Chapter 14: Other Infections

14.1: URINARY TRACT INFECTION

14.1.1: We suggest that all KTRs receive UTI prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 months after transplantation. *(2B)*

14.1.2: For allograft pyelonephritis, we suggest initial hospitalization and treatment with intravenous antibiotics. *(2C)*

KTRs, kidney transplant recipients; UTI, urinary tract infection.

Background

A urinary tract infection (UTI) is an infection causing signs and symptoms of cystitis or pyelonephritis (including the presence of signs of systemic inflammation), which is documented to be caused by an infectious agent. Kidney allograft pyelonephritis is an infection of the kidney allograft that is usually accompanied by characteristic signs and symptoms of systemic inflammation and a positive urine and/or blood culture. Occasionally, pyelonephritis is diagnosed by allograft biopsy. Antibiotic prophylaxis is the use of an antimicrobial agent (or agents) to prevent the development of a UTI.

Rationale

- UTI is a frequent and potentially important complication of kidney transplantation.
- The use of antibiotic prophylaxis can reduce the risk of UTI.
- Kidney allograft pyelonephritis may be associated with bacteremia, metastatic spread, impaired graft function and even death.
- KTRs with clinical and laboratory evidence suggestive of kidney allograft pyelonephritis should be hospitalized and treated with intravenous antibiotics.

Observational studies have documented a high incidence of UTI in KTRs (402). Pyelonephritis of the kidney allograft is a common complication in KTRs (402). It may cause graft failure, sepsis and death. The use of antibiotic prophylaxis with trimethoprim–sulfamethoxazole has been demonstrated to decrease the frequency of bacterial infections, including UTI in KTRs (403). The use of trimethoprim–sulfamethoxazole for the first 9 months following kidney transplant was associated with statistically significant decreases in number of any bacterial infection, overall number of UTI and number of noncatheter UTI. There is moderate-quality evidence that the benefit of UTI prophylaxis (primarily preventing infection, but unclear evidence for reducing mortality or preventing graft loss) outweighs the risks (see Evidence Profile and accompanying evidence in Supporting Tables 50–51 at http://www3.interscience.wiley.com/journal/118499698/toc).

Based upon this, and several other small studies, prophylactic trimethoprim–sulfamethoxazole for 6–12 months following kidney transplantation is warranted.

Although the use of ciproflaxicin also appeared effective in the prevention of UTI after KTRs, patients treated with this regimen were at risk for, and developed *Pneumocystis jirovecii* pneumonia (PCP) (see Recommendation 14.2) (404). Accordingly, the use of trimethoprim–sulfamethoxazole is preferred over ciprofloxacin at least during the first 6 months after transplantation.

Although some investigators have recommended indefinite use of trimethoprim–sulfamethoxazole, data are not available demonstrating clinical benefit beyond the first 9 months following kidney transplantation. Evidence suggests that late UTIs tend to be benign, without associated bacteremia, metastatic foci or effect on long-term graft function (405). For this reason, we recommend providing prophylaxis for a minimum of 6 months. For patients who are allergic to trimethoprim–sulfamethoxazole, the recommended alternative agent would be nitrofurantoin. This agent, which is widely recommended as an alternative to trimethoprim/sulfamethoxazole, is chosen over ciprofloxacin (despite demonstrated effectiveness in KTRs) in an effort to limit the likelihood of emergence of antibacterial resistance.

Kidney allograft pyelonephritis may be associated with bacteremia, metastatic spread, impaired graft function and even death. Accordingly, KTRs with clinical and laboratory evidence suggestive of kidney allograft pyelonephritis should be hospitalized and be treated with intravenous antibiotics for at least the initial course of therapy. This is particularly true in early infections (first 4–6 months following kidney transplantation). Recognition of the morbidity and mortality associated with allograft pyelonephritis led to recommendations in the 1980s to treat UTIs with as long as a 6-week course of antimicrobials for early UTI following transplantation. More recently, UTI after kidney transplantation has been associated with considerably lower morbidity and mortality (405). Accordingly, a less-prolonged course may be required, although patients experiencing relapsing infection should be considered for a more prolonged therapeutic course.

Because of the potential for serious complications, KTRs with kidney allograft pyelonephritis should be hospitalized and treated with intravenous antibiotics, at least initially. Although evidence derived from RCTs on the optimal duration of therapy for kidney allograft pyelonephritis are not available, it is anticipated, in the absence of a kidney abscess, that 14 days should be adequate.

