Current Fungal Infection Reports (2021) 15:143–150
https://doi.org/10.1007/s12281-021-00425-7

FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Coccidioidomycosis and Solid Organ Transplantation

Muskan Agarwal[1] · **Brandon Nokes**[2] · **Janis E. Blair**[3]

Accepted: 20 September 2021 / Published online: 7 October 2021

Abstract

Purpose of Review This review discusses the epidemiology, microbiology and pathogenesis, prevention, diagnosis, and treatment of coccidioidomycosis in solid organ transplant recipients.

Recent Findings Coccidioidomycosis is associated with a high mortality in solid organ transplant recipients than in immunocompetent individuals. Within the endemic area, strategies to reduce the incidence and mortality among solid organ transplant recipients include pretransplantation screening and treatment of coccidioidomycosis among donors and recipients, use of universal azole prophylaxis after transplantation, and more aggressive treatment of asymptomatic or primary pulmonary coccidioidomycosis after transplantation.

Summary Coccidioidomycosis is an endemic infection in the southwestern United States that is associated with high rates of dissemination and mortality among solid organ transplant recipients. Patients can acquire coccidioidomycosis after transplantation via primary infection after transplantation, reactivation of prior infection, or infection acquired from the transplanted organ. Although some solid organ transplant recipients with coccidioidomycosis may be asymptomatic, in general, solid organ transplant recipients have more severe disease and a higher mortality rate than immunocompetent persons. Various strategies have been used to reduce the incidence and mortality among solid organ transplant recipients. Fluconazole is commonly used as the first-line treatment of asymptomatic or primary pulmonary coccidioidomycosis, but other azole therapy may be useful in patients intolerant to fluconazole. In patients with rapidly progressive coccidioidomycosis, amphotericin B is often used first, followed by fluconazole.

Keywords Coccidioidomycosis · Solid organ transplant · Epidemiology · Immunology · Pathogenesis · Prophylaxis · Treatment

Abbreviations

EIA	Enzyme-linked immunosorbent assay
CF	Complement fixation
ID	Immunodiffusion
IgM	Immunoglobulin M
IgG	Immunoglobulin G
ATS	American Thoracic Society
IDSA	The Infectious Disease Society of America
AST	American Society of Transplantation
CDC	Centers of Disease Control and Prevention
HIV	Human immunodeficiency virus

Introduction

Coccidioidomycosis is an endemic fungal infection primarily in the southwestern United States that has a high mortality rate among solid organ transplant recipients [1, 2]. As domestic and international travel have become more common, solid organ transplant recipients living in non-endemic areas have been found to have coccidioidomycosis. Therefore, it is important for physicians practicing in endemic and non-endemic areas to be aware of the different diagnostic modalities and treatment options for coccidioidomycosis in solid organ transplant recipients. This paper will discuss the epidemiology, pathogenesis, diagnosis, prevention, and

This article is part of the Topical Collection on *Fungal Infections in Transplantation*

✉ Janis E. Blair
Blair.Janis@mayo.edu

[1] Department of Medicine, Mayo Clinic in Arizona, Phoenix, AZ, USA

[2] Division of Pulmonary, Critical Care, Sleep Medicine, and Physiology, University of California San Diego, San Diego, CA, USA

[3] Division of Infectious Diseases, Mayo Clinic in Arizona, Phoenix, AZ, USA

treatment of coccidioidomycosis in patients with solid organ transplants.

Epidemiology

Coccidioidomycosis is a fungal infection endemic to the southwestern United States, Washington, Mexico, and parts of Central and South America [3]. In 2019, 18,407 new cases of coccidioidomycosis were reported to the Centers of Disease Control and Prevention (CDC). The highest incidence of coccidioidomycosis cases was reported in Arizona, which accounted for 56% of all new cases reported in the USA. Arizona reported 10,359 new cases (approximately 142 per 100,000). Following Arizona, California accounted for 40% of all the new cases, with 7408 new cases (approximately 19 per 100,000). All other states each accounted for < 1% of the new coccidioidomycosis cases in the USA. California, New Mexico, and Nevada had the third and fourth highest incidences of coccidioidomycosis, accounting for 0.9% (164 cases or approximately 8 per 100,000) and 0.6% (117 cases, 0.6%, 4 per 100,000) of the cases, respectively. All other states combined had less than 100 new cases of coccidioidomycosis [4].

The incidence of coccidioidomycosis in solid organ transplant patients largely depends on location. Because Arizona has the largest population burden of coccidioidomycosis [4], Arizona transplant recipients may have the highest risk of coccidioidomycosis after solid organ transplantation. Early studies in Arizona showed an incidence of 4–8% [5] of coccidioidomycosis in solid organ transplant patients, while early studies in California showed an incidence of 0.59% [6]. Although the overall incidence of coccidioidomycosis increased by 1–2% or 1000–3000 cases every year [4], the incidence of coccidioidomycosis among solid organ transplant patients has decreased with increasing use of fluconazole prophylaxis, and in Arizona specifically, the incidence of coccidioidomycosis among solid organ transplant patients decreased to 1–3% [7–9].

