15 Prevention and Treatment of Other Opportunistic Infections: Nocardiosis, Toxoplasmosis, Chagas and Pneumocystis Disease

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15.1 Nocardiosis

15.1.1 Introduction

Nocardiosis is an uncommon opportunistic infection that primarily affects immunocompromised hosts with defects in cell-mediated immunity such as solid organ transplant recipients [1]. There are several species that can cause disease depending on geography. These include *N. nova*, *N. brasiliensis*, and *N. farcinica* [2]. Two of the key features that are characteristic of *Nocardia* spp. include (1) the ability to cause disseminated disease (the lung, central nervous system, and skin are common sites) and (2) a high probability of relapse or recurrent disease once treated. Among solid organ transplant recipients, the risk of infection is highest in the first year following transplantation. Particular risk groups include those who have received glucocorticoid therapy, have high calcineurin inhibitor concentrations, and have had antecedent cytomegalovirus infection. Heart and lung transplant recipients are disproportionally represented among solid organ transplant recipients, but all solid organ transplant patients are at risk.

15.1.2 Clinical Presentation

Transplant patients often present non-specifically. A common presentation is the patient who gets evaluated for pulmonary nodules and other findings seen on chest imaging as

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part of a workup for fevers or can be incidentally found [3]. However as the "great imitator," *Nocardia* commonly affects other organ systems as well such as the central nervous system (brain abscess, meningitis) and skin (subcutaneous abscesses) [4]. One clinical pearl is that central nervous system disease is often asymptomatic. All transplant patients presenting with pulmonary or cutaneous disease should be evaluated clinically and/or radiologically for central nervous system disease.

15.1.3 Diagnosis

Nocardia is a gram-positive bacterium that is quite unusual in appearance. It is distinguished by its delicate filamentous gram-positive branching rods that appear almost fungal in morphology. It is weakly acid-fast in contrast to *Actinomyces* species which can have a similar appearance otherwise. It can be easily missed by non-experienced microbiologists. Clinicians with a high pretest probability should alert laboratory staff accordingly and order a modified acid-fast stain for BAL samples, abscess, and biopsy specimens. Newer diagnostic methods such as 16S ribosomal sequencing and other molecular methods are increasingly being used given the poor sensitivity of current methods. Given the wide variation in susceptibilities based on the specific species, we always recommend identification at the species level with susceptibility testing once empiric treatment has been started [5].

15.1.4 Treatment

The principles of treatment for infection with *Nocardia* in solid organ transplant recipients are as follows: (1) treat for a prolonged period in the order of 6–12 months given the tendency for *Nocardia* to relapse (a shorter course may be adequate if no CNS disease or if localized cutaneous disease but most treat for 12 months) [6]; (2) treat with dual therapy while awaiting susceptibilities, including one IV agent at least, while the patient is critically ill; (3) use TMP-SMX in the regimen if that option is available [7]; and (4) surgically drain if necessary. Given the multiple species and unpredictable susceptibilities, we request identification and susceptibility testing for all our isolates. For sick patients, we typically use a carbapenem and TMP-SMX empirically (Table 15.1). Other options before final susceptibilities are known include linezolid, minocycline, and amikacin.

15.1.5 Prevention

We do not currently recommend prophylaxis for *Nocardia* in at-risk patients such as solid organ transplant recipients. Interestingly, most of these patients are on

Table 15.1 Prevention and treatment regimens for nocardiosis, toxoplasmosis, Chagas disease, and *Pneumocystis*

	Prevention	Treatment[a]
Nocardiosis	None	Non-severe: TMP-SMX 15 mg/kg orally of the trimethoprim component in 3–4 divided doses Severe: TMP-SMX 15 mg/kg IV of the trimethoprim component in 3–4 divided doses *and* Amikacin 7.5 mg/kg IV every 12 h *or* Imipenem 500 mg IV every 6 h *or* Linezolid 600 mg IV/orally every 12 h
Toxoplasmosis	Primary prophylaxis First line: TMP-SMX 1 DS tablet (800 mg/160 mg) orally per day *or* TMP-SMX 1 DS tablet orally three times per week *or* TMP-SMX 1 SS tablet orally per day Second line: Dapsone 50 mg orally per day *and* Pyrimethamine 50 mg orally per week *and* Leucovorin 25 mg orally per week Third line: Atovaquone 1500 mg orally per day (with or without pyrimethamine 50 mg orally per week *and* Leucovorin 25 mg orally per week)	First line: Sulfadiazine 1000 mg orally four times per day (if ≥60 kg, 1500 mg four times per day) *and* Pyrimethamine 50 mg orally per day (if ≥60 kg, 75 mg per day), after a 200 mg loading dose *and* Leucovorin 10–25 mg orally per day Second line: Clindamycin 600 mg IV/orally four times per day *and* Pyrimethamine 50 mg orally per day (if ≥60 kg, 75 mg per day), after a 200 mg loading dose *and* Leucovorin 10–25 mg orally per day *or* TMP-SMX 5 mg/kg IV/orally of the trimethoprim component two times per day
Chagas disease		First line: Benznidazole 10 mg/kg orally per day in two divided doses for 60 days Second line: Nifurtimox 8–10 mg/kg orally per day in 3–4 divided doses for 90–120 days

