Chapter 12
Preventive Health in the Adult Solid Organ Transplant Recipient

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Cancer Screening in Solid Organ Transplant Recipients

Cancer is one of the leading causes of death in solid organ transplant recipients, in addition to cardiovascular disease and infections. Overall, solid organ transplant recipients have a twofold increased incidence of all types of cancers and a three- to fivefold increased rate of cancer mortality, as compared with respective rates in the general population. The most extensive cohort study involving 175,732 solid organ transplant recipients (58.4% kidney, 21.6% liver, 10% heart, and 4% lung) in the United States showed a cancer standardized incidence ratio of 2.1 [1]. The risk was increased for a total of 32 different malignancies. The cancers with the highest risk relative to the general population included Kaposi sarcoma (KS); non-Hodgkin lymphoma; and lip, nonmelanoma skin, liver, vulvar, and anal cancers. Immunosuppression is associated with an increased incidence in HPV-related cancers (vulva, vagina, cervix, anus) [2]. Skin cancers are the most frequent malignancy seen in the solid organ transplant population, accounting for more than 40% of post-transplant malignancies [3].

The risk of specific malignancies varies according to the organ transplanted. Lung transplant recipients have a twofold increase in non-Hodgkin lymphoma compared to other solid transplant recipients [1]. Lung cancer is more common in lung and heart transplant recipients than in kidney or liver recipients. Liver and kidney cancers are more common in liver and kidney transplant recipients, respectively. Solid organ transplant recipients with primary sclerosing cholangitis are at increased risk for colorectal cancer and those with alcoholic liver disease are at increased risk for esophageal and head/neck cancers compared with patients undergoing lung transplants for other indications [4].

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Risk factors for cancer in solid organ transplant recipients include immunosuppression, oncogenic viruses, and disease-specific associations. Traditional risk factors such as tobacco use, sun exposure, and history of cancer also are important. Donor-derived malignancy rarely occurs.

Cancers in solid organ transplant recipients are more advanced at diagnosis, more aggressive and difficult to treat, and have worse outcomes than the general population [5]. Unfortunately, the optimal screening strategy remains uncertain as randomized controlled cancer screening trials have not been performed in the solid organ transplant population. Furthermore, screening trials that might improve outcomes are unlikely to be conducted since solid organ transplant recipients are relatively few in number compared to the general population.

A systematic review of 12 clinical practice guidelines for adult solid organ transplant recipients found that although most of the guidelines made recommendations for cancer screening, they varied considerably by transplanted organ, were largely based on expert opinion, and were derived primarily from cancer screening guidelines for the general population [6]. However, screening for two types of cancer, cervical and skin, in solid organ transplant recipients deserves further discussion.

**Cervical Cancer Screening**

Recommendations for cervical cancer screening among non-HIV immunosuppressed women remain limited because of lack of quality studies. The 2018 US Preventive Services Task Force guidelines on cervical cancer screening did not include recommendations for solid organ transplant recipients. In the review of clinical practice guideline recommendations for solid organ transplant recipients, eight of twelve guidelines recommended cervical cancer screening but with varying screening intervals: two recommended screening every 3 years, five recommended annual screening, and one recommended screening every 3–5 years [6].

A panel of cervical cancer researchers concluded that there is a consistent increase in the risk of cervical neoplasia and invasive cervical cancer in kidney, heart/lung, liver, and pancreas transplant recipients, and that using the CDC cervical cancer screening guidelines for HIV-infected women was a reasonable approach for screening and surveillance in the solid organ transplant population [7]. Cervical cancer screening recommendations among HIV-infected women have been supported by evidence from retrospective and prospective studies. The purpose of more frequent screening in high risk populations is to identify low-grade lesions before progression to high-grade squamous intraepithelial lesions or carcinoma. The recommendations are as follows: [7]

1. Women under age 30 should undergo annual cytology tests (i.e., Papanicolaou smear test), and if results of three consecutive cytology tests are normal, then subsequent cytology can be done every 3 years.
2. Women of age 30 and older have two screening options:
(a) Annual cytology, and if three consecutive tests are normal, then repeat testing can be done every 3 years
(b) Cytology and HPV co-testing at baseline, and if both are normal, then repeat co-testing can be done every 3 years

3. Continue screening throughout lifetime (do not stop at age 65 even if normal prior testing)

The American Society of Transplantation recommends more frequent screening using Pap testing every 6 months for the first year, then annually indefinitely if first tests are negative. These guidelines provide the option of high-risk HPV testing to determine if more frequent testing is indicated. They also recommend considering increasing the frequency back to every 6 months if a patient has been treated for rejection, necessitating an increased level of immunosuppression [8]. The direct effect of specific immunosuppressants on gynecologic cancers is not well studied and data is conflicting. Risk factors for developing squamous cell HPV-related cancers of the cervix, vulva, and vagina include multiple sexual partners or male partners with multiple sexual partners, current tobacco use, and infection with other sexually transmitted diseases. Cervical cancer screening (test, type, and frequency) should be discussed with the patient after reviewing the potential benefit, risks of harms, and their personal preferences. The decision to stop screening should be made based on co-morbidities, life expectancy, and personal factors.

Skin Cancer Screening

Nonmelanoma skin cancers are among the most common of all malignancies in solid organ transplant recipients. The risk of cutaneous squamous cell carcinoma (SCC) is 65 times that of the general population and the risk is threefold for malignant melanoma (MM) [3]. Risk factors include male gender, fair skin, sun exposure, geographic location, history of previous nonmelanoma skin cancer, age 50 years or older at the time of transplant, a recipient of a thoracic organ, and having a longer time elapsed since transplant [3]. Squamous cell cancers tend to develop at a younger age, are more aggressive, and metastasize more often [9]. Primary care providers should have a low threshold to biopsy any suspicious lesion and aggressively treat actinic keratoses or other precancerous lesions. Patients should be advised to seek evaluation for any new skin lesion as soon as it is noticed, minimize sun exposure, and always use sunscreen and wear hats. Most clinical practice guidelines for solid organ transplant recipients recommend annual skin and lip cancer screening by either a primary care physician or dermatologist [6]. These recommendations are in contrast to those of the US Preventive Services Task Force for the general population, which cite insufficient evidence to recommend for or against skin cancer screening [10]. A diagnosis of cutaneous SCC is associated with a higher risk of subsequently developing a non-cutaneous SCC [9]. These include cancers of the oral cavity/pharynx,
lip, tongue, lung, and HPV-related cancers (anal and female genital cancers). Therefore, it is important for primary care providers to be diligent in evaluating any new symptoms that arise in these areas if a solid organ transplant recipient has a history of SCC.

