Infectious complications in liver transplantation

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INTRODUCTION

Infectious complications are major sources of morbidity and mortality in liver transplant recipients.

The specific factors (preoperative and postoperative) that increase the risk for infection in liver transplant recipients will be reviewed here. The most common pathogens responsible for infection at three key time points (the first month after transplant, months 1 through 6, and after the initial six months) will also be discussed. General issues related to liver transplantation and infections in solid organ transplant recipients are presented separately. (See "Infection in the solid organ transplant recipient" and "Evaluation for infection before solid organ transplantation" and "Prophylaxis of infections in solid organ transplantation".)

Hepatitis C virus infection and Hepatitis B virus infection in solid-organ transplantation is also discussed separately. (See "Hepatitis C virus infection in liver transplant candidates and recipients" and "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

EPIDEMIOLOGY

Despite advances in liver transplantation, morbidity and mortality due to infectious complications remain major problems. Older data have noted that up to two-thirds of all liver

transplant patients have at least one episode of infection [1]. Other series have observed infection rates of 1 to 2.5 episodes per patient [2-4]. As an example, a Swiss study of 577 liver transplant recipients found that 55 percent of recipients experienced an infection within 12 months after transplant; bacteria, viruses, and fungi caused 59 percent, 33 percent, and 8 percent of infections, respectively [5]. Infection accounted for 42 percent of the deaths occurring in the study period. Another review of 317 liver transplant recipients showed that 45 percent developed an infection in the first six months after transplant and more than one infectious episode per patient was associated with higher mortality [6].

Infection is often cited as the most frequent cause of death following liver transplantation, particularly in the first year after transplant [7]. In an autopsy series, infections were the cause of death in 64 percent of 321 transplant patients who died between 1982 and 1997 [8]. The most common types of infection were bacterial (48 percent), fungal (22 percent), and viral (12 percent). And, in an analysis of 64,977 liver transplants in the UNOS database from 2002 to 2016, infection was the most frequent cause of mortality from 30 to 180 days post-transplant [1].

GENERAL PRINCIPLES

Several principles of infection in solid organ transplant recipients are important to recognize [9,10]:

- Signs and symptoms of infection are often attenuated in the setting of immunosuppression, and infection may be more difficult to diagnose.
- Noninfectious causes of fever may mimic infection (eg, allograft rejection, medications).
- The variety of possible pathogens is quite broad but is influenced by the timing of infection in relation to transplantation.
- Antimicrobial agents used to treat infections can have important drug interactions with immunosuppressive medications.
- Infection may be more severe and progress more rapidly compared with immunocompetent hosts.
- Infection risk is determined by a patient's "net state of immunosuppression" [9], a balance contributed to by factors such as the dose, type, and duration of immunosuppressive therapy, the presence of indwelling devices such as catheters, nutritional status, metabolic conditions, certain immunomodulating viral infections, graft function, and underlying

diseases. (See "Infection in the solid organ transplant recipient", section on 'Net state of immunosuppression'.)

RISK FACTORS

Identification of risk factors for infection before transplantation permits the optimal use of strategies for preventing infections in the post-transplant setting. Although the ability to accurately predict a patient's risk of infection after transplantation remains limited, there are some risk factors that can be modified when recognized, such as the cytomegalovirus (CMV) serostatus of the transplant donor and recipient. (See 'Prevention of herpes virus infections' below.)

- **Latent infection in donor or recipient** − One important risk factor is the presence of a latent or unrecognized infection in either the transplant donor or recipient. Such infections may reactivate and cause significant morbidity after the introduction of immunosuppressive therapy. As a result, potential transplant donors and recipients are routinely screened for infections such as those due to CMV and other herpesviruses, tuberculosis, hepatitis B and C, syphilis, and human immunodeficiency virus (table 1). This is discussed in detail separately. (See "Evaluation for infection before solid organ transplantation".)

- **Active infection in the donor** − Infection in the donor that is active at the time of organ procurement may also be transferred to the recipient [10]. For example, bacteremic donors have transmitted bloodstream infection to transplant recipients despite administration of appropriate antimicrobial prophylaxis, and liver transplant recipients may be at increased risk for donor-derived bacteremias [11]. (See "Infection in the solid organ transplant recipient", section on 'Donor-derived infections'.)

- **Pretransplant colonization with certain organisms** − Pretransplant colonization of liver transplant recipients with organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant Enterobacteriaceae, or vancomycin-resistant *Enterococcus* (VRE) can lead to post-transplant infection with these organisms and increased mortality [12-19]. However, colonization by these organisms are not contraindications to transplantation [18,20]. An increased prevalence of multidrug-resistant gram-negative bacilli (eg, extended-spectrum beta-lactamase-producing Enterobacteriaceae, including *Escherichia coli* and *Klebsiella pneumoniae*; carbapenem-resistant Enterobacteriaceae) has been observed not only in the general population but also in solid organ transplant recipients [18,21]. Transplant recipients often have several risk factors for acquisition of

resistant bacteria, such as prior antimicrobials, devices, exposure to the health care environment, and underlying illness [21].