(continued)

Table 15.1 (continued)

	Prevention	Treatment[a]
Pneumocystis	Primary prophylaxis First line: TMP-SMX 1 DS tablet (800 mg/160 mg) orally per day *or* TMP-SMX 1 DS tablet orally three times per week *or* TMP-SMX 1 SS tablet orally per day Second line: Dapsone 100 mg orally per day in 1–2 divided doses *or* Atovaquone 1500 mg orally per day *or* Dapsone 50 mg orally per day *and* Pyrimethamine 50 mg orally per week *and* Leucovorin 25 mg orally per week *or* Pentamidine 300 mg inhaled monthly	First line: TMP-SMX 15–20 mg/kg IV/orally of the trimethoprim component in 3–4 divided doses Second line: Clindamycin 900 mg IV three times per day (or 600 mg IV four times per day or 600 mg orally three times per day) *or* Primaquine 30 mg (base) orally per day *or* Pentamidine 4 mg/kg IV once daily Adjunctive glucocorticoids (if PaO2 < 70 mmHg) Prednisone 40 mg orally two times per day for 5 days, followed by 40 mg orally once daily for 5 days, followed by 20 mg orally once daily for 11 days

TMP-SMX trimethoprim-sulfamethoxazole, *DS* double-strength oral tablet, *SS* single-strength oral tablet
Amikacin not preferred in renal transplant recipients
[a]Adjust dose in renal impairment

TMP-SMX prophylaxis for *P. jirovecii* which should theoretically prevent *Nocardia* as well. However, this does not appear to provide complete benefit with several instances of breakthrough infection reported.

15.2 Toxoplasmosis

15.2.1 Introduction

Toxoplasmosis is a rare disease caused by *Toxoplasma gondii*, an intracellular parasite with a worldwide distribution. There are classic risks for infection such as eating raw or undercooked meat and cat exposure. However, because more than half of patients do not have identifiable risk factors, using epidemiologic features to stratify transplant donors at risk is not useful. Serology is used to define risk of disease transmission in transplant recipients. The highest risk of transmission is in the scenario where the organ of an exposed donor (D+) is placed in an unexposed (R−)

recipient. Among solid organ transplant recipients, the highest risk of disease is among heart transplant patients, as the *Toxoplasma* cysts are commonly found in muscle when infection occurs [8]. However, there is increasing recognition that D+ donors can also cause disease in non-heart R− recipients [9]. It is important for transplant professionals to know these risks and institute prophylaxis accordingly.

15.2.2 Clinical Presentation

Solid organ transplant recipients may develop disease in two scenarios: either as reactivation of old disease or in the setting of donor-derived infection. In most individuals, primary infection is asymptomatic or may be seen as patients presenting with lymphadenopathy, chorioretinitis, hepatitis, or flu-like symptoms (fever, headache, myalgias, malaise). In solid organ transplant recipients, reactivation may be seen as some of the symptoms in primary infection but in many cases with brain abscesses, encephalitis, myocarditis, rash, and widely disseminated disease [10].

15.2.3 Diagnosis

In the general population, *T. gondii* acute infection is diagnosed indirectly with serology. Following acute infection, *Toxoplasma*-specific IgM antibodies appear first, followed by IgG antibodies 2 weeks later. The *Toxoplasma*-specific IgG antibodies persist for life. Transplant and other immunocompromised patients may not be able to mount an antibody response rendering the serology test insensitive [11]. Although there are no standardized polymerase chain reaction (PCR) assays, commercially available PCR tests may be helpful for diagnosis of organ-specific disease (e.g., pneumonia, central nervous system, eye) in immunocompromised patients. Pathology on biopsy may be diagnostic if characteristic tachyzoites or cysts are seen.