**Adherence to Cancer Screening in Solid Organ Transplant Recipients**

Adherence to cancer screening has not been well studied in solid organ transplant recipients but a large study in Canada suggests that adherence is very low [11]. A population cohort was studied between 1997 and 2010 to determine the uptake of breast, cervical, and colorectal cancer screening. They found that 4436 were eligible for colorectal screening, 2252 for cervical cancer screening, and 1551 for breast cancer screening. Of those, 77.5%, 69.8%, and 91.4%, respectively, were not up to date in cancer screening tests during the observed period. More surprisingly, greater than 30% had not been screened at all during the study period for colorectal, cervical, and breast cancer. The screening rates were lower than in the general population. The reason for these low screening rates is not clear but it does suggest that there is room for significant improvement and better communication between transplant specialists and primary care providers in the routine care of these patients.

Table 12.1 summarizes cancer screening in solid organ transplant recipients. See also Chap. 10 for further discussion.

**Risk of Cardiovascular Disease and Diabetes**

Solid organ transplant recipients are at increased risk for cardiovascular disease (CVD), and in many solid organ transplant populations, cardiovascular disease is a leading cause of non-graft related death [12, 13]. In a review of managing CVD risk [14], the authors categorized risk factors into four categories: pre-transplant risk factors (including usual risk factors, e.g., obesity, hyperlipidemia, diabetes, and smoking), transplant-related risk factors (e.g., immunosuppression, graft dysfunction, rejection, and anemia), donor risk factors (smoking, age of donor, quality of organ donated, ischemic time prior to transplantation), and other risk factors (e.g., increased C-reactive protein, prothrombosis, and proteinuria). Although transplant-related and donor risk factors are generally not modifiable, it is important to consider these non-traditional factors in solid organ transplant recipients so as not to misjudge CVD risk. For example, as a result of unique risk factors related to solid organ transplant, traditional risk models such as the Framingham Heart Study risk score, tend to underestimate CVD risk in solid organ transplant recipients [15].
As multiple non-traditional and often non-modifiable factors contribute to solid organ transplant recipients’ overall CVD risk, it is important to identify and manage modifiable risk factors such as hypertension, hyperlipidemia, obesity, and diabetes in primary care. Even adjusting for transplant-specific risk factors, solid organ transplant recipients are at increased risk for the usual risk factors above [14].

Transplant medications can lead to multiple side effects, increasing the risk for hypertension, diabetes, and cardiovascular disease. Calcineurin inhibitors are associated with increased risk of hypertension, diabetes, hyperlipidemia, hypomagnesemia, and hyperuricemia [16]. Corticosteroids are associated with increased risk of hypertension, diabetes, and increased weight. (Also see Chap. 3)

Given the frequency of routine lab testing and office visits for solid organ transplant recipients driven by transplant specialists, much of the data needed for screening for these conditions will be ordered by the transplant team and can be reviewed.

**Table 12.1 Cancer screening in solid organ transplant recipients**

| Cancer risk | Risk factors | Modified screening recommendations a |
|-------------|--------------|-------------------------------------|
| Overall >2× general population | Type of transplant: Lung transplant > other transplants | Cervical cancer screening b: Women < age 30: Annual cytology If 3 consecutive cytology tests are normal, then repeat every 3 years |
| Most common: Nonmelanoma skin cancer | Immunosuppression (esp. calcineurin inhibitors) | Women ≥ age 30: Annual cytology; if 3 consecutive tests are normal, then repeat testing every 3 years; Or Cytology and HPV co-testing at baseline; if both normal, then repeat co-testing every 3 years |
| Others at increased frequency: Kaposi sarcoma (KS) | Smoking | Note some guidelines recommend cytology testing every 6 month for the first year post-transplant, then yearly if testing is negative Continue after age 65 if indicated |
| Liver cancer (esp. in liver transplant recipients) | Alcohol (both pre- and post-transplant) | Skin cancer screening: Annual skin exam |
| Lung cancer (esp. in lung transplant recipients) | EBV serostatus | |
| Kidney and urothelial cancer (esp. in kidney transplant recipients) | HPV infection | |
| HPV-associated: Cervical, vulvar, penile, anal, oral squamous cell carcinomas | | |
| Post-transplant lymphoproliferative disorder (PTLD)/non-Hodgkin lymphoma | | |
| Colorectal cancer | | |
| Head and neck cancer | | |
| Thyroid cancer | | |

aScreening for cancers not listed here is similar to the general population
bSee text for details; guidelines vary. Shown are recommendations similar to cervical cancer screening for patients with HIV

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in primary care as well. However, the primary care provider should ensure that blood pressure is monitored at each visit, lipids are measured, and diabetes is screened for annually. Counseling patients on the benefits of regular exercise and maintaining a healthy diet is very important.

Recommendations for assessment of cardiovascular risk and diabetes at outpatient clinic visits are shown in Table 12.2. Management of cardiovascular risk factors, including the use of aspirin and statins for primary prevention, and treatment of hypertension and dyslipidemia are addressed in Chap. 11.

**Metabolic Bone Disease**

Solid organ transplant recipients are at significantly increased risk for osteoporosis. Osteoporosis risk includes preexisting factors (e.g., smoking, prednisone use, poor nutrition, and vitamin D deficiency) as well as transplant-specific factors, specifically corticosteroids and possibly calcineurin inhibitors [17]. This risk is particularly increased within the first 6–12 months of organ transplantation coinciding with higher doses of corticosteroids.

| Table 12.2 Routine outpatient assessment of cardiovascular risk and diabetes in solid organ transplant recipients |
|---|---|
| **History** | Review risk factors including: |
|  | Smoking |
|  | Exercise |
|  | Nutrition |
|  | Body-mass index |
| **Exam** | Blood pressure, height, weight |
|  | Cardiopulmonary exam |
| **Laboratory** | Often ordered routinely by the transplant team |
|  | Diabetes screening every 3 months for the first year, then yearly if normal |
|  | Lipid panel annually if normal |
| **Other testing** | Heart transplant recipients: review surveillance for cardiac allograft vasculopathy |
| **Risk stratification** | Existing risk tools may underestimate risk in solid organ transplant recipients |
| **Chemoprevention** (see Chap. 11) | Aspirin used in all heart transplant recipients; variable use in kidney transplant recipients |
|  | Statin therapy used in all heart transplant recipients; commonly used in kidney transplant recipients |
All Solid Organ Transplant Recipients—History

At outpatient visits, the primary care provider should assess risk factors:

- **Smoking status:** Active smoking is a contraindication to lung transplantation, and strongly discouraged prior to other solid organ transplants. Patients should be asked about whether they have started or resumed tobacco use after transplantation.

