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# Infections in Transplant Patients

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## KEYWORDS

- Solid organ transplant • Common infections • Primary care
- Opportunistic infections

## KEY POINTS

- Primary care providers must prepare themselves to care for an increasing population of solid organ transplant (SOT) patients.
- SOT recipients require lifelong immunosuppression, and therefore are chronically at increased risk for infections.
- Typical signs of infection may be subtle or absent in the setting of immunosuppressive medications.
- Expedited, comprehensive diagnostic testing for infectious symptoms is important, and sometimes invasive procedures may be warranted.

## Generalists must learn to care for infectious complications in solid organ transplant patients.

Primary care providers (PCPs) in North America must prepare themselves to see a growing number of solid organ transplant (SOT) patients. More SOTs are being performed, and SOT patients are living longer.<sup>1</sup> Based on transplant data analyzed from 2008 for 104 countries, around 100,800 SOTs are performed every year worldwide: 69,400 kidney transplants (46% from living donors), 20,200 liver transplants (14.6% from living donors), 5400 heart transplants, 3400 lung transplants, and 2400 pancreas transplants.<sup>2</sup>

Data from the Health Resources and Services Administration showed that more than 27,000 solid organs were transplanted in the United States in 2008.<sup>3</sup> Over the past decade, graft survival and patient survival has improved for nearly every organ. The most gains occurred in living liver donor recipients and heart-lung transplants, with 11% to 34% increased survival. More manifestations of chronic diseases

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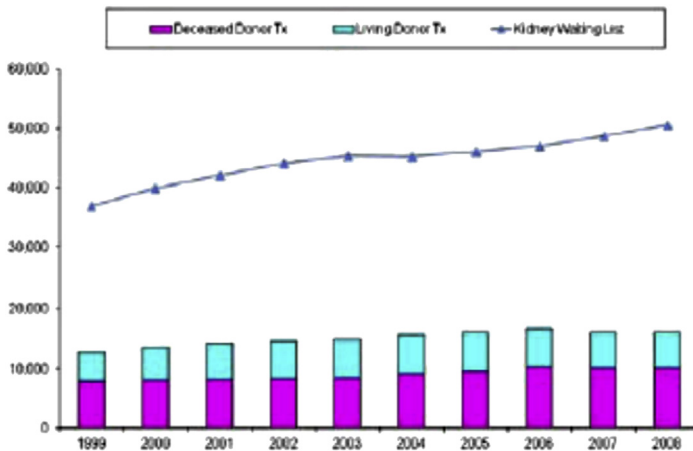
commonly seen by generalists now qualify patients for SOT, including symptomatic chronic conditions such as congestive heart failure (CHF), chronic obstructive lung disease (COPD), chronic hepatitis, and chronic kidney disease (CKD). Given the prevalence of these chronic conditions, more than 100,000 people are on waiting lists in the United States for SOTs. While wait-list length is influenced by changes in demand, listing practices, death rates, donation rates, and allocation policies, it is important to be aware that the demand for SOT is increasing (Fig. 1).<sup>3</sup>

**SOT recipients are at risk for infections in the short and long term, resulting in higher morbidity and mortality.**<sup>4</sup>

Unlike the vast majority of hematopoietic cell transplant recipients who eventually have immunosuppressive medications discontinued, SOT patients require lifelong immunosuppression and therefore remain at lifelong increased risk of infection.<sup>5</sup> To avoid transplant rejection the commonly used immunosuppression regimens are broadly acting, decreasing both cellular and humoral immunity. Reduced cellular immunity leaves hosts susceptible to viral, fungal, and intracellular pathogens while decreased humoral immunity increases the risk for encapsulated bacteria. In most SOT recipients the degree of immunosuppression, and hence the infectious risk, tends to decrease over time, but never returns to a normal baseline. For those who develop recurrent or chronic organ rejection and require intensification of their immunosuppressive regimen, the risk for infection remains high. Usual immunosuppressive regimens include a corticosteroid, a calcineurin inhibitor, and an antimetabolite.<sup>5</sup>

**More care is decentralized from major transplant centers.**

Even patients who live in rural and geographically isolated areas are receiving SOTs. Because the risk of many transplant-related complications tends to decrease after 3 to



**Fig. 1.** Number of transplants and size of active waiting list. There was a very large gap between the number of patients waiting for a transplant and the number receiving a transplant. This gap widened over the decade, meaning that the waiting times from listing to transplant continued to increase. The number of living-donor transplants grew until 2004 while the number of deceased donor transplants continued to rise gradually until 2006. (Data from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: Clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48(8):1003–32.)

6 months posttransplant, patients generally are referred back to their PCPs/specialists by around 3 months after the transplant. Hence, subacute and long-term management is now being done by generalists with the transplant center providing a consultative role if needed. Most transplant centers will provide the patient and primary physician a packet with transplant-specific care guidelines, recommended monitoring, and follow-up requirements. PCPs of new SOT patients should request this information from the transplant center (**Box 1**).

## PRACTICAL ISSUES IN THE MANAGEMENT OF SOT INFECTION

### Typical signs and symptoms of infection are muted by immunosuppressive agents.

In immunocompetent hosts, the signs and symptoms of inflammation (rubor, dolor, calor) can be important clues to infection. However, the immunosuppressive agents that SOT recipients receive can blunt this inflammatory response (the mechanism by which they prevent rejection), thereby making the signs and symptoms of inflammation much more subtle.<sup>5</sup> Thus, it is important for PCPs and patients to remain vigilant of even subtle manifestations of infections. Common urgent-visit concerns such as low-grade fevers, new cough, or diarrhea can portend serious infections. This article reviews common presenting symptoms that should be approached differently in SOT patients than in immunocompetent persons.

