Chapter 9
Common Symptoms in the Adult Solid Organ Transplant Recipient

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Introduction

Solid organ transplant (SOT) recipients often return to the primary care setting after the first few months following transplantation, especially if their course has been free of serious complications. While they will still have contact with their transplant team—the frequency of which varies by transplant center as well as the patient’s complications—they may present to primary care when they develop new symptoms. Patients may be unsure if the new symptoms are related to the transplanted organ, their immunosuppression, side effects of medications, or an unrelated illness. This chapter explores several common symptoms and offers an approach to the initial evaluation. As will be discussed, if the patient’s presentation is concerning, close coordination with the transplant team is advised, and often transfer to an acute care setting (e.g., emergency department or admission to the hospital) may be indicated for expedited evaluation and treatment.

Respiratory Symptoms

Respiratory symptoms, including shortness of breath and cough, are common concerns of patients presenting to primary care. Cough alone is among the most common reasons for ambulatory visits: excluding visits for general follow-up, medication management, checkups, and postoperative evaluation, it is the number one reason for outpatient visits in the United States [1]. The following section focuses on addressing cough and dyspnea in solid organ transplant recipients who present to care in the outpatient setting.
General Approach

Assess Clinical Stability

- Patients with new-onset hypoxia, severe tachypnea, signs of sepsis, or respiratory distress will need rapid evaluation and treatment in an emergency setting.
- Solid organ transplant recipients are at risk of rapid decompensation in cases of severe infection, and it is generally best to err on the side of caution when considering whether to transfer to a higher level of care.

History

History should be directed toward infectious and non-infectious causes of respiratory symptoms.

- Core transplant history: Important initial information to gather includes the time since transplantation and prior episodes of rejection, as the types of infections to which a solid organ transplant recipient is more susceptible may vary based on this history. (For more in-depth discussion, see Chap. 8).
- Medications: A thorough medication history should be taken. The degree of immunosuppression may be helpful in triaging the potential for opportunistic infections as well as the risk of decompensation.
- Habits: In most cases, solid organ transplant recipients have stopped smoking cigarettes prior to transplantation. However, prior smoking can still lead to complications, including lung cancer and chronic obstructive pulmonary disease. Additionally, patients may have returned to using cigarettes or vaping after transplantation. Patients should be asked about substance use, as inhaled marijuana has been associated with pulmonary aspergillosis in renal transplant recipients [2], although its precise contribution to pulmonary aspergillosis in solid organ transplant recipients overall is uncertain.
- Exposures: As with the general population, recent hospitalization increases the risk for multi-drug resistant organisms, and recent travel should prompt consideration for infectious illnesses not endemic to the current location.
- Associated symptoms:
  - Symptoms such as fever and rhinorrhea may point to an infectious source. Solid organ transplant recipients may contract community-acquired viral infections such as the common cold. However, one must be careful not to prematurely narrow the differential diagnosis if the patient is at higher risk for other opportunistic infections due to increased levels of immunosuppression. Prolonged viral infections may lead to secondary bacterial infection. Due to immunosuppression, the solid organ transplant recipient may not present with typical fevers and the absence of a fever is not reliable enough to rule out infection.
  - While a cough may be infectious (e.g., caused by an upper or lower respiratory tract infection), it is important not to assume an infectious source.
Interstitial and obstructive lung diseases, pulmonary edema, gastroesophageal reflux, and lung cancer all may feature cough as their presenting symptom. Sputum character does not reliably distinguish one cause from another. Hemoptysis should always be evaluated further—history should include asking about other symptoms of infection, including risk factors for tuberculosis, as well as symptoms of malignancy such as systemic symptoms.

- Dyspnea alone (for example, absent symptoms such as rhinorrhea, cough, angina, fever) should lead to a similar differential diagnosis as in the general population, including pulmonary embolism, congestive heart failure, pulmonary hypertension, interstitial lung disease, obstructive lung disease, and systemic illnesses such as anemia. However, one should still consider an atypical presentation of infection as well as malignancy (for example, lung cancer with a pleural effusion) (See Chap. 10).

- **Time course**: Duration and tempo of symptoms cannot solely distinguish among causes of respiratory symptoms, but may nevertheless provide clues.

  - Acute (1–2 days): Consider acute infections more highly on the differential diagnosis, especially if other infectious symptoms are present. Additionally, acute pulmonary embolism should be considered, especially if risk factors are present. However, even chronic conditions may present acutely (e.g., a lung cancer may present with an effusion that becomes symptomatic, or a decreased cardiac ejection fraction may be subclinical until it presents with decompensated heart failure).

  - Sub-acute (2 weeks): Infections, including opportunistic, may still occur. *Pneumocystis jirovecii* pneumonia may present subacutely with cough and dyspnea, although more severe and acute cases can occur in solid organ transplant recipients compared to patients with HIV. Other non-infectious causes should still be in the differential diagnosis.

  - Chronic (weeks to months): In a stable patient with chronic cough, consider traditional causes such as gastroesophageal reflux disease, postnasal drip, and reactive airways disease. Medication side effects and interstitial lung disease should also be considered. For stable outpatients with dyspnea, all causes should be considered, including anemia, heart disease, and lung disease.

  - For all of the above considerations, in the heart or lung transplant recipient, respiratory symptoms should raise concern for rejection or other transplanted organ dysfunction (see below).

- **Special mention should be made for lung and heart transplant recipients.**

  - Lung transplant recipients presenting with dyspnea or cough should have their workup coordinated with the lung transplant specialist, as the transplant team will often recommend an urgent workup for rejection, re-evaluate graft function, and also may perform additional tests for infection (see Chap. 7). Other diagnostic considerations include lung cancer, in which the risk is higher in lung transplant recipients compared to other solid organ transplant recipients (see Chap. 10), and airway stenosis, a unique complication of lung transplantation. Additionally, it is important to know whether the patient received a single
or double lung transplant. In single lung transplant recipients, the native lung may still be diseased—for example, in a patient with a single lung transplant for smoking-related COPD, the native lung remains at increased risk for infection, malignancy, and other complications such as pneumothorax.

Heart transplant recipients have a denervated donor organ, so may not present with typical angina. Dyspnea on exertion may be a sign of coronary artery disease as well as heart failure. As with lung transplant recipients, heart transplant recipients who present with dyspnea without a readily apparent non-cardiac etiology should have their care coordinated with the transplant team, as an expedited workup is likely warranted (see Chap. 6).

Examination

- Examination should include vital signs and a thorough upper respiratory tract, pulmonary, and cardiovascular exam.
- Abdominal exam may be useful if an intra-abdominal process leading to pulmonary symptoms is suspected.
- In patients with dyspnea, assessment should include looking for signs of anemia or other systemic illnesses.

Differential Diagnosis

Infectious

(Infections are covered more in Chap. 8)

- **Pneumonia**: Precise estimates on incidence of pneumonia in solid organ transplant recipients are difficult to obtain. A point-prevalence study in Europe estimated an incidence of 10 per 1000 patients per year [3]. The incidence was highest in lung transplant recipients. The majority presented late (defined as >6 months). Although this sample included outpatient care, the cases identified were primarily in hospitalized patients. Similarly, prior single-center studies showed a high mortality rate, but cases were predominantly nosocomial and early after transplantation [4].

Several fungal infections can cause pneumonia in solid organ transplant recipients. *Pneumocystis jirovecii* is an important causative agent of opportunistic infections in the solid organ transplant population, so much so that most solid organ transplant recipients receive prophylaxis against *P. jirovecii* within the first 6–12 months after transplantation (protocols vary), with lifelong prophylaxis given to lung transplant recipients. Patients with *Pneumocystis jirovecii* pneumonia may present acutely with hypoxia and dyspnea, more commonly than in patients with HIV infection, who often present subacutely with several weeks of progressive symptoms. While prophylaxis is credited to dramatic reductions in *P. jirovecii* pneumonia, cases still occur, especially after prophylaxis has been discontinued, and have been associated with episodes of acute rejection (and
therefore increased immunosuppression), as well as cytomegalovirus (CMV) viremia; additionally, heart and lung transplant recipients are at higher risk compared to other solid organ transplant recipients [5, 6].

Infections due to *Aspergillus fumigatus* are more common than those due to *Pneumocystis jirovecii* and other fungal infections in solid organ transplant recipients [7]. Risk factors include lung and heart transplantation, CMV infection, the degree of immunosuppression, and environmental exposure [7]. Nosocomial infections may occur early after transplantation, but late infections (> 6 months post-transplant) also occur. Pulmonary infections caused by *Aspergillus* may present with cough, fever, hemoptysis, chest pain, and malaise. Patients may manifest symptoms in other organs if the infection has already spread at the time of presentation [7]. Prophylaxis is typically administered in the first few months post-transplant for lung transplant recipients and in some heart transplant recipients (protocols vary) [7].