- **Alcohol use:** Alcohol use has been most studied in liver transplant recipients who had alcoholic cirrhosis and subsequently return to using alcohol after transplantation. In addition to other health risks, alcohol is associated with osteoporosis [18].

- **Weight-bearing exercise:** Solid organ transplant recipients should be counseled to maintain weight-bearing exercise, unless contraindicated by their medical conditions.

- **Medications:** Corticosteroid use is typically lowered over time, and in lower risk transplants (e.g., liver), it often can be discontinued completely. However, patients may be treated with higher doses of corticosteroids for longer periods of time, or indefinitely, if they have had episodes of rejection or other indications for use. Increased exposure to corticosteroids may merit more frequent bone mineral density testing. Other medications not related to transplantation should be reviewed for risk of lowering bone density (e.g., depot medroxyprogesterone for contraception, certain anti-epileptic medications, high-dose acid-suppressive medications, and thiazolidinediones for diabetes).

- **Malabsorption:** Some solid organ transplant recipients have continued risk factors for malabsorption. For example, a lung transplant recipient for cystic fibrosis may continue to have significant gastrointestinal disease, or a liver transplant recipient for primary sclerosing cholangitis may have ongoing inflammatory bowel disease symptoms after transplantation. Mycophenolate therapy commonly causes mild to moderate diarrhea, but rarely it can cause an enterocolitis with malabsorption.

- **Nutrition and body weight:** Many solid organ transplant recipients have difficulty maintaining body weight prior to transplantation due to cachexia from their organ failure. After transplantation, they should be monitored closely for maintenance of normal body weight.

- **Family history:** Although nonmodifiable, the patient’s family history of fracture should be reviewed.

- **Personal history:** Patients should be asked about a prior history of fracture. When the solid organ transplant recipient presents for an initial primary care visit, it is advisable to review the pre-transplant workup, as most transplant recipients will have received bone mineral density testing prior to transplantation (see Chap. 2).
Screening Tests and Preventive Therapy

While guidelines for average risk adults recommend screening dual-energy X-ray absorptiometry (DXA) to assess bone density for women starting at age 65 years, and continuing interval screening depending on baseline risk [19], in general, all solid organ transplant recipients should be screened with DXA scans within the first-year post-transplant. Following initial screening, guidelines vary with regard to suggested interval screening depending on risk factors and which organ is transplanted (Table 12.3).

- Liver transplant recipients: The 2012 American Association for the Study of Liver Diseases (AASLD) and American Society of Transplantation (AST) guidelines [13] recommend continuing screening every 2–3 years for liver transplant recipients without osteopenia and annually if osteopenia is present for the first 5 years following transplant. The AASLD and AST guidelines also recommend all post-liver transplant patients with or at risk for osteopenia take 1000–1200 mg daily calcium supplementation, maintain vitamin D levels above 30 ng/mL, and engage in regular, weight-bearing exercise.

- Heart transplant recipients: Heart transplant practice guidelines [20] recommend screening with a DXA scan as part of the pre-transplant workup with evaluation and treatment of osteoporosis as appropriate prior to transplant. All adult heart transplant recipients are recommended bisphosphonate therapy in the first year after transplant in addition to calcium and vitamin D supplementation and regular, weight-bearing exercise. Following the first year post-transplant, if corticosteroids are discontinued, continuation of bisphosphonate therapy is to be determined based on clinical risk; for example, if BMD > −1.5, guidelines suggest that it is reasonable to stop treatment. These recommendations were mainly based on expert opinion with authors citing insufficient evidence for bisphosphonate therapy in heart transplant patients. A subsequent meta-analysis, however, including 425 heart transplant patients did find efficacy of bisphosphonate therapy in reducing vertebral bone loss without additional medication-associated adverse events; given limitations of data, fracture prevention was not formally evaluated [21].

- Kidney transplant recipients: The risk of osteoporosis in kidney transplant recipients is higher, and screening and treatment are more complicated than in other organ transplant populations due to preexisting metabolic bone disease associated with end-stage renal disease. The fracture risk after renal transplant is estimated to be almost four times higher than that of the general population [22]. Age, female gender, and duration of pre-transplant dialysis increased the risk of hip fracture [22]. Similar to other solid organ transplant recipients, kidney transplant recipients have the most rapid decrease of bone density within the first 6–12 months after transplant. However, unlike other solid organ transplant recipients whose risk of osteoporosis decreases thereafter, the risk in kidney transplant recipients persistently increases at a slower rate following the first year after transplant [23].
Table 12.3 Screening for osteoporosis in solid organ transplant recipients