In this time of heightened awareness of medical costs and growing resistance to antimicrobial therapy, the usual approach to average-risk ambulatory patients is to be judicious and pragmatic in our use of diagnostic and therapeutic interventions.<sup>6</sup> Several features of infection in SOT patients mandate a different approach than is used in immunocompetent patients (the clinical presentation can be more subtle,

#### Box 1

##### What the PCP should expect from the transplant center

*Checkout Materials, Including the Following Information:*

- Standard monitoring
  - Labs, immunosuppressive level targets, imaging
  - Frequency of routine clinic appointments
  - Frequency of transplant clinic appointments
  - Assessment for common complications/side effects
    - Hypertension, hyperlipidemia, osteoporosis, diabetes, dental disease
    - Secondary cancer surveillance
- Troubleshooting recommendations for common presentation of infection
  - Fever, cytomegalovirus, typical infections
- Preventive care issues
  - Vaccinations
  - Nutrition, activity, travel
  - Pregnancy
  - Cancer screening

*Adapted from UWMC SOT patient/provider materials.*

multiple pathogens may be present concomitantly, and the progression of infection may be more rapid). As a result, in general more comprehensive diagnostic testing and earlier escalation to advanced imaging and invasive diagnostic procedures are warranted for SOT patients.<sup>5</sup> Although empiric therapeutic interventions have their place in SOT patients, thorough efforts to identify and characterize the etiologic agent(s) of infection are imperative.

Some tests used to diagnose infections in immunocompetent patients are much less sensitive in SOT patients. For example, tests that rely on the host's immune system (eg, serology) may be less sensitive than direct detection of the pathogen. Although serologic tests can help identify latent infections, antibody development to acute infections may be delayed or never develop in immunosuppressed patients. Instead, direct detection of pathogens using culture, polymerase chain reaction (PCR), and so forth, from optimal specimens is preferred.<sup>5,7</sup>

To add to the complexity, SOT patients are more likely than immunocompetent patients to have rapid progression of infection because of the lack of an appropriate immune response. An example is pneumonia, which can be safely treated in the ambulatory setting in most immunocompetent patients but can often result in hospitalization in SOT patients.<sup>8</sup> SOT patients are more likely to have multiple pathogens and resistance patterns that complicate the choice of antimicrobial therapy.<sup>7</sup> Early involvement of infectious disease specialists may be warranted.

**PCPs should familiarize themselves with the timeline of susceptibility to infections.**

In general, the intensity of immunosuppression decreases with the time from transplant and, as a result, the risk for serious opportunistic infections tends to decrease with time. However, if episodes of rejection occur, immunosuppressive medications are intensified and patients again become more vulnerable to opportunistic infections that might more typically be seen in the earlier period posttransplant.<sup>5,7</sup>

**The first month after transplant is a vulnerable time for nosocomial infections with multidrug-resistant organisms, including those related to complicated surgery.**

Nosocomial infections may be related to the transplant surgery itself or exposures to the hospital environment.<sup>5,7</sup> Many such infections are the results of venous and urinary catheterization as well as intubation. Most SOT patients are aggressively treated for known infections before transplantation, given the risks of immunosuppression. protocols exist to screen donors for infections, but the short time frame necessitates limited diagnostic testing. Although serologic testing for viral hepatitis, human immunodeficiency virus (HIV), herpesviruses, and microbiological testing with blood and urine cultures can identify active bacterial and fungal infections, donor-related infections are well described.<sup>9</sup> During the first posttransplant month, bacterial and fungal infections are more common than viral infections, and often these nosocomial pathogens are drug-resistant strains. SOT patients in this time frame will typically still be under the direct care of the transplant center.

**The effects of immunosuppressive medications typically manifest in months 1 to 6, so this is when opportunistic infections tend to be most common.**

Donor-acquired conditions, or reactivation of recipient infections such as hepatitis B and C, are apt to infect the patient after the first month.<sup>7,9</sup> By 3 months posttransplant, if all is going well, immunosuppression will typically be tapered and most patients will leave the direct care of the transplant program. Patients will be receiving prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP) (trimethoprim/sulfamethoxazole or dapsone, or monthly inhaled pentamidine) and cytomegalovirus (CMV) (commonly

valganciclovir).<sup>5</sup> Reactivation of latent infections can occur during this time period, including *Mycobacterium tuberculosis* and *Strongyloides stercoralis*. SOT patients are susceptible during this period to endemic mycoses including *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Cryptococcus*.<sup>7</sup> Prophylactic medications are typically discontinued by 6 to 12 months after transplant. The need for prophylaxis diminishes over time, but SOT patients will always be susceptible to typical community-acquired viral and bacterial infections.

#### Further concerns are raised 6 months or more posttransplant.

Most stable SOT patient are on reduced doses of immunosuppression, and therefore have decreased risk for opportunistic infections. CMV, Epstein-Barr virus, herpes simplex virus, and hepatitis viruses remain a concern, but more commonly SOT patients are infected with seasonal respiratory and gastrointestinal viruses, community-acquired pneumonias, and urinary tract infections during this period.<sup>7,10</sup> In patients who experience allograft rejection, doses of immunosuppressive medication are increased. In those who require higher levels of immunosuppression, the risk for opportunistic infections may be as high as during the 1- to 6-month posttransplant period; this would include an increased risk for PJP, *Nocardia*, *Varicella*, and *Aspergillus* (Fig. 2).<sup>7</sup>

### CASES OF INFECTIOUS DISEASE IN SOT PATIENTS

#### Case 1

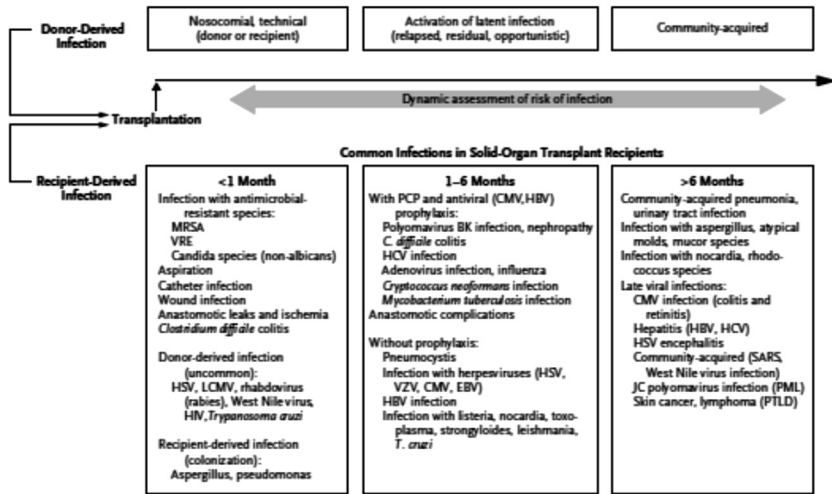
A 45-year-old man, 2 years post orthotopic liver transplant, presents to your clinic in January with 5 days of rhinorrhea, mild sore throat, dry cough, mild headache, and chills. ROS is negative for pleurisy or dyspnea, but positive for fatigue. Vital signs (VS): temperature (T) 37.7°C, heart rate (HR) 100 beats/min, blood pressure (BP) 110/70 mm Hg, respiratory rate (RR) 22 breaths/min, oxygen saturation (O<sub>2</sub> sat) 98%. His examination shows clear nasal secretions, mild pharyngeal erythema, and no adenopathy, and his lungs are clear to auscultation bilaterally. His transplanted liver is nontender on palpation, and he is hydrating orally and urinating without difficulty. He had an influenza vaccination 2 months prior.