Risk factors for coccidioidomycoses in solid organ transplant recipients include a recent history of coccidioidomycosis or positive serology before transplantation, immunosuppression [10], and treatment of acute rejection [5]. Concurrent immunosuppressing diseases such as diabetes [11, 12], HIV [13–15], and malignancy [16] also increase the risk of coccidioidomycosis, and risk factors for severe or disseminated disease among immunocompetent individuals include tobacco use [16], pregnancy, low income, black race, and older age [17]; however, whether these comorbid illnesses or risk factors further increase the risk among transplant recipients is not known.

Microbiology and Pathogenesis

Coccidioidomycosis is a fungal infection caused by the genus *Coccidioides*, which consists of *Coccidioides immitis* and *Coccidioides posadasii*. The two species of *Coccidioides* are clinically indistinguishable, and so, they are often referred to by their genus, *Coccidioides*. *Coccidioides* lives in the top layers of desert soil as mycelium. As it matures, it disarticulates into smaller, 2–4 μm in diameter, arthroconidia [18]. The small arthroconidia are easily aerosolized when soil is disrupted and can be inhaled. Primary coccidioidomycosis infection is caused by the inhalation of arthroconidia. Once in the lungs, arthroconidia transform into mature spherules. The mature spherules release thousands of endospores that can cause local or disseminated infection (Fig. 1). The cycle repeats as the endospores transform into mature spherules and release thousands of more endospores [18–20].

In immunocompetent individuals, the innate and adaptive immune systems are typically successful in controlling coccidioidal infections. Most cases of coccidioidomycosis are asymptomatic (60%) [21] and are limited to the respiratory tract (95%) [22]. As such, coccidioidomycosis in immunocompetent individuals are typically a self-limited disease [21]. In patients with solid organ transplantation, however, rates of dissemination and mortality can be as high as up to 72–75% and 50–60%, respectively, when prophylactic fluconazole is not used.

Multiple arms of the innate and adaptive immune response are involved in quelling coccidioidal infections [23]. Phagocytic cells in the innate immune system engulf arthroconidia, endospores, and spherule initials, but these

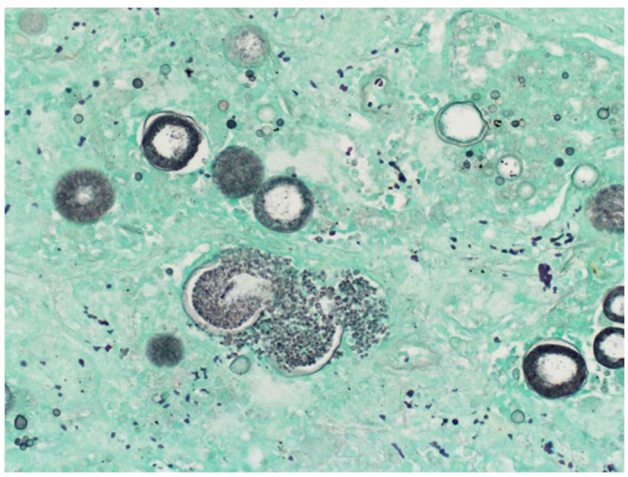

Fig. 1 GMS stain 200X, lung tissue with spherules (arrows), and endospores (arrowheads). Image courtesy of Brandon Larsen, MD PhD

phagocytes are too small to engulf the larger, mature spherules. The adaptive immune system is critical for control of coccidioidomycosis infection [23–25]. Each of the 4 classes of pattern recognition receptors, the IL12 receptor axis, CD4, CD8, Th17, monocytic priming by dendritic cells, and phagocytic activity from macrophage and neutrophils are all important in the immunologic response to coccidioidomycosis[26]. CD8 cells aid coccidioidal adaptive responses, and although both immunoglobulin M and G appear during active coccidioidomycosis infections, their importance in combatting coccidioidal infections is less clear [25]. With the exception of pattern recognition receptors, each of these arms of the immune system is hindered amidst common post-transplant immunosuppressive regimens. Tapering antirejection medications improves delayed-type hypersensitivity in transplanted patients [27], and is an adjunctive treatment strategy in achieving control of coccidioidomycosis [28].

There are three major mechanisms through which solid organ transplant recipients acquire coccidioidomycosis: primary infection after transplantation, reactivation of prior infection, or infection acquired from the transplanted organ.

Clinical Manifestations

Of the patients who develop coccidioidomycosis after solid organ transplantation, 70% typically develop coccidioidomycosis within the first year [5], likely reflecting higher levels of antirejection treatments. Coccidioidomycosis exists in a spectrum of disease. Similar to immunocompetent patients, some patients with solid organ transplants are asymptomatic and are found to be seropositive on routine screening. One study showed that 27% of solid organ transplant patients with coccidiomycosis were asymptomatic and were found to have positive serology on routine testing [7].