14.2: *PNEUMOCYSTIS JIROVECII* PNEUMONIA

14.2.1: We recommend that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for 3–6 months after transplantation. *(1B)*

14.2.2: We suggest that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 weeks during and after treatment for acute rejection. *(2C)*

14.2.3: We recommend that KTRs with PCP diagnosed by bronchial alveolar lavage and/or lung biopsy be treated with high-dose intravenous trimethoprim–sulfamethoxazole, corticosteroids, and a reduction in immunosuppressive medication. *(1C)*

14.2.4: We recommend treatment with corticosteroids for KTRs with moderate to severe PCP (as defined by PaO_2 <70 mm Hg in room air or an alveolar gradient of >35 mm Hg). (*1C*)

KTRs, kidney transplant recipients; PaO_2, partial pressure of oxygen in arterial blood; PCP, *Pneumocystis jirovecii* pneumonia.

Background

Pneumocystis jirovecii (formally known as *Pneumocystis carinii*) is an opportunistic fungal pathogen known to cause life-threatening pneumonia in immunocompromised patients, including KTRs. *P. jirovecii* pneumonia (PCP) is defined as the presence of lower respiratory-tract infection due to *P. jirovecii*. A definitive diagnosis of PCP is made by demonstration of organisms in lung tissue or lower respiratory tract secretions. Because no specific diagnostic pattern exists on any given imaging test, it is imperative that the diagnosis of PCP be confirmed by lung biopsy or bronchoalveolar lavage.

Rationale

- Infection with *P. jirovecii* is life-threatening in KTRs.
- Prophylaxis with trimethoprim–sulfamethoxazole is safe and effective.
- Although thrice-weekly dosing of trimethoprim–sulfamethoxazole is adequate prophylaxis for PCP, daily dosing also provides prophylaxis for UTI and may be easier for patient adherence.

- Treatment of PCP with high-dose, intravenous trimethoprim–sulfamethoxazole and reduction of immunosuppressive medications are the treatments of choice for PCP.
- Based upon data from HIV-infected adults, the use of corticosteroids has been uniformly recommended for all patients experiencing moderate to severe PCP.

PCP prophylaxis

Pneumocystis jirovecii is an important opportunistic pathogen known to cause life threatening PCP in KTRs (406). The most typical time of onset of symptoms of PCP is 6–8 weeks following initiation of immunosuppressive therapy. Although PCP is potentially a life-threatening complication of KTRs, the use of chemoprophylaxis has been shown to be extremely effective in preventing the development of clinical disease attributable to this pathogen. The use of trimethoprim–sulfamethoxazole prophylaxis resulted in a RR of 0.08 (95% CI 0.023–0.036) of developing PCP compared to either a placebo, control or no intervention (403). Treatment also decreased mortality.

There was no difference in efficacy for PCP when trimethoprim–sulfamethoxazole was given daily or three times per week (407). However, in KTRs, the use of daily trimethoprim–sulfamethoxazole may be associated with a decreased risk of bacterial infection (403). Although definitive evidence for the duration of PCP prophylaxis is not available, most experts agree that it should be continued for at least 6 months (and perhaps as long as 1 year) following transplantation (406). Because most KTRs will remain on immunosuppression for the rest of their lives, some experts recommend a more prolonged and perhaps even indefinite use of PCP prophylaxis. Indications for the use of alternative preventive agents include the development of allergic reactions and/or drug-induced neutropenia from trimethoprim–sulfamethoxazole. Potential alternative agents include dapsone, aerosolized pentamidine, atovaquone or the combination of clindamycin and pyrimethamine (Table 17).

PCP treatment

Prior to the use of trimethoprim–sulfamethoxazole, mortality from PCP in KTRs was very high (409,410). The treatment of PCP includes both the use of intravenous trimethoprim–sulfamethoxazole as well as corticosteroids for KTRs with significant hypoxemia (406). RCTs have demonstrated that the use of corticosteroids in the first 72 hours of PCP in HIV patients resulted in improved outcome, including morbidity, mortality and avoidance of intubation (406). The usual duration of treatment is 2–3 weeks. The use of intravenous pentamidine isethionate should be considered in patients with proven trimethoprim–sulfamethoxazole allergy. Other treatment strategies should be restricted to patients with mild PCP only.