Other fungi such as Candida species, Cryptococcus, Zygomycetes species, the endemic mycoses coccidioidomycosis and histoplasma all may cause pulmonary infections. Histoplasmosis tends to occur in the later post-transplant period with disseminated disease but can have subacute pulmonary symptoms [7]. In contrast, coccidioidomycosis tends to occur earlier post-transplant and represent reactivation [7]. Blastomycosis is considered rare even in this population [7] (see Chap. 8).

Mycobacterial infections can be divided into infections caused by *Mycobacterium tuberculosis* and those by all non-tuberculous mycobacteria. Pulmonary tuberculosis does occur, and level of suspicion is dependent on exposure and local epidemiologic risk factors. Non-tuberculous mycobacterial pulmonary infections are less common than other pathogenic infections in the solid organ transplant population, but they do occur and should be suspected in patient with chronic cough and especially if systemic symptoms are present. (See Chap. 8).

**Viral infections.** Most solid organ transplant recipients receive prophylaxis against CMV during the first 6–12 months after transplantation (see Chap. 8). Although considered an “early” post-transplant infection, because of effective prophylaxis in the initial post-transplant period, late cases do occur. While multiple immunosuppressive agents decrease T-cell function and increase the risk of CMV, mammalian target of rapamycin (mTOR) inhibitors do not appear to increase risk and may even lower the risk of CMV infection [8]. CMV not only may cause a viral syndrome with non-specific symptoms but also may cause end-organ damage, including pneumonia. As noted above, CMV infection increases the risk for subsequent *Aspergillus* and *P. jirovecii* infections.

A multitude of other viruses may cause respiratory infections—those that may cause lower respiratory tract symptoms include influenza and respiratory syncytial virus (RSV).

- **Upper respiratory tract infections:** Solid organ transplant recipients are susceptible to the common respiratory viruses that cause the common cold, similar to the general population, including rhinovirus and coronavirus. Patients with rhinorrhea and other upper respiratory tract infection (URI) symptoms, without evidence of bacterial sinusitis or lower respiratory tract disease, may be considered to have an iso-
lated URI. However, any patient with a cough or dyspnea should have a broader differential considered in the evaluation. For lung transplant recipients, even mild respiratory viral infections may be associated with a decline in graft function and, therefore, the lung transplant team should be notified (see Chap. 7).

- **COVID-19**: COVID-19 (SARS-CoV-2) became a worldwide pandemic in 2020. At the time of this book’s publication, the presentation, prognosis, and optimal treatment in solid organ transplant recipients is continuing to be studied. Testing should be initiated promptly depending on local epidemiology, and consultation with infectious disease specialists is warranted in this population.

### Non-infectious

Immunosuppression should raise suspicion for infection in a solid organ transplant recipient who presents with respiratory symptoms. However, certain other conditions also have a higher prevalence in the solid organ transplant population.

- **Cancer**: Solid organ transplant recipients have an increased overall risk of malignancy compared to the general population, as well as higher mortality when cancers occur [9]. While studies vary, there is an increased incidence of cancers that may present with pulmonary symptoms, including lung cancer, lymphoma, melanoma, and kidney cancer, in all solid organ transplant recipients [10, 11]. Primary lung cancer, metastatic cancer to the lung, and lymphoma in the lung may present with cough or hemoptysis. Additionally, pleural effusions due directly or indirectly to malignancy may cause dyspnea and pleuritic chest pain (see Chap. 10).

- **Pulmonary embolism**: The risk of venous thromboembolism (VTE) has been shown to be increased in the postoperative period, especially in lung transplant recipients [12]. Long-term VTE risk has been reported in other solid organ transplant recipients, but the majority of studies are retrospective and the incidence rates vary widely [13, 14]. Some studies suggest an ongoing risk for renal-transplant recipients, with increased risk associated with chronic kidney disease, and not associated with immunosuppression [15, 16]. In the absence of more definitive data, one should consider that solid organ transplant recipients presenting to primary care may be at higher risk for VTE, even after the immediate post-transplantation period. As the precise degree of risk is uncertain, providers should continue to assess for traditional VTE risk factors.

- **Interstitial lung disease**: Interstitial lung disease typically presents with a variety of chronic to subacute symptoms, including dyspnea and cough. In addition to exploring traditional risk factors for ILD, in the solid organ transplant recipient, there have been case reports of ILD associated with immunosuppressive medications, including the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus [17–19].

- **Lung transplant recipients**: Lung transplant recipients may present with acute rejection. Acute symptomatic rejection may present with acute dyspnea and cough. Symptoms may be subtle and, therefore, lung transplant centers routinely monitor lung function. In cases of suspected rejection, consultation with the
transplant pulmonologist is critical, and other causes of dyspnea such as airway stenosis and infection will often need to be evaluated urgently (see Chap. 7). Chronic symptoms in lung transplant recipients may arise from Chronic Lung Allograft Dysfunction (CLAD), of which there are two main types – bronchiolitis obliterans syndrome (BOS), and restrictive allograft syndrome (RAS). CLAD may present with chronic dyspnea and cough (See Chap. 7).

- **Heart disease:** Cardiac causes of respiratory symptoms should be considered. Although solid organ transplant recipients are screened pre-transplantation for heart disease (see Chap. 2), they may still develop cardiovascular disease after transplantation. Solid organ transplant recipients are at increased risk of the metabolic risk factors that lead to cardiovascular disease, including diabetes, hypertension, and hyperlipidemia. Cardiovascular disease is increased in kidney transplant recipients, although data on risk in liver transplant recipients is not consistent [14, 20]. Lung transplant recipients have not been shown to have increased mortality from cardiovascular disease, possibly due to the earlier onset of graft dysfunction and lower overall mortality [20]. Heart transplant recipients are at risk for allograft vasculopathy, a form of rejection in the coronary arteries (see Chap. 6).

Causes of dyspnea or cough in solid organ transplant recipients are summarized in Table 9.1.

### Table 9.1 Causes of dyspnea or cough in solid organ transplant recipients

| Infectious                        | Non-infectious                                           |
|----------------------------------|----------------------------------------------------------|
| Upper respiratory tract infection| Pulmonary/lung disease                                    |
| Viral rhinosinusitis             | COPD exacerbation                                         |
| Bacterial sinusitis              | Asthma exacerbation                                       |
| Lower respiratory tract infection| Interstitial lung disease                                 |
| Pneumonia                        | Pulmonary embolism                                        |
| Bacterial                        | Pulmonary hypertension                                    |
| Viral (e.g., CMV); emerging:     | Lung transplant recipients: rejection, chronic lung       |
| COVID-19                         | allograft dysfunction, airway stenosis                    |
| Fungal (e.g., *Aspergillus*, *P. jirovecii*, *Candida* species, endemic mycoses) |                            |
| Mycobacterial                    | Malignancy                                                |
| Bronchitis                       | Primary lung cancer                                       |
| Viral                             | Lymphoma/PTLD in the lungs or mediastinum                 |
| Bacterial                        | Pleural effusion associated with malignancy               |
|                                  | Metastatic disease to the lung                            |
|                                  | Head and neck cancer/laryngeal                            |
|                                  | **Cardiac**                                               |
|                                  | Heart failure                                             |
|                                  | Coronary artery disease                                   |
|                                  | Heart transplant recipients: cardiac allograft vasculopathy; rejection |
|                                  | Medication side effect                                    |
|                                  | ACE inhibitors (cough)                                    |
| **Gastrointestinal**             | Gastroesophageal reflux disease                           |
|                                  | **Upper airway**                                          |
|                                  | Postnasal drip/upper airway cough syndrome                |
| **Metabolic**                    | Anemia                                                    |

9 Common Symptoms in the Adult Solid Organ Transplant Recipient
Additional Testing and Treatment

- Imaging: While one cannot recommend a one-size-fits-all approach, in general one should have a lower threshold to obtain imaging in solid organ transplant recipients who present with respiratory symptoms due to the increased risk of infection and malignancy, as well as their potentially blunted inflammatory response to infection. A chest X-ray is a reasonable first imaging test, but in patients with concerning symptoms, a chest CT is more sensitive.

- Specific tests for respiratory pathogens: While testing for respiratory viruses other than influenza is uncommonly performed in the general population, for solid organ transplant recipients presenting with potentially infectious respiratory symptoms, it is recommended to obtain a nasopharyngeal swab to send for PCR-based tests for viral pathogens.