Symptomatic coccidioidomycosis predominantly presents as pulmonary coccidioidomycosis in transplant and non-transplant patients. Common symptoms of pulmonary coccidioidomycosis include fever, cough, and pleuritic chest pain. However, transplant patients have a greater propensity to develop disseminated coccidioidomycosis. Early studies in Arizona showed an incidence of 4–8% [5] of coccidioidomycosis in solid organ transplant patients, with a rate of dissemination of 72–75% [1, 2] and mortality of 50–62% [1, 2]. With the increasing use of prophylactic fluconazole, more recent studies in Arizona show a lower incidence of coccidioidomycosis in solid organ transplant patients (1–3% [7–9]) with a dissemination rate of 33% and mortality of 33% [9].

Disseminated coccidioidomycosis can be identified anywhere in the body and does not always include pulmonary disease. A review of 38 transplant recipients with disseminated coccidioidomycosis showed that 14 patients (37%) had no evidence of pulmonary disease. The most common site of dissemination is the central nervous system; of the 38, 10 patients (26%) developed meningitis and 4 patients (10%) developed brain lesions, including abscesses [5, 29, 30]. Other common areas of dissemination include the spleen (9 patients, 24%), liver (7 patients, 18%) [31], genitourinary areas (7 patients, 18%) [32], skin (6 patients, 16%) [33–35], joints (6 patients, 16%) [31], thyroid (5 patients, 13%) [36], and the pancreas (3 patients, 8%) [5]. Coccidioidomycosis also infects lymph nodes, kidneys, adrenal glands, bones/bone marrow [36], colon, heart, peritoneum, choroid (eye), and parathyroid gland [5].

Diagnosis

Clinical symptoms and history of travel to or residence within endemic areas help suggest an active coccidioidal infection. However, the final diagnosis relies on laboratory testing. Clinical specimens that demonstrate spherules or grow *Coccidioides* sp. are diagnostic. In many situations, however, such testing requires an invasive test. Serology is a common adjunctive testing strategy. As physicians order and interpret the different diagnostic modalities available, they should be aware of the sensitivities and specificities of these tests in solid organ transplant recipients.

Transplant patients are less likely to test positive on serologic testing as they are less likely to mount a detectable immunological response to coccidioidomycosis. Although 95% of immunocompetent patients with clinical coccidioidomycosis test positive via serological testing (enzyme-linked immunosorbent assay [EIA] IgG or IgM, complement fixation [CF], or immunodiffusion [ID] IgG or IgM), only 71–77% of solid organ transplant recipients with clinical coccidioidomycosis tested positive via serological testing [37, 38]. One institution in an endemic area reported the positive rates of various tests among twenty-seven transplant recipients with newly acquired symptomatic coccidioidomycosis. Patients were tested for coccidioidomycosis at the onset of symptoms and 1 month after the onset of symptoms, and in all cases, the sensitivities of the serologies increased at the 1-month follow-up testing (Table 1) [38]. Although the sensitivities of the individual serological tests are low (most are < 50%), collectively, the sensitivity increases to 77% (at the onset of symptoms) and 92% (1 month after the onset of symptoms) (Table 1) [38]. Therefore, the American Thoracic Society (ATS) recommends using more than one diagnostic modality in the diagnosis of coccidioidomycosis. Table 2 shows that non-serological testing for coccidioidomycosis also have low sensitivities (< 60%). However, the sample size for the testing modalities in Table 2 is small [38].

Table 1 Summary of serological test results in 27 solid organ transplant patients with active coccidioidomycosis

Type of test	No. of patients positive/no. tested (%)	
	First test at the onset of symptoms	Second test one month from the onset of symptoms
EIA		
IgM	7/25 (28%)	8/25 (32%)
IgG	14/25 (56%)	16/25 (64%)
ID		
IgM	2/10 (20%)	7/24 (29%)
IgG	9/24 (38%)	9/24 (38%)
CF ≥ 1:2	7/25 (28%)	9/25 (36%)
Any positive serology	20/26 (77%)	24/26 (92%)

Table was adapted from "The Utility of Diagnostic Testing for Active Coccidioidomycosis in Solid Organ Transplant Recipients" by Mendoza et. Al. with permission

Table was adapted from "The Utility of Diagnostic Testing for Active Coccidioidomycosis in Solid Organ Transplant Recipients" by Mendoza et al. with permission

Table 2 Summary of non-serological test results in 27 solid organ transplant patients with active coccidioidomycosis

Type of test	No. of patients positive/no. tested (%)
Culture	
Respiratory specimen	9/17 (53%)
Expectorated sputum	3/7 (43%)
Bronchial washings	3/3 (100%)
Bronchioalveolar lavage specimens	3/5 (60%)
Endotracheal cultures	0/1 (0)
Protected catheter brushing	0/1 (0)
Tissue biopsy or swab	4/7 (57%)
Pleural fluid	½ (50%)
Any positive culture	14/26 (54%)
Other tests	
Cytology	2/10 (20%)
Tissue pathology	9/24 (38%)
Rapid PCR	7/25 (28%)