- **Surgical approach and surgical complications** − Various other risk factors for infection after liver transplantation have been reported. Many are related to surgical complications of the transplant operation. As an example, in a series of 101 patients, risk factors for infection included a prolonged operative time (>12 hours) and reoperation [22]. In other reports, the risk of bacterial infections was increased in patients who had undergone Roux-en-Y biliary anastomosis rather than choledochocholedochostomy, had multiple abdominal surgeries, or had CMV infection in the postoperative period [1,23]. Similar risk factors have been identified for post-transplant fungal infections [1,24-26].

- **Other factors** − Graft dysfunction and pre-existing critical illness also confer an increased risk for post-transplant infection [10]. CMV infection increases the risk of other infections, which may in part be due to the immunomodulatory effects of this virus [23,27,28]. Patients who develop rejection or who have poor graft function after transplant are also at increased risk of infection, at least in part because they receive a more aggressive immunosuppressive regimen.

PREVENTION

In addition to screening potential liver donors and recipients for infection as noted above, there are some general approaches to the prevention of infections in liver transplant patients. These include vaccination, the universal administration of prophylactic antimicrobials to patients at increased risk for specific infections (both perioperative surgical prophylaxis and post-transplant prophylaxis), and pre-emptive therapy [27]. "Targeted prophylaxis" and "educated avoidance" are additional approaches [10].

Vaccination — Patients awaiting liver transplantation should receive appropriate vaccinations before transplantation since antirejection immunosuppressive medications may prevent optimal responses to vaccination post-transplantation (table 2) [29]. Although efficacy is decreased after transplantation, particularly in the first few months after transplant or during other periods of intensified immunosuppression [29], certain vaccines such as pneumococcal and influenza vaccines should be repeated after transplantation in an attempt to lower the risk for these diseases. As a general rule, live vaccines should be avoided in transplant recipients due to the risk of disseminated disease. (See "Immunizations in solid organ transplant candidates and recipients" and "Immunizations for adults with chronic liver disease" and "COVID-19: Issues related to solid organ transplantation", section on 'Vaccination'.)

Antibacterial prophylaxis — The rate of surgical site infection (SSI) is higher in liver transplant recipients compared with other solid organ transplant types and ranges from 10 to 37 percent [19]. These infections can cause considerable morbidity and mortality [19,30]. Antibiotics are administered at transplantation in an attempt to prevent SSIs, including wound and intra-abdominal infection, although they do not provide complete protection [31]. Skin and intestinal flora are common SSI pathogens, and liver transplant candidates and recipients can be colonized by multidrug-resistant organisms (MDROs) [17-19], as discussed further below. Thus, it is important to recognize local epidemiologic patterns and recent colonizing or infecting organisms in the transplant recipient and donor when choosing antibiotics for prophylaxis. The use of antibacterial agents around the time of transplantation is discussed separately. (See "Prophylaxis of infections in solid organ transplantation", section on 'Antibacterial prophylaxis'.)

Pneumocystis prophylaxis — In patients without sulfonamide allergy, trimethoprim-sulfamethoxazole is generally administered for 6 to 12 months after liver transplantation [32], primarily to reduce the risk of *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia (PCP), but it also helps to prevent infections with *Listeria monocytogenes*, *Toxoplasma gondii*, and many common urinary, respiratory, and gastrointestinal bacterial pathogens [27,32-34].

Trimethoprim-sulfamethoxazole prophylaxis has also been associated with reducing the rate of nocardiosis in solid organ transplant recipients but breakthrough infections have been described [35]. One single-strength tablet taken daily or one double-strength tablet taken three times weekly are appropriate doses for PCP prevention. Optimal dosing of trimethoprim-sulfamethoxazole for the prevention of other pathogens is not well established. Routine use of trimethoprim-sulfamethoxazole prophylaxis has virtually eliminated PCP infection in the post-transplant setting [32], in comparison with a 10 to 12 percent incidence in earlier series [33]. (See "Treatment and prevention of Pneumocystis pneumonia in patients without HIV".)

In patients who are intolerant of trimethoprim-sulfamethoxazole, second-line PCP prophylaxis agents can be used, including dapsone, aerosolized pentamidine, or atovaquone. However, these medications do not provide the broad-spectrum activity that trimethoprim-sulfamethoxazole does against pathogens other than PCP [32].

