Coccidioidomycosis in Solid Organ Transplantation

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Coccidioidomycosis is an endemic fungal infection of the southwestern United States. Normally a self-limited infection in healthy hosts, coccidioidomycosis can become a serious complication in patients who have had solid organ transplantation. Among patients whose solid organ transplantation was complicated by coccidioidomycosis, the infection has a variety of clinical presentations. Disseminated disease is common and has substantial morbidity. Patients at risk for coccidioidal infection should be identified so that antifungal prophylactic therapy can be initiated. Treatment options include amphotericin B or azoles. Secondary prophylaxis is recommended because relapse is frequent.

Coccidioidomycosis is an endemic fungal disease caused by Coccidioides immitis. The region of endemcity is restricted to the Western Hemisphere; in North America, the region of endemcity includes the southwestern United States, northern Mexico, and parts of Central America. In the United States, desert regions of California and Arizona are the major areas of endemcity [1, 2]. In healthy persons, coccidioidomycosis usually manifests with influenza-like symptoms or, less commonly, with pneumonia [2, 3]. Rarely, the disease can disseminate to extrapulmonary sites. Risk factors for disseminated disease include diabetes mellitus, pregnancy, male sex, race with dark pigmentation (African American, Filipino, Hispanic, and others), and immunodeficiency (such as HIV infection or organ transplantation) [1, 2].

In 1971, the death of a child due to disseminated coccidioidomycosis after renal transplantation prompted Murphey et al. [4] to recommend that potential transplant candidates with any evidence of prior coccidioidal infection should be excluded. Other authors have reiterated similar ideas [5].

Despite these concerns, solid organ transplantation has flourished in locations of high endemicity for coccidioidomycosis. We review the current literature from a few transplant centers on coccidioidomycosis and solid organ transplantation.

METHODS

A search of the medical literature for all papers published from January 1960 through September 2000 was conducted with use of the MEDLINE, EMBASE, and PubMed (National Library of Medicine) databases. Key words included “coccidioidomycosis” and “organ transplantation.” Also, the references from these papers were used to identify other relevant references. The search was limited to English-language sources. Papers relating to bone marrow transplantation were not included.

RESULTS

The MEDLINE search identified many individual case reports and 6 case series documenting coccidioidomycosis in organ transplant recipients. Seventy-three cases were identified, and clinical information was provided for 68 patients in 26 articles [4, 6–30]. Abstracted...
information included the following: age; sex; race; year of transplantation; year report was published; organ transplanted; antirejection therapy (if any); characteristics of pretransplantation coccidioidomycosis infection, if known, including time to transplantation; treatment; use of prophylactic therapy after transplantation; characteristics of the posttransplantation clinical presentation of coccidioidal infection, including time after transplantation; organ(s) involved; sites cultured; serological findings; treatment; outcome; follow-up; and autopsy findings. This collection of cases was reviewed and is referred to herein as the “Coccidioidomycosis in Transplantation” (CIT) data set.

Table 1 summarizes the features of patients presenting with pulmonary coccidioidomycosis, table 2 summarizes the features of patients presenting with extrapulmonary coccidioidomycosis, and table 3 summarizes the group of patients with evidence of coccidioidal infection before transplantation.

### Demographics
Reports of coccidioidomycosis complicating solid organ transplantation have appeared in the medical literature since 1967. Coccidioidomycosis complicated the postoperative course of renal [4, 6, 8–10, 14, 16, 18, 20–25, 27–30], heart or heart-lung [6, 11, 13, 15, 22, 31], liver [7, 12, 32], or small bowel transplant recipients [17]. Most of the case series and many of the individual case reports were from areas of endemicity, most notably from the University of Arizona in Tucson [8, 14, 22, 33]. Most of the patients in whom coccidioidomycosis was diagnosed outside an area of endemicity were residents or former residents of an area of endemicity. In a few cases, brief visits were adequate for the infection to be acquired [11, 13, 30].

Race was specified for 45 of 69 patients in the CIT data set: 26 patients were white, 2 were black, 13 were Hispanic, 2 were Native American, 1 was Filipino, 1 was Korean, and 1 was Samoan. Except for 2 children who were 6 and 10 years old, the patients in the CIT data set were adults (range, 16–69 years).