You recommend:

- A. Chest radiograph (CXR), rapid influenza test, empiric therapy with levofloxacin
- B. Reassurance, conservative measures, acetaminophen 500 mg every 6 hours for headache push fluids, strict return precautions
- C. CXR, rapid influenza test, empiric oseltamivir
- D. Sinus computed tomography (CT) scan, levofloxacin
- E. Lumbar puncture, admission with ceftriaxone, ampicillin, acyclovir, fluconazole

Correct answer: C.

The Infectious Disease Society of America (IDSA) guidelines recommend that clinicians consider influenza for all patients with acute onset of fever and respiratory symptoms during the influenza season.<sup>11</sup> The IDSA does not have a unique diagnostic algorithm for immunosuppressed patients during or outside of the influenza season, but does warn that chronically ill/immunosuppressed patients could present atypically and have more severe consequences of infection with influenza.<sup>11</sup> Otherwise healthy patients can forgo diagnostic testing and be treated empirically if they present for care



**Fig. 2.** Changing timeline of infection after organ transplantation. Infections occur in a generally predictable pattern after solid organ transplantation. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV), or Epstein-Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis carinii* pneumonia; PML, progressive multifocal leukoencephalopathy; PTLD, posttransplantation lymphoproliferative disorder; SARS, severe acute respiratory syndrome; VZV, varicella zoster virus; VRE, vancomycin-resistant *Enterococcus faecalis*. (From Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357(25):2601–1; with permission. Copyright © 2007 Massachusetts Medical Society.)

within 48 to 72 hours of the onset of symptoms, but SOT patients should be approached differently.

Although the rate of influenza infection in SOT patients appears to be similar to the general population (2%–4% in SOT vs 3%–5% in the general population), the severity of infections is higher.<sup>12</sup> The type of organ transplant may influence the risk of complications. Lung transplant recipients are most vulnerable, followed by liver, then kidney transplant patients.<sup>13</sup> Whereas healthy patients typically shed the virus 1 day prior and up to 1 week following the onset of symptoms, SOT patients can be infectious for weeks to months because of their inability to clear the virus,<sup>14</sup> and are more likely to present with atypical symptoms including no or only a low-grade fever (50%–80% of SOT patients with influenza present with fever). Hence, symptoms of rhinorrhea, dry cough, sore throat, or gastrointestinal symptoms of stomach upset and diarrhea commonly seen in noninfluenza respiratory or gastrointestinal viral infections may be the only presenting symptoms of influenza. When fever is present in the setting of symptoms of upper respiratory tract infection, it is a very predictive sign for influenza in SOT patients.<sup>12</sup>

SOT patients are more prone to develop lower respiratory tract infections, including influenza pneumonia (47% of hospitalized SOT patients), secondary bacterial pneumonia (*Streptococcus* and *Staphylococcus*, 17% of hospitalized SOT patients), other bacterial superinfections, and extrapulmonary manifestations such as central nervous system or myocardial involvement.<sup>12</sup> As a result, SOT patients may require hospitalization and aggressive management of influenza infection more commonly than immunocompetent patients.

Whereas empiric therapy or supportive therapy alone is acceptable in many otherwise healthy ambulatory patients, SOT patients benefit from specific identification of the pathogen(s). Immunocompetent patients should be tested as soon as symptoms begin, ideally within less than 5 days. However, regardless of the timing of symptom onset, it is appropriate to test SOT patients for influenza when the suspicion arises. Whereas nasopharyngeal washes and aspirates are superior in immunocompetent patients, upper and lower respiratory tract specimens can be helpful in SOT patients.<sup>11</sup>

#### **What is the appropriate workup of transplant patients suspected of influenza?**

Rapid antigen tests have limited sensitivity for the diagnosis of influenza, and a negative test does not exclude the diagnosis. More sensitive tests such as respiratory virus PCR panels are becoming the gold standard at many laboratories. These tests are appropriate for use in symptomatic patients but can cause confusion by identifying multiple viruses in asymptomatic patients, making it difficult to determine if the identified viruses are pathogens. If patients have lower respiratory tract symptoms or clinical or radiographic evidence of lower tract infection, they should undergo bronchoscopy with testing.<sup>12</sup> For more information on testing, the reader is advised to visit the seasonal flu Web site of the Centers for Disease Control and Prevention: (<http://www.cdc.gov/flu/professionals/diagnosis/labprocedures.htm>).

Because of increasing resistance patterns to M2 inhibitors such as amantadine in influenza A and H1N1, neuraminidase inhibitors such as oral oseltamivir and inhaled zanamivir are considered the first-line therapy. The optimal duration of therapy is not well defined. In immunocompetent individuals the typical course is 5 days. However, SOT patients can continue to shed the virus for a longer duration. Active treatment for 10 to 14 days with weekly PCR monitoring should be considered.<sup>12</sup> Given the higher rate of bacterial superinfection or coinfection, antibiotics should be considered, especially in SOT patients with lower respiratory infection symptoms, while awaiting results of diagnostic studies.