The most common adverse effect of trimethoprim-sulfamethoxazole is allergy. Myelosuppression can also occur, but it is uncommon at the doses used for prophylaxis. Oral trimethoprim-sulfamethoxazole in combination with cyclosporine can affect tubular secretion of creatinine and increase serum creatinine levels without necessarily decreasing renal function [36]. In higher doses (such as those needed to treat PCP), it can also exacerbate the nephrotoxicity of cyclosporine or tacrolimus. Rarely, it may cause hyperkalemia.

Prevention of herpes virus infections — Cytomegalovirus (CMV) remains the most important viral infection in liver transplant recipients. CMV infection, the presence of the virus in blood, tissue, or body fluids, should be distinguished from CMV disease, which is CMV infection accompanied by signs and symptoms of CMV [37]. Ganciclovir and valganciclovir have been incorporated into strategies designed to prevent CMV disease in patients at risk of CMV reactivation [38-41]. As a result, the incidence of CMV disease in the post-transplant setting has declined [42,43].

Other herpesviruses including herpes simplex virus (HSV) types 1 and 2 and varicella-zoster virus (VZV) can be significant pathogens after transplantation. Without prophylaxis, approximately 50 percent of patients with HSV will have a recurrence [44]. Antiviral agents used to prevent CMV infection also have activity against HSV and VZV but do not have clinical benefit against other herpes viruses such as Epstein-Barr virus and human herpes virus 6. (See "Treatment of genital herpes simplex virus infection" and "Vaccination for the prevention of shingles (herpes zoster)" and "Treatment and prevention of herpes simplex virus type 1 in immunocompetent adolescents and adults".)

Prophylactic and pre-emptive CMV therapy — Patients at greatest risk of cytomegalovirus (CMV) infection and disease are those without pre-existing immunity. As a result, liver transplant recipients who are seronegative for CMV and receive an organ from a CMV-seropositive donor (D+/R-) have the highest risk for developing CMV disease, while CMV-seropositive recipients (R+) have a modest risk, and CMV D-/R- recipients have the lowest risk [45,46]. (See 'Cytomegalovirus' below.)

CMV not only has direct effects on tissues that it infects but also has indirect effects resulting from its ability to modulate the immune system [47]. CMV infection is associated with an increased risk of bacteremia and invasive fungal infections and an almost fourfold increase in the risk of death within one year of transplantation [48-50]. In addition, CMV infection has been associated with an accelerated course of hepatitis C virus recurrence and allograft loss after liver transplantation [51,52]. Thus, strategies to reduce the risk of CMV reactivation can also reduce the risk of related infections [48].

Several studies have described varied approaches to prevention including prophylaxis and pre-emptive therapy [53-58]. CMV prophylaxis refers to giving an anti-CMV drug to those at increased risk of CMV reactivation (eg, CMV D+/R-, D+/R+, D-/R+), while pre-emptive therapy refers to giving an anti-CMV drug only when there is evidence of CMV replication (eg, by detection of CMV nucleic acids in serum via polymerase chain reaction or CMV antigenemia). Both strategies have been shown to reduce the risk of CMV disease in solid organ transplant recipients [59-61]. In one randomized trial evaluating over 200 CMV seronegative liver

transplant recipients, the incidence of CMV disease over a 12-month period was reduced by 10 percent (95% CI 0.5 versus 19.6 percent) when comparing pre-emptive therapy with continuous antiviral prophylaxis [61]. However, there was no difference in the incidence of allograft rejection, opportunistic infections, neutropenia, or mortality with preemptive therapy when compared with continuous prophylaxis. Further study is needed to determine if these results are reproducible and generalizable, and transplant centers need to consider the findings in the context of the resources and logistics required for weekly CMV monitoring to day 100 after transplant.

Valganciclovir, a valyl ester prodrug of oral ganciclovir, has a bioavailability of nearly 70 percent (compared with 7 percent for oral ganciclovir) and at doses of 900 mg daily produces serum ganciclovir levels that are similar to those measured with intravenous (IV) administration of ganciclovir administered at 5 mg/kg daily. (See "Clinical manifestations, diagnosis, and management of cytomegalovirus disease in kidney transplant patients", section on 'Antiviral therapy'.)

Although valganciclovir has been approved by the US Food and Drug Administration (FDA) for the prevention of CMV reactivation in renal, lung, and pancreas transplant recipients, it was not approved for liver transplant recipients because the initial clinical trial comparing valganciclovir with oral ganciclovir showed an increased incidence of CMV disease compared with those who received oral ganciclovir in patients who had undergone liver transplantation [43,47]. Despite concerns raised by this trial, valganciclovir is used widely among liver transplant recipients because its bioavailability and ease of administration make it a more attractive option than the intravenous formulation of ganciclovir [62]. Oral ganciclovir is no longer manufactured in the United States.