Table was adapted from "The Utility of Diagnostic Testing for Active Coccidioidomycosis in Solid Organ Transplant Recipients" by Mendoza et. Al. with permission

Coccidioides antigen testing and the serum (1,3)-beta-D-glucan tests may in theory be helpful in immunosuppressed patients as they test for the fungal antigen, rather than the patient's immunological response to the organism (via IgG or IgM) [39]. However, the utility of these tests has not been studied systematically in a cohort of solid organ transplant recipients with coccidioidomycosis. Though data is scant, ATS recommends considering the use of *Coccidioides* antigen testing in immunocompromised patients [39]. The sensitivity of the new *Coccidioides* antigen EIA test among 18 immunosuppressed patients was 77%. Two of 2 solid organ transplant recipients with coccidioidomycosis tested positive by both *Coccidioides* antigen tests available. The specificity of the *Coccidioides* antigen EIA has not been tested in the transplant population; however, in the general population without other endemic mycosis, the specificity is 99.3%, and in the general population with other endemic mycosis, it is 96.4% [40, 41]. The (1,3)-beta-D-glucan test, when using a cutoff value of ≥ 80 pg/ml, has a sensitivity of 43.9% and specificity of 91.1% [42] in the general population.

Occasionally, pathology specimens are needed to obtain a diagnosis (Fig. 1), but this is the least common diagnostic modality owing to its invasive nature. Imaging can aid in detecting coccidioidomycosis. One study showed that 16 of 25 patients (64%) had chest X-ray abnormalities at the onset of symptoms [38]. The abnormalities included consolidations, pleural effusions, multifocal nodules, cavitary lesions, and hilar adenopathy [31, 31]. Repeat chest X-rays in 1 week showed increased sensitivity (21 of 35 patients, 84%). Chest computed tomography identified abnormalities in 19 of 22 (86%) patients at the onset of symptoms but repeat imaging did not identify new individuals with radiological abnormalities [38]. The "classic" coccidioidomycosis imaging shows cavitary lesions and nodules (Fig. 2), but the radiographic findings in pulmonary coccidioidomycosis are highly variable[43].

Prevention of Coccidioidomycosis in Solid Organ Transplant Patients

Endemic Areas

Screening and Treatment Before Transplantation

Because patients with a history of coccidioidomycosis or positive serological testing prior to transplantation have a higher risk of developing complications from coccidioidomycosis after transplantation [5], it is paramount to identify and treat patients with active or latent coccidioidomycosis prior to transplantation. Different centers use different screening strategies. Kidney transplant patients at the University of California, Los Angeles, were screened for coccidioidomycosis prior to transplantation with EIA IgG and IgM antibodies [44]. At Mayo Clinic Arizona, all patients undergoing transplantation are screened for coccidioidomycosis through clinical history, serologic testing (EIA gG and IgM antibodies, ID IgG and IgM antibodies, and CF), and a chest radiograph. Because the sensitivities of individual tests are lower than the combined sensitivities of multiple modalities

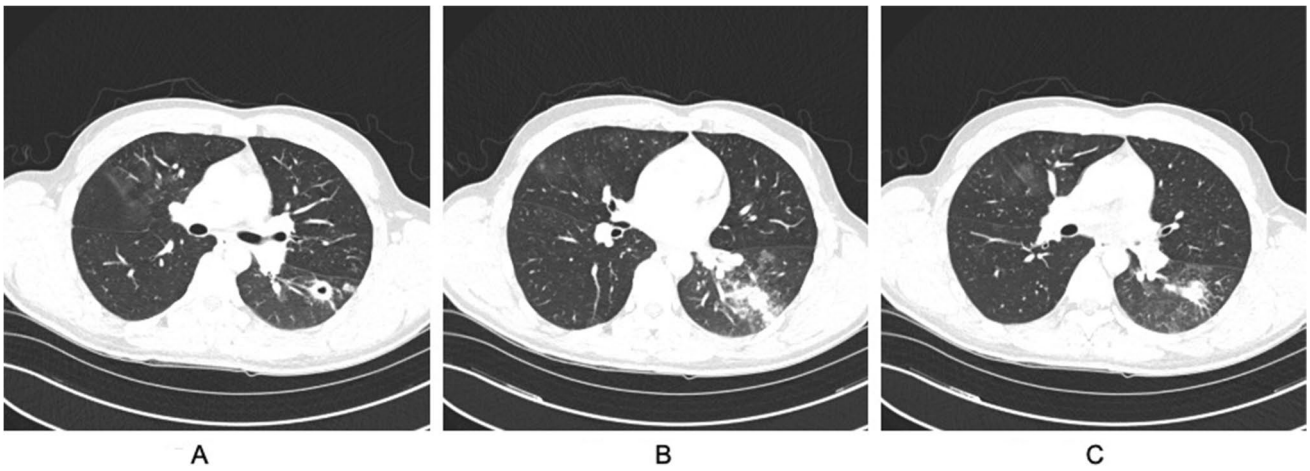

Fig. 2 CT chest, non-contrast. Dominant 1.9 cm cavitary nodule (panel **A**) in the left lower lobe with a nodular consolidation located immediately inferior (panels **B** & **C**), consistent with history of coccidioidomycosis

of diagnostic testing, combination serological testing (EIA IgG and IgM antibodies, ID IgG and IgM antibodies, and CF) and radiological testing may be beneficial in identifying patient who have active or latent coccidioidomycosis.