- Additional testing: Solid organ transplant recipients with serious illnesses such as pneumonia frequently require additional testing such as sputum samples, bronchoscopy, and in some cases biopsy depending on the presentation, imaging findings, and response to treatment.

- If CMV is considered, consultation with an infectious disease specialist is appropriate. Imaging findings are typically bilateral, patchy, and may include ground glass opacities, air-space disease, and small nodules; however, most imaging studies of CMV pneumonitis included only a small number of SOT recipients [21]. CMV disease (in any organ) is diagnosed definitively by tissue. The CMV antigenemia assay is not sufficiently sensitive in the SOT population [22] and has been replaced by PCR [8]. Serology should be determined from reviewing the transplantation history, as CMV-negative hosts who receive organs from CMV-positive donors are at highest risk, but it is not helpful to recheck these tests in the acute setting. While in some cases if other causes are ruled out or are deemed of low likelihood, pneumonitis with CMV viremia may prompt initial treatment for presumed CMV disease, followed by invasive testing if the patient does not respond to initial treatment. However, if other causes are also likely and unable to be ruled out, then early invasive testing with bronchoalveolar lavage may be indicated both to assess for the cytopathic presence of CMV in the lung and to investigate other causes of the patient’s symptoms. In lung transplant recipients in particular, bronchoscopy may be especially important to assess for rejection – consultation with the transplant pulmonologist should be obtained.

- Early consultation is generally recommended for patients with higher risk or more serious presentations. The primary care provider should have a low threshold to consult with the transplant specialist and an infectious disease specialist, and transfer to a higher level of care if necessary.

- Empiric treatment: If influenza is suspected, treatment should be initiated while waiting for confirmatory testing. For suspected community-acquired pneumonia, patients should be triaged for consideration of hospitalization for inpatient treatment. If deemed stable for outpatient treatment for community-acquired pneumonia, then empiric, guideline-concordant treatment should be started, with appropriate assessment of potential drug interactions and whether the patient is at risk for drug-resistant organisms. Empiric treatment should generally not be
started in stable patients in whom opportunistic infections are suspected, as guidance by an infectious disease specialist is usually warranted to identify appropriate testing and management. As noted above, for lung transplant recipients, the transplant team should be contacted prior to empiric treatment, as they may have recommendations to guide choice of treatment and what testing should be performed to help assess for both infection and rejection (see Chaps. 7 and 8).

- Corticosteroids: Corticosteroids for obstructive lung disease exacerbation and reactive airways should be used with caution, as it may affect evaluation of organ rejection—in lung transplant recipients in particular, corticosteroids should not be given (unless emergent) without first consulting the transplant pulmonologist.
- IV fluids: IV fluids should generally not be given to solid organ transplant recipients in the primary care setting. If the patient is sick enough to require IV fluids, then transfer to an acute care setting is indicated. In particular, IV fluids should be administered with caution and only in a well-monitored setting for lung transplant recipients, as the disruption in the lymphatic system makes these patients more susceptible to pulmonary edema. Heart transplant recipients should also generally not be given IV fluids without consultation with the transplant cardiologist, as their volume status and graft function will likely need more urgent assessment.

### Follow-Up

As with any patient, if the solid organ transplant recipient being treated for a pulmonary condition does not improve, one should reconsider the initial diagnosis as well as consider co-infection with more than one organism.

### Key Points

- As with all solid organ transplant recipients presenting with a new symptom, a thorough history and directed exam should be performed.
- Solid organ transplant recipients presenting with potentially infectious respiratory symptoms should generally have a nasopharyngeal swab sent for respiratory virus PCR testing.
- Solid organ transplant recipients are more likely to need advanced imaging and invasive testing for the diagnosis and treatment of serious respiratory conditions.
- Stable lung transplant recipients should not receive empiric IV fluids or corticosteroids without consulting with the transplant specialist first—they are sensitive to pulmonary edema from IV fluids, and corticosteroids can affect workup for rejection.
- A broad differential diagnosis is required for pneumonia in solid organ transplant recipients—in stable patients over 6 months since transplantation, community-acquired pneumonia is common, but other opportunistic infections can still occur.
- Solid organ transplant recipients are at increased risk for cancers that may present with respiratory symptoms.
Urinary Symptoms

Urinary symptoms are common reasons for primary care visits. Once a solid organ transplant recipient is returned to the primary care setting, it is quite likely that if the patient has urinary symptoms, the initial site of contact may be the primary care clinic rather than the specialist’s office. In this section, we consider the solid organ transplant recipient who presents with dysuria and/or hematuria.

General Approach

Assess Clinical Stability

- Patients with signs of sepsis from a urinary tract source will need more rapid evaluation and treatment in an emergency setting.
- SOT recipients are at higher risk of rapid decompensation in cases of severe infection, and it is generally best to err on the side of caution.

History

- Core transplant history: Important initial information to gather includes the time since transplantation and prior episodes of rejection, as the types of infections to which a solid organ transplant recipient is more susceptible may vary based on this history. (For more in-depth discussion, see Chap. 8.)
- Medications: A thorough medication history should be taken. The degree of current immunosuppression may be helpful in triaging the potential for opportunistic infections as well as the risk of decompensation.
- Habits: A history of smoking increases the risk for urinary tract malignancies. Solid organ transplant recipients are generally required to stop smoking prior to transplantation. However, prior smoking continues to pose a risk for future cancers: the risk of bladder cancer is higher in former smokers compared to those who have never smoked [23].
- Exposures: Recent hospitalization increases the risk for multi-drug resistant organisms, and recent travel should prompt consideration for infectious illnesses not endemic to the current location. As with the general population, certain chemical exposures increase the risk for bladder cancer.
- Risk factors for urinary tract infections (UTIs): Risk factors for UTIs in solid organ transplant recipients include age, female gender, and post-transplant dialysis [24]. Other risk factors identified in kidney transplant recipients include age, history of increase in immunosuppression, prior reflux kidney disease, and having a deceased donor [25]. Patients who have had urinary catheters or instrumentation are also at higher risk of UTI.
• *Prior UTIs and local resistance patterns:* Many patients have recurrent UTIs and it is helpful to review prior microbiological data to identify the prior organisms and their antimicrobial resistance.

• *Associated symptoms:*
  
  – Urethral discharge may be a sign of urethritis from a sexually transmitted infection. Patients should be asked about exposure history, including number of partners, type of sexual activity, and condom use, if appropriate.
  
  – Flank pain, fever, chills are suggestive of systemic infection such as pyelonephritis.
  
  – Colicky abdominal or groin pain is suggestive of nephrolithiasis.
  
  – Gross hematuria may be a sign of nephrolithiasis, bladder stones, coagulopathy, benign prostatic hyperplasia, or urinary tract malignancy.

• Special mention should be made for kidney transplant recipients (see Chap. 4):
  
  In the renal transplant recipient, pyelonephritis of the transplanted kidney may present with pain in the lower abdominal quadrant where the transplanted organ is typically located.

### Examination

• Vital signs.

• Examination of the flank and abdomen.

• If present, vaginal symptoms should be evaluated and may require a pelvic examination.

• Prostate exam if symptoms of prostatitis.

• Kidney transplant recipients should have an examination of the abdomen that includes assessment of the transplant site (typically in the left or right lower quadrant).

### Differential Diagnosis

**Infectious**

(Infections are covered more in Chap. 8)

• Urinary tract infections are common in all solid organ transplant recipients in the first several months after transplantation [24]. During this period, the patient will most likely remain primarily in the care of the transplant team. However, even after the first few months post-transplant, urinary tract infections continue to occur in all solid organ transplant recipients, although the incidence is highest in kidney transplant recipients [24]. UTI is a common cause of bacteremia in kidney transplant recipients [26].
• The main issues for UTIs in non-renal transplant recipients are diagnostic accuracy and choice and duration of antibiotic therapy.
• While opportunistic infections do occur in the genitourinary tract, they are less common compared to opportunistic infections at other sites. Candida UTIs do occur, with higher risk in renal transplant recipients.
• Prostatitis may occur in solid organ transplant recipients, but the exact incidence is unknown. It should be suspected if a patient has recurrent UTIs or typical symptoms. While there are case reports of unusual pathogens, including CMV and Cryptococcus, initially typical urinary pathogens should be suspected.
• Urethral discharge, vaginal discharge, and sexual contact should raise concern for sexually transmitted infections. There is little data on the solid organ transplant population as to prevalence, however.