#### **What is the best way to handle influenza vaccination in transplant patients?**

SOT patients should be vaccinated with an inactivated influenza vaccine before and after transplantation. There is some controversy about the optimal timing of vaccination posttransplant, but the prudent approach is to vaccinate SOT patients as soon as the seasonal vaccine is available before influenza season. The efficacy of vaccination may be lower in SOT patients than in immunocompetent patients, but does appear to be safe. One study found that of the population of SOT patients diagnosed with influenza, 50% had received the vaccination and none of these patients had protective levels of antibodies against influenza at the time of admission. The same study showed that influenza vaccination decreased the risk of associated pneumonia (relative risk 0.3) in comparison with SOT patients who were not immunized.<sup>15</sup> There is no evidence that additional benefit is gained from high-dose vaccines or intradermal inoculation. The live attenuated nasal vaccine is contraindicated in immunocompromised persons, including those who have received a SOT. Evidence does not show an increased risk for graft rejection or failure with influenza vaccination.<sup>16</sup>



**Case 2**

A 52-year-old woman 3.5 months status post living-related kidney transplant presents to your clinic to reestablish care after her transplant. She reports 7 days of subjective fevers and a nonproductive cough. She has no rhinorrhea, sore throat, nausea, vomiting, diarrhea, or body ache, but she has had anorexia and some mild night sweats. She has had many well-wishers at her home since returning and suspects she could have had an infectious exposure. VS: T 38.1°C, HR 96, BP 132/90, RR 24, O<sub>2</sub> sat 94% on room air. On examination she is speaking in full sentences but looks tired. She has scattered shoddy cervical adenopathy, no nuchal rigidity, and some scattered inspiratory crackles bilaterally. There are wheezes, and her lungs are equally resonant on percussion. Her heart is regular without a murmur, she has a reassuring soft abdominal examination, and her transplant kidney is nontender on palpation.

Allergies: sulfamethoxazole

CXR: bilateral nodular infiltrates

*Which management strategy would you choose?*

- A. Empiric treatment with azithromycin, calculate CURB-65 and if less than 2, treat as an outpatient with 1 week follow-up
- B. Admit for workup including CT scan and likely bronchoscopy
- C. Empiric treatment with levofloxacin, calculate CURB-65 and if less than 2, treat as an outpatient with 1 week follow-up
- D. Empiric treatment with azithromycin and oseltamivir, calculate CURB-65 and if less than 2, treat as an outpatient

Correct answer: B.

The differential diagnosis for nodular infiltrates in SOT patients includes:

- Fungal infections (*Aspergillus*, *Cryptococcus*)
- Mycobacterial infections (*Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare* complex)
- Bacterial infections (*Nocardia*, *Legionella*, *Rhodococcus equi*)
- Malignancy (lymphoma)

Features of this case that mandate an aggressive diagnostic evaluation include immunosuppression, onset within the posttransplant period at highest risk for opportunistic infection, and the nodular nature of the pulmonary infiltrates.

Community-acquired pneumonia (CAP) in SOT patients is common (3 times higher incidence than in immunocompetent individuals) and dangerous (11%–43% mortality rate).<sup>17,18</sup> A Canadian case-control study found that immunosuppressive medications increased the risk for CAP, with an odds ratio of 15.<sup>17</sup> Despite the uniquely higher risk facing SOT patients, the IDSA and the American Thoracic Society (ATS) do not specifically consider immunosuppressed patients in their consensus guidelines for CAP. Rather, the guidelines address CAP and separate guidelines address nosocomial pneumonia (recent hospitalization or institutional settings).<sup>19</sup> For this patient, the presentation in the 3- to 6-month posttransplant period increases her risk for opportunistic infections, given the effects of longer duration and higher dose of immunosuppressive medications. Viral infections such as CMV and respiratory viruses can cause primary lung infections during this time, and can also complicate matters by further decreasing immunity and increasing the risk for opportunistic infections such as *Aspergillus fumigatus* and PJP.<sup>10</sup>

Causes of CAP in immunocompromised patients, in order of frequency, are<sup>17</sup>:

- *Streptococcus pneumoniae*
- *Legionella pneumophila*
- *Haemophilus influenzae*
- Gram-negative rods (GNRs): *Pseudomonas aeruginosa*
- *Nocardia* spp
- *Staphylococcus aureus*
- Viral (influenza, respiratory syncytial virus)

ATS and IDSA recommend the use of assessment tools of pneumonia severity to determine the appropriate care setting: ambulatory, inpatient, or ICU. CURB-65 is a recommended tool that gives 1 point for Confusion, Uremia, Respiratory rate greater than 30/min, Blood pressure less than 90 mm Hg, and age 65 or older. A score greater than or equal to 2 on CURB-65 should spur providers to consider hospitalizing patients. The pneumonia severity index (PSI) is the other recommended tool, and has 11 initial elements to the assessment. If patients have any of the 11 elements they are risk stratified into 4 higher-risk classes that correlate to 30-day mortality risk, as does CURB-65.<sup>19</sup> PSI has a higher discriminatory power and is more accurate in lower-risk patients. Neither tool specifically considers immunosuppression or SOT as a risk factor for severe disease. Hence, it is important for PCPs to use such tools with caution in SOT patients. Current guidelines recommend these tools be used for supplemental data, and that the physician's determination of the patient's global risk be the primary determinant of the treatment plan.<sup>19</sup>

In SOT patients with lower respiratory symptoms of cough, dyspnea, increased respiratory rate, or fever, testing should include complete blood count, chemistry panel, blood cultures, sputum culture, and a chest radiograph. Although chest radiographs have lower sensitivity in immunosuppressed people, the pattern of disease on radiography can still be helpful. Focal airspace disease is correlated with bacterial (and mycobacterial) pneumonia. Multifocal airspace disease and nodular infiltrates have a much broader differential (as discussed earlier). Diffuse and interstitial patterns are concerning for pneumocystis or viral infections. In immunocompromised patients with pulmonary infiltrates, chest CT scan and bronchoscopy have clearly shown benefit in distinguishing among infectious and noninfectious causes.<sup>20,21</sup>

Consensus guidelines recommend empiric treatment with institutionally tailored antibiotic choices that should reflect the resistance in the community. PCPs should not delay empiric therapy while waiting for testing. Usual choices of a respiratory fluoroquinolone, macrolides, or broader-spectrum  $\beta$ -lactams + a macrolide are also reasonable empiric therapy for SOT patients.<sup>19</sup> Depending on clinical presentation, severity scores, reliability and level of home support, some patients can be treated as an outpatient with very close follow-up, whereas others need to be managed in the inpatient setting. Hospitalizing immunosuppressed SOT patients and putting them at risk for nosocomial infections is an important consideration. Early consultation with pulmonary and infectious disease specialists, very close follow-up, and rapid escalation of the intensity of both diagnostic and therapeutic efforts depending on response are appropriate.