In patients who are found to have active or latent coccidioidomycosis, treatment with antifungal therapy to control the infection prior to transplantation is recommended, if clinically feasible, even if this treatment delays transplantation. At one institution, patients are treated with antifungal therapy for at least 6 months. Patients are monitored for symptomatic, serologic, and radiological (chest X-ray) improvement. Additionally, CF titers are monitored, and patients are treated until the titers are equivalent or below 1:2 or 1:4 on two separate occasions and have demonstrated at least 2-dilution drop after the initiation of antifungal therapy. Once the patient clinically and radiologically improves, meets the decreasing titers criteria, and has completed at least 6 months of antifungal therapy, the patient is then reassessed by an infectious disease specialist for clearance to undertake transplantation while continuing antifungal therapy. In one institution, seronegative patients receive fluconazole 200 mg daily for 1 year after transplantation to prevent new coccidioidal infections. However, seropositive recipients receive fluconazole 400 mg daily for at least 1 year to prevent relapsed coccidioidomycosis. An infectious disease specialist determines whether continued fluconazole would benefit the patient [22].

Candidates for Antifungal Prophylaxis

The Infectious Disease Society of America (IDSA) recommends antifungal prophylaxis for all transplant recipients living an endemic area [28]. A study of Arizona liver transplant recipients evaluated targeted antifungal prophylaxis (fluconazole prophylaxis given only to recipients with evidence of coccidioidomycosis) vs universal antifungal prophylaxis. In the targeted prophylaxis cohort, 8 of 349 patients (2.3%) developed asymptomatic seropositive coccidioidomycosis and 10 of 349 (2.9%) patients developed symptomatic coccidioidomycosis. Nine of 10 of the patients that developed symptomatic coccidioidomycosis did not have a history of coccidioidomycosis, and so had not received prophylactic fluconazole. In the universal prophylaxis group, 0 of 143 patients developed coccidioidomycosis [45]. Universal prophylaxis likely reduces incidence of coccidioidomycosis among transplant patients by preventing newly acquired coccidioidomycosis after transplantation, recrudescent infection, or infection via transplant.

Duration of Antifungal Prophylaxis

IDSA recommends azole prophylaxis for the duration of 6 to 12 months after transplantation [28]. A study of Arizona transplant recipients evaluated the duration of antifungal prophylaxis. A retrospective assessment of antifungal prophylaxis demonstrated that 6 of 134 (4.5%) patients who received antifungal prophylaxis for 1–2 months developed infection. By contrast, 0 of the 65 patients that received antifungal prophylaxis for at least 3 months developed coccidioidomycosis [9]. This study highlights that longer durations of antifungal prophylaxis help reduce the incidence of coccidioidomycosis among solid organ transplant patients. Because patients are given the highest amounts of immunosuppressive therapy in the first year, and because 70% of coccidioidomycosis cases occur within the first year of transplantation, it is reasonable to continue antifungal prophylaxis for 1 year [5]. The regimen of fluconazole 200 mg daily for 6–12 months following transplantation has been

studied and has been shown to reduce the incidence of coccidioidomycosis [22, 45, 46].

There have been many reports of reactivated coccidioidomycosis in patients with primary coccidioidomycosis who discontinued antifungal prophylaxis after transplantation [2, 28, 47], and based on these data, IDSA recommends lifelong antifungal prophylaxis in patients with primary coccidioidomycosis after transplantation. However, this is an area that requires further study.

Non-endemic Areas

Patients living in non-endemic areas are at a low risk of acquiring coccidioidomycosis. As such, the American Society of Transplantation (AST) only recommends screening in patients with a history of history of travel to or residence in an endemic area [48]. If the patient is found to have active or latent coccidioidomycosis, treatment and evaluation by an infectious disease specialist are recommended prior to transplantation. For patients who re-locate to an endemic area after transplantation, some experts recommend prophylaxis with fluconazole 200 mg daily for lung transplant recipients, but not other solid organ recipients [22].

Donor-Derived Solid Organ Transplantation

Donor

Donors with asymptomatic coccidioidomycosis or history of treated coccidioidomycosis may still harbor viable organisms in granulomas. Transplantation of an organ with these viable organisms may result in transmission of coccidioidomycosis from donor to recipient. As the lung is the most commonly infected organ in patients with coccidioidomycosis, lung transplant recipients may be at the highest risk of donor derived coccidioidomycosis. However, recipients with heart, liver, and kidney transplants have also been found to have donor-derived coccidioidomycosis. Some of these donors have a known history of disseminated coccidioidomycosis, while other donors did not [49, 50].