### Incidence of Coccidioidomycosis after Transplantation
The incidence of coccidioidomycosis after transplantation in areas of high endemicity is summarized in table 4. The earliest of these studies was a review of all cases of coccidioidomycosis

| Table 1. Summary of patients who presented with pulmonary coccidioidomycosis after solid organ transplantation, review of the literature, 1960–2000. |
|---|---|---|---|---|---|---|
| Type of transplantation (reference) | Year of publication | Race, sex | Time of disease presentation after transplantation | Serological results | Antifungal treatment | Outcome, follow-up |
| Kidney | 1971 | W, M | 7 months | NG | NG | Died, disseminated disease |
| [10]a | 1977 | H, F | <1 weekb | Negative | None | Died, disseminated disease |
| [8] | 1982 | W, F | 50 months | Negative | | Died, disseminated disease |
| [8] | 1982 | H, M | 7 months | ID positive; CF 1:32 | AmB 0.5 g | Died |
| [8] | 1982 | W, F | 1 month | CF 1:256 | AmB 2.7 g | Alive, 8 months |
| [8] | 1982 | W, M | 9 months | CF 1:2 | AmB 1.9 g | Alive, 7 months |
| [8] | 1982 | W, M | 48 months | CF 1:4 | AmB 1.5 g | Alive, 22 months |
| [25] | 1986 | NG, M | 3 weeks | CF repeatedly negative; CIE negative twice, then positive at 9 weeks | AmB 2.6 g | Alive at discharge, lost to follow-up |
| [25] | 1986 | NG, M | 2 months | CF 1:64, increased to 1:512 | AmB 1.6 g, then Ket | Alive at 3 months, lost to follow-up |
| Liver | 1997 | W, M | 72 months | ID positive; CF <1:2 | AmB 1.0 g, then Flu | Recovered, then relapsed after discontinuation of Flu |
| Heart or heart-lung | 1985 | NG, M | 11 months | NG | NG | Died, disseminated disease |
| [23] | 1985 | NG, M | 1 month | Negative | AmB 0.8 g, then Ket | Died, multiple pulmonary infections |
| [23] | 1985 | NG, M | 7 months | NG | AmB 0.9 g, then Ket | Alive, receiving Ket indefinitely |
| [22] | 1985 | NG, F | 1 month | CF 1:4 | AmB 1.0 g, then Ket | Alive, receiving Ket indefinitely |
| [30] | 2000 | K, M | 1.5 months | NG | AmB 380 mg, then lipid-associated AmB 1450 mg | Died |

**NOTE.** AmB, amphotericin B; CF, complement-fixation antibody test; CIE, counterimmunoelectrophoresis; F, female; Flu, fluconazole; H, Hispanic; ID, immunodiffusion antibody test; K, Korean; Ket, ketoconazole; M, male; NG, not given; TP, tube-precipitin antibody; W, white.

a Two transplantations.
b After second transplantation.
Table 2. Summary of patients who presented with extrapulmonary coccidioidomycosis after solid organ transplantation, review of the literature, 1960–2000.