15.2.4 Treatment

We usually treat up front with sulfadiazine and pyrimethamine (Table 15.1). Clindamycin and pyrimethamine is an alternative combination. In any pyrimethamine-based regimen, leucovorin is added to prevent bone marrow toxicity. The initial regimen is usually given for 6 weeks, followed by maintenance therapy which is usually the same drugs used for initial therapy but at lower doses.

15.2.5 Prevention

In general, heart transplant patients who are seronegative recipients of seropositive donors receive from 6 months to lifelong prophylaxis. There is limited data, but many centers opt to provide lifelong prophylaxis in this setting. Prophylaxis in

seronegative recipients from positive donors has now been expanded to non-heart solid organ recipients given several reports of donor-derived infections involving these organs [12]. Trimethoprim-sulfamethoxazole (TMP-SMX) is usually already given for the prevention of *Pneumocystis* pneumonia but is also highly effective for toxoplasmosis primary prophylaxis for the targeted high-risk D+R− population (Table 15.1). Most patients receive TMP-SMX. An alternative for primary prophylaxis is dapsone-pyrimethamine. There is less data for atovaquone, but this is also a potential option for patients intolerant to TMP-SMX or dapsone-pyrimethamine.

15.3 Chagas Disease (American Trypanosomiasis)

15.3.1 Introduction

Chagas disease is a vector-borne infection caused by *Trypanosoma cruzi* (a protozoan parasite) and is transmitted by the reduviid bug. These insects naturally occur only on the American continent. Outside the Americas, infected immigrants may transmit the infection acting as blood or organs donors. Infected mothers may vertically transmit the infection to their offspring, explaining infection occurring in people born from non-endemic areas. International travel (with extended stays in rural areas) is another way to acquire infection among people from non-endemic areas. Among transplant recipients, there are three ways we consider infection risk: (1) in patients who have end-stage cardiac disease due to Chagas disease and who need heart transplantation, (2) in those who have chronic Chagas infection who need a solid organ transplant for a non-Chagas reason, and (3) in those with donor-derived infection from a donor with chronic Chagas infection. Patients with chronic Chagasic cardiomyopathy with heart transplantation have survival rates better than patients who were transplanted because of other heart conditions. Heart, kidney, kidney-pancreas, and liver transplantation have been successfully performed in patients with chronic Chagas infection. Reactivation has been reported in 20–50% of kidney transplant recipients and in less than 20% of liver transplant recipients with Chagas disease [13]. Finally, with the proper molecular monitoring protocol in place, it is safe to accept non-heart organs from donors with chronic *T. cruzi* infection [14].

15.3.2 Clinical Presentation

In humans, the disease has an acute and a chronic phase. The acute stage may be asymptomatic, or it may present only mild clinical symptoms such as a malaise, fever, anorexia, and lymphadenopathy, which usually resolve spontaneously in 8–12 weeks. In most cases, the immune response controls the parasitic infection, but (in the absence of specific anti-parasitic drug treatment) is ineffective to clear it. The infection results in clinical latency (chronic or indeterminate phase), which may last 10–30 years or lifelong. The infection is evident only by positive serology, with extremely low and intermittent parasitemia. After several years of

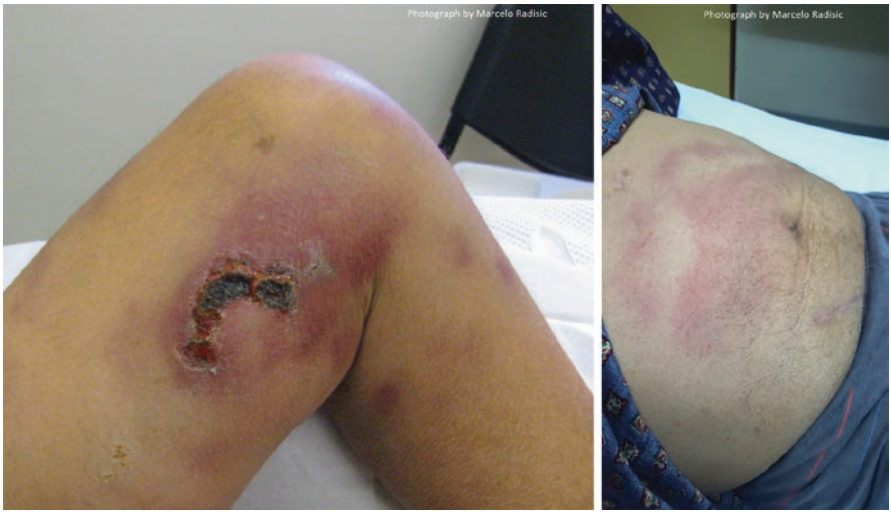

Fig. 15.1 Skin lesions caused by Chagas reactivation in kidney transplant patients

asymptomatic disease, progression to symptomatic Chagas may be observed in 20–30% of infected patients who may develop Chagasic cardiomyopathy (90%) and, less frequently, gastrointestinal (15–20%) and peripheral nervous system disease (10%) [13].