Non-infectious

• Gross hematuria should always be evaluated. Sources can include the kidney itself (glomerulonephritis, renal cysts, renal cell carcinoma), nephrolithiasis or bladder stones, other urothelial tract malignancy, the prostate, and, for kidney transplant recipients, acute rejection.
• In renal transplant recipients, acute rejection may be asymptomatic and found only on laboratory studies, but it may also present with fever, malaise, and tenderness of the transplanted kidney. If these symptoms are present along with an increased level of creatinine, and especially if no infection is found, the transplant nephrologist should be consulted to evaluate for acute rejection.

Additional Testing and Treatment

Solid organ transplant recipients presenting with UTI symptoms (dysuria, frequency, or urgency) should have a clean-catch urinalysis performed.

• Solid organ transplant recipients are at risk for less common pathogens, drug-resistant organisms, and more severe illness. Therefore, it is recommended that solid organ transplant recipients who present with urinary tract infection symptoms should always have urine testing performed, including a culture. This practice is in contrast to low-risk patients in the general population who may be treated empirically with antibiotics based on local resistance patterns without obtaining a formal culture.
• For solid organ transplant recipients, the definition of asymptomatic bacteriuria is the same as for the general population and is defined as a urine culture with \( \geq 10^5 \) colony-forming units/mL in a patient with no symptoms of cystitis and no systemic symptoms [26]. Note however, that in most cases, it is not recommended to obtain a urine culture if a patient is not symptomatic.
The definition of acute uncomplicated cystitis in a solid organ transplant recipient is the following: the presence of local symptoms (dysuria, urinary frequency or urgency, or suprapubic pain) without systemic symptoms or urinary tract instrumentation. The colony count threshold in a urine culture is a matter of some debate. Some guidelines specify a colony count of \( \geq 10^5 \) colony-forming units/mL, the same number as for asymptomatic bacteriuria [28]. However, many authors recommend using a lower threshold in symptomatic patients even in the general population, as some cases of true cystitis are associated with lower colony counts of between \( 10^2 \)–\( 10^5 \) colony-forming units/mL [27].

In kidney transplant recipients, the definitions are similar, with formal classification as shown in Table 9.2 [26]. Some laboratories appropriately offer “reflexive” cultures to be done if pyuria is present. However, because pyuria is not an absolute criterion (although the absence should broaden the differential diagnosis), especially in patients with neutropenia, a culture should be obtained in most cases in patients with urinary tract symptoms.

Empiric treatment:

- For acute, uncomplicated cystitis, a fluoroquinolone, amoxicillin-clavulanate, or a third-generation cephalosporin is recommended as empiric therapy, pending culture results [26]. Guidelines vary with regard to the use of fosfomycin as first-line therapy [26, 28].
- The choice of initial antibiotic should also be modified based on prior UTI results, if available, and local resistance patterns and whether there is a history of hospitalization or instrumentation.
- Note that some guidelines do not recommend nitrofurantoin in solid organ transplant recipients due to risk of adverse effects [28], whereas others allow for its use if the creatinine clearance is \( >60 \) mL/min, and possibly even if \( >40 \) mL/min [26].

Treatment duration: In contrast to simple cystitis in female patients, in which a 3-day course is appropriate, for solid organ transplant recipients (both female and male), the treatment duration is recommended for a longer period, 5–10 days [26, 28].

Pyelonephritis: If the patient’s clinical presentation is consistent with pyelonephritis, in most cases the patient should be transferred to an acute-care setting, as the patient will require IV antibiotics, additional blood tests, and blood cultures, and need close monitoring for risk of sepsis. Diagnostic criteria for pyelonephritis vary. General criteria for pyelonephritis in solid organ transplant recipients (other than kidney transplant) are the following [28]:

- Urine culture \( \geq 10^5 \) colonies/mL and/or bacteremia and fever.
- Costovertebral angle pain (or renal allograft pain in a kidney transplant recipient), chills, or cystitis criteria met (bacteriuria plus symptoms).

Table 9.2 shows the classification of simple cystitis and pyelonephritis in guidelines specifically created for kidney transplant recipients. The differences in criteria for pyelonephritis between kidney transplant and other solid organ transplants.
are subtle, and both guidelines require that the patient have significant systemic symptoms. In a solid organ transplant recipient, such systemic symptoms should generally prompt urgent acute care treatment and further evaluation. Blood cultures should be drawn prior to antibiotic initiation. Further treatment is beyond the scope of this chapter.

- For further discussion of urinary pathogens, risk factors, and treatment, see Chap. 8.
- The workup for gross hematuria is similar to the workup in the general population. The evaluation for infection and kidney stones is straightforward. If this evaluation is negative, then additional testing for malignancy is indicated; generally, consultation with a urologist should be undertaken to discuss cross-sectional imaging and cystoscopy. Solid organ transplant recipients are at increased risk for malignancies.

| Classification                        | Description                                                                 | Laboratory investigations of urine |
|---------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|
| Asymptomatic bacteriuria              | No urinary or systemic symptoms of infection                                | >10^5 CFU/mL uropathogen^ab       |
| Acute simple cystitis                 | Dysuria, urinary urgency/frequency, or suprapubic pain; but no systemic symptoms and no ureteral stent/nephrostomy tube/chronic urinary catheter | >10^3 CFU/mL uropathogen^b       |
| Acute pyelonephritis/complicated UTI  | Fever, chills, malaise, hemodynamic instability, or leukocytosis (without other apparent etiology); flank/allograft pain; or bacteremia with same organism as in urine Dysuria, urgency, frequency, suprapubic pain may or may not be present | >10^4 CFU/mL uropathogen^b       |
| Recurrent UTI                         | ≥ 3 UTIs in prior 12-month period                                           | As above                          |

WBC white blood cell. CFU/mL colony-forming units/milliliter

Reprint from Goldman, et al., with permission [26]  
^aWhile routine treatment of AB is not recommended (see Treatment section), if considering treatment of AB (e.g., in the immediate post-transplantation period), a repeat urine culture is recommended (with care to minimize contamination) to assess the persistence of the same uropathogen. Spontaneous resolution is common.

^bStaphylococcus epidermidis (except if ureteral stent), Lactobacillus, and Gardnerella sp. are unlikely to be uropathogens. Regarding CFU/mL: while most patients with UTI will have >10^9 CFU/mL of a uropathogen in a midstream urine sample, some patients with pyelonephritis may have only 10^4–10^5 CFU/mL of a uropathogen and some patients with cystitis may have even fewer CFU/mL (most data on cystitis with low CFU/mL are only for E. coli). Not all labs report <10^3 CFU/mL.

^cWhile not an absolute criterion (depending on the performance characteristics of the urinalysis or presence of neutropenia), <10 WBC/mm^3 should prompt consideration of a diagnosis other than UTI

Table 9.2 Classification of asymptomatic bacteriuria (AB) and urinary tract infection (UTI) in renal transplant recipients

| Classification                        | Description                                                                 | Laboratory investigations of urine |
|---------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|
| Asymptomatic bacteriuria              | No urinary or systemic symptoms of infection                                | >10^5 CFU/mL uropathogen^ab       |
| Acute simple cystitis                 | Dysuria, urinary urgency/frequency, or suprapubic pain; but no systemic symptoms and no ureteral stent/nephrostomy tube/chronic urinary catheter | >10^3 CFU/mL uropathogen^b       |
| Acute pyelonephritis/complicated UTI  | Fever, chills, malaise, hemodynamic instability, or leukocytosis (without other apparent etiology); flank/allograft pain; or bacteremia with same organism as in urine Dysuria, urgency, frequency, suprapubic pain may or may not be present | >10^4 CFU/mL uropathogen^b       |
| Recurrent UTI                         | ≥ 3 UTIs in prior 12-month period                                           | As above                          |

WBC white blood cell. CFU/mL colony-forming units/milliliter

Reprint from Goldman, et al., with permission [26]  
^aWhile routine treatment of AB is not recommended (see Treatment section), if considering treatment of AB (e.g., in the immediate post-transplantation period), a repeat urine culture is recommended (with care to minimize contamination) to assess the persistence of the same uropathogen. Spontaneous resolution is common.

^bStaphylococcus epidermidis (except if ureteral stent), Lactobacillus, and Gardnerella sp. are unlikely to be uropathogens. Regarding CFU/mL: while most patients with UTI will have >10^9 CFU/mL of a uropathogen in a midstream urine sample, some patients with pyelonephritis may have only 10^4–10^5 CFU/mL of a uropathogen and some patients with cystitis may have even fewer CFU/mL (most data on cystitis with low CFU/mL are only for E. coli). Not all labs report <10^3 CFU/mL.

^cWhile not an absolute criterion (depending on the performance characteristics of the urinalysis or presence of neutropenia), <10 WBC/mm^3 should prompt consideration of a diagnosis other than UTI
that affect the urinary tract. In addition, kidney transplant recipients are at particularly increased risk for kidney cancer (see Chap. 10).