| Organ    | Osteoporosis incidence | Screening recommendations | Prevention recommendations |
|----------|------------------------|---------------------------|----------------------------|
| **Lung** | Common pre-transplant: [26] Osteopenia 36% Osteoporosis 31% At 1-year post-transplant: [26] Osteopenia: 33% Osteoporosis: 40% Osteoporotic fracture rate post-transplant: 19–225 per 1000 person-years [27, 28] (note: Limited data, few studies) | No consensus guideline recommendations Some authors recommend: [29] Baseline DXA (time not specified, most would assess within first year) Osteopenia: Repeat DXA every 2–3 years Osteoporosis: Treat and measure annually | No consensus guideline recommendations Some authors recommend: [29] Calcium 1000–1500 mg/d Vitamin D 400–800 IU/d |
| **Heart*** | Osteoporosis 13% pre-transplant [30] Vertebral fractures: 21% at 1-year post-transplant [30] Total osteoporotic fractures: 36% at 1-year post-transplant [31] | DXA 1-year post-transplant. Normal BMD: Repeat DXA every 3 years Osteopenia: Repeat DXA every 2 years (IIa/C) | Bisphosphonate therapy in first year post-transplant (IB), afterward depending on risk Calcium 1000–1500 mg/d (IC) Cholecalciferol 400–1000 IU/d to maintain 25(OH) vitamin D > 30 ng/mL (IC) Regular weight-bearing exercise (IB) |
| **Liver** | Common pre- and post-transplant At 1-year post-transplant: [32] Osteopenia 39% Osteoporosis: 44% | For the first 5 years after transplant: Osteopenia: Repeat DXA yearly Normal BMD: Repeat DXA every 2–3 years DXA (2B) [13] | If osteopenia or at risk of osteopenia: Calcium 1000–1200 mg/d Maintain 25(OH) vitamin D > 30 ng/mL Regular weight-bearing exercise (1A) [13] |
| **Kidney*** | Hip fracture rate: 3.3 per 1000 person-years [22] All fractures: 22.5% within 5-year post-transplant [33] | DXA within 3 months of transplant if treated with corticosteroids or have other risk factors (2D) [24] Insufficient evidence later post-transplant [25] | Take into account if chronic kidney disease mineral and bone disorder is present; consider assessing calcium, phosphate, PTH, alkaline phosphatases, and 25(OH) vitamin D levels (2C) [25] |

DXA dual-energy X-ray absorptiometry  
BMD bone mineral density  
*ISHLT guidelines use the American College of Cardiology/American Heart Association system for Class of Recommendation (I, IIa, IIb, III) and Level of Evidence (A, B, C) prior to its revision in 2015  
**AASLD guidelines use a modified version of the GRADE system for strength of recommendation (Strong =1, Weak = 2) and Level of Evidence (High = A, Moderate = B, Low = C)  
***KDIGO guidelines use the GRADE system unmodified for strength of recommendation (Strong =1, Weak = 2) and Level of Evidence (High = A, Moderate = B, Low = C, Very low = D)
The 2009 KDIGO guidelines [24] recommend measurement of BMD before and within 3 months of transplant. Updated guidelines in 2017 for metabolic bone disease [25] specifically recommend considering treatment for low BMD with vitamin D, calcitriol, and/or antiresorptive agents within the first year after transplant. However, they cite equivocal evidence for antiresorptive agents in kidney transplant recipients and highlight that there is not sufficient current data to demonstrate decreased fracture risk with antiresorptive treatment in kidney transplant population. They also recommend considering bone biopsy (an ungraded recommendation) in order to characterize bone osteodystrophy to guide treatment in renal transplant patients with osteoporosis and/or elevated fracture risk. The 2017 guidelines state that there is insufficient evidence to make recommendations past the first year after kidney transplant. Because of the complexity of management considerations in kidney transplant recipients, the primary care provider should address modifiable risk factors and if osteopenia or osteoporosis is identified, work with the transplant nephrologist to optimize therapy.

• Lung transplant recipients: There is relatively less data regarding the incidence of osteoporosis in lung transplant recipients (few studies with small number of patients); however, in a retrospective analysis of 72 lung transplant recipients, 36% had osteopenia prior to transplant and 31% had osteoporosis without significant changes in bone mineral density (BMD) a year following transplant; authors therefore recommended DXA scan as part of pre-transplant workup [26]. There are no current guidelines for osteoporosis screening in the lung transplant population.

Contraception and Pregnancy in Solid Organ Transplant Recipients

Contraception

More and more women of child-bearing age are receiving solid-organ transplants. In 2018, there were 13,904 solid organ transplants in women and 35% (4881) of them were of child-bearing age [34]. It is important that primary care providers appropriately counsel their solid organ transplant recipients on their fertility before and after transplantation and their contraception options. Prior to transplantation, many women have decreased fertility, especially those with end-stage renal disease and end-stage liver disease. Dysfunction of the hypothalamic-pituitary-ovarian axis in women with chronic renal failure or severe hepatic disease results in anovulation and reduced fertility. It has been found that conception rates are approximately 0.5% per year in women undergoing peritoneal dialysis or hemodialysis [35]. Fertility is often restored within months of a successful organ transplantation and ovulatory cycles may begin as soon as 1 month after transplantation [36]. Unfortunately, many solid organ transplant recipients are not
informed of this change in fertility. In one survey of 309 female solid organ transplant recipients, it was found that 44% were unaware that they could become pregnant after transplant [37]. Another study of 217 female solid organ transplant recipients aged 18–45 found that 33% were unaware of the necessity to use contraception within the first year after transplantation [38]. Approximately one-third of pregnancies are unintended in solid organ transplant recipients, which likely represents an underestimate given that some women may not report pregnancies that were terminated [39].

Contraception is best started before or shortly after receiving the transplanted organ. Pregnancy should be delayed at least 1 year after transplant to stabilize transplant function and reduce immunosuppressant medications to maintenance levels. The risks of an unintended pregnancy after a transplant are much greater than the risks of any contraceptive method. Two forms of contraception should be used until pregnancy is desired with condoms as one of the methods to protect against sexually transmitted infections.

Contraceptive choice will depend on the woman’s preference, co-morbidities, side effects, costs, and reversibility. The Centers for Disease Control (CDC) updated the US version of the Medical Eligibility Criteria (US MEC) guide for contraceptive use to evaluate the risks and benefits of contraception among women with certain medical conditions including solid organ transplantation [40].