Regarding follow-up, because this patient is in the highest-risk time frame for opportunistic infections, and has nodular infiltrates on her chest radiograph conferring a broader range and possibly higher-risk situation, an infectious disease consultation should be initiated as well as hospitalization for intensified diagnostic and therapeutic interventions. Typically recommended regimens for CAP requiring hospitalization

(ceftriaxone + azithromycin, respiratory fluoroquinolone) would not be active against the cause of this patient's pneumonia.

*Nocardia* was diagnosed on Gram stain (beaded, branching, filamentous gram-positive rod) and culture of a bronchial alveolar lavage (BAL) sample. Invasive procedures are often necessary to make the diagnosis of pulmonary nocardiosis (44% in one study).<sup>22</sup> *Nocardia* is a soil-borne bacterium that more commonly presents as an opportunistic infection in immunosuppressed patients, although it can cause self-limited indolent disease in immunocompetent patients. SOT patients are particularly vulnerable when their T-cell immunity is suppressed, often when corticosteroid doses are higher.<sup>23</sup> Because *Nocardia* has a propensity to disseminate to other sites (brain, bones, skin), the patient should be carefully clinically assessed for these complications, with further imaging clinically appropriate. The primary treatment is typically with sulfamethoxazole-based antibiotics. This patient had no evidence of dissemination outside her lungs and was treated with imipenem initially, given her sulfamethoxazole allergy, then converted to linezolid orally for 6 months.

### Case 3

A 48-year-old woman, 2 years post liver transplant for autoimmune hepatitis, presents with watery, profuse diarrhea for 3 days, resulting in 3 lb (1.36 kg) of unintentional weight loss. She reports no nausea, vomiting, blood in the stool, or tenesmus, but has had a low-grade fever. She has no recent travel, change in her medications, or unusual or risky food ingestions or sexual behavior. However, on further questioning she is a girl-scout leader for her 10-year-old daughter's group, and they recently had a day outing to a local water park. On examination she is tired, without jaundice. VS: T 38.1°C, HR 95, BP 110/65. Her abdominal examination is minimally tender without guarding or rigidity, and her liver is nontender on examination.

*What testing would you pursue?*

- A. None indicated. Treat her with supportive therapy as she has no blood, or severe VS abnormality.
- B. Ova and parasite stool sample × 3
- C. Enteric pathogen stool culture
- D. Enteric pathogens, *Clostridia difficile*, *Giardia* and *Cryptosporidium*, *Isopora*, *Cyclospora* × 3

Correct answer: D.

Diarrhea is a common symptom in both the general and SOT populations. Noninfectious and infectious causes are prevalent, but morbidity and mortality in susceptible immunocompromised SOT patients is much higher.<sup>24</sup> SOT patients can present with infectious causes of diarrhea, with acute onset and chronic presentations. The differential diagnosis favors infectious causes, then medication side effects, and in the setting of prolonged immunosuppression, posttransplant lymphoproliferative disease (PTLD) should be considered.<sup>24</sup> Unlike in stem cell transplant recipients, graft-versus-host disease is an uncommon reason for diarrhea following solid organ transplantation. CMV, *C difficile*, and bacterial pathogens are common infectious causes; parasitic infections are less common (Table 1).<sup>25</sup>

*C difficile*-associated diarrhea (CDAD) is the most common nosocomial antibiotic-associated diarrhea in SOT populations.<sup>26</sup> In the general population we worry about risk factors such as hospitalizations, gastrointestinal surgery, advanced age, uremia, and multiple comorbidities. Most cases of CDAD in SOT patients occur during the first 3 months, owing to associated risk factors of prolonged hospitalization, prolonged

**Table 1**  
**Differential diagnosis of diarrhea in SOT patients**

|               |  |
|---------------|--|
| Infectious    |  |
| Viral         | Cytomegalovirus, rotavirus, norovirus, herpesviruses, adenovirus   |
| Bacterial     | <i>Escherichia coli</i> (shiga toxin-producing strains), <i>Salmonella</i> , <i>Shigella</i> , <i>Clostridium difficile</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Vibrio</i> |
| Parasite      | Cryptosporidia, <i>Isospora</i> , <i>Cyclospora</i> , <i>Giardia</i>   |
| Fungal        | Microsporidia  |
| Noninfectious |  |
| Medications   | Antibiotics, azathioprine, mycophenolate mofetil, sirolimus, tacrolimus  |
| Other         | Idiopathic enteritis or colitis, inflammatory bowel disease, posttransplant lymphoproliferative disease, graft-vs-host disease   |

antibiotic exposure, and the intensity of immunosuppression. Late-onset CDAD in SOT can happen months to years after transplantation, and is associated with intensification of immunosuppression to address rejection or antibiotic exposure.<sup>9,26</sup> The presentation can vary from mild diarrhea to life-threatening sepsis.

A prospective Canadian study of more than 1300 SOT patients found that the incidence of CDAD increased from 4.5% in 1999 to 21% in 2005, and with interventions decreased to 9.5% in 2010. The study showed that CDAD resulting in graft loss, colectomy, or death was more likely in those with a white blood cell count of greater than 25,000, and the finding of pancolitis on CT scan. The presence of both conferred an increased risk for these complicated events by 42%. In such patients, disease progressed despite timely and appropriate antimicrobial therapy.<sup>26</sup> PCPs should be aggressive in their approach to diagnosis and treatment of SOT patients with suspected CDAD and should have a low threshold for hospitalizing SOT patients for expedited care.