| Type of transplantation (reference) | Year of publication | Race, sex | Time of disease presentation after transplantation | Organs or sites involved | Serological results | Antifungal treatment | Outcome, follow-up |
|-----------------------------------|---------------------|-----------|---------------------------------------------------|--------------------------|---------------------|---------------------|-------------------|
| **Kidney**                        |                     |           |                                                   |                          |                     |                     |                   |
| [8, 14]                            | 1977                | W, M      | 1.5 months<sup>a</sup>                            | Lungs, urine             | Negative             | AmB 0.05 g         | Died, disseminated disease |
| [8, 14]                            | 1977                | W, M      | 2 months                                          | NG                       | CF:1:32             | None                | Died, disseminated disease |
| [8, 14]                            | 1977                | W, F      | 14 months                                         | Lungs, bone marrow       | CF:1:32             | AmB 0.04 g         | Died, disseminated disease |
| [8, 14]                            | 1977                | W, M      | 23 months                                         | Lungs, urine, skin, knee | CF:1:256            | AmB 4.0 g          | Alive, receiving suppressive Ket |
| [8, 14]                            | 1977                | W, M      | 48 months                                         | Lung, urine, spleen      | TP:1:10;            | AmB 1.1 g          | Died, disseminated disease |
| [8, 14]                            | 1977                | B, M      | 11 months                                         | Lung, thyroid            | CF:1:8              | AmB 1.3 g          | Died, disseminated disease |
| [16]                              | 1980                | NG, M     | 2 months                                          | CNS<sup>c</sup>          | NG                  | None                | Died, disseminated disease |
| [26]                              | 1980                | W, M      | 4 years                                           | Lung, CNS, skin          | CF:1:32             | AmB ic, intracisternally, Mic iv | Alive, 18 months |
| [8]                               | 1982                | W, M      | 0.5 months                                        | Lung, spleen             | CF:1:256            | AmB 0.02 g         | Died, disseminated disease |
| [8]                               | 1982                | W, M      | 2 months                                          | Lung, peritoneum, CNS    | CF:1:2              | AmB 2 g            | Died, disseminated disease |
| [8]                               | 1982                | NA, M     | 2 months                                          | Lung, liver              | CF:1:16             | AmB 0.01 g         | Died, disseminated disease |
| [8]                               | 1982                | H, M      | 27 months                                         | Joints, skin, urine      | CF:1:512            | Ket                | Alive, 21 months |
| [8]                               | 1982                | W, M      | 1 month                                           | Urine                    | Negative            | None                | Alive, 60 months |
| [8]                               | 1982                | W, M      | 32 months                                         | Lung, urine, skin, brain | CF:1:32             | AmB 3.7 g          | Alive, 90 months |
| [22]                              | 1985                | NA, M     | 9 months                                          | CNS                       | CF:1:4              | AmB intracisternally, Ket | Died, bacterial pneumonia |
| [22]                              | 1985                | H, M      | 89 months                                         | Lung, bones, urine       | CF:1:8              | Ket                | Alive |
| [22]                              | 1985                | H, F      | 17 months                                         | Skin, joints, meningies  | NG                  | AmB 1.2 g, Ket     | Died, cocci meningitis |
| [22]                              | 1985                | H, M      | 7 months                                          | Lung, skin               | CF:1:256            | AmB 2.5 g          | Died, bacterial pneumonia |
| [23]                              | 1995                | NG, M     | 10 years                                          | Knee                      | NG                  | AmB 1.0 g, then Ket, then Flu | Alive, 120 months |
| [18]                              | 1996                | NG, F     |          | Forearm lesion                                     | NG                       | Surgical excision   | Alive, 12 months |
| [9]                               | 1996                | NG, NG    | 3 weeks                                           | Brain                     | NG                  | AmB, then Flu      | NG |
| [9]                               | 1996                | Fil, M    | NG                                               | Septic arthritis         | NG                  | AmB, then Flu      | Alive |
| **Liver**                         |                     |           |                                                   |                          |                     |                     |                   |
| [7, 12]                           | 1990                | H, M      | 2 months                                          | Lung, liver, blood       | ID positive; CF:1:16 | AmB 0.8 g          | Died 3 months after transplantation |
| [7]                               | 1997                | H, F      | 16 months                                         | Lung, meningies, blood   | ID positive; CF:1:256 | AmB intrathecally, AmB iv 0.59 g, Flu | Died |
| [7]                               | 1997                | W, M      | 1.5 months                                        | Liver                     | ID negative; CF:1:64 | AmB 1.5 g, then Flu | Alive, receiving Flu indefinitely |
| [7]                               | 1997                | H, M      | 1 month                                           | Monoarticular arthritis  | ID positive; CF:1:256 | AmB 4.0 g, then Flu | Alive, receiving Flu indefinitely |
| **Heart or heart-lung**           |                     |           |                                                   |                          |                     |                     |                   |
| [15]                              | 1981                | NG, M     | 1.5 month                                         | Lung, CNS, urine         | CSF CF:1:24         | Mic iv, AmB iv, intrathecally | Alive, follow-up NG |
| [31]                              | 1982                | W, M      | 1 month                                           | Lung, CNS                | CF:1:256            | AmB iv 3.1 g, intrathecally 16.9 mg | Initial response for 1 year; died, disseminated disease |
| [11]                              | 1987                | W, M      | <1 month                                          | Lung, extremity cellulitis | NG                | None                | Died 21 days after transplantation, disseminated disease |
| [13]                              | 1998                | NG, M     | 6 years                                           | Blood, arm, thyroid      | NG                  | AmB, Flu            | Alive |

**NOTE.** AmB, amphotericin B; B, black; CF, complement-fixation antibody test; CIE, counterimmunoelectrophoresis; F, female; Fil, Filipino; Flu, fluconazole; H, Hispanic; ID, immunodiffusion antibody test; Ket, ketoconazole; M, male; Mic, miconazole; NA, Native American; NG, not given; TP, tube-precipitin antibody; W, white.