The category risks are as follows:

| Category 1 | A condition for which there is no restriction for the use of the contraceptive method. |
|------------|---------------------------------------------------------------------------------------|
| Category 2 | A condition for which the advantages of using the method generally outweigh the theoretical or proven risks. |
| Category 3 | A condition for which the theoretical or proven risks usually outweigh the advantages of using the method. |
| Category 4 | A condition that represents an unacceptable health risk if the contraceptive method is used. |

The CDC categorizes a patient’s medical condition after transplant as either complicated or uncomplicated. Complicated conditions include acute and chronic graft failure, graft rejection, and cardiac allograft vasculopathy [40]. Table 12.4
Table 12.4  Contraception management in solid organ transplant recipients

| Method                              | Advantages                                                   | Disadvantages                              | CDC category (uncomplicated) | CDC category (complicated) |
|-------------------------------------|--------------------------------------------------------------|--------------------------------------------|------------------------------|---------------------------|
| Copper-T IUD                        | Most effective, long acting, reversible                      | Heavy menses                              | 2                            | Initiation: 3              |
|                                     |                                                              |                                            |                              | continuation: 2            |
| Progestin IUD                       | Most effective, long acting, reversible, decreased anemia    | Irregular bleeding                        | 2                            | Initiation: 3              |
|                                     |                                                              |                                            |                              | continuation: 2            |
| Depot medroxyprogesterone acetate   | Highly effective, decreased anemia                           | Decrease in BMD, irregular bleeding, possible cholestatic effect | 2                            | 2                         |
| Progestin implant                   | Most effective, long acting, no BMD decrease                | Irregular bleeding                        | 2                            | 2                         |
| COC                                 | Menstrual regulation, decreased anemia                      | Contraindicated in those with uncontrolled hypertension, active liver disease, and personal history of myocardial infarction, stroke, or DVT; first-pass liver metabolism; gastrointestinal disturbance may decrease absorption | 2                            | 4                         |
| Contraceptive patch                 | First-pass liver metabolism avoided                        | Higher circulating levels of estrogen; contraindicated in those with uncontrolled hypertension, active liver disease, and personal history of myocardial infarction, stroke, or DVT | 2                            | 4                         |
| Vaginal ring                        | First-pass liver metabolism avoided, lower circulating estrogen | Contraindicated in those with uncontrolled hypertension, active liver disease, and personal history of myocardial infarction, stroke, or DVT | 2                            | 4                         |
summarizes the different contraceptive options and their advantages/disadvantages and CDC categories for solid organ transplant recipients [41].

For women with uncomplicated solid organ transplants, all forms of contraceptive (except barrier methods) are classified as Category 2, meaning that the advantages for using the method generally outweigh the theoretical or proven risks. In women with a complicated solid organ transplant, estrogen-containing methods of contraception are considered Category 4 and intrauterine devices (IUDs) are considered Category 3. However, if a woman already has an IUD in place, then it is considered a Category 2 and she should continue with it.

The methods with the lowest failure rate (<1%) include permanent methods (female and male sterilization) and long-acting reversible methods (IUD and the subdermal progestin implant). Male sterilization is safer, less expensive, and less invasive than female sterilization (for women in a monogamous relationship with a male partner). Immunosuppressive medications do not alter the efficacy of the IUD or increase the risk of pelvic inflammatory disease [39]. IUDs are an excellent option for this patient population and should be highly recommended [42]. The subdermal progestin implant is very effective and there is no hepatic first pass effect which results in fewer drug interactions.

Depot medroxyprogesterone is highly effective with correct use (<1%), but with typical use it has a 6% failure rate. A disadvantage is that it reduces bone density which is important in solid organ transplant recipients who may be at high risk for bone loss due to chronic corticosteroid use and renal osteodystrophy (see Section “Metabolic Bone Disease” above). Combined hormonal contraceptives (pills, patches, rings) have a high failure rate with typical use (9%) and therefore are not considered first-line options. If chosen, these combined hormone contraceptives should be initiated at least 6 months after a liver transplant when organ stability is clear. If combined hormone therapy is chosen, then the ring or patch may be better options as they bypass the liver resulting in less drug interactions.

| Method                  | Advantages                                                                 | Disadvantages                                                      | CDC category (uncomplicated) | CDC category (complicated) |
|-------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------|------------------------------|---------------------------|
| Progestin-only pill     | Less effective than COC; first-pass liver metabolism                       |                                                                     | 2                           | 2                         |
| Condoms                 | No drug interactions, protects from sexually transmitted diseases          | Less effective                                                     | 1                           | 1                         |
| Cervical cap/ diaphragm | No drug interactions                                                       | Less effective                                                     | 1                           | 1                         |

Data from Centers for Disease Control and Prevention. Adapted from https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/appendixk.html#transplantation [41]

BMD bone mineral density, CDC Centers for Disease Control and Prevention, COC combined oral contraceptive, DVT deep vein thrombosis, IUD intrauterine device
Additionally, it is advisable to inform the transplant team when starting systemic hormonal treatment.

Unfortunately, the most highly effective contraceptive methods may not be used the most by transplant recipients. A cross-sectional survey study of 32 female solid organ transplant recipients found that the most common contraceptive method used in the year before and after transplant was condoms (18% failure rate with typical use) [43]. This finding along with the high unintended pregnancy rate among solid organ transplant recipients highlights the need for primary care physicians to address contraception with their solid organ transplant patients of child-bearing age.

### Table 12.5
Classifications for emergency contraception, including the copper-containing intrauterine device, ulipristal acetate, levonorgestrel, and combined oral contraceptives in solid organ transplant recipients [40]

|                      | Cu-IUD | UPA | LNG | COC |
|----------------------|--------|-----|-----|-----|
| Complicated: Graft failure (acute or chronic), rejection, or cardiac allograft vasculopathy | 3      | 1   | 1   | 1   |
| Uncomplicated        | 2      | 1   | 1   | 1   |

Abbreviations: COC combined oral contraceptive, Cu-IUD copper-containing intrauterine device, LNG levonorgestrel, UPA ulipristal acetate

Additionally, it is advisable to inform the transplant team when starting systemic hormonal treatment.

Emergency Contraception

Solid organ transplant recipients can use all the emergency contraception methods (see Table 12.5) currently available which include copper IUD (Cu-IUD), levonorgestrel, ulipristal acetate, and combined oral contraceptive pills [40]. The only exception is that the copper IUD should not be used in women with complicated transplants: graft failure (acute or chronic), rejection, or cardiac allograft vasculopathy.

### Pregnancy

Pregnancy in solid organ transplant recipients should be carefully planned and delayed until at least 1 year after transplant [42]. Pregnancy during the first 12 months after a transplant is associated with graft dysfunction, rejection or loss, and pre-term delivery [44]. Solid organ transplant recipients benefit from pregnancy planning by a collaborative multidisciplinary approach with the transplant team, maternal-fetal medicine specialists, and pharmacists. Solid organ transplant recipients have an increased risk of miscarriage, gestational hypertension, preeclampsia, gestational diabetes, fetal prematurity, and low birth weight. It is also important that chronic medical problems such as diabetes or hypertension are well controlled. Immunosuppressive drugs with risks to the fetus need to be discontinued prior to pregnancy. Exposure to mycophenolate is associated with higher rates of
miscarriages and birth defects compared to pregnancies without that exposure [45]. Mammalian target of rapamycin inhibitors (everolimus, sirolimus) are associated with increased risks of preterm delivery, decreased fetal weight, and skeletal ossification. The incidence of birth defects in infants exposed to prednisone, azathioprine, cyclosporine, or tacrolimus in utero is about 3–5% which is similar to the general population [46].