Table 17: Antimicrobial agents for the prevention of PCP in KTRs[a]

Agent	Adult dose	Pediatric dose
Trimethoprim/ sulfamethoxazole[b]	Single-strength pill (80 mg as trimethoprim) or double-strength pill (160 mg as trimethoprim) daily or three times per week	150 mg/m^2/day as trimethoprim daily or three times per week
Aerosolized pentamidine	300 mg inhaled every 3–4 weeks via Respirgard II^{TM} nebulizer	For children ≥5 years old, 300 mg inhaled monthly via Respirgard II^{TM} nebulizer
Dapsone[c]	100 mg/day as a single dose or 50 mg twice a day	Can be administered on a daily or weekly schedule as 2.0 mg/kg/day (maximum total dosage of 100 mg/day) or 4.0 mg/kg/week (maximum total dosage of 200 mg/week) orally. Approximately two thirds of patients intolerant to Trimethoprim/sulfamethoxazole can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or aerosolized pentamidine but slightly less effective than Trimethoprim/sulfamethoxazole
Atovaquone	1500 mg/day	Administered with a meal as an oral yellow suspension in single dosage of 30 mg/kg/day for patients 1–3 months and >24 months of age, and 45 mg/kg/day for infants aged 4–24 months

KTRs, kidney transplant recipients; PCP, *Pneumocystis jirovecii* pneumonia.
[a]Excerpted from (408).
[b]This is first-line therapy. All other agents should be considered second-line therapy.
[c]Must screen for glucose 6-phosphate dehydrogenase deficiency prior to using dapsone, as this is a risk factor for development of methemoglobinemia associated with use of dapsone.

14.3: TUBERCULOSIS

14.3.1: We suggest that TB prophylaxis and treatment regimens be the same in KTRs as would be used in the local, general population who require therapy. (2D)

14.3.2: We recommend monitoring CNI and mTORi blood levels in patients receiving rifampin. (1C)

14.3.2.1: Consider substituting rifabutin for rifampin to minimize interactions with CNIs and mTORi. (Not Graded)

CNI, calcineurin inhibitor; KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s); TB, tuberculosis.

Rationale

- KTRs are at increased risk of developing disease due to tuberculosis (TB).
- KTRs with latent TB, identified by a positive purified protein derivative (PPD) skin test or a history of TB disease without adequate treatment, are at highest risk of developing clinical TB after transplantation and are therefore good candidates for chemoprophylaxis with isoniazid.
- Treatment of TB in KTRs has been shown to respond to standard antimycobacterial therapy.
- The use of rifampin is associated with numerous drug–drug interactions through its activation of the CYP3A4 pathway.
- This interaction can affect drug levels for CNIs as well as mTORi.

- Rifabutin achieves similar therapeutic efficacy while minimizing the potential for drug–drug interactions.

The incidence of TB among KTRs varies according to geographic locations, with rates of 0.5–1.0% reported in North America, 0.7–5% in Europe and 5–15% in India and Pakistan (411,412). This represents a marked (50- to 100-fold) increase in the frequency of TB compared to the general population. In addition, there is also a marked increase in severity of disease in KTRs with mortality rates 10-fold higher than in immunocompetent individuals with TB.

The most frequent source of TB infections in KTRs is reactivation of quiescent foci of *Mycobacterium tuberculosis* that persist after initial asymptomatic infection (413). Accordingly, screening and identification of individuals with evidence of prior latent infection with TB should allow treatment prior to development of clinical disease, resulting in improved outcome.

Data from a variety of immunosuppressed populations demonstrate that treatment of latent TB markedly reduces the risk of subsequent progression to clinically active TB (414). A limited number of RCTs have evaluated the benefit of prophylactic treatment with isoniazid for KTRs (415) or organ transplant patients, including KTRs (416,417). Results of these studies suggest a benefit to KTRs, although study size and design limit the strength of these observations. The use of prophylactic isoniazid in patients with a past or current positive PPD skin test, and/or a history of TB without adequate documented treatment, has been previously recommended by the European Best Practice Guidelines for Renal Transplantation (411) and the American Society of Transplantation Guidelines for the

Prevention and Management of Infectious Complications of Solid Organ Transplantation (418).