Universal CMV prophylaxis has additional benefits since ganciclovir and valganciclovir are active against other herpesviruses including VZV and HSV [27]. The use of CMV prophylaxis also reduces the risk of other infections and complications by reducing infections that occur more commonly in patients with CMV reactivation [59]. As an example, in a retrospective study of 192 liver transplant recipients, there was a significant reduction of bacteremia in patients who had received greater than 14 days of CMV prophylaxis [48]. In addition, CMV prophylaxis reduced the risk of biopsy-proven rejection in liver transplant recipients [63]. In a large retrospective multicenter cohort of more than 7000 hospitalized liver transplant recipients, sepsis diagnosed >100 days after transplant was associated with prior CMV disease [64].

We recommend either CMV prophylaxis or pre-emptive monitoring in CMV D+/R- and CMV R+ liver transplant recipients, depending on the capacity of the transplant center to perform pre-emptive monitoring. These recommendations are in accordance with the 2019 American Society

of Transplantation (AST) guidelines on the management of cytomegalovirus in solid organ transplantation [65]. The 2018 international consensus guidelines on the management of cytomegalovirus in solid organ transplantation also state that either universal prophylaxis or pre-emptive therapy is acceptable for D+/R- and R+ liver transplant recipients [46]. The choice of drug and duration of prophylaxis vary among transplant centers, but most centers use antiviral CMV prophylaxis for three to six months after transplant and during intensification of immunosuppression for rejection [41]. Approaches for the prevention of CMV disease in other types of solid organ transplantation are discussed separately. (See "Clinical manifestations, diagnosis, and management of cytomegalovirus disease in kidney transplant patients" and "Prevention of cytomegalovirus infection in lung transplant recipients".)

It is important to note that patients who complete CMV prophylaxis after transplantation are at risk for late-onset CMV disease, which may be associated with graft loss and increased mortality [64,66]. In the retrospective study noted above involving hospitalized liver transplant recipients, late-onset CMV disease occurring >100 days after transplant was more common than early-onset CMV disease (4.3 versus 2 percent) and was associated with death [64]. Late-onset CMV disease is relatively uncommon in patients who are managed with pre-emptive CMV therapy [65]. A "hybrid strategy" of prophylaxis followed by pre-emptive monitoring after prophylaxis is complete has been investigated and is employed at some centers [46,65]. However, in a study of 71 high-risk (CMV D+/R-) solid organ transplant recipients, weekly virologic monitoring of patients who completed prophylaxis was ineffective at predicting CMV disease [67]. Pre-emptive therapy was successfully used in only 3 of 19 (16 percent) viremic patients, with no progression to CMV disease. The remaining patients with detectable viremia cleared low-level viremia spontaneously (3 patients; 16 percent) or had CMV disease (13 patients; 68 percent), either at the first detection of viremia or before pre-emptive therapy initiation because of rapid viral load doubling. Adequate data are lacking for this type of monitoring strategy [46,65].

In patients who do not receive CMV prophylaxis, an antiviral with activity against HSV and VZV (acyclovir, valacyclovir, famciclovir) should be given for at least the first month after transplantation and during periods of intensified immunosuppression (treatment of graft rejection) [68].

Prevention of fungal infections — A large review of >9000 solid organ transplant recipients in Canada found that the probability of invasive fungal infection one year after liver transplant was 1.8 percent with an all-cause mortality of 39 percent [69].

- **Candida prophylaxis** – *Candida* is the predominant fungal infection encountered after liver transplantation [69,70], with a shift toward infection due to non-albicans *Candida* spp [70], which are more likely to be fluconazole resistant. As an example, a fluconazole-

resistant hospital-acquired *Candida auris* outbreak was reported in liver transplant recipients [71].

The 2019 AST candidiasis guidelines recommend *Candida* prophylaxis for adult liver transplant recipients with one or more of the following risk factors [72]:

- Prolonged or repeat operation
- Retransplantation
- Renal failure requiring dialysis
- High transfusion requirement (ie, transfusion of ≥40 units of cellular blood products including platelets, packed red blood cells, and auto transfusion)
- Choledochojejunostomy
- *Candida* colonization during the perioperative period

It is unclear if there is additive risk for candidiasis when more than one risk factor is present [72], but targeted prophylaxis for individuals with at least one risk factor for invasive candidiasis appears effective [73,74].

Fluconazole 400 mg orally (or IV if the patient is not taking oral medications) daily is appropriate for many patients, but an echinocandin (micafungin, caspofungin, anidulafungin) or a lipid formulation of amphotericin B 3 to 5 mg/kg IV daily should be used if there is a high rate of non-albicans *Candida* infections or intolerance to fluconazole. The duration of *Candida* prophylaxis should be one to four weeks or for as long as risk factors persist.