A study in Arizona showed that approximately 2.1% of prospective kidney and liver transplant donors were seropositive for coccidioidomycosis [51]. Donor-derived coccidioidomycosis is associated with a high rate of transmission (43–61%) and mortality (28–38%) in patients who do not receive fluconazole prophylaxis or early treatment of coccidioidomycosis [49, 52]. However, the transmission rate can be as low as 0% in non-lung transplant recipients who receive antifungal prophylaxis [51]. In most cases (71–83%) of donor-derived coccidioidomycosis, the donor has a known history of travel or residence in an endemic area [49].

Because of the high mortality associated with donor-derived coccidioidomycosis, AST recommends screening all live donors in endemic areas for active coccidioidomycosis and recommends treatment prior to transplantation. Screening prior to organ procurement includes serology (EIA, ID, and CF) and imaging. Cultures of respiratory secretions or tissue specimens may also be obtained based on the results of serology and imaging. Complement fixation titers greater than 1:16 in immunocompetent individuals may be associated with disseminated disease [53] and warrant further evaluation for extrapulmonary disease. If a patient is found to have active or latent coccidioidomycosis, AST recommends resolution of infection prior to organ procurement. Resolution of disease is defined as improvement in clinical symptoms, improvement in radiographic abnormalities, and a reduction of complement fixation titers by fourfold [54].

Recipients

AST recommends pre-transplant coccidioidomycosis screening in recipients with donors with a history of travel to or residence in an endemic area. This would serve as a baseline comparison if the recipient developed symptoms later. If a donor is found to have active or latent coccidioidomycosis, the physicians of the recipients should be informed. ATS recommends prophylaxis with fluconazole 400 mg daily in these recipients given the high mortality associated with donor transmitted coccidioidomycosis. Because lung transplant recipients may be at a higher risk of transmission, lifelong fluconazole 400 mg daily prophylaxis is recommended for lung transplant recipients with positive donors. For non-lung transplant recipients, lifelong treatment with fluconazole 400 mg daily is recommended when the donor has disseminated coccidioidomycosis. If the donor did not have disseminated coccidioidomycosis, reduction or discontinuation of fluconazole prophylaxis after 1 year is recommended [22, 54].

Treatment

The ATS and IDSA have recommendations on the treatment of coccidioidomycosis in solid organ transplant patients. Both societies recommend the treatment of disseminated coccidioidomycosis. For primary pulmonary coccidioidomycosis in solid organ transplants, ATS recommends consideration of treatment, while the IDSA simply recommends treatment [28, 55].

Per IDSA, all solid organ transplant patients with coccidioidomycosis should be treated with antifungal therapy, regardless of severity of disease. In clinically stable patients with a normal renal function, IDSA prefers fluconazole 400 mg daily for 3–6 months as the initial treatment strategy [28]. ATS offers itraconazole 200 mg BID for 3–6 months as an alternative first-line treatment for primary pulmonary coccidioidomycosis in immunosuppressed patients [55].

Patients with refractory disease or intolerance to fluconazole can be treated with posaconazole or voriconazole [45, 56, 57].

Azoles have been shown to be effective in the treatment of coccidioidomycosis and have a lower side effect profile compared to amphotericin B, and so they are the first-line treatment in clinically stable coccidioidomycosis. However, amphotericin B has a perceived faster onset of action and so it is used as first-line therapy in rapidly progressing coccidioidomycosis [58]. Once the patient has clinically stabilized, a less toxic drug, such as fluconazole, can be initiated. Therefore, in patients with disseminated disease or rapidly progressing pulmonary disease, IDSA recommends treatment with amphotericin B until the patient has stabilized, and then fluconazole is recommended [28].

In solid organ transplant patients with clinically stable coccidioidomycosis, per IDSA, reduction of immunosuppression is not necessary. However, in rapidly progressing or disseminated disease, reduction of immunosuppression is recommended to help patients mount an immune response [28, 59].

When azole therapy is initiated, all patients may require dose reduction of immunosuppressive agents due to drug-drug interactions. All azoles inhibit CYP3A4, which is responsible for metabolizing many immunosuppressive agents (cyclosporine, tacrolimus, sirolimus, and everolimus). Fluconazole, which has the lowest potency for CYP3A4, has been shown to increase sirolimus levels in transplant patients in a dose dependent manner [60]. Therefore, careful monitoring of immunosuppressive medication levels is warranted in transplant patients on azole therapy.

Conclusions

Although great progress has been made in the field of identifying, preventing, and treating coccidioidomycosis in the transplant recipient, much work remains. With a host of diagnostic antigen-based testing in development, we anticipate optimizing our diagnostic armamentarium.