The American Society of Transplantation recommends that the following clinical criteria be met prior to pregnancy: [47]

- No rejection within the previous year
- Stable graft function
- No acute infection that might affect the fetus
- Immunosuppressant drugs at stable doses

With appropriate preconception planning and subsequent careful management by the transplant team and high-risk obstetrician, solid organ transplant recipients can have successful pregnancies and healthy infants. Because of demographics and other factors, successful pregnancies are more commonly reported in kidney and liver transplant recipients compared to other solid organ transplant recipients [48]. The primary care provider should ask about family planning in solid organ transplant recipients of child-bearing age and make early referrals to specialty care. Additionally, the primary care provider can assist in the control of other medical conditions, standard preconception care including ensuring adequate folate intake, avoidance of tobacco and alcohol, and reviewing other medications for safety in pregnancy.

**Immunizations in Solid Organ Transplant Recipients**

Solid organ transplant recipients should receive the same vaccinations as the general population except for live vaccines which are contraindicated. Recommendations are based on the routine schedule for immunocompetent individuals according to age, vaccination status, and exposure history and are summarized in Table 12.6 [49]. Primary care providers and specialists share the responsibility for ensuring that appropriate vaccinations are administered to solid organ transplant recipients and for recommending appropriate vaccinations for household members and close contacts [50].

Since solid organ transplant recipients receive life-long immune suppression, they may have lower rates of serological conversion, lower mean antibody titers, and waning of protective immunity over a shorter period as compared to the general population [51]. Therefore, it is important that vaccines, especially live vaccines, be given to the patient prior to transplant if possible. Live vaccines should be given at least 4 weeks before transplant, whereas inactivated vaccines can be given up to 2 weeks before. Most transplant centers review and update vaccines as part of the pre-transplant evaluation. However, if transplants are done more urgently,
Vaccinations are not always given. At the initial primary care visit, the patient’s pre-transplant vaccination history should be reviewed.

After transplantation, it is extremely important that patients are kept up to date in their immunizations as they are more susceptible to infections and their complications. For example, a systematic review of the incidence of invasive pneumococcal disease (IPD) in immunocompromised patients found that the IPD incidence was 465/100,000 in solid organ transplant recipients vs only 10/100,000 in healthy controls [52]. There is no evidence that vaccines lead to allograft rejection in solid organ transplant recipients, so there should be no hesitation in administering them except for the Shingrix® vaccine (discussed below) [53]. For patients that are non-immune, vaccines can be administered starting 2–6 months after transplant. Vaccinations should be withheld from solid organ transplant recipients during intensified immunosuppression, including the first 2 months after transplant, or in the setting of treatment for rejection, because of the likelihood of inadequate immune response [51]. It is not routine to measure serologic responses to immunizations given after transplant as there is no data showing that booster doses are helpful. Vaccine guidelines change frequently and primary care providers will need to check updated recommendations from either the CDC or the WHO, as well as their local public health organizations. The following information is relevant for solid organ transplant recipients regarding specific vaccines:

| Vaccine                  | Schedule                          | Comments                                                                 |
|--------------------------|-----------------------------------|--------------------------------------------------------------------------|
| Influenza                | One dose annually                 | Inactivated or recombinant vaccines, trivalent or quadrivalent, high-dose trivalent may be preferred [54] |
| Tdap                     | Single dose ≤2 yrs after last Tetanus-diptheria (Td) | Td booster every 10 years                                                |
| Prevnar® (PCV13)         | Once regardless of age            | If given after PPSV23, then wait >1 y                                    |
| Pneumovax® (PPSV23)      | ≥ 8 weeks after Prevnar            | One booster after 5 years and then again ≥ age 65 at least 5 years after most recent booster |
| Shingrix®                | Not yet determined                | The CDC has not provided guidance on its use in solid organ transplant recipients |
| HPV                      | 3 doses through age 26            | 9-valent                                                                 |
| Meningococcal (MenACWY)  | 1–2 doses depending on the indication | Those treated with ecilizumab or another indication Booster every 5 years if ongoing risk |
| MenB                     | 2 or 3 doses depending on vaccine | Those treated with ecilizumab                                             |
| Hepatitis B              | 2 or 3 doses depending on vaccine | Wants protection or is at risk (consider 40 mcg dose)                     |
| Hepatitis A              | 2–3 doses depending on vaccine    | Wants protection or is at risk                                           |

Table 12.6 Vaccine recommendations for adult solid organ transplant recipients
• **Pneumococcal vaccine.** The current recommendations for solid organ transplant recipients are one dose of PCV13 followed by one dose of PPSV23 at least 8 weeks later. Another dose of PPSV23 should be given at least 5 years after the previous PPSV23. At age 65 years or older, one dose of PPSV23 should be given if it has been at least 5 years since the last PSV23. No further doses are indicated. If pneumococcal vaccines are given prior to transplantation, they do not need to be repeated after transplantation.

• **Influenza vaccine.** There are two types of inactivated vaccines: trivalent and quadrivalent. The high-dose trivalent is safe and immunogenic in solid organ transplant recipients. It is recommended that it be given 1–3 months after transplant as immunogenicity may be reduced if given earlier. However, it can be administered within 1 month after transplant during an influenza outbreak and revaccination at 3–6 months after transplant if outbreak is ongoing [50]. In one study, the high-dose trivalent vaccine demonstrated significantly better immunogenicity than the standard dose in adult transplant recipients and may be the preferred influenza vaccine for this population [54].

• **Meningococcal vaccine.** Meningococcal disease does not occur at higher rates after transplant, so it is not routinely prescribed for solid organ transplant recipients except for those with risk factors. Risk factors include those receiving eculizumab which is used for treatment of antibody-mediated rejection post-transplant [55], history of splenectomy, military recruits, or travel to high-risk areas. The quadrivalent conjugated vaccine (MenACWY) is preferred as it provides a T-cell-dependent immune response, immune memory, and long-term protection. It requires two doses at 0 and 2 months. Those treated with eculizumab should also receive MenB.