- ***Aspergillus* prophylaxis** − The subgroup of liver transplant recipients who would most benefit from anti-*Aspergillus* prophylaxis is unclear. Reported risk factors for *Aspergillus* infection after liver transplantation have included fulminant hepatic failure, reoperation, retransplantation, post-transplant renal or hepatic failure, concurrent cytomegalovirus infection, hepatitis C infection, and high-dose glucocorticoids [75], however, these risk factors were largely identified from studies in the 1990s and early 2000s [76].

  The 2019 AST guidelines on invasive aspergillosis in solid organ transplant recipients recommend targeted *Aspergillus* prophylaxis in liver transplant recipients with any of the following risk factors [76]:

  - Retransplantation
  - Renal failure requiring dialysis within 7 days of transplantation
  - Reoperation involving the thoracic or intra-abdominal cavity

We generally decide whether to provide prophylaxis against *Aspergillus* on a case-by-case basis, taking into account the epidemiology of invasive fungal infections in the transplant center caring for the patient because the predictive value of the above risk factors is not certain. One retrospective study of the predictive value of standard risk factors for mold infection (ie, retransplantation, renal failure, reoperation, fulminant hepatic failure) showed poor performance among a cohort of 534 liver transplant recipients. The incidence of mold infections was similar regardless of the presence of risk factors [77]. The authors concluded that center-specific data may be more important than reliance on traditional risk factors for informing the use of antimold prophylaxis in liver transplant recipients. In addition, because azoles interact with many immunosuppressive medications (eg, tacrolimus, cyclosporine, sirolimus), dose adjustments and careful monitoring of drug levels is typically needed when using these agents concurrently. In the 2016 Infectious Diseases Society of America aspergillosis guidelines [75], no specific antifungal agents are recommended for *Aspergillus* prophylaxis in non-lung solid organ transplant recipients.

An echinocandin (micafungin, caspofungin, anidulafungin) or voriconazole for 14 to 21 days is recommended in this setting, although a lipid formulation of amphotericin B at a dose of 3 to 5 mg/kg can be considered [76].

The role of prophylaxis for fungal infections in liver transplantation has been studied in small randomized trials, and prophylaxis has demonstrated some efficacy for fungal-related outcomes, although it has not been associated with overall survival benefit [78-81]. Studies comparing different antifungal agents have generally evaluated their efficacy for preventing invasive fungal infection overall (ie, *Candida* infections, *Aspergillus* infections, and other fungal infections as a composite outcome). In an open-label randomized trial that compared micafungin with center-specific standard care (fluconazole, liposomal amphotericin B, caspofungin) in high-risk liver transplant recipients, similar rates of clinical success (defined as absence of proven/probable invasive fungal infection and no need for additional antifungals) were observed with micafungin and standard care (98.6 versus 99.3 percent) [73].

A meta-analysis of 10 randomized trials of antifungal prophylaxis in 1106 liver transplant recipients revealed that antifungal prophylaxis did not reduce total mortality, although fluconazole prophylaxis decreased invasive fungal infections by 75 percent [82]. An observational study of 189 liver transplant recipients revealed that prophylaxis using a fixed dose of 400 mg of fluconazole for 14 days in liver transplant recipients with at least one risk factor (operative time >10 hours, reoperation within 30 days, retransplantation, pretransplant dialysis, pretransplant *Candida* colonization, choledochojejunostomy, allocation model for end-

stage liver disease >35, pretransplant hospitalization for >7 days, and operative transfusion of >40 cellular blood products) can significantly reduce invasive fungal infection but not mortality [74].

Breakthrough fungal infections and fungal infections due to drug-resistant fungi have been observed in the setting of prophylaxis [71,74,83]. In the *C. auris* outbreak noted above, three of the four liver transplant recipients with infection had received fluconazole prophylaxis and the fourth had prior fluconazole exposure. A prospective multicenter study reported that 5 percent of liver transplant recipients receiving targeted antifungal prophylaxis developed breakthrough invasive fungal infections consisting of *Candida* or *Aspergillus* [83]. In univariate analysis, breakthrough infection was associated with pretransplant *Candida* colonization, post-transplant CMV viremia >100,000 copies/mL and reoperation. Of note, adherence to the targeted antifungal protocol was only 64 percent [83]. Thus, determining the optimal patients for antifungal prophylaxis and the ideal antifungal agent, dose, and length of treatment will require additional studies.

The use of antifungal agents around the time of transplantation is discussed in greater detail separately. (See "Prophylaxis of infections in solid organ transplantation", section on 'Antifungal prophylaxis'.)