In addition, the immunology of coccidioidomycosis and the transplantation recipient is still unfolding; numerous questions exist: can patients with prior quiescent coccidioidomycosis regain their immunity to this organism following transplantation? Do all transplant recipients whose course is complicated by coccidioidomycosis require lifelong antifungal prophylaxis, or can we identify a cohort whose prophylaxis can safely be withdrawn? Will future vaccines replace antifungal prophylaxis strategies? Future study will help us elucidate answers to these and other questions.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Cohen IM, et al. Coccidioidomycosis in renal replacement therapy. Arch Intern Med. 1982;142(3):489–94.
2. Holt CD, et al. Coccidioidomycosis in liver transplant patients. Clin Infect Dis. 1997;24(2):216–21.
3. Valley Fever Maps. Available from: https://www.cdc.gov/fungal/diseases/coccidioidomycosis/maps.html.
4. 2019 Annual Tables of Infectious Disease Data. Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System, CDC Division of Health Informatics and Surveillance: Atlanta.
5. Blair JE, Logan JL. Coccidioidomycosis in solid organ transplantation. Clin Infect Dis. 2001;33(9):1536–44.
6. Blair JE. Coccidioidomycosis in liver transplantation. Liver Transpl. 2006;12(1):31–9.
7. Blair JE. Coccidioidomycosis in patients who have undergone transplantation. Ann N Y Acad Sci. 2007;1111:365–76.
8. Blair JE, Douglas DD, Mulligan DC. Early results of targeted prophylaxis for coccidioidomycosis in patients undergoing orthotopic liver transplantation within an endemic area. Transpl Infect Dis. 2003;5(1):3–8.
9. Braddy CM, Heilman RL, Blair JE. Coccidioidomycosis after renal transplantation in an endemic area. Am J Transplant. 2006;6(2):340–5.
10. Bergstrom L, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004;50(6):1959–66.
11. Santelli AC, Blair JE, Roust LR. Coccidioidomycosis in patients with diabetes mellitus. Am J Med. 2006;119(11):964–9.
12. Wheeler C, Lucas KD, Mohle-Boetani JC. Rates and risk factors for Coccidioidomycosis among prison inmates, California, USA, 2011. Emerg Infect Dis. 2015;21(1):70–5.
13. Ampel NM, Dols CL, Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. Am J Med. 1993;94(3):235–40.
14. Fish DG, et al. Coccidioidomycosis during human immunodeficiency virus infection. A review of 77 patients. Medicine (Baltimore). 1990;69(6):384–91.
15. Woods CW, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994–1997: incidence, risk factors, and prevention. J Infect Dis. 2000;181(4):1428–34.
16. Leake JA, et al. Risk factors for acute symptomatic coccidioidomycosis among elderly persons in Arizona, 1996–1997. J Infect Dis. 2000;181(4):1435–40.
17. Rosenstein NE, et al. Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern County, California, 1995–1996. Clin Infect Dis. 2001;32(5):708–14.