• **Zoster vaccine.** Although Shingrix® is a recombinant vaccine, it has not yet been approved for solid organ transplant recipients due to a concern that its immunogenicity may affect allografts by causing rejection.

In addition to keeping up to date in vaccinations, solid organ transplant recipients need to take many precautions due to their high risk for infections. Food and water safety are very important. They must take care to minimize direct contact with pathogens, so frequent handwashing and avoidance of others with respiratory or gastrointestinal illnesses are recommended. Household members and other close contacts should be up to date in their vaccinations. They can receive both live and inactivated vaccines except for the live polio vaccine which is easily transmitted via the oral-fecal route and therefore is unsafe for the solid organ transplant recipients [49]. With the COVID-19/SARS-CoV-2 worldwide pandemic, solid organ transplant recipients are considered in the highest risk category, and they should follow local public health guidelines to avoid exposure. At the time of this publication, data are continuing to be analyzed to better characterize the risk to solid organ transplant recipients. Recommendations are summarized in Table 12.7.
Travel Immunizations and Recommendations

Solid organ transplant recipients are living longer and traveling internationally—it is important that they receive the appropriate travel advice, as they are at increased risk of developing opportunistic and non-opportunistic infections. Surveys of transplant centers found significant rates of illness in transplant recipients during foreign travel with insufficient rates of pre-travel counseling and interventions [57]. Travel clinics provide the best comprehensive care for solid organ transplant recipients, but these are not always available, so primary care providers need to be able to appropriately counsel and provide medical care for them. Travel recommendations change frequently as international conditions change; therefore, primary care providers should check for updated guidelines prior to making recommendations.

- **Immunizations:** All individuals should be up to date in routine immunizations (tetanus, influenza, pneumococcal). The specific vaccines needed for travel will depend on the travel agenda, including the specific areas in the countries that will be visited and exposure risks, and the patient’s vaccination status. In general, solid organ transplant recipients should avoid traveling to countries with yellow fever or other endemic outbreaks such as typhoid, dengue, measles, polio, and chikungunya. Ideally, vaccines should be given several months before travel to allow for an optimal immune response. Comprehensive information regarding travel vaccines for solid organ transplant recipients can be found at the Centers for Disease Control and Prevention Traveler’s Health website [58], but a few recommendations are highlighted below:

- **Hepatitis A.** For those who have not been vaccinated or are on higher levels of immunosuppression and plan to travel within 2 weeks, IM pooled immunoglobulins should be given as they provide 85–90% protection against hepatitis A. A

### Table 12.7 Strategies for disease prevention in solid organ transplant recipients [56]

| **Foodborne illness:** |
|------------------------|
| Avoid unpasteurized dairy products, undercooked meats, unwashed fruits/vegetables, raw seafood (*Vibrio vulnificus*). A handout on food safety can be found at: [http://www.fda.gov/Food/FoodborneIllnessContaminants/PeopleAtRisk/ucm312570.htm](http://www.fda.gov/Food/FoodborneIllnessContaminants/PeopleAtRisk/ucm312570.htm) |

| **Water sources** |
|-------------------|
| Avoid drinking water from private wells and ingesting water exposed to human or animal waste |

| **Hand hygiene** |
|------------------|
| Wash hands after eating or preparing food, touching plants or dirt, using the restroom, changing diapers, touching animals, etc. |

| **Avoid exposures** |
|--------------------|
| Avoid visiting prisons, homeless shelters, or other TB high-risk areas, tattooing, self-piercing, sharing needles, and close contact with individuals with respiratory/gastrointestinal illnesses or herpes zoster outbreak* |

*SOT recipients should follow guidelines for high risk populations during the COVID-19/SARS-CoV-2 pandemic. These guidelines are expected to continue to evolve.*
dose of 0.02 ml/kg provides up to 3 months of protection. The first dose of the hepatitis A vaccine should also be given.

- Typhoid. This must be given in the inactivated IM form and is protective for 2 years. It should be given at least 2 weeks before departure.
- Hepatitis B. High-dose hepatitis B (40 mcg) should be used. Also, accelerated schedules 0, 7, 21, and 28 days or 0, 1, and 2 months (both with a booster at 6 months) are acceptable.
- Measles. If solid organ transplant recipients must travel to an endemic area, their immunity should be checked (those born before 1957, evidence of two vaccinations, positive IgG titer, or clear h/o clinical disease). If non-immune, then immunoglobulin may be administered for short-term protection.

**Travel Precautions**

Ideally, solid organ transplant recipients should not travel for 1 year after transplant or during treatment for rejection. Once they are on maintenance doses of immunosuppressants and the allograft has stabilized, then it is safer for them to travel. It is important for them to carefully follow food and water precautions to prevent infections. They should drink only boiled or bottled water, and avoid ice in drinks, raw food, and food rinsed with tap water. Solid organ transplant recipients need to minimize their sun exposure as they are at high risk for developing skin cancers, especially squamous cell cancer. Diarrhea, the most common illness of travelers, can be life threatening for solid organ transplant recipients. Dehydration can lead to decreased renal function, especially those taking tacrolimus. Complications include bacteremia and altered absorption and metabolism of immunosuppressive drugs. Patients should be prescribed ciprofloxacin or azithromycin to take at the onset of symptoms; however, these medications can potentially interact with transplant medications and should be discussed with the transplant team first. The threshold for treatment is more than three unformed stools in 24 hours. Anti-motility agents should be used with caution. Bismuth-containing antidiarrheal medications should be avoided as they put solid organ transplant recipients at risk for salicylate toxicity if the patients have decreased renal function. Patient should not take an antibiotic prophylactically as this can lead to antibiotic resistance, *C. difficile* infection, and drug interactions. Additionally, the COVID-19/SARS-CoV-2 pandemic has restricted travel for high risk populations. Solid organ transplant recipients who desire to travel during this pandemic should follow public health guidelines and should be strongly cautioned against travel that would increase exposure to areas with high rates of infection, or travel via indoor settings in which they cannot sufficiently reduce their risk of exposure. Table 12.8 summarizes the recommendations for solid organ transplant recipients who plan to travel internationally.
Behavioral Health and Substance Use in Transplant Recipients

Behavioral Health

Behavioral health diagnoses are prevalent in solid organ transplant recipients, although further research is needed to better characterize the incidence and impact of these conditions following solid organ transplant. The most evidence is for depression. Solid organ transplant recipients are at higher risk for developing depression post-transplant compared to the general population. In a survey of liver transplant recipients, approximately 50% of those surveyed met criteria consistent with at least mild depression based on Patient Health Questionnaire-9 (PHQ-9) responses [60]. A diagnosis of depression post-transplant is correlated with worse outcomes. A 2015 systematic review and meta-analysis found that post-transplant depression was associated with a 65% greater risk of mortality. The same analysis examined the impact of anxiety on post-transplant mortality and found a non-significant increased risk; however, the authors noted that these data were likely unreliable due to far fewer studies and less precision of results as compared to those for depression [61].