Tuberculosis prevention — A systematic review of seven studies estimated that, compared with the general population, liver transplant recipients have an 18-fold increase in the prevalence of active *Myobacterium tuberculosis* infection and a fourfold increase in the case-fatality rate [84]. It is optimal to treat latent tuberculosis prior to transplantation, and daily rifampin for four months has become a preferred regimen over isoniazid for treatment of latent tuberculosis [85]. While the use of three months of weekly isoniazid plus rifapentine is another preferred regimen [85], it is challenging to use isoniazid in liver transplant candidates due to the risk of hepatotoxicity. Still, isoniazid has been used in this setting with very close monitoring of liver function tests [86-89]. Some experts favor beginning latent tuberculosis therapy after transplantation once liver function has normalized, in which case isoniazid would be preferred due to the significant drug-drug interactions between rifampin and standard immunosuppressive medications such as calcineurin inhibitors. A trial of nine months of levofloxacin prophylaxis in transplant candidates was discontinued due to a high rate of tenosynovitis (18.2 percent) [90]. (See "Tuberculosis in solid organ transplant candidates and recipients", section on 'Treatment of latent tuberculosis' and "Treatment of tuberculosis infection (latent tuberculosis) in nonpregnant adults without HIV infection".)

Targeted prophylaxis — Immune-monitoring tests that assess an individual's risk for infection may be useful in guiding prophylaxis and/or adjusting immunosuppression [46,91,92]. For

example, the QuantiFERON-CMV assay (which is not FDA approved in the United States) measures interferon-gamma secretion in response to CMV-specific peptides and has been shown in liver transplant recipients to correlate with risk of CMV viremia [92]. There is also a CMV T cell immunity panel, which measures CMV-specific CD4+ and CD8+ responses via intracellular cytokine staining and flow cytometry after stimulation of whole blood with CMV antigens [93]. The ImmuKnow assay measures adenosine triphosphate production in response to immune cell stimulation; however, its clinical usefulness for predicting infection is not well established [91].

Educated avoidance — Transplant recipients should be instructed on practices that can minimize exposure to infectious pathogens that may be encountered in daily life [94]. Such recommendations should include hand and respiratory hygiene, ways to prevent food- and waterborne infections, how to decrease infection risks during travel, and precautions for pet owners or those coming in contact with animals.

TIME COURSE OF INFECTIONS

The risk of infection and types of infections encountered differ based upon the timing after transplantation, although with changes in immunosuppressive agents over time and the institution of prophylaxis for various infections, the timeline of infection has been altered [10,27]. Nevertheless, most postoperative infections can be grouped into three major periods: transplant to one month, one month to six months, and after six months (figure 1). (See "Infection in the solid organ transplant recipient", section on 'Risk of infection following transplantation'.)

Transplant to one month — Infections occurring immediately following transplantation are often similar to those seen in immunocompetent hosts following surgery. Bacterial infections predominate; they usually have a nosocomial source, such as central vascular or urinary catheters, or are related to surgical complications such as bleeding, impaired wound healing, strictures or biliary leaks. In addition, donor-derived infections may present in the initial month after transplant and should be considered if there are unexplained syndromes consistent with infection [10].

The two major sites of infection during this time period are the abdomen and the lungs, both of which may be associated with bacteremia [22,31,95,96].

- Abdominal abscesses and infections of the peritoneum can result from operative complications including biliary leaks or hematomas, with the predominant pathogens

being enteric organisms.

- Intrahepatic abscesses may manifest as the result of hepatic artery thrombosis or bile duct ischemia occurring in the perioperative period.
- Cholangitis may occur after biliary tract obstruction.
- Wound infections are common.

Nosocomial pneumonias are particularly frequent in patients who require prolonged mechanical ventilation. *Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii* are often recovered from respiratory tract specimens in this setting [97]. Other common bacterial pathogens associated with pneumonia include *S. aureus, Stenotrophomonas maltophilia*, and *Citrobacter freundii* [2,97]. (See "Epidemiology of pulmonary infections in immunocompromised patients" and "Epidemiology, pathogenesis, microbiology, and diagnosis of hospital-acquired and ventilator-associated pneumonia in adults".)

Clostridioides difficile colitis can also occur, particularly in the early period following transplantation and in patients requiring prolonged hospitalization. In fact, liver transplantation has been identified as a significant risk factor for *C. difficile* acquisition in the hospital [98,99]. (See "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology" and "*Clostridioides difficile* infection in adults: Clinical manifestations and diagnosis" and "*Clostridioides difficile* infection in adults: Treatment and prevention".)

The incidence of *C. difficile* colitis was noted to be 8 percent in a series of 467 liver transplant recipients followed from 5 to 1999 days after transplantation, with more than half of these cases occurring in the first month post-transplant [100]. Another study confirmed the early onset of *C. difficile* colitis after liver transplantation (41 percent occurred within one week after transplant); the majority of patients did not have fever or leukocytosis [101]. The intense immunosuppression and frequent exposure to antimicrobial agents that occur shortly after transplantation likely contribute to the increased risk for *C. difficile* infection in this period. Gastric acid suppression, hypogammaglobulinemia, intra-abdominal hemorrhage, systemic infection, and biliary complications may be additional risk factors [100,102,103]. Studies have associated *C. difficile* colitis in organ transplant recipients with poorer outcomes, including length of stay and mortality [104,105].