If, according to these guidelines, vaccination with BCG can give a 'false-positive' PPD skin test, then some patients may be treated unnecessarily. Most believe that the effect of BCG should not persist for more than 10 years (419). The use of BCG vaccine is especially common in regions where the prevalence of TB is high. In these regions, it is therefore difficult to distinguish PPD skin tests that are positive due to BCG from those that are positive due to prior infection with *M. tuberculosis*. Accordingly, it is recommended that the history of BCG vaccination should be ignored and that a 9-month course of prophylactic isoniazid should be used (411). It is also possible that dialysis and transplant patients frequently have false-negative PPD skin tests. Accordingly, some experts have recommended use of isoniazid prophylaxis in selected KTRs with a negative PPD skin test. These would include those with history of active TB that was not adequately treated, those with radiographic evidence of previous TB without a history of treatment and those who have received an organ from a donor with a history of a positive PPD skin test (418).

Interferon-gamma release assays such as T-SPOT.TB and QuantiFERON are an alternative to the tuberculin skin test for detecting latent TB infection. Their sensitivity and specificity, however, have not been systematically evaluated in KTRs. Data from CKD stage 5 patients suggest important limitations for detecting latent TB infection which preclude their routine use at present (420–423).

Extensive experience in the treatment of immunosuppressed patients (including transplant recipients) suggests that the response to treatment is the same as in immunocompetent patients. Unfortunately, rifampin is a strong inducer of the microsomal enzymes that metabolize CNIs and mTORi, and it may be difficult to maintain adequate levels of these immunosuppressive drugs to prevent rejection. The use of rifampin has required doses of CNIs to be increased two- to threefold (418). One potential alternative is to substitute rifabutin for rifampin. Rifabutin has activity against *M. tuberculosis* that is similar to rifampin, but rifabutin is not as strong an inducer of CYP3A4 as rifampin. However, there is little published experience with rifabutin in KTRs.

There are reports of successful treatment of posttransplant TB with rifampin-sparing regimens (415). In this report, rifampin is substituted with a fluoroquinolone along with isoniazid, ethambutol and pyrazinamide for the first 2 months. At this point, the latter two are stopped and fluoroquinolone and isoniazid continued for another 10–12 months. According to the authors, the success rate is 100% (424–426).

Finally, the rate of recovery of drug-resistant TB is increasing. Since both KTRs and their donors may come from diverse geographic locations where the prevalence of drug resistance may vary, all isolates of TB recovered from KTRs should be submitted for susceptibility testing. Modifications in treatment should be made once the results of susceptibility testing become available.

14.4: *CANDIDA* PROPHYLAXIS

14.4.1: We suggest oral and esophageal *Candida* prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole for 1–3 months after transplantation, and for 1 month after treatment with an antilymphocyte antibody. *(2C)*

Rationale

- KTRs are at increased risk for oral and esophageal infections due to *Candida* species.
- The use of oral clotrimazole troches or nystatin provides effective prophylaxis without systemic absorption and hence without concerns for side effects.
- Although data regarding the duration of prophylaxis are not available for KTRs, prophylaxis should logically be continued until patients are on stable, maintenance immunosuppression, particularly corticosteroids.

Observational studies have reported a high incidence of oral and esophageal *Candida* infections in KTRs. There are limited data supporting the use of antifungal therapy in KTRs, although it is beneficial in liver transplant recipients (427). The standard immunosuppressive agents typically used in KTRs are associated with an increased risk of developing *Candida* infections. The most common source for these infections is colonization of the oral mucosa. Accordingly, use of topical antifungal therapies such as clotrimazole troches and nystatin offer the opportunity to eradicate fungal colonization without associated risks that may be present for systemically absorbed antifungal agents. However, a recent report suggested a potential drug–drug interaction between clotrimazole and tacrolimus (428). It is important to note that there are drug–drug interactions between fluconazole and CNIs.

Although data regarding the appropriate duration of prophylaxis for these agents are not available for KTRs, the risk is greatest early after transplantation when patients are receiving their highest levels of immunosuppression, and are more likely to be exposed to antibacterial agents that increase the risk for *Candida* infections. Accordingly, these agents can likely be discontinued once the patient is on maintenance immunosuppression, particularly when steroid doses are stable and low.

Research Recommendations

- RCTs are needed to determine the optimal duration and type of prophylaxis for *Candida* infections in KTRs.