<sup>a</sup> Two transplantations.
<sup>b</sup> After second transplantation.
<sup>c</sup> Lesion possibly not from coccidioidomycosis.

in the kidney transplantation program at the University of Arizona, Tucson, from 1970 to 1979 [8]. The annual incidence was highest (5%) in the first posttransplantation year and lower (2%–3%) in years 2–5. No patients presented with coccidioidomycosis >5 years after transplantation. In the later series of patients (1985 or later), the incidence appears to be lower, although application of the Pearson χ² statistic did not demonstrate statistical significance (15 [4%] of 363 vs. 22 [7%] of...
Table 3. Summary of patients with coccidioidomycosis before solid organ transplantation, review of the literature, 1960–2000.

| Reference | Date of report | Patient age in years, sex | Years before transplantation | Organs involved | Treatment | Serological results | Posttransplantation antifungal prophylaxis | Organ transplanted | Outcome |
|-----------|---------------|---------------------------|----------------------------|----------------|-----------|-------------------|------------------------------------------|-------------------|---------|
| [28]      | 1967          | 19, M                     | 4; 3*                      | Lung, brain    | AmB       | CSF CF 1:1        | AmB                                      | Kidney            | Meningitis recurred when AmB discontinued; died 3 years after transplantation |
| [27]      | 1969          | 33, F                     |                            | Lung           | NG        | NG                | None                                     | Kidney            | Died of disseminated disease |
| [21]      | 1972          | 27, M                     | 4                          | Lung           | NG        | None              | None                                     | Kidney            | Died of disseminated disease after treatment with AmB, then Flu |
| [29]      | 1975          | 34, F                     | 4                          | Lung           | None      | None              | None                                     | Kidney            | Died of disseminated disease 2 months after transplantation |
| [10]      | 1977          | 39, M                     | 2                          | Lung           | Nodule resection, AmB | TP NR; CF NR | AmB                                      | Kidney            | No evidence of disease 60 months after transplantation |
| [22]      | 1985          | 10, M                     | 1.1                        | Lung           | NG        | CF 1:8            | AmB                                      | Kidney            | No evidence of disease (follow-up NG) |
| [22]      | 1985          | 34, M                     | 3                          | Lung           | NG        | CF NR; ID positive| None                                     | Kidney            | No evidence of disease (follow-up NG) |
| [22]      | 1985          | 37, M                     | 0.4                        | Lung           | Ket for 2 months | CF 1:8   | Ket                                      | Heart            | Chronic Ket; no evidence of disease |
| [22]      | 1985          | 31, F                     | 2 months                   | Unk            | NS        | ID positive       | Mic, Ket                                 | Kidney            | Alive |
| [6]       | 1993          | 63, M                     | 1                          | Lung           | Ket for 2 months | TP NR; CF NR | Ket                                      | Heart            | No evidence of disease 17 months after transplantation |
| [6]       | 1993          | 63, M                     | 1                          | Lung           | NG        | TP NR; CF 1:2     | Ket                                      | Heart            | No evidence of disease 19 months after transplantation |
| [6]       | 1993          | 6, M                      | 1                          | Lung           | None      | TP NR; CF 1:16    | AmB                                      | Kidney            | No evidence of disease 139 months after transplantation |
| [6]       | 1993          | 36, M                     | 1.8                        | Lung           | None      | TP NR; CF 1:1     | Ket                                      | Heart            | No evidence of disease 126 months after transplantation |
| [6]       | 1993          | 31, M                     | 3                          | Lung           | Cavity resection | TP NR; CF NR | None                                     | Kidney            | No evidence of disease 132 months after transplantation |
| [6]       | 1993          | 23, M                     | Unk                        | Lung           | Resection of lung mass | CF 1:2; TP negative | None                                     | Heart            | Alive 60 months |
| [6]       | 1993          | 29, F                     | Unk                        | Lung           | Ket        | CF 1:1; TP positive| Ket                                      | Kidney            | Alive 115 months |
| [6]       | 1993          | 36, M                     | Unk                        | Lung           | Ket        | CF 1:1; TP negative| None                                     | Kidney            | Died of pneumonia |
| [6]       | 1993          | 29, M                     | Unk                        | Lung           | Ket        | CF range 1:1–1:8 | None                                     | Kidney            | Died of coccidioidal meningitis |
| [9]       | 1996          | Unk                       | Yes, but no details given  | NG             | None      | Positive         | Flu for 2 months                          | Kidney            | Septic arthritis occurred after discontinuation of Flu, recovered after treatment with AmB, then Flu |
| [7]       | 1997          | 69, F                     | Unk                        | NG             | None      | CF 1:2; ID negative| None                                     | Liver             | Died, disseminated disease |
| [7]       | 1997          | 55, M                     | Unk                        | NG             | None      | CF >1:16; ID positive| None                                     | Liver             | Died, disseminated disease after treatment with AmB 0.2 g Flu |

**NOTE.** AmB, amphotericin B; CF, complement-fixation antibody test; F, female; Flu, fluconazole; ID, immunodiffusion antibody assay; Ket, ketoconazole; M, male; Mic, miconazole; NG, not given; NR, nonreactive; TP, tube-precipitin antibody; Unk, unknown.