Infection is often suspected when patients develop a fever. However, as mentioned above, fever is not always present and, when present, it may also be due to noninfectious causes, such as malignancy, rejection, transfusion reactions, medications, or adrenal insufficiency. In the series

mentioned above, noninfectious etiologies accounted for 22 percent of febrile episodes in liver transplant recipients [106].

If a bacterial infection is suspected in a liver transplant recipient, empiric broad-spectrum antibiotics should be initiated until the specific bacterium and its sensitivities can be identified. Antibiotic regimens used for empiric therapy in the early posttransplantation period should provide coverage for gram-positive cocci, gram-negative bacilli, and anaerobes; while awaiting microbiologic test results, coverage should include agents that treat resistant organisms that have already been documented in the patient. In addition, it is important to consider local hospital epidemiology and resistance patterns in the selection of empiric antimicrobial coverage. Aminoglycosides are usually avoided in solid organ transplant recipients due to their nephrotoxicity, particularly in combination with calcineurin inhibitors.

In recent years, there has been a shift toward an increased proportion of infections in transplant recipients caused by gram-negative organisms, and particularly multidrug-resistant organisms (MDROs) [107]. This may necessitate treatment with newer broad-spectrum agents active against extended spectrum beta-lactamase-producing bacteria and carbapenem-resistant Enterobacteriaceae (CRE) [21]. A multicenter study of the impact of CRE on transplant outcomes identified 60 organ transplant recipients (30 liver) who were colonized or infected prior to transplant [18]. Post-transplant infection occurred in 24 patients (40 percent), mostly manifesting as surgical site and bloodstream infections, and post-transplant CRE infection adversely impacted survival. A single-center study that screened liver transplant candidates for MDRO colonization reported that colonization increased with time on the transplant waiting list and was associated with death on the waiting list [108]. While MDRO colonization overall was not associated with post-transplant mortality, there was a trend toward increased post-transplant mortality in patients colonized with carbapenem-resistant gram-negative bacteria.

Candida is also an important pathogen during the first month after transplantation. The bloodstream, surgical wounds, and the urinary tract are common sites for primary infection, which may then disseminate [70]. *Candida* infections may also manifest as esophagitis and superficial infections of the skin (folliculitis) or oral cavity [2].

Any candidemia should be treated, since fungemia is associated with high mortality [70]. In addition, as noted above, a greater proportion of invasive *Candida* infections among liver transplant recipients in recent years has been due to non-albicans *Candida* spp, a finding that has significant implications for outcome and treatment as these organisms have been associated with higher mortality and may be less susceptible to fluconazole than *C. albicans* [70]. (See "Management of candidemia and invasive candidiasis in adults".)

Except for herpes simplex virus (HSV) and unusual situations like donor-transmitted viral illnesses such as that due to West Nile virus [109], viral infections are uncommon during the first month following transplantation. Without prophylaxis, reactivation of HSV occurs in approximately 50 percent of patients who are seropositive prior to transplant, usually as genital or oral ulcers [110]. (See "Treatment and prevention of herpes simplex virus type 1 in immunocompetent adolescents and adults".)

One to six months — Opportunistic infections tend to occur one to six months after transplant due to the cumulative effect of relatively high-dose immunosuppression.

Cytomegalovirus — Cytomegalovirus (CMV) prophylaxis has changed the pattern of this infections after transplant [9]. CMV can largely be prevented during the period of antiviral prophylaxis but in many cases, primary CMV infection is merely delayed rather than prevented and often occurs after prophylaxis has been stopped [64,111]. In the absence of prophylaxis, CMV reactivation occurs in approximately 50 to 60 percent of patients; 20 to 30 percent of these will develop CMV-related disease such as pneumonitis, enteritis, or hepatitis [1].

Liver transplant recipients who were initially seronegative for CMV but received a graft from a CMV-positive donor are at greatest risk for CMV disease, similar to what is seen with other solid organ transplants. Furthermore, CMV D+/R- liver transplant recipients have a higher risk of graft loss and overall mortality compared to liver transplant recipients of other serostatus types [112]. A retrospective analysis of United States liver transplant outcomes in 54,000 adults reported that, unlike other CMV serostatus groups, CMV D+/R- serostatus was independently associated with graft loss (adjusted hazard ration [aHR] 1.07, 95% CI 1.05-1.22) and mortality (aHR 1.13, 95% CI 1.05-1.22). These associations persisted beyond the first year after transplant, adding to the evidence that CMV's impact extends beyond its immediate direct effects. (See "Clinical manifestations, diagnosis, and management of cytomegalovirus disease in kidney transplant patients".)