- If rejection is considered in kidney transplant recipients, urgent consultation with the renal transplant specialist is indicated.

**Key Points**

- As with all solid organ transplant recipients presenting with a new symptom, a thorough history and directed exam should be performed.
- If a urinary tract infection is suspected, urinalysis with culture should be obtained for all solid organ transplant recipients.
- Treatment for uncomplicated UTI in solid organ transplant recipients is typically 5–10 days.
- Consultation with the kidney transplant team is indicated for kidney transplant recipients who present with a UTI.
- For severe infections (e.g., pyelonephritis), transfer to an acute care setting should strongly be considered.

**Gastrointestinal Symptoms: Diarrhea**

Diarrhea is a common complaint in solid organ transplant recipients with a prevalence ranging from 20% to 50% [29]. Solid organ transplant recipients are particularly susceptible to complications from diarrheal illnesses, including volume depletion, increased toxicity of medications, organ rejection, and death. The evaluation and management of diarrhea in a solid organ transplant recipient differ compared to the general population due to a higher risk of infections, side effects due to immunosuppressive medication, and rapid clinical deterioration.

**General Approach**

**Assess Clinical Stability**

- Patients will need more rapid evaluation and treatment in an emergency setting if they have any of the following:
  - Vital sign instability
  - Signs of sepsis from a gastrointestinal (or other) source
  - Severe volume depletion requiring IV fluid resuscitation
  - Frailty and ongoing large-volume diarrhea, anticipating that volume depletion will occur imminently even if not present on initial evaluation
- Symptoms or signs of acute gastrointestinal bleeding in addition to diarrhea
- Acute abdomen, signs of peritonitis on exam
- Inability to take oral medications—including immunosuppressive medications, due to ongoing nausea and vomiting

- Solid organ transplant recipients are at higher risk of rapid decompensation in cases of severe infection, and it is generally best to err on the side of caution.

**History**

- Core transplant history: Important initial information to gather includes the time since transplantation, prior episodes of rejection, as the types of infections a solid organ transplant recipient is more susceptible to may vary based on this history. (For more in-depth discussion, see Chap. 8.)
- Time course: Acute diarrhea (< 14 days) without obvious non-infectious source is often from an acute infectious etiology. Chronic diarrhea (> 30 days) may be infectious, but an expanded list of pathogens should be considered (see Differential Diagnosis below), as well as other non-infectious sources.
- Associated symptoms:
  - Blood may be associated with bacterial infections (dysentery), but it is not specific—it may also be seen in inflammatory bowel disease and bowel ischemia.
  - Nausea and emesis may indicate an ileus, obstruction, or upper gastrointestinal tract problem; however, it is nonspecific. Many infectious diarrheal illnesses do not typically cause nausea and vomiting, however.
  - Malabsorption: Patients may give a history of an “oily sheen” in the toilet, or intolerances to certain foods.
  - Abdominal pain: Many medication-induced causes of diarrhea may cause cramping but not typically severe pain. Severe pain should raise concern for severe bacterial infection, perforation, ischemia, and inflammatory bowel disease.
- Stool pattern: Unremitting diarrhea without association with food intake is more likely to be secretory than malabsorptive or osmotic, and more likely to be infectious. Symptom pattern in the immunosuppressed patient is not completely reliable, however.
- Medication history:
  - Level of immunosuppression: higher doses (for example, patients with lung and heart transplants tend to have higher maintenance dosing, or patients with a history of rejection requiring recent pulse doses of corticosteroids or a higher maintenance dose) are associated with a higher risk of opportunistic infections.
  - Mycophenolate is a component of the most commonly used regimen for many solid organ transplant recipients and frequently causes diarrhea. The medication history should be reviewed for any recent initiation or increase in dose of mycophenolate.
– Immunosuppressive medications such as tacrolimus also commonly cause magnesium wasting, requiring oral magnesium supplementation, which may in turn cause diarrhea.
– Diarrhea may affect medication levels. For chronic diarrhea, immunosuppressive medication trough levels should be reviewed and rechecked if necessary.

• Exposures:
  – Antibiotics: Patients should be asked about any recent infections that may have been treated with antibiotics, including urgent care visits or dental infections. Antibiotic exposure increases the risk of antibiotic-associated diarrhea, Clostridioides difficile infection, as well as resistant pathogens.
  – Hospitalization: Recent hospitalization increases the risk of hospital-acquired organisms.
  – Travel: Solid organ transplant recipients frequently travel and do not always have pre-travel counseling (See Chap. 12). Given the increased susceptibility to opportunistic infections, if the patient has traveled recently, they may have acquired other infectious organisms not typically seen in the patient’s home region.
  – Food: Untreated sources of water may be a source of parasitic infections.

Examination

• Vitals signs
• Mucous membranes, skin turgor, and other assessment of volume depletion
• Cardiopulmonary exam
• Abdominal exam, assess for tenderness, peritoneal signs, masses
• Stool for appearance of melena, emesis (if present) for appearance of blood

Differential Diagnosis

Infectious causes of diarrhea in solid organ transplant recipients are discussed in more detail in Chap. 8. Following is a brief list (Table 9.3):

• Clostridioides difficile infection (CDI). Clostridioides difficile is the leading cause of infectious diarrhea in solid organ transplant recipients with incidence rates ranging from <1% to 23% [29, 30]. Higher rates occur in liver and lung transplant recipients and the lowest rates are in patients with kidney transplants [29, 31]. Compared to the general population, solid organ transplant recipients are at even greater risk for CDI due to immunosuppression, recent surgery, antibiotic treatments, ganciclovir prophylaxis, gastric acid suppression, and prolonged hospital stays [30]. Additional risk factors include enteral feeding, gastrointestinal surgery, obesity, cancer chemotherapy, hematopoietic stem cell transplantation, inflammatory bowel disease, and cirrhosis [32]. Although the use of multiple antibiotics, broad-spectrum antimicrobials, and longer durations
of antibiotic therapy clearly increase the risk for CDI, in immunosuppressed patients CDI is more likely to occur even in the absence of antibiotic use [33]. The illness spectrum of CDI ranges from asymptomatic carrier to mild or moderate diarrhea all the way to fulminant pseudomembranous colitis. In solid organ transplant recipients the development of CDI increases rates of graft dysfunction and other infections such as cytomegalovirus (CMV) or pneumonia, results in mortality rates between 2.3% and 8.5%, and is an independent predictor of death [29].

- **Cytomegalovirus.** CMV infection is defined as the presence of CMV replication in the blood (positive DNA by PCR or nucleic acid amplification testing, positive CMV antigenemia, or positive CMV culture) and can be symptomatic or asymptomatic. CMV disease is defined as CMV infection accompanied by clinical signs and symptoms. CMV disease may result in a CMV syndrome (fever, malaise, atypical lymphocytosis, leukopenia or neutropenia, thrombocytopenia, and elevated hepatic transaminases) or end-organ CMV disease, including gastrointestinal disease, pneumonitis, hepatitis, nephritis, myocarditis, pancreatitis, encephalitis, and retinitis. CMV has a predilection to infect the transplanted allograft, hence more likely causing symptoms and end-organ damage in the grafted organ [34].

CMV infections most often occur between 30 days and 6 months after transplantation, as this is the time when immunosuppression tends to be maximal. In patients not receiving CMV prophylaxis (duration depending on the type of transplanted organ, patient and donor serostatus, and transplant center protocols), CMV infection typically occurs within 3 months of transplantation. The onset of

**Table 9.3** Causes of diarrhea in solid organ transplant recipients

| Infectious                | Non-infectious            |
|---------------------------|---------------------------|
| **Bacterial**             | **Medication side effect**|
| Enteric pathogens (e.g., E. coli, Shigella, Salmonella, Campylobacter) | Mycophenolate |
| C. difficile              | Magnesium                 |
| Viral (e.g., CMV, norovirus, rotavirus)* | Antidepressants |
| Parasitic (e.g., Giardia, Cryptosporidium, Cystoisospora, Microsporidium, Cyclospora) | Stool softeners, laxatives |
| Gastrointestinal          | Proton pump inhibitors    |
| Irritable bowel syndrome  | Metformin                 |
| Inflammatory bowel disease| Antibiotics               |
| Microscopic colitis       | Gastrointestinal Lymphoma/PTLD |
| Small intestine bacterial overgrowth | Colon cancer |
| Malabsorption             | Neuroendocrine tumors     |

*The emerging coronavirus COVID-19 (SARS-CoV-2) may present with gastrointestinal symptoms including diarrhea. At the time of this publication, data on this virus’ symptoms in solid organ transplant recipients continues to evolve.*
disease may be delayed among patients receiving anti-CMV prophylaxis and also tends to occur within 3–6 months after completion of antiviral prophylaxis in CMV donor-positive/recipient-negative solid organ transplant recipients [34]. Donor and recipient CMV serostatus prior to transplantation is the most significant risk factor with the highest risk of infection occurring in CMV-seronegative recipients of a CMV-seropositive donor organ. In solid organ transplant recipients, the most common site of tissue invasive disease is the gastrointestinal tract, potentially causing esophagitis, gastritis, enteritis, and/or colitis. Typical symptoms include abdominal pain, diarrhea, and fever; however, signs may be subtle and present as mild epigastric discomfort or dyspepsia. CMV gastrointestinal disease has been associated with disorders such as inflammatory bowel disease as well as co-infection with C. difficile. CMV hepatitis, cholangitis, cholangiopathy, and pancreatitis also occur and may or may not have associated diarrhea [29].