Recommendations for diagnostic testing and the initial treatment of acute diarrhea, including *C difficile*, have been previously published. IDSA guidelines specifically consider immunosuppression for diarrhea lasting 7 days or more. However, SOT patients are at higher risk than immunocompetent populations, and for acute diarrhea, regardless of duration, providers should have a high suspicion of bacterial, viral, and parasitic causes.<sup>24</sup> The unique risks in SOT (chronic immunosuppression, medications that commonly cause diarrhea, risk of exposure to antibiotics) can make finding a diagnosis a complex process. Endoscopy with biopsy should be considered in those with a negative noninvasive evaluation. Reported rates of abnormality on colonoscopy and histology range from 20% to 40%, but only 10% of colonoscopy findings lead to a change in medical management.<sup>25</sup>

Regarding follow-up, this patient was diagnosed with cryptosporidiosis via special staining and PCR of a fresh stool sample. Supportive therapy and antimotility agents were initiated alongside a cautious reduction in immunosuppression.

*Cryptosporidium* is a fecal-orally transmitted, water-borne protozoan found worldwide, including in the United States. It is a highly resistant parasite whose oocysts can survive for 3 to 10 days in water despite appropriate levels of iodine and chlorine treatment.<sup>27</sup> Water-borne outbreaks of cryptosporidiosis have been traced to water parks and public fountains. Food-borne outbreaks have also been linked to infected food handlers and unpasteurized apple cider, and person-to-person contact has been described at daycare centers.<sup>27</sup> Whereas it can cause self-limited mild diarrhea in the general population, in children and immunocompromised people

**Box 2****Diarrhea pearls**

- Routine diagnostic studies for the workup of diarrhea in the general population should be used for SOT patients but, if the etiology remains obscure and symptoms persist, meticulously assess for viral, bacterial, and parasitic infections including abdominal imaging and colonoscopy.
- Consider *C difficile* in patients with risk factors, even for community-acquired diarrhea.
- Consider cryptosporidiosis in SOT patients with a history of travel or exposures to water parks.
- *Cryptosporidium* can shed oocysts intermittently, so serial testing on 3 separate days is appropriate. Providers should ask specifically for *Cryptosporidium* testing, as it may not be included on standard ova and parasite testing.
- Immunosuppressive medications may cause diarrhea. Monitor immunosuppressive levels closely, and proactively adjust doses to avoid related toxicities.
- Hand washing with water and soap is an important preventive strategy. Many causes of infectious diarrhea (rotavirus, norovirus, *Cryptosporidium*) are not effectively killed with alcohol-based hand sanitizers.

cryptosporidiosis can cause severe and prolonged diarrhea. A literature review showed *Cryptosporidium* to be an important cause of more severe infectious diarrhea in the SOT population; this is especially true for children with SOT or recipients of intestinal grafts. A retrospective cohort found an increased risk for cryptosporidiosis in men, and in those with a longer duration of diarrheal symptoms and increased tacrolimus (TAC) levels. Cases of cryptosporidiosis that were associated with higher TAC levels also correlated with a self-limited but important increase in creatinine (**Box 2**).<sup>28</sup>

UTIs are very common in adult renal, and kidney-pancreas (K-P) transplant patients (6%–86%),<sup>29,30</sup> being reported in up to 40% of pediatric renal SOT patients.<sup>31</sup> UTIs also affect other SOT recipients but typically occur in the first month posttransplant, owing to the inherent risks of urinary catheterization.<sup>29</sup> In nonrenal SOT patients risk

**Case 4**

A 37-year-old woman with history of renal transplant 5 months ago and history of recurrent urinary tract infections presents with concern for a urinary tract infection (UTI). She endorses 2 days of frequency, urgency, and dysuria. She is mildly nauseated but has no chills, vomiting, or flank pain. She thinks her urine is mildly malodorous and cloudy. Her medications include tacrolimus, prednisone, mycophenolate mofetil, amlodipine, and trimethoprim/sulfamethoxazole SS as pneumocystis prophylaxis. VS: T 38.2°C, HR 88, BP 115/70. She appears well, has no rash or flank tenderness, she has mild tenderness over her surgical site and transplanted kidney, and in the suprapubic area. Her urine dipstick is positive for leukocyte esterase and nitrites.

In addition to sending urinalysis and urine culture, you should treat her empirically with:

- Nitrofurantoin ER
- Trimethoprim/sulfamethoxazole DS
- Ciprofloxacin
- Fosfomycin
- Amoxicillin

Correct answer: C.

factors include female gender, increased age, and diabetes. In renal and K-P transplant patients, the risk of UTI is high for the first year after transplantation. Risk factors include a history of posttransplant dialysis, age, and female gender.<sup>29</sup> Factors that may increase the risk for recurrent UTI include ureteric stricture, vesicoureteral reflux, prolonged urinary catheterization, and overimmunosuppression.<sup>29</sup>

UTIs occur at higher frequency with increased morbidity in renal transplant recipients. Studies are mixed, and have not convincingly demonstrated an increased risk for graft rejection or increased mortality due to UTIs.<sup>29,31,32</sup> Whereas some studies have found that specific immunosuppressive regimens and intensity of immunosuppression appear to increase the risk of UTIs, other studies do not support the notion that UTIs are opportunistic infections in SOT patients. Rather, the increased risk is thought to be due to other factors (**Table 2**) and posttransplant anatomic changes that effectively define all UTIs in renal transplant patients as “complicated UTIs.”<sup>29,30</sup>

Asymptomatic bacteriuria (ASB) without signs and symptoms of infection is common in renal transplant patients. ASB has been associated with increased risk for UTI in the first year, but significant controversy exists about whether it should be treated within that time frame.<sup>33</sup> Candiduria is common, affecting up to 10% of renal transplant patients, but it is mostly asymptomatic.<sup>33</sup> The approach to asymptomatic candiduria is also controversial, given the paucity of available data on this topic. No convincing data exist to show that graft survival, morbidity, or mortality improves with treatment of asymptomatic candiduria in kidney transplant patients.<sup>33</sup>