There is emerging data regarding post-traumatic stress disorder (PTSD) following solid organ transplant. A systematic review found 10–17% cumulative incidence of post-transplant PTSD. Poor social support and pre-existing psychiatric diagnoses were correlated with post-transplant PTSD. Post-transplant PTSD was associated with worse mental health-related quality of life [62].

There is no consensus recommendation for screening for psychiatric diagnoses post-transplant, although many recommend at least regular interval screening for depression [63].

Substance Use

Substance use is screened and monitored heavily as part of pre-transplant evaluations. After solid organ transplant, substance use (e.g., alcohol and tobacco) is associated with higher rates of graft failure [64, 65]. Although precise estimates are unknown, a
A meta-analysis of studies in solid organ transplant recipients found a 1–4% rate of post-transplant substance use (defined as tobacco, alcohol, or illicit drug use) [66]. Still, comprehensive screening guidelines are lacking for the solid organ transplant population.

Substance use after transplant is best studied in patients who received liver transplant for alcoholic liver disease. In a study surveying 67 liver transplant recipients, approximately 20% reported alcohol use; however, only 4.5% reported at-risk behavior (as defined by the Alcohol Use Disorders Identification Test (AUDIT)), 30% reported tobacco use, and a minority (3%) reported non-marijuana drug use [60].

Alcohol use after liver transplant is associated with worse outcomes regardless of reason for transplant [67]. The AASLD and AST guidelines [13] recommend that patients who receive a liver transplant for alcoholic liver disease should be encouraged to abstain from alcohol. However, there are not specific guidelines for screening patients who do not have a prior diagnosis of alcoholic liver disease. Guidelines for care of kidney transplant recipients include avoidance of alcohol and other behaviors associated with worse outcomes in the evaluation of adherence; however, no specific screening recommendations are given [24].

Tobacco use in solid organ transplant recipients is associated with poorer graft function and significantly worse survival [68]. Currently, only lung transplant guidelines cite tobacco use as an absolute contraindication to transplant [69]. While there are not clear guidelines regarding screening for tobacco use in solid organ transplant recipients, it is recommended, given the clear correlation with worse outcomes and the demonstrated substantial rates of recurrent use in recipients who smoked prior to transplant [64].

Increasingly, states are legalizing medical and recreational marijuana, yet there is little guidance as to how to screen and counsel solid organ transplant recipients regarding use. Studies that have looked at the effect of marijuana use in solid organ transplant recipients have not found significant differences in graft function and/or survival as compared to non-marijuana users [70, 71, 72]. However, there remain concerns regarding marijuana’s potential inhibition of metabolic pathways that could lead to medication toxicity, infectious risks in the context of immunosuppression, end organ risks that may be amplified in immunosuppression, as well as addiction behaviors and impacts on cognition that might worsen adherence to medical therapy [73].

**Conclusion**

Solid organ transplant recipients are at increased risk for a broad spectrum of common conditions, several of which are discussed in this chapter. We emphasize the importance of contraception and pregnancy planning in women and vaccinations for all recipients. Travel planning and precautions are also addressed.

For many of the conditions reviewed, there are still unclear or absent guidelines with respect to screening. For example, we were unable to find any guidelines for screening for osteoporosis in lung transplant recipients, although there is an
increased risk. This can cause uncertainty, especially among primary care physicians, as to what to recommend to patients. More frequently updated guidelines and further research is needed to establish effective screening modalities and intervals for different medical problems in the solid organ transplant population.

Primary care providers play an important role in providing optimal healthcare for solid organ transplant recipients. The checklist below (Table 12.9) summarizes most

| Screening/prevention category | Recommendations |
|------------------------------|-----------------|
| **Cancer** | - Cervical cancer screening: Cytology +/- HPV at 1–3 year intervals; continue after age 65 if indicated (see Table 12.1 for additional detail and age-specific recommendations)  
- Skin cancer screening: Annual skin and lip cancer screening |
| **Cardiovascular disease and diabetes** | - Monitor blood pressure each visit  
- Annual lipids  
- Exercise and diet counseling  
- Diabetes screening every 3 months for first year, then annually |
| **Osteoporosis** | - DXA at least within the first year of transplant  
- Consider calcium/vitamin D supplementation (see Table 12.3 for additional detail and transplanted-organ specific recommendations) |
| **Pregnancy** | - If pregnancy desired:  
  - Contraception at least through first-year post-transplant; delay pregnancy until graft and immunosuppressive medications are stable (LARC preferred)  
  - After the first year, early involvement with maternal-fetal medicine specialist in pregnancy planning  
- If pregnancy not desired:  
  - Address contraception (see Table 12.4) |
| **Immunizations** | - Influenza: annually  
- PCV13: once  
- PPSV23: ≥ 8 weeks after Prevnar; one booster after 5 years (additional booster ≥65 years and 5 years since prior booster)  
- TdaP: Single dose ≤2 yrs after lastTd and then Td booster every 10 years  
- Shingrix®: not yet approved for solid organ transplant recipients – avoid until further guidance (see Table 12.6 for additional vaccine recommendations) |
| **Behavioral health** | - Depression screening (PHQ-2 and/or PHQ-9) at least annually b  
- Alcohol screening at least annually b  
- Tobacco screening at least annually b |

aOnly cancer screening recommendations that are different than for the general population are shown  
bNo consensus guidelines
topics covered in this chapter and can serve as a tool for primary care physicians to ensure solid organ transplant recipients receive regular screening and appropriate preventive care.

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