In addition to causing direct symptoms and tissue-invasive disease, CMV infection can cause indirect effects such as allograft dysfunction or rejection and increased susceptibility to other opportunistic infections and death. One study demonstrated graft dysfunction in one of six patients with CMV-associated colitis [35].

• **Norovirus.** More than 90% of non-bacterial infectious diarrhea cases are due to norovirus with outbreaks occurring year-round but most commonly during the winter months. Transmission occurs via fecal-oral route, contact with contaminated surfaces, or via inhalation of aerosols from vomitus. In immunocompetent patients, norovirus tends to cause acute diarrhea lasting a few days; however, either acute or chronic diarrhea can occur in solid organ transplant recipients. Many solid organ transplant recipients with norovirus will develop weight loss and acute renal failure due to volume depletion.

• **Parasitic** causes of diarrhea in solid organ transplant recipients are less common but important to consider especially when other etiologies are not identified. Giardia and cryptosporidium are among the most common parasites to cause infection. If no diagnosis is made, then further investigation should be undertaken for more unusual pathogens such as Microsporidia, Cystoisospora, Cyclospora, and other ova and parasites [29]. As endemic parasites vary worldwide, local epidemiology should be considered.

Non-infectious Causes

• **Drug-induced diarrhea.** Drug-induced diarrhea is common in solid organ transplant recipients and may be due to the direct effects of the immunosuppressive drugs or due to other medications commonly administered including antibiotics, colchicine, or laxatives.

  – Compared to other immunosuppressive medications, mycophenolate mofetil (MMF) or mycophenolic acid (MPA) are more commonly associated with gastrointestinal side effects including nausea, vomiting, and diarrhea [35, 36].
The diarrhea associated with MMF and MPA is dose-dependent due to direct enterocyte damage. Diarrhea caused by mycophenolate may be bothersome but usually is not severe; however, in some cases, it may lead to dehydration, gastrointestinal hemorrhage, or perforations [37]. Additionally, a rarer disease similar to inflammatory bowel disease can occur.

- Calcineurin inhibitors such as tacrolimus or cyclosporine can cause diarrhea due to their macrolide effects, which can increase gut motility [29].
- Although less common, sirolimus and everolimus can also cause diarrhea.
- Non-immunosuppressive medications commonly used in solid organ transplant recipients that are frequently implicated in causing diarrhea include anti-bacterials, anti-arrhythmics, diabetic agents, laxatives, proton pump inhibitors, and magnesium supplementation. A careful review for these medications with dose adjustments or discontinuation may be appropriate with the guidance of the transplant team [29].

- **Graft-versus-host disease (GVHD).** GVHD is a multisystem disorder that occurs when the immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient. GVHD is most commonly a complication of allogeneic hematopoietic cell transplant (HCT). It is a rare complication in solid organ transplant recipients, generally only occurring in liver and small intestine transplantation [29]. Acute GVHD usually occurs between 2 and 6 weeks after liver transplantation; however, this can be variable with late onset cases seen in other transplant settings [38]. (Small intestine transplantation is not covered in this book). The clinical presentation of solid organ transplant-associated GVHD includes skin rash, diarrhea, abdominal pain, gastrointestinal bleeding, fever, and in most cases quickly advances to become a multisystem disease affecting the bone marrow and other non-transplanted organs [29, 38]. The characteristic skin rash presents as red to violet maculopapular lesions first appearing on the hands and soles but may progress to the whole body, coalesce, and in severe cases lead to the development of vesicles or bullae. The mortality rate of SOT-associated GVHD can exceed more than 75% [38]. Diagnosis is based on clinical symptoms, pathologic changes in biopsied tissues, and systemic lymphoid chimerism.

- **Post-transplant lymphoproliferative disorder (PTLD).** Post-transplant lymphoproliferative disorder (PTLD) is an important malignancy to recognize in solid organ transplant recipients. It is a lymphoproliferative disorder with varying subtypes, often similar to B-cell lymphoma, and is associated with higher levels of immunosuppression as well as unfavorable Epstein-Barr virus serostatus (donor positive, recipient negative). PTLD can affect virtually any organ system and has a variable presentation. Extranodal masses occur in more than half of the cases of PTLD and can involve the gastrointestinal (GI) tract, lungs, skin, liver, central nervous system, and allograft. When PTLD occurs extra-nodally, the gastrointestinal system is most commonly affected. Since PTLD can occur anywhere along the GI system, symptoms may include chronic diarrhea, weight loss, protein-losing enteropathy, abdominal pain, and anorexia [29].
• **Small intestine bacterial overgrowth (SIBO).** Small intestine bacterial overgrowth may account for more than 10% of cases of chronic diarrhea in solid organ transplant recipients. SIBO occurs when bacteria colonize the upper small bowel leading to malabsorption and diarrhea. Immunosuppression, exocrine pancreatic insufficiency, achlorhydria, anatomic abnormalities (e.g., ileocecal resection and blind loop syndrome), and small bowel motility disorders predispose to SIBO. In many cases, the etiology may be multifactorial. Patients may be asymptomatic or symptoms can range from mild, mimicking irritable bowel syndrome (abdominal pain or discomfort, bloating, cramping, flatulence, chronic diarrhea), to severe, resulting in steatorrhea, malabsorption, and weight loss [39].

• **Inflammatory bowel disease (IBD).** Inflammatory bowel disease may occur de novo in solid organ transplant recipients but more commonly it presents as an exacerbation of preexisting disease. De novo development of IBD is ten times the incidence of IBD in the general population and is increased in CMV mismatch patients (seropositive donor, seronegative recipient). Recurrent IBD following transplantation appears to have a more aggressive course than de novo IBD and many patients will require escalation in medical therapy or colectomy for refractory disease. The risk of IBD recurrence post-transplantation includes active disease at the time of transplantation, short duration of IBD prior to transplantation, and the use of tacrolimus. Azathioprine and 5-aminosalicylates appear to be protective [39, 40].

• **Microscopic colitis.** Either subtype—lymphocytic colitis or collagenous colitis—can cause chronic watery diarrhea. In one study of kidney and kidney-pancreas transplant patients, the incidence of microscopic colitis was 50-fold higher in the solid organ transplant recipients compared to the general population. A definitive diagnosis requires histologic evaluation of large bowel biopsies [39].

• **Colon cancer.** Colon cancer risk may be increased in solid organ transplant recipients, and although rare, it may manifest as post-transplant diarrhea. Several studies have demonstrated a two- to threefold increased risk of colon cancer in transplant recipients. Cancers may also develop at a younger age and behave more aggressively [39].

### Additional Testing and Treatment

Given the broad differential diagnosis, solid organ transplant recipients who present with diarrhea require at least basic testing. With the above history, exam, and differential diagnosis in mind, a suggested approach is shown in Fig. 9.1.

• The clinically unstable patient should be immediately transferred to an acute care setting such as the emergency department or admitted to the hospital. Signs of clinical instability include tachycardia, hypotension, orthostatic vital signs, intractable nausea or vomiting, severe abdominal pain or acute abdomen, melena, and hematemesis. Clinical judgment should be exercised in patients who are not
immediately unstable but appear to be at risk of becoming unstable—this category includes patients who are not yet volume depleted but whose diarrhea is so profuse that they are not expected to be able to maintain hydration and patients who cannot tolerate oral intake in whom vital immunosuppressive medications may be missed. Additionally, strong consideration should be made for admitting frail or elderly solid organ transplant recipients who present with severe diarrhea, as the likelihood of volume depletion is high. The workup after admission is beyond the scope of this book, but it would typically include volume resuscitation, stool testing, consultation with transplant team, infectious disease and/or gastroenterology specialists.