The diagnosis of cystitis is the same in SOT patients as it is for the general population. The important caveats are that urine culture should be obtained in all SOT patients given the higher risk of multidrug-resistant bacterial infections, and that upper tract (ie, kidney allograft) infections are very common in kidney transplant recipients. Pyelonephritis should be considered in kidney transplant patients with signs/symptoms of cystitis accompanied by fever, bacteremia, increased creatinine, leukocytosis, chills, or pain/tenderness over the transplanted kidney.<sup>29</sup>

| <b>Table 2</b>  |                    |
|---|--------------------|
| <b>Major risk factors for bacterial urinary tract infection and pyelonephritis in renal transplant recipients</b> |                    |
| <b>Risk Factor</b> <sup>Refs</sup>  | <b>OR (95% CI)</b> |
| <b>Bacterial urinary tract infection</b> <sup>13,24,54,57</sup>   |                    |
| Female gender   | 5.8 (3.79–8.89)    |
| Age (per year)  | 0.02 (1.01–1.04)   |
| Reflux kidney disease before transplantation  | 3.0 (1.05–8.31)    |
| Deceased donor  | 3.64 (1.0–12.7)    |
| Duration of bladder catheterization   | 1.50 (1.1–1.9)     |
| Length of hospitalization before UTI  | 0.92 (0.88–0.96)   |
| Increase in immunosuppression   | 17.04 (4.0–71.5)   |
| <b>Acute pyelonephritis</b> <sup>4,25</sup>   |                    |
| Female gender   | 5.14 (1.86–14.20)  |
| Acute rejection episodes  | 3.84 (1.37–10.79)  |
| Number of UTIs  | 1.17 (1.06–1.30)   |
| Mycophenolate mofetil   | 1.9 (1.2–2.3)      |

*Abbreviations:* CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

*Data from* Rice J, Safdar N. Urinary tract infections in solid organ transplant recipients. *Am J Transplant* 2009;9(Suppl 4):S267–72.

Many transplant centers use trimethoprim/sulfamethoxazole as prophylaxis against *Pneumocystis* in renal transplant patients during the first 6 to 12 months after transplantation, and this appears to also decrease the risk of UTI. However, this has also been associated with breakthrough infections caused by trimethoprim/sulfamethoxazole-resistant organisms. Long-term prophylaxis has been shown to decrease the incidence of UTI, although the growing resistance to trimethoprim/sulfamethoxazole among GNRs, reportedly more than 80% in some settings, limits the utility of long-term antibiotic prophylaxis.<sup>29,33</sup>

A multicenter, prospective cohort study followed 4000 SOT patients over 2 years of follow-up, during which 208 episodes of UTI occurred in renal transplant recipients. The vast majority were due to GNRs (>50% *Escherichia coli*, 10% *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, 6% other gram negatives) and only 7% due to *Enterococcus* species.<sup>29</sup> Several studies also identify *Staphylococcus* species as common pathogens in renal SOT patients.<sup>30,33</sup> An alarming amount of antibiotic resistance was observed, with more than one-quarter identified as extended-spectrum  $\beta$ -lactamase resistance (ESBL). Carbapenem-resistant *Klebsiella*, *Pseudomonas aeruginosa*, and vancomycin-resistant *Enterococcus* are all increasing in frequency.<sup>34</sup>

Regarding follow-up, this patient has typical symptoms of cystitis; however, she also has tenderness over her transplanted kidney and fever, suggesting associated allograft pyelonephritis. It is inappropriate to use antibiotics that are effective only for lower UTIs (eg, nitrofurantoin and fosfomycin). The infection has occurred while receiving prophylactic trimethoprim/sulfamethoxazole, making this inappropriate empiric therapy. Despite evidence of growing resistance in some strains, fluoroquinolones remain a reasonable option for empiric therapy.<sup>29</sup> However, at centers with high rates of resistance to fluoroquinolones, treatment with broader-spectrum antibiotics might be appropriate. Other common pathogens causing cystitis/graft pyelonephritis in kidney transplant patients include *Enterococcus* and *Pseudomonas*.

Clinically stable SOT patients without signs of sepsis but with evidence of cystitis can be appropriately managed in the ambulatory setting. However, any concern for graft pyelonephritis should trigger hospitalization and further evaluation. The rate of predisposing anatomic abnormalities is relatively high in kidney transplant recipients with graft pyelonephritis, so further diagnostic workup typically includes CT imaging of the kidneys and/or urological evaluation (for structural or functional abnormalities).<sup>30</sup>

#### Case 5

A 48-year-old woman with history of renal transplant 6 years ago requests a routine preventive care examination. In addition to her usual SOT monitoring, she also requests "booster" shots of any vaccinations you recommend.

Past immunization history: influenza last year, Td 3 years ago, standard childhood vaccinations.

You recommend:

- A. Intramuscular influenza vaccination only
- B. Td only
- C. Flumist (nasal flu vaccine), check titers for tetanus and diphtheria, and revaccinate if low
- D. Yearly influenza vaccination, pneumococcal vaccination with pneumococcal vaccine 13 (PCV13) then pneumococcal polysaccharide vaccine 23 (PPSV23), one-time Tdap (tetanus, diphtheria, acellular pertussis)

Correct answer: D.

As more SOT patients are living longer, PCPs should be prepared to address preventive care concerns. This section focuses on vaccine preventive care issues unique to the infectious risks facing SOT patients, and does not cover noninfectious preventive care.

The key pearls for vaccination in SOT patients are that in general, live vaccines are contraindicated posttransplant, and that the immunologic response to routine vaccinations may be diminished, especially in the first 3 to 6 months after transplantation.<sup>35</sup> This situation suggests that PCPs must be proactive; if a patient's chronic disease condition progresses on a path toward possible SOT, then appropriate live vaccinations (this may include measles, mumps, rubella, zoster, and varicella) should be administered pretransplant, before the patient is immunosuppressed. The American Society of Transplantation (AST) 2009 guidelines recommend that any live vaccines be administered at least 4 weeks before transplant.<sup>36</sup> Even inactivated/killed vaccinations should be considered pretransplant when possible, because of the anticipated better response rate. Although end-stage chronic illnesses that necessitate SOT might be associated with reduced immune response to vaccinations, immunologic response to vaccinations is thought to be even further suppressed in the posttransplant period.<sup>35</sup>

### ***Influenza***

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Three of 4 studies on the response to vaccination to influenza in SOT patients reported significantly reduced protective titers in comparison with normal controls. Lower responses were correlated to SOT patients on combination immunosuppressive therapy. Specifically, mycophenolate mofetil (MMF) and cyclosporine were implicated.<sup>37</sup> Given the substantial morbidity and mortality associated with influenza in immunosuppressed populations, yearly inactivated influenza vaccination is recommended.<sup>35</sup> Live attenuated influenza vaccine is contraindicated in SOT patients.