*a Pulmonary infection 4 years before transplant; meningitis 3 years before transplant.**

306; P = .085; 95% CI for the difference in incidence, −0.5 to 6.6). If a true decrease in the incidence exists, it may be because efforts have been made to identify patients at risk for coccidioidal disease and administer prophylactic therapy.

**Clinical Characteristics**

**Risk factors for coccidioidomycosis.** Immunosuppression has long been recognized as a risk factor in the presentation of coccidioidomycosis after transplantation. In 1977, Smithline et al. [14] reported increased mortality among renal transplant recipients with disseminated coccidioidomycosis who received high-dose corticosteroid treatment. Since that report, immunosuppressive regimens have changed, and prednisone doses have decreased substantially. All patients in the CIT data set were receiving corticosteroids as part of their immunosuppressive regimen, although details of dose and duration were not consistently reported. It is not known how other components of immunosuppressive regimens affect the presence or clinical presentation of active coccidioidal infections.

Treatment of acute rejection is also a risk factor for coccidioidal infection. In the CIT data set, 13 patients with coccidioidomycosis had antirejection therapy of some kind (high-dose corticosteroids, polyclonal antilymphocyte or antithymocyte preparations, and monoclonal therapy such as OKT3) [4, 6–10, 12, ...
of these, 9 had fatal disseminated disease. In 1996, Serota [9] reviewed his experience with a cohort of 160 renal transplant recipients over a 5-year period and concluded that among other factors, patients requiring ≥2 courses of antirejection therapy had an increased risk of coccidioidomycosis.

Concurrent immunosuppressing illnesses may be present in transplant recipients; these include diabetes mellitus, malignant neoplasms, uremia, HIV infection, and collagen-vascular disease [2]. Although these illnesses may increase the likelihood of disease dissemination in patients who have not received a transplant [10, 20, 27, 29, 35], there is insufficient information from our CIT data set to conclude that these concurrent illnesses influence the presentation of coccidioidomycosis in transplant recipients [9, 22]. In 1 series, renal transplant recipients with diabetes who had coccidioidomycosis did not differ significantly from a control group of transplant recipients who had diabetes but who did not have coccidioidomycosis [8].

The risk of coccidioidomycosis after transplantation is increased by either a prior history of coccidioidomycosis or any positive serological findings obtained just before transplantation [6, 22, 33, 34]. The increased risk of active disease in patients with a positive history or serological test may be attenuated postoperatively by initiating antifungal prophylactic therapy. The clinical course of patients with evidence of coccidioidomycosis before transplantation is summarized in table 3. Of the 21 patients listed, 11 received antifungal prophylactic therapy after transplantation. Seven of the 10 patients who did not receive this treatment died of disseminated coccidioidomycosis. Nine of the 11 patients who received antifungal prophylactic therapy survived without complications; the other 2 patients had prophylactic therapy discontinued, resulting in 1 patient dying [28] and the other having septic arthritis [9]. At the University of Arizona, 9 of 21 patients who had a history of coccidioidomycosis before transplantation were given antifungal prophylactic therapy, and none of them had postoperative recurrence of coccidioidomycosis. However, 10 of the other 12 patients who did not receive antifungal prophylactic therapy developed active coccidioidomycosis [6, 33].

Risk factors for disseminated disease in the noncompromised host include race, male sex, pregnancy, blood type, and HLA type [2]. Disseminated coccidioidomycosis has an increased likelihood of developing in the following racial groups: blacks, Filipinos, Hispanics, and Native Americans [2]. In the CIT data set, the distribution of transplant recipients with coccidioidomycosis does not clearly have an overrepresentation of the high-risk racial groups, but the absence of an association cannot be excluded because the racial distribution in the denominator is not known. Race was not a significant factor for the presence of coccidiodal infection in renal transplant recipients [8], although a follow-up report from the same institution showed disseminated coccidioidomycosis in 3 Hispanics and 1 Native American [22]. The latter report did not indicate whether this racial distribution was atypical of the area’s patient population.

Blood type B and male sex (but not HLA type) are additional risk factors for disseminated coccidioidomycosis but not for the mere presence of coccidioidomycosis [8]. In the CIT data set, 12 of 18 patients presenting with pulmonary coccidioidomycosis (table 1) and 24 of 29 patients with disseminated coccidioidomycosis (table 2) were male.