Fig. 9.1  Suggested approach to evaluation of diarrhea in solid organ transplant recipients*

- In a stable patient, a workup is still recommended in almost all cases. This practice is in contrast to the general population, many of whom may be diagnosed clinically with a viral gastroenteritis and be treated with supportive care alone.
  - Medications: It is recommended to stop any medications that may be causing or worsening diarrhea. However, any potential changes in immunosuppressants should be directed by the transplant specialist. Medications are less
likely to be causal if the diarrhea is acute and severe in onset without recent medication changes; if there is associated nausea and vomiting; if there is severe abdominal pain or signs of bleeding; and if there are other signs of infection such as fever and chills.

– Acute diarrhea (<14 days):

Compared to immunocompetent patients, the evaluation of diarrhea in solid organ transplant recipients should be worked up more expeditiously due to the risk of severe complications. For very acute cases (e.g., diarrhea of 1–3 days’ duration) in solid organ transplant recipients who are >6 months since transplantation, evaluation for common bacterial pathogens and common viruses, as well as *C. difficile* is indicated. A serum CMV PCR is also a reasonable initial test as CMV colitis can occur late after transplantation, although this test by itself does not make a diagnosis of CMV colitis. For acute diarrhea in the 7–14 day period, it is additionally reasonable to consider early testing for parasitic causes, depending on the results of the initial testing (if completed) and exposure history.

If available, a stool enteric pathogen PCR panel that includes bacterial pathogens, *C. difficile*, and common viruses is a good initial assay in addition to the serum CMV PCR. If not available, then bacterial and viral pathogens can be tested separately from the Giardia antigen and ova and parasite testing.

If the initial testing is negative and the diarrhea persists, then consultation with a gastroenterologist is indicated, as workup for CMV colitis with endoscopy, and/or testing for SIBO, may be required.

– Persistent (14–30 days) and chronic diarrhea (>30 days):

If the patient presents late in the course with prolonged diarrhea, then all testing for acute causes should still be performed, although bacterial enteric pathogens become less likely to be a cause. In solid organ transplant recipients, viruses such as norovirus can lead to a chronic diarrhea not typical of immunocompetent hosts. In addition, testing for parasitic causes should be performed. As mentioned above, a serum CMV PCR and a stool multi-assay for bacterial pathogens, viruses, *C. difficile*, and parasites are reasonable first steps if available.

If the initial testing is negative, then consultation with a gastroenterologist familiar with immunosuppressed patients is appropriate for consideration of colonoscopy and possible upper endoscopy to evaluate for CMV infection, inflammatory bowel disease, microscopic colitis, and malignancy, depending on the overall clinical suspicion. Note that the definitive diagnosis of CMV infection requires biopsy for histopathology and that the CMV viral load by blood test can be negative but tissue gastrointestinal examination positive—when uncertain, a transplant infectious disease specialist should be consulted.

• Treatment is directed at the underlying etiology if found. Empiric treatment (e.g., antibiotics) is generally discouraged in a stable patient, with preference to making a correct diagnosis.

• If no clear cause is found, the primary care provider should continue to work with the transplant team and gastroenterology consultant to consider adjustments in medications, as well as further workup for malabsorption and less common causes
of diarrhea. Empiric treatment with anti-diarrheal medications is appropriate if infectious causes are ruled out; some authors also recommend a trial of probiotics.

- For a more detailed discussion of infectious causes, see Chap. 8. Note that the evaluation algorithm above differs slightly from infectious disease guidelines to reflect triage for clinical factors and time course.
- COVID-19/SARS-CoV-2: The novel coronavirus may present with gastrointestinal symptoms. Depending on local epidemiology, this virus should be considered in the differential diagnosis of solid organ transplant recipients presenting with diarrhea. However, optimal diagnostic and treatment strategies are still being determined–local public health guidelines in combination with transplant infectious disease specialists should be consulted regarding assessment for and treatment of COVID-19 in this population.

### Key Points

- As with all solid organ transplant recipients presenting with a new symptom, a thorough history and directed exam should be performed.
- An early workup for infectious causes is generally indicated for solid organ transplant recipients who present with diarrhea, especially if other infectious symptoms are present and no obvious recent medication change was made.
- Infectious workup generally includes serum CMV PCR and stool tests for enteric bacterial pathogens (more likely in acute diarrhea), *C. difficile* (any duration), viruses (any duration), and parasitic causes (more likely persistent or chronic).
- Invasive testing with colonoscopy may be required if initial testing is negative, or to assess for CMV gastrointestinal disease and inflammatory bowel disease.
- Consultation with a gastroenterologist and infectious disease specialist is often indicated if the initial workup is negative, or to assist with prioritizing testing and empiric treatment.

### Dermatologic Issues in Solid Organ Transplant Recipients

Skin manifestations occur commonly in solid organ transplant recipients. The most common occurrence is skin cancer. Infections, graft versus host disease, and cosmetic complications of immunosuppressive agents should also be considered.

### Malignancy

The risk of malignancy increases in solid organ transplant recipients due to the long-term use of immunosuppressive therapies (see Chap. 10). The most common site to develop malignancy is the skin, accounting for up to 40% of malignancies in solid organ transplant recipients. Skin cancers in solid organ transplant recipients are more aggressive, invasive, and metastatic compared to healthy controls [41]. A
variety of factors increase the development of skin cancer, including intensity and duration of immunosuppression, ethnic background, sun exposure history, and geographic location. More than 50% of skin cancers will develop in white solid organ transplant recipients with rates of approximately 6% in nonwhite solid organ transplant recipients [42, 43]. Interestingly, as opposed to white patients, in nonwhite patients two-thirds of these skin cancers develop in partial sun-exposed areas or sun-protected areas including the genitals [44]. (Note the terms “white” and “nonwhite” are listed here because these categories were used in these studies).

Regular skin exams are important in the care of the solid organ transplant recipient. The frequency of skin examination may range from once yearly if there is no history of skin cancer or actinic keratosis (AK) to every 3–6 months in the setting of nonmelanoma skin cancers, AKs, and melanomas. The recommended frequency of skin exams varies depending upon risk factors, medical history, degree of immunosuppression, and history of type and number of skin cancers. Rapidly developing tumors, aggressive tumors, or metastatic skin cancer requires more frequent exams usually every 4–6 weeks. Skin cancer exams should also include palpation of lymph nodes. Involvement of dermatologists in the care of solid organ transplant recipients is often indicated. The use of chemoprevention of skin cancer may be appropriate in some patients and should be guided by dermatologists.

**Nonmelanoma Skin Cancers (NMSC)**

Nonmelanoma skin cancers including squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) occur the most often. However, solid organ transplant recipients are also at risk for melanoma and Kaposi sarcoma. As compared to the general population in whom BCCs are more common, solid organ transplant recipients are 65–250 times more likely to develop SCC and 6–16 times more likely to develop BCC [43, 45, 46]. As the time from transplantation increases, the risk of skin cancer also increases. Based on a large cohort of over 10,000 adult United States transplant recipients who received their primary transplant in 2003 and were followed for a median time of 6 years, the predictors of post-transplant skin cancer included the following (in order of importance): white race, history of pre-transplant skin cancer, age at transplantation ≥50 years, male sex, and thoracic organ transplant [47]. Several other large studies found similar findings and predictors for skin cancer [48, 49].

The proposed pathogenesis for higher rates of skin cancer in solid organ transplant recipients includes the effects of immunosuppressive medications in reducing immune surveillance and leading to the survival and proliferation of atypical cells; direct or contributory carcinogenic effects of the calcineurin inhibitors such as azathioprine and cyclosporine; or proliferation of oncogenic viruses [41].

In patients with very little natural skin pigment, SCC most often develops in sun-exposed areas. The development of SCC on non-sun-exposed areas is much less common overall; however, SCC in sun-protected areas more commonly occurs in patients with more pigmented skin. The development of SCC within areas of chronic inflammation and scarring is also more likely to occur in patients with more pigmented skin. In addition to examining sun-exposed areas, close inspection of the
anus, genitalia, and periungual region (most often due to HPV exposure) and sites of chronic inflammation and scarring is important. SCC arising on the external ear or at mucocutaneous interfaces such as the lips, genitalia, and perianal areas tend to be more aggressive with rates of metastasis estimated to range from 10% to 30% [50].

The typical description of an SCC in immunocompetent patients includes the development of one or more red, scaly, well-demarcated superficial plaques. Lesions may also be papular, nodular, skin-colored, or pigmented or present as a cutaneous horn. The pigmented variant is more common in patients with more darkly pigmented skin. The appearance of SCC may change depending upon the location and one should maintain a high level of suspicion when evaluating persistent skin lesions.