### ***Pneumococcal***

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SOT patients are at higher risk than the general population for invasive pneumococcal infections.<sup>8</sup> Although pneumococcal vaccination has been shown to be safe in SOT patients, response rates to vaccination are reduced, ranging from 13% to 50% depending on the serotype measured.<sup>38</sup> Major guidelines (AST, ACIP) recommend pneumococcal vaccination in immunosuppressed patients, including those who have received a solid organ transplant, and recent updated guidelines that incorporate both the polysaccharide and conjugate vaccines have recently been published.<sup>39</sup>

- Vaccine-naïve SOT patients are advised to have PCV13 followed by PCV23 8 weeks later.
- In SOT patients who have previously received PPSV23, a dose of PCV13 should be given at least 1 year after the dose of PCV23.
- SOT patients younger than 65 years should have a repeat PPSV23 at 5 years, and those vaccinated before age 65 should have a repeat PCV23 at 65 or 5 years after the first dose.

### ***Tetanus/Diphtheria/Pertussis***

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Immunologic response to tetanus is close to normal in SOT patients, and should be repeated every 10 years as per IDSA/ACIP guidelines. Diphtheria immunity wanes significantly even after the first year, but current guidelines do not recommend checking titers for diphtheria.<sup>36</sup> A single booster dose of pertussis vaccine (Tdap) should be given to adults older than 19 years.<sup>35,40</sup>



### Human Papilloma Virus

The human papilloma virus (HPV) vaccine has not been well studied in SOT patients. It is not a live vaccine and should therefore theoretically be safe in the posttransplant population. The indications for HPV vaccination are similar to those in non-SOT patients.<sup>36,40</sup>

It is safe to give hepatitis A and B, meningococcal, and *H influenzae* B vaccinations after transplant in patients with indications. The first 6 months after SOT, when immunosuppression is at its peak, is not the ideal time for vaccination administration because the immunologic response is significantly diminished.<sup>35</sup>

Because household/other close contacts are presumed to be a primary source for many important infections, it is important for PCPs to counsel SOT patients' families and close contacts on the importance for them to be appropriately immunized. PCPs should add this to their list of annual preventive care reminders for their SOT patients (Table 3).

The risk for cervical cancer is reportedly increased (up to 11-fold) in immunosuppressed patients in comparison with the general population.<sup>41</sup> As such, the recommendation from the United States Preventive Task Force Service (USPSTF) and the American College of Obstetrics and Gynecology is for yearly Papanicolaou smear and pelvic examination for cervical cancer screening in immunosuppressed patients.<sup>42,43</sup> However, this practice is best supported for people immunosuppressed

**Table 3**

**Vaccination recommendations in adults with SOT, and household contacts, before and after solid organ transplantation**

| Vaccination                                | SOT Recipients |      | Household Contacts |      |
|--|----------------|------|--------------------|------|
|  | Pre            | Post | Pre                | Post |
| <b>Inactive</b>                            |                |      |                    |      |
| Influenza                                  | Yes            | Yes  | Yes                | Yes  |
| Hepatitis A                                | Yes            | Yes  | Yes                | Yes  |
| Hepatitis B                                | Yes            | Yes  | Yes                | Yes  |
| Td   | Yes            | Yes  | Yes                | Yes  |
| Tdap                                       | Yes            | Yes  | Yes                | Yes  |
| <i>Streptococcus pneumoniae</i>            | Yes            | Yes  | Yes                | Yes  |
| <i>Haemophilus influenzae</i> <sup>a</sup> | Yes            | Yes  | Yes                | Yes  |
| Human papilloma virus <sup>a</sup>         | Yes            | Yes  | Yes                | Yes  |
| Polio (inactive) <sup>a</sup>              | Yes            | Yes  | Yes                | Yes  |
| <i>Neisseria meningitides</i> <sup>a</sup> | Yes            | Yes  | Yes                | Yes  |
| <b>Live Attenuated</b>                     |                |      |                    |      |
| Influenza (nasal)                          |                | No   | Yes                | No   |
| Varicella (Varivax) <sup>a</sup>           | Yes            | No   | Yes                | Yes  |
| Varicella (Zostavax) <sup>a</sup>          | Yes            | No   | Yes                | Yes  |
| Measles <sup>a</sup>                       | Yes            | No   | Yes                | Yes  |
| Mumps <sup>a</sup>                         | Yes            | No   | Yes                | Yes  |
| Rubella <sup>a</sup>                       | Yes            | No   | Yes                | Yes  |

<sup>a</sup> Optional based on risk factors.

Adapted from ATS 2009 immunization guidelines for SOT, ATS 2009 immunization guidelines for household members of SOT.

by HIV infection. The evidence that HPV causes cervical cancer is excellent, and the increased risk of cervical cancer evidenced in HIV immunosuppression has been extrapolated to apply to SOT patients. However, in 2011 Engels and colleagues<sup>44</sup> evaluated data from a United States registry of more than 400,000 SOT patients and found no increased risk of cervical cancer. In addition, a 10-year prospective case-control study of 48 renal and K-P SOT patients showed no increased risk of cervical cancer in the SOT patients.<sup>45</sup>

Despite the emerging data that immunosuppression in SOT recipients might not necessarily increase the risk of cervical cancer, at present PCPs should follow updated USPSTF cervical cancer screening guidelines from 2012, which explicitly exclude immunosuppressed patients from lengthening the screening interval beyond 1 year.<sup>43</sup>

## SUMMARY

SOT recipients need PCPs who are familiar with their unique needs. Understanding the lifelong infectious risks faced by SOT patients because of their need for lifelong immunosuppressive medications is fundamental. SOT recipients can present with atypical and muted manifestations of infections. The savvy, prepared PCP will keep a careful eye on the patient and initiate a comprehensive evaluation for infectious etiology. PCPs should work together with their local (infectious disease and other) specialists to generate care plans if the diagnosis or management is in question.

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