**Clinical presentation.** The first reports of coccidioidomycosis after transplantation described disseminated disease with catastrophic outcome. Retrospective case series from areas of endemicity identified less dramatic cases of coccidioidomycosis, often limited to the lungs. Patients with pulmonary infection presented variably, some with an acute illness consisting of fever, productive cough, shortness of breath, altered sensorium, or fulminant respiratory failure with septic shock [30]. Other patients presented more insidiously, with anorexia, weight loss, fatigue, and the absence of fever or pulmonary symptoms. Asymptomatic cavitary lung lesions were discovered in 2 liver transplant recipients during a radiographic evaluation for an unrelated reason [7].

In noncompromised hosts, extrapulmonary dissemination is rare. The most common sites are skin, bone and joints, and meninges [2]. In transplant recipients with coccidioidal infection, dissemination to multiple sites is common, up to 75% in 1 series [8], with or without concurrent pulmonary involvement [36]. Table 5 summarizes the sites of dissemination in patients from the CIT data set. Multiple sites of dissemination were common. The transplant graft was infected in 10 of the cases.

**Timing of infection.** Coccidioidomycosis after solid organ transplantation can occur at any time; the highest risk is during the first year [8, 22]. In the CIT data set, the time of infection was reported for 47 patients [4, 7, 8, 10, 13–15, 19–26, 28]. Of these, 24 (51%) presented with infection within 3 months after transplantation and 33 (70%) presented within 1 year. After the first year, there was no particular distribution in the time of presentation.

**Postinfection time to transplantation.** In areas of endemicity for coccidioidomycosis, primary coccidioidomycosis may develop in a patient awaiting transplantation. How long should a patient wait before transplantation can be performed safely? The interval (range, 2 months to 4 years) between active coccidioidomycosis and organ transplantation was known for 13 patients in the CIT data set (table 3) [6, 10, 22, 27–29]. Eleven of these 13 patients had transplantation ≥1 year after the episode of coccidioidomycosis. One patient had a heart transplantation performed successfully 5 months after an episode of pulmonary coccidioidomycosis [22]; this patient was given ketoconazole preoperatively and postoperatively. For pa-
patients who contract an acute coccidioidal infection, transplantation should be delayed as long as possible (ideally, 1 year) and done when the infection is clinically controlled. These patients should receive uninterrupted antifungal prophylactic therapy throughout the transplantation process, continuing long into the posttransplantation period (perhaps indefinitely). A registry of organ transplant recipients who have had antecedent coccidioidal infections has been established [6] to facilitate a better understanding of the risks and benefits of transplantation in this setting.

**Mortality.** Early reports of transplant recipients with coccidioidomycosis indicated that mortality was high [14]; overall mortality was 63% in the first case series of kidney transplant recipients with coccidioidomycosis and 72% in patients with disseminated infection [8]. Recent reports from Arizona kidney and heart transplantation programs indicate that the mortality is lower than in earlier years, ranging from 0 [34] to 25% [22]. However, in a recent retrospective review of mortality among liver transplant recipients with coccidioidomycosis at the University of California Los Angeles during 1984–1994, overall mortality was 50% (4 of 8 cases); all of the patients in this series who died had disseminated infection [7]. The decrease in coccidioidomycosis-related mortality in the Arizona transplant programs may be the result of a greater appreciation of the problem and more rapid diagnosis and initiation of therapy [33]. The use of less toxic antifungal therapy may also be a factor.

**Laboratory Studies**

**Skin tests.** Tests for delayed hypersensitivity to coccidioidin or spherulin antigens have been done to determine whether a patient has had previous exposure to *C. immitis*. Immunocompromised hosts, including transplant recipients, react poorly to skin tests; this type of evaluation is not sensitive for patients with active disease [14]. In a retrospective review of coccidioidomycosis in the heart transplant service at the University of Arizona, Hall et al. [6] reported 13 asymptomatic cardiac transplant recipients whose skin tests for coccidioidomycosis were positive. Recurrent coccidioidomycosis did not develop in any patient after transplantation, and only 2 patients received antifungal therapy after transplantation. Thus, a positive skin test result was not predictive of the development of coccidioidomycosis after transplantation and should not exclude an otherwise acceptable candidate for transplantation. Commercially produced skin test antigens are not currently available and may not be reintroduced into the market.

**Serological evaluation.** The serological evaluation of coccidioidomycosis has been recently reviewed [33]. The tests primarily use 2 antigens. The first is the tube-precipitin antigen, which detects antibodies relatively early in the course of primary infection. The second is the complement-fixing antigen, which detects antibodies that arise later in the course of infection; the concentration of the latter roughly correlates with the extent of infection and can be monitored serially to follow the course of infection. A commercially available ELISA uses a proprietary antigen to detect antibodies in patients with antibodies to both the tube-precipitin and complement-fixing antigens [33].