Numerous SCC or actinic keratosis may develop in solid organ transplant recipients especially if they have light natural skin pigment and a history of extensive sun exposure. The scalp and back of the hands are common sites for multiple SCC or AKs. The incidence and mortality of SCC are increased in transplant recipients. Solid organ transplant recipients are also more likely to develop lip cancer [51]. Pain is not a typical symptom of SCC; however, in solid organ transplant recipients, this could indicate an invasive tumor which may be associated with increased overall mortality [52].

Nodular basal cell skin cancer is the most common type of BCC; however, there are other subtypes of BCC including superficial, pigmented, and infiltrating. Therefore, high clinical suspicion is needed for BCC when not presenting in the more familiar nodular manner. The typical presentation of nodular BCC in immunocompetent and solid organ transplant recipients is as a pearly papule(s) or nodule(s) with rolled borders and overlying telangiectasias in sun-exposed areas. Ulceration and focal pigmentation are often seen.

Shave, punch, or excisional biopsies may be used for the diagnosis of SCC or BCC. Ideally, biopsies should extend to at least the mid-reticular dermis in order to allow for adequate evaluation of invasive disease. Once diagnosis is confirmed, referral to dermatology surgery for additional resection is often needed.

**Melanoma**

Melanoma risk is increased in solid organ transplant recipients. Based on information from a large investigation conducted in the United States, it has been shown that the incidence of melanoma increases sharply in the first 4 years after transplantation before declining steadily. Risk also increases with the intensity and duration of immunosuppression. Compared to the general population, the risk of melanoma is more than twofold higher in solid organ transplant recipients with higher rates in kidney transplant recipients than in liver or lung recipients. Male sex, increasing age, and azathioprine maintenance therapy were also associated with increased rates of melanoma [53]. These risk factors along with the use of cyclosporine or sirolimus were confirmed by another large study in renal transplant recipients [54]. Transmission of melanoma from organ donors to organ recipients has also been reported. Compared
to non-transplanted patients, melanoma-specific mortality is higher in transplant recipients even when stage and treatment are taken into account [55].

Although melanoma is more common in patients with less skin pigment, the risk of melanoma may still be increased in patients with more skin pigment with certain solid organ transplants. Based on a large study of renal transplant patients, it has been shown that the annual incidence of melanoma was 17 times greater in African-American transplant recipients than in the African-American general population [56].

There are four main subtypes of melanoma: superficial spreading (most common type), nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma (the least common type). The appearance of the melanoma will vary based on the subtype but several features will be shared. Utilizing the rules of the ABCDEs when evaluating pigmented lesions is helpful. These include Asymmetry of pigmented lesions, irregularity of Borders, change or variegation of Color, large Diameter (greater than 6 mm), and Evolution. Ulceration and bleeding are generally late signs. The majority of melanomas arise de novo; however, about 30% may arise from a preexisting nevus. Although most melanomas are pigmented, some may appear to lack or contain little pigment and are referred to as amelanotic melanoma.

When suspicion for melanoma is high, punch or excisional biopsy is recommended. Sampling the entire lesion is recommended when possible. Ideally, the biopsy should reach the subcutaneous fat plane. This provides enough depth of tissue for the dermatopathologist to visualize the melanoma and provide accurate staging parameters that guide treatment decisions and prognosis.

Kaposi Sarcoma

Immunosuppression increases the risk of the herpes human virus-8 (HHV-8)-associated Kaposi sarcoma (KS). Rates of KS are highest in males, patients with less skin pigment, and lung transplant recipients. KS develops rapidly after organ transplantation with a mean interval of 13 months [42].

KS lesions may be faint, red-purple macules, papules, plaques, tumors, or nodules. They are often oval and may form along the lines of skin cleavage. In people with more skin pigment, lesions may be more subtle and easy to miss. Assessing for KS should including looking for hues of red and purple on a darker background, and assessment of associated local lymphadenopathy. Koebnerization (lesions occurring in areas of trauma) can occur. Cutaneous and/or mucosal lesions occur approximately 90% of the time. Most common areas of involvement are the trunk and central face, especially the nose. Visceral involvement develops in 25–30% of renal transplant recipients and 50% of heart or liver transplant recipients. The most frequently involved organs include the GI tract, lungs, and lymph nodes [42].

Punch or excisional skin biopsy is recommended for diagnosis and allows for the evaluation of the dermis and subcutis.
Infection

Immunosuppression in the setting of solid organ transplantation predisposes patients to the development of dermatologic infections. Etiology may be bacterial, mycobacterial, viral, or fungal. Often patients will experience co-infections. Human papilloma virus–associated warts are also common. The characteristic appearances of these infections may be altered in the setting of a transplant. Consequently, microbiologic and histologic tests should not be delayed. Within the first 3 months after transplantation, common bacterial and viral infections predominate. In the later period after transplantation, more rare bacterial infections and opportunistic infections such as those caused by fungi may be seen. (See Chap. 8).

Graft-Versus-Host Disease (GVHD)

GVHD is a multisystem disorder which is most commonly a complication of allogeneic hematopoietic cell transplant (HCT) and occurs when the immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient. The development of GVHD is very rare in solid organ transplant patients but it is potentially lethal. Solid organ transplant–associated GVHD most commonly occurs in liver and small bowel transplants recipients usually between 2 and 6 weeks after transplantation. Late onset cases, however, have been seen in other transplant settings [38].

The clinical presentation of solid organ transplant–associated GVHD is variable. The organs most frequently involved are the skin, liver, and intestinal mucosa. In most cases, GVHD quickly advances to a multisystem disease that affects the bone marrow and other non-transplanted organs [38].

There is both an acute and a chronic form of cutaneous GVHD. Acute disease usually develops within 2–4 weeks of stem cell infusion around the time of engraftment. Chronic cutaneous GVHD usually develops within a mean of 4 months after transplantation [57]. Acute disease typically presents as red to violet maculopapular lesions first appearing on the hands and sole but may progress to the whole body, coalesce, and in severe cases lead to the development of vesicles or bullae or a toxic epidermal necrolysis-like picture. Chronic cutaneous GVHD manifests with mucocutaneous lesions and sclerotic (resembling scleroderma) and non-sclerotic (lichen planus-like) skin lesions. In rare cases, hyperacute cutaneous GVHD can occur with the onset prior to day 14 following transplant. Hyperacute GVHD manifests with high fevers and more severe skin disease [58].

The mortality rate of solid organ transplant–associated GVHD can exceed more than 75% [38]. Skin biopsy may support clinical impression; however, skin biopsies are not always reliable in differentiating GVHD from drug eruptions, viral exanthems, eruption of lymphocyte recovery, and toxic erythema or chemotherapy.
Dermatology involvement is encouraged to aid in diagnosis and treatment. Systemic therapy is generally required for management of patients with acute GVHD. High-potency topical steroids may be helpful in patients with limited skin disease and no systemic involvement.

**Cosmesis**

Immunosuppressive medications have been associated with a variety of cosmetic skin changes, including but not limited to acne, alopecia, hypertrichosis, sebaceous hyperplasia, stomatitis, gingival hyperplasia, and Cushingoid features. When new dermatologic conditions develop, a review of potential medication side effects is necessary. Common immunosuppressives that may cause cosmetic skin changes include azathioprine, cyclosporine, glucocorticoids, mycophenolate mofetil, rapamycin, and tacrolimus.

**Key Points**

- Routine skin exams are recommended for solid organ transplant recipients because of the high incidence of skin cancers.
- A complete skin exam is indicated, as skin cancers may arise in partial sun-exposed areas or sun-protected areas, especially in patients with more skin pigment.
- The incidence of both basal cell carcinoma and squamous cell carcinoma is increased in solid organ transplant recipients, but in contrast to the general population, squamous cell carcinoma is relatively more common than basal cell carcinoma.

**Conclusion**

Care of the solid organ transplant recipient will require the primary care provider to be familiar with common symptoms that may be first encountered in the outpatient clinic, including respiratory symptoms, urinary symptoms, diarrhea, and skin problems. The initial approach to evaluating these symptoms requires recognizing key differences between solid organ transplant recipients and the general population, including having an expanded differential diagnosis, being aware of medication side effects, considering an increased risk of infection and malignancy, and knowing when a workup needs to be performed more quickly or with more testing. In many cases, earlier consultation or triage to a higher level of care is necessary. With attentive care, the primary care provider can appropriately evaluate, triage, and manage the solid organ transplant recipient who presents to the outpatient clinic with these symptoms.
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