In SOT recipients, most reactivated cases have parasitemia with positive PCR or/and Strout tests (see below) but with no clinical manifestations of disease. Less frequently, the patient may present with fever and skin lesions (usually very painful solitary or multiple subcutaneous nodules and rarely panniculitis and ulcers) (Fig. 15.1). Skin lesions are predominantly located in the limbs. Severe disease may sporadically occur (usually with a high level of parasitemia), presenting as Chagasic meningoencephalitis, tumorlike brain lesions (Chagomas), and acute myocarditis. In heart transplant recipients, Chagasic myocarditis is more frequent than in non-heart transplant recipients and must be differentiated from rejection. The risk of Chagas reactivation seems to be related to the amount of immunosuppression. Possible risk factors for reactivation are mycophenolate mofetil use for maintenance immunosuppression, rejection episodes, and neoplasias.

Patients with donor-derived infection with *T. cruzi* may present asymptomatically if detected on molecular monitoring (see below). However, they may also present with disseminated disease as above typically in cases where donor screening and recipient PCR monitoring have not occurred.

15.3.3 Screening and Diagnosis

Pretransplant serological screening for Chagas should be part of routine evaluation in transplantation donors and recipients in endemic areas. In non-endemic areas,

screening should be performed in people who were born or who lived in endemic areas and in people who received blood transfusions or whose mothers were born in endemic areas [14]. Serological screening may be done with enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination (HA), and indirect fluorescent antibody (IFA) tests. Health agencies from endemic areas recommend obtaining positive results from at least two of three different methods to diagnose Chagas. Radioimmunoprecipitation (RIPA), Western blot, immunoblot, and IFA have the highest specificity and sensitivity and are considered confirmatory tests [13].

FDA-licensed screening tests for blood or organ donors include Ortho *T. cruzi* ELISA Test System and ABBOTT PRISM Chagas chemiluminescent immunoassay (ChLIA) with sensitivity and specificity close to 100%. Depending on the country and setting, there may be additional tests available.

Reactivation of chronic Chagas disease may occur with immunosuppression therapy, especially in the first months after transplantation, or with intensification of the immunosuppressive regimen. Therefore, sequential monitoring for early detection of parasitemia (reactivation) and implementation of preemptive treatment are recommended. Monitoring is done weekly or every 2 weeks for the first 6 months after transplantation and monthly thereafter until 1 year. Weekly monitoring for 2 months after intensification of immunosuppression is also recommended.

Parasitemia may be detected by direct observation of motile trypanosomes using microscopic examination of the buffy coat, thin or thick blood films stained with Giemsa, or by a concentration method (Strout test) or microhematocrit. Real-time PCR for *T. cruzi* has a higher sensitivity for low-grade parasitemia, preceding a positive Strout test or clinical signs of disease [15, 16].

PCR sensitivity may differ regarding whether they amplify nuclear (nPCR) or kinetoplast (kPCR) *T. cruzi* DNA. The best performing PCR methods for detection of *T. cruzi* in human blood samples have a high sensitivity (83–94%) and specificity (85–95%).

Pathology can be also used to diagnose active disease. On pathological examination, skin nodules show nests of intracytoplasmic *T. cruzi* amastigotes. Both rejection and Chagas reactivation in the heart can present with lymphocytic infiltrates with edema and areas of necrosis in endomyocardial biopsies. However, Chagas disease is diagnosed by identification of *T. cruzi* (either by immunohistochemistry and/or tissue-based PCRs).