Diminished immunocompetence can make the diagnosis of coccidioidomycosis difficult. In an early series [14], all 5 renal transplant recipients with disseminated coccidioidal infection had no response to coccidioidin skin testing, and 3 of the 5 had no detectable serological reaction. This lack of serological reactivity has also been noted at our institution (unpublished data) and others [8, 10, 22, 25].

False-positive coccidioidal serological results have been documented in candidates for lung transplantation who had underlying cystic fibrosis. This finding was likely from high circulating levels of nonspecific or cross-reacting serum proteins that interfered with the test [37].

**Cultures.** The definitive method of diagnosis is to isolate the fungus in a clinical specimen. *C. immitis* is not a fastidious organism; it grows well on most media used in clinical microbiology laboratories and can be detected within 5 days.

*C. immitis* has been isolated from cultures of various body fluids. Because coccidioidomycosis typically localizes to the lungs, expectorated sputum samples are frequently sent to the laboratory for culture but may be negative in the presence of active infection. The yield can be improved with the use of bronchoscopy [8].

The ability to establish the diagnosis of disseminated coccidioidomycosis is enhanced by the use of a urine fungal culture.

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**Table 4. Incidence of coccidioidomycosis (CDM) after solid organ transplantation, review of the literature, 1960–2000.**

| Reference | Program location, Arizona | Organ transplanted | Years | No. of patients | No. of CDM cases | Incidence (%) |
|-----------|---------------------------|--------------------|-------|----------------|-----------------|---------------|
| [8]       | Tucson                    | Kidney             | 1970–1979 | 260             | 18               | 6.9           |
| [9]       | Scottsdale                | Kidney             | 1989–1994 | 160             | 6               | 3.8           |
| [22]      | Tucson                    | Heart              | 1979–1984 | 46              | 4               | 8.7           |
| [34]      | Tucson                    | Heart              | 1985–1991 | 203             | 9               | 4.4           |
The principal diagnostic tool in 6 of 10 renal transplant recipients with disseminated coccidioidomycosis was a positive result from urine fungal culture [8]. Blood cultures occasionally yield positive results for patients presenting with overwhelming infection [7, 8, 12, 13].

**Radiology.** No predominant pattern of pulmonary disease was seen in a retrospective study of radiographic findings of renal transplant recipients presenting with coccidioidomycosis [36]. Lobar, nodular, alveolar, or miliary infiltrates noted in ≥1 lobe were all seen. Cavitary disease was unusual. Pulmonary patterns of disease were similar whether infection was isolated to the lungs or part of disseminated disease. The time to radiographic resolution after antifungal therapy among survivors ranged from 14 to 120 days.

**Leukopenia.** Neutropenia has not been associated with coccidioidomycosis in transplant recipients. However, many transplant recipients have lymphopenia as a result of their immunosuppressive regimens. A lymphocyte count of <1000 cells/mm³ occurred in 4 of 5 kidney recipients with pulmonary coccidioidomycosis and in 10 of 12 recipients with disseminated disease [8].

**Miscellaneous laboratory findings.** Thyrotoxicosis and recurrent hypercalcemia occurred in a heart transplant recipient with disseminated coccidioidomycosis involving the thyroid [13]. The mechanism of the hypercalcemia was consistent with extrarenal production of 1,25-dihydroxyvitamin D.

**Pathology.** The presence of a mature spherule of *C. immitis* in any tissue is pathognomonic of coccidioidal infection. A single specimen may show numerous spherules in all stages of maturation [12]. The surrounding tissue may show a granulomatous [38] or suppurrative inflammation with prominent polymorphonuclear cells [10, 19, 21]. Well-defined granulomas with giant cells accompanied by either caseating [30, 31] or noncaseating [12] granulomas have been reported.

### Table 5. Sites involved among 38 solid organ transplant recipients with disseminated coccidioidomycosis, review of the literature, 1960–2000.

| Site              | No. of patients |
|-------------------|-----------------|
| Lungs             | 24              |
| Transplant graft  | 10              |
| Kidney            | 3               |
| Heart             | 3               |
| Liver             | 3               |
| Lung              | 1               |
| Meninges          | 10              |
| Spleen            | 9               |
| Liver             | 7               |
| Genitourinary     | 7               |
| Skin              | 6               |
| Joint             | 6               |
| Thyroid           | 5               |
| Brain             | 4               |
| Pancreas          | 3               |
| Lymph nodes       | 3               |
| Kidney            | 2               |
| Adrenal           | 2               |
| Bone              | 1               |
| Bone marrow       | 1               |
| Colon             | 1               |
| Heart             | 1               |
| Peritoneum        | 1               |
| Choroid (eye)     | 1               |
| Parathyroid       | 1               |

**NOTE.** Data are from [4, 6–16, 18–23, 26–28, 31]. Total exceeds 38 because coccidioidomycosis disseminated to >1 site for some patients.

