompromised patients and those with severe symptoms caused by mycotic disease may be more often correctly diagnosed and hence identified through laboratory-based surveillance (although *Aspergillus* may be an exception to this, as difficulties with the case definition may have led to the inclusion of patients with less severe mycotic disease). The mycoses in which mild and subclinical forms are common will not be fully ascertained by laboratory surveillance. Like passive reporting, active laboratory surveillance not only can underestimate the true disease incidence but also may distort the demographic and risk characteristics of the patient population.

The practical difficulties encountered during laboratory-based surveillance highlight two major problems of diagnostic mycology that hinder fungal disease surveillance. First, for some mycoses, a positive culture is not a specific predictor of invasive disease. Second, a prolonged or unsuccessful diagnostic process in the laboratory may affect the clinical diagnosis in several ways. The result may not be known early enough to affect clinical management or to allow confirmation of an isolate’s clinical significance (when this is uncertain) by methods such as tissue biopsy or additional cultures.

Death, surgical intervention, “blind” antifungal treatment, and symptom resolution may occur in the interim, so that the microbiological diagnosis is not confirmed. This may impair descriptive or epidemiological studies that might otherwise promote awareness among physicians of the clinical presentations of these infections. The development of better and more timely diagnostic tests would be a useful step toward understanding the importance of some of the less-well-described fungal pathogens and their associated clinical syndromes.

A major factor leading to the emergence of fungal infections is the growing number of susceptible patients [23, 28, 31, 57, 58], of victims of “new” diseases such as HIV infection, and of treatments such as organ transplantation and immunosuppressive chemotherapy that prolong the lives of susceptible patients. Further research should be directed toward the timely and accurate diagnosis of these infections. Improved, comprehensive surveillance techniques are needed to monitor incidence trends and to be used as a basis for epidemiological studies to evaluate risk factors for the invasive mycoses. The results of such research may highlight an increasing need for awareness among clinical and laboratory staff of the potential importance of invasive mycotic infections.

Acknowledgments

The authors gratefully acknowledge the members of the Mycotic Diseases Active Surveillance Group: Gretchen Rothrock, Nicholas Czap, Pamala Daily, Lisa Gelling, and Nandeeni Mukerjee (California) and Laura Conn (CDC). They also thank Dr. Arvind A. Padhye (CDC) and the staff of all participating laboratories in the San Francisco Bay Area.

References