15.3.4 Treatment

Patients with reactivated Chagas disease usually respond very well to benznidazole treatment (Table 15.1) (10 mg/kg/day in two divided doses for 60 days). Nifurtimox (8–10 mg/kg/day orally in three or four divided doses for 90–120 days) could also be effective, but its side effects are considerable. The adverse side effects of these drugs include dermatitis, peripheral polyneuropathy, weight loss, gastrointestinal disease, hematologic disorders, and an increased incidence of lymphoma. Posaconazole has activity against *T. cruzi*, but clinical results when treating chronic

indeterminate Chagas disease demonstrate inferiority to benznidazole [17]. Allopurinol also has good in vitro activity against *T. cruzi*. There is anecdotal experience of successful use (dose 600–900 mg/day for 2–3 months) for the treatment of reactivation following heart transplantation.

Parasitemia clearance and remission of clinical manifestations are usually obtained in the first week of treatment. In the heart transplant patients, relapses may occur. They may be multiple and may be observed many years after the first reactivation episode, with parasitemia or clinical manifestations; however, these individuals have had good responses to subsequent treatment courses. Mortality related to Chagas disease reactivation in heart transplantation has been reported to be 0.3% [13].

15.3.5 Prevention

Prevention strategies include identification of donors and recipients at risk of *T. cruzi* infection. In endemic countries, up to 5% of all deceased donors are patients chronically infected with Chagas disease [13]. In non-endemic countries, transmission by unscreened deceased organ donors and unscreened blood transfusions has been reported. Donor screening should be considered in when risk factors for Chagas are present (Fig. 15.2). The decision to accept Chagasic organ donors should be made balancing the risk of expected mortality in the waiting list against expected morbidity from eventual Chagas transmission. The likelihood of transmission appears to vary by organ type [14]. Transmission by infected donors to negative kidney recipients was reported to be from 0 to 18%. In liver transplant recipients,

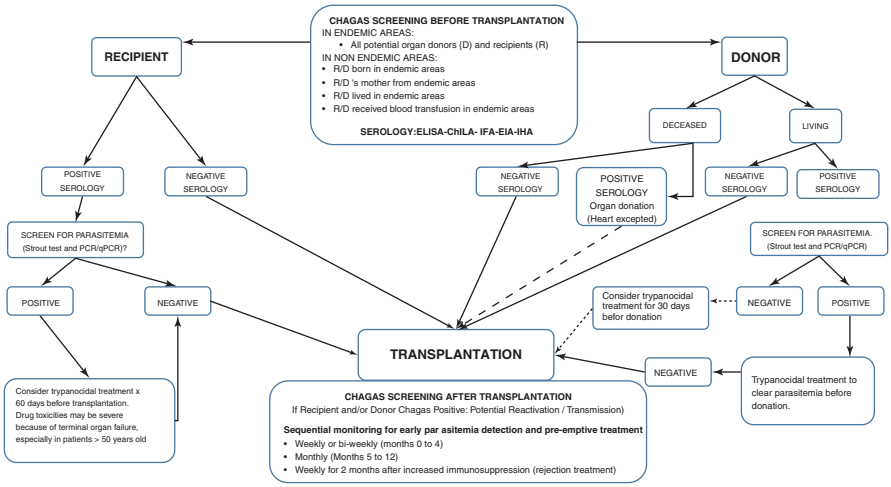

Fig. 15.2 Screening of transplant donors and recipients at risk for *T. cruzi* infection. Key: *R/D* recipient/donor, *ELISA* enzyme-linked immunosorbent assay, *ChILA* Chagas chemiluminescent immunoassay, *IFA* indirect fluorescent antibody, *EIA* enzyme immunoassay, *IHA* indirect hemagglutination

infection from positive donors was 0% (with prophylactic treatment with benznidazole) and 0–22% without prophylaxis [13, 15]. When transplant recipients are monitored for *T. cruzi* transmission from infected donors, treatment with benznidazole is highly effective, with no mortality attributable to Chagas disease. Therefore, in endemic countries (with appropriate informed consent), organs from infected deceased donors are considered acceptable (with exception of the heart) for infected recipients and for uninfected kidney recipients and for uninfected lung and liver recipients in emergency situations. It is recommended that infected living donors receive trypanocidal treatment for 30 days prior to donation to decrease the risk of transmission, and donation should take place immediately after treatment completion [13]. When transplantation is performed on a non-infected patient who resides in or who moves to an endemic area, the patient may be exposed to vector transmission, as has been reported in a few cases.