**Prophylaxis and Treatment**

Most patients reported in the CIT data set received amphotericin B (tables 1 and 2) before azoles were available. After initial control of the infection, many patients had recurrent infection that required retreatment. Azoles were used in the more recent cases to suppress recurrent infection. Medical treatment alone was sometimes inadequate to control the infection, and reduction of immunosuppression was required [28].

The treatment of coccidioidomycosis after transplantation is similar in many respects to the treatment of coccidioidomycosis in the noncompromised host. After coccidioidal infection is diagnosed, it is important to determine the extent of infection. Treatment recommendations for specific manifestations of coccidioidomycosis have been reviewed recently [39].

Specific antifungal therapy for the treatment of coccidioidomycosis includes amphotericin B (0.5–0.7 mg/kg/day) and azoles (ketoconazole, 400 mg/day; fluconazole, 400–800 mg/day; or itraconazole, 200 mg b.i.d.) [39]. Generally, for rapidly progressing nonmeningeal infections, many physicians familiar with coccidioidomycosis select amphotericin B as initial therapy because its antifungal effect appears to have a more rapid onset than that of azoles [33, 39]. After improvement has been seen with amphotericin B, therapy can be changed to a less toxic azole. Subacute or chronic infections are more likely to be treated initially with an azole [39]. Meningitis is also an indication for either fluconazole or itraconazole [39].

Two patients in the CIT data set received ketoconazole alone (table 2). Both patients had widely disseminated infection and both survived. No other published data were found for the use of azoles as initial therapy for transplant recipients with coccidioidomycosis. In other immunocompromised patients such as those infected with HIV, available data agree with the statements that azoles can be used initially in the treatment of less.
severe infections [40] and that fluconazole is effective in treating HIV-infected patients with coccidioidal meningitis [41].

Azoles have been used for both primary prophylaxis for high-risk patients and secondary prophylaxis for patients who had initial therapy with amphotericin B. Typically, doses of 100–200 mg/day have been used for primary prophylaxis and 200–400 mg/day for secondary prophylaxis [9]. The optimal duration of prophylactic therapy is unknown and tends to be prolonged (6–12 months or longer) and individualized [6, 7]. The azoles bind and inhibit the hepatic cytochrome P-450 system regulating cyclosporine metabolism, frequently causing increased cyclosporine levels [42], and increase the risk of nephrotoxicity. A similar phenomenon has been observed in patients given tacrolimus [43]. Cyclosporine or tacrolimus levels should be monitored when fluconazole doses are >100 mg daily [43]. The cost of long-term fluconazole for fungal prophylaxis is partially offset by the savings from a decreased cyclosporine dose [9]. Azole-induced hepatotoxicity was not reported in the CIT data set [9, 32].

Lipid formulations of amphotericin became available after the majority of patients in the CIT data set were treated. When compared with conventional amphotericin B, lipid formulations of amphotericin B cause less nephrotoxicity in cyclosporine-treated transplant recipients [44] and have equal efficacy in immunosuppressed patients with systemic fungal infections [45]. The efficacy of lipid amphotericin B preparations in treating transplant recipients with coccidioidomycosis has not been reported but may warrant future study.

Cumulative doses of amphotericin B were reported for 33 patients in the CIT data set and ranged from 10 mg to 4.0 g. Of the 13 patients who received <1 g of amphotericin B, 3 (23%) survived. Twenty patients received ≥1 g of amphotericin B and 11 (55%) survived. Twenty-two patients received treatment with azoles; 2 patients received primary azole therapy, and 20 received azole therapy concurrent with or after a course of amphotericin B. Of these patients given azoles, 11 (50%) survived. Survival was associated with higher cumulative doses of amphotericin B and azole suppression.

**SUMMARY**

A review of the medical literature was conducted to summarize the reports of transplant recipients whose posttransplantation courses were complicated by coccidioidomycosis. Generally, the incidence of posttransplantation coccidioidomycosis is low, but its morbidity and mortality may be high, especially among patients with disseminated infection. Patients at risk for coccidioidal infection should be identified so that antifungal prophylactic therapy can be initiated. Transfer recipients with coccidioidomycosis can have various clinical presentations, and dissemination is common. Treatment with amphotericin B is commonly required. Secondary prophylactic therapy is recommended because relapse is frequent. Many questions persist regarding coccidioidomycosis in transplantation; future studies should refine screening, prophylactic therapy, and treatment for these patients.

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