18. Prevention, C.f.D.C.a., Biology of Coccidioidomycosis. https://www.cdc.gov/fungal/diseases/coccidioidomycosis/pdf/coccidiomycosis-lifecycle508c.pdf.
19. Stevens DA. Coccidioidomycosis. N Engl J Med. 1995;332(16):1077–82.
20. Hector RF, Laniado-Laborin R. Coccidioidomycosis–a fungal disease of the Americas. PLoS Med. 2005;2(1):e2.
21. Smith CE, Beard RR, et al. Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases. Am J Public Health Nations Health. 1946;36(12):1394–402.
22. Nokes BT, Blair JE. Coccidioidomycosis in transplantation. In: Morris MI, Kotton CN, Wolfe C, editors. emerging transplant infections: clinical challenges and implications. Cham: Springer International Publishing; 2020. p. 1–18.
23. Hung CY, et al. A review of innate and adaptive immunity to coccidioidomycosis. Med Mycol. 2019;57(Supplement_1):S85–92.
24. Diep AL and Hoyer KK. Host Response to coccidioides infection: fungal immunity. Front Cell Infect Microbiol. 2020;10(692).
25. Castro-Lopez N and Hung CY. Immune response to coccidioidomycosis and the development of a vaccine. Microorganisms. 2017;5(1).
26. Ampel NM. The complex immunology of human coccidioidomycosis. Ann N Y Acad Sci. 2007;1111:245–58.
27. van Besouw NM, et al. Tapering immunosuppressive therapy significantly improves in vivo cutaneous delayed type hypersensitivity responses. Transpl Immunol. 2008;19(3–4):229–34.
28. Galgiani JN, et al. 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis. Clin Infect Dis. 2016;63(6):e112–46.
29. Kotton CN, et al. Coccidioidal meningitis after liver transplantation in a nonendemic region: a case report. Transplantation. 2006;81(1):132–4.
30. Carvalho C, et al. Cerebral coccidioidomycosis after renal transplantation in a non-endemic area. Transpl Infect Dis. 2010;12(2):151–4.
31. Yoshino MT, Hillman BJ, Galgiani JN. Coccidioidomycosis in renal dialysis and transplant patients: radiologic findings in 30 patients. AJR Am J Roentgenol. 1987;149(5):989–92.
32. Chandler JW, Kalina RE, Milam DF. Coccidioidal choroiditis following renal transplantation. Am J Ophthalmol. 1972;74(6):1080–5.
33. Diaz MA et al. Coccidioides in lung transplant: case report. BMJ Case Rep. 2020;13(4).
34. Vartivarian SE, Coudron PE, Markowitz SM. Disseminated coccidioidomycosis. Unusual manifestations in a cardiac transplantation patient. Am J Med. 1987;83(5):949–52.
35. Theodoropoulos N, Angarone M. Photo quiz. Lip lesion in a solid organ transplant recipient. Clin Infect Dis. 2012;54(9):1332, 1373–13321374.
36. McAninch EA, et al. Coccidiomycosis thyroiditis in an immunocompromised host post-transplant: case report and literature review. J Clin Endocrinol Metab. 2014;99(5):1537–42.
37. Blair JE, et al. Serologic testing for symptomatic coccidioidomycosis in immunocompetent and immunosuppressed hosts. Mycopathologia. 2006;162(5):317–24.
38. Mendoza N, Blair JE. The utility of diagnostic testing for active coccidioidomycosis in solid organ transplant recipients. Am J Transplant. 2013;13(4):1034–9.
39. Hage CA, et al. Microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200(5):535–50.
40. Kuberski T, et al. Diagnosis of coccidioidomycosis by antigen detection using cross-reaction with a Histoplasma antigen. Clin Infect Dis. 2007;44(5):e50–4.
41. Durkin M, et al. Diagnosis of Coccidioidomycosis with use of the coccidioides antigen enzyme immunoassay. Clin Infect Dis. 2008;47(8):e69–73.
42. Thompson GR 3rd, et al. Serum (1->3)-β-D-glucan measurement in coccidioidomycosis. J Clin Microbiol. 2012;50(9):3060–2.
43. Jude CM, et al. Pulmonary coccidioidomycosis: pictorial review of chest radiographic and CT findings. Radiographics. 2014;34(4):912–25.
44. Phonphok K, et al. Screening Coccidioides serology in kidney transplant recipients: a 10-year cross-sectional analysis. Transpl Infect Dis. 2018;20(5):e12932.
45. Kahn A, Carey EJ, Blair JE. Universal fungal prophylaxis and risk of coccidioidomycosis in liver transplant recipients living in an endemic area. Liver Transpl. 2015;21(3):353–61.
46.• Asbury K, et al. De novo coccidioidomycosis among solid organ transplant recipients 1 or more years after transplant. Am J Transplant. 2019;19(9):2517–24. **Incidence and presentation of de novo Coccidioidomycosis 1 year after transplantation**.
47. Blair JE. Coccidioidal pneumonia, arthritis, and soft-tissue infection after kidney transplantation. Transpl Infect Dis. 2004;6(2):74–6.
48.• Miller R, Assi M. Endemic fungal infections in solid organ transplant recipients-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13553. **American Society of Transplantation recommendations on diagnosis, prevention, and treatment of Coccidioidomycosis in solid organ transplant recipients**.
49. Kusne S, et al. Coccidioidomycosis transmission through organ transplantation: a report of the OPTN Ad Hoc Disease Transmission Advisory Committee. Am J Transplant. 2016;16(12):3562–7.
50. Nelson JK, et al. Donor-derived Coccidioides immitis endocarditis and disseminated infection in the setting of solid organ transplantation. Open Forum Infect Dis. 2016;3(3):ofw086.
51. Blair JE, Mulligan DC. Coccidioidomycosis in healthy persons evaluated for liver or kidney donation. Transpl Infect Dis. 2007;9(1):78–82.
52. Dierberg KL, et al. Donor-derived organ transplant transmission of coccidioidomycosis. Transpl Infect Dis. 2012;14(3):300–4.
53. Pappagianis D, Zimmer BL. Serology of coccidioidomycosis. Clin Microbiol Rev. 1990;3(3):247–68.
54. Singh N, et al. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. Am J Transplant. 2012;12(9):2414–28.
55. Limper AH, et al. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011;183(1):96–128.
56. Kim MM, et al. Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. Clin Infect Dis. 2011;53(11):1060–6.
57. Puing AG, et al. Simultaneous coccidioidomycosis and phaeohyphomycosis in a kidney transplant recipient: a case report and literature review. Transpl Infect Dis. 2020;22(6):e13365.
58. Galgiani JN. Coccidioidomycosis. Curr Clin Top Infect Dis. 1997;17:188–204.
59. Kaplan JE, Zoschke D, Kisch AL. Withdrawal of immunosuppresive agents in the treatment of disseminated coccidioidomycosis. Am J Med. 1980;68(4):624–8.
60. Cervelli MJ. Fluconazole-sirolimus drug interaction. Transplantation. 2002;74(10):1477–8.