15.4 Pneumocystis

15.4.1 Introduction

Pneumocystis jirovecii is an important fungal etiologic agent of pneumonia in transplant recipients. The risk is highest in heart and heart-lung recipients (with incidence of up to 40% in the absence of prophylaxis) and lowest in kidney transplant recipients [18]. Infection in humans is likely transmitted by the airborne route and is usually acquired in childhood. Reactivation of dormant infection may occur with acquired immunosuppression. *Pneumocystis* outbreak reports in transplantation units suggest person-to-person transmission or a common environmental source of *Pneumocystis* [19]. The risk of *Pneumocystis* pneumonia (PCP) is related to the net state of immunosuppression of the patient and seems to be highest during the first 6–12 months after transplantation, but rejection, cytomegalovirus, and other immunomodulating infections may allow late infections to appear [20].

15.4.2 Clinical Presentation

Pneumocystis should be considered in the differential diagnosis of pneumonia in solid organ transplant recipients. In this setting, symptomatic progression often is acute or subacute and develops in few days, though progression over 1–2 weeks may also be observed. Dry cough, fever, and dyspnea out of proportion to physical findings are common, but co-infection may be present, changing the clinical presentation.

15.4.3 Diagnosis

Chest X-ray may be normal or reveal diffuse bilateral interstitial pulmonary infiltrates. Chest computed tomography may demonstrate disease not observed on plain

chest X-ray [18]. The etiological diagnosis of pneumonia in transplanted patients usually requires sampling from deep airways by bronchoalveolar lavage (BAL), although *P. jirovecii* may be detected in sputum and oral wash samples. The most sensitive staining method is with specific immunofluorescent (IF) monoclonal antibodies. When IF is not available, calcofluor white and Gomori methenamine silver are the most sensitive methods, although the microorganism can be observed with other stains (Gram-Weigert, Wright-Giemsa, modified Papanicolaou stains, or toluidine blue). PCR techniques of BAL fluid, induced sputum, or oral wash increase the diagnostic yield over conventional staining alone [18]. Quantitative assays may increase specificity, as false positives (asymptomatic carrying) may be observed with qualitative PCR. *P. jirovecii* may also be observed in transbronchial biopsies, which should be considered when performing bronchoscopy for diagnosis of pulmonary infiltrates. Measurement of plasma (1 → 3) β-D-glucan levels may aid in the diagnosis of PCP. However, this assay may be positive in other invasive fungal infections and lacks specificity for PCP.

15.4.4 Treatment

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice (Table 15.1). When treatment with TMP-SMX is not feasible (due to allergy or toxicities), intravenous pentamidine is an effective second-line agent. Pentamidine pancreatic toxicity is a potential concern when treating pancreas or islet cell transplant recipients. In severe disease (patients with hypoxemia, i.e., pAO2 < 70 mmHg on room air), adjunctive treatment with 40–60 mg of prednisone (or equivalent) is recommended along with antimicrobial therapy, ideally starting within the first 72 h of antimicrobial treatment. Steroids should be given for 5–7 days and tapered over the following 2–3 weeks. The recommended antimicrobial therapy duration is generally 21 days, particularly in those with severe disease. Echinocandins in combination with TMP-SMX or clindamycin have also been reported as salvage therapy in case reports.

15.4.5 Prevention

The risk of PCP is highest within the first 6 months after transplant. In most transplant centers, prophylaxis is routinely used during the first 6–12 months after transplantation. In patients with risk factors (heavy immunosuppression, cytomegalovirus infection, prior PCP), prophylaxis extension (even lifelong as in the case of HIV-infected transplant recipients) may be considered, as PCP has been described at any time after transplantation. TMP-SMX is the drug of choice for PCP prophylaxis [18]. Side effects of TMS-SMX that may occur are bone marrow toxicity (more common when other myelotoxic drugs are administered along) and cutaneous allergic manifestations, which can be severe (Stevens-Johnson syndrome, toxic epidermic necrolysis, and, less commonly, hepatitis, aseptic meningitis, interstitial nephritis, and hyperkalemia). In patients with glucose 6 phosphate dehydrogenase

(G6PD) deficiency, TMX-SMX may produce hemolysis [18]. Dapsone may be used as a second-line agent for PCP prophylaxis, whenever TMP-SMX use is not feasible. However, patients with severe allergy to TMP-SMX may present similar reactions to dapsone. Hemolytic anemia and methemoglobinemia may also occur with the use of dapsone, especially when there is G6PD deficiency [18]. Other alternatives for PCP prophylaxis are atovaquone [21] and inhaled or intravenous pentamidine [22, 23]. Prophylaxis failures have been described [18, 20]. There is a potential for airborne transmission from infected patients, suggested from reports of PCP outbreaks in transplantation units. Formal infection control policies could be considered for PCP patients [19].

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