Approximately 40 to 60 percent of healthy adults are seropositive for CMV and, following liver transplantation, these patients can experience reactivation of latent virus leading to CMV disease. Antithymocyte globulin use, retransplantation, and older age are additional risk factors for CMV reactivation in the post-transplant period [1,38,113]. The lowest risk is present in a seronegative recipient who receives a liver from a seronegative donor [38,44,114].

CMV disease can present with a variety of symptoms, the most common of which are fever, leukopenia, thrombocytopenia, malaise, and arthralgias [115,116]. Less frequent manifestations include pneumonia, gastroenteritis, hepatitis, encephalitis, and retinitis.

CMV may also affect the allograft. CMV hepatitis may be difficult to distinguish from graft rejection, which is also common during this period. A liver biopsy is helpful in this setting. Findings on liver biopsy suggesting CMV disease include the presence of viral inclusions associated with a mononuclear cell infiltrate and microabscesses. Although somewhat controversial, CMV has also been implicated as a risk factor for ductopenic (ie, chronic) rejection [117,118].

Of the various methods that have been developed to diagnose CMV infection (molecular testing, serologic studies, histopathology, and shell vial assays), assays that allow for rapid identification and quantification of CMV have proven to be most valuable in the post-transplant setting. Quantitative polymerase chain reaction (PCR) of the blood is generally preferred, CMV antigenemia is another option. The approach to diagnosis of CMV infection and tissue invasive disease is discussed separately. (See "Approach to the diagnosis of cytomegalovirus infection" and "Overview of diagnostic tests for cytomegalovirus infection".)

Other viruses — Varicella-zoster virus (VZV), Epstein-Barr virus (EBV), respiratory syncytial virus (RSV), human herpesvirus 6 (HHV-6), influenza, adenovirus, and other respiratory viruses may also occur during the period of one to six months following transplant.

- **EBV and PTLD** − EBV is one of the most important because of its potential to cause post-transplant lymphoproliferative disease (PTLD).

  EBV replication can be detected in approximately 20 to 30 percent of transplant recipients and in approximately 80 percent of patients receiving antithymocyte globulin and high doses of immunosuppressants [33]. EBV infection has a wide range of clinical manifestations including a benign mononucleosis-like syndrome, but the most serious complication of EBV is PTLD [27]. A major risk factor for PTLD is primary EBV infection after transplant, which occurs when an EBV-seronegative recipient receives an organ from a seropositive donor. (See "Treatment and prevention of post-transplant lymphoproliferative disorders".)

- **HHV-6** − HHV-6 is the cause of roseola infantum in childhood and has become appreciated as contributing to adverse outcomes in liver transplant recipients [119]. The virus, like other herpesviruses, remains latent after initial infection and can reactivate during times of immunosuppression. Detection of HHV-6 post-transplant has been associated with fever, rash, cytopenias, encephalitis, interstitial pneumonitis, and hepatitis [119]. HHV-6 may cause these syndromes by directly damaging tissues or via immunomodulatory effects that enhance CMV reactivation, infection by other pathogens, or allograft dysfunction [120,121], and HHV-6 infection has been associated with graft failure,

mortality, and worsening of coinfections like hepatitis C [119]. However, the degree to which HHV-6 reactivation causes disease after liver transplantation is not firmly established. As an example, in one trial, 129 liver transplant recipients were randomized to routine monitoring for HHV-6 reactivation by PCR versus usual care. Among monitored patients, 36 percent developed HHV-6 viremia but none were symptomatic. Thus, we do not routinely monitor for HHV-6 reactivation [119,122]. (See "Clinical manifestations, diagnosis, and treatment of human herpesvirus 6 infection in adults".)

- **Respiratory viruses** − The prevalence of infection due to respiratory viruses (eg, RSV, parainfluenza, influenza, adenovirus, severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) is similar to the general population, although respiratory viral infections can be more severe and have a greater likelihood to disseminate in transplant recipients. SARS-CoV-2 infection in liver transplant recipients is discussed further below.

Aspergillus species — As noted above, most fungal infections following liver transplantation are caused by *Candida* spp, but *Aspergillus* infections can also occur. In one 10-year retrospective series of 554 liver transplant recipients, *Aspergillus* accounted for 35.7 percent of all fungal infections [123]. A study of solid organ transplant patients in Spain over a 10-year period reported that the incidence of invasive aspergillosis in liver transplant recipients was 1.8 percent [124]. In a multicenter Swiss cohort, the median time from liver transplant to invasive aspergillosis was 18 days (interquartile range 9 to 122 days) [125].

The most common site of aspergillosis is the lung, although it may disseminate to other sites including the central nervous system (CNS). It is the most common cause of CNS infection in liver transplant recipients, accounting for 55 percent of brain abscesses in one series [126]. Mortality of aspergillosis in early series of liver transplant recipients approached 100 percent [127], but more recent data suggest the outcomes may be improving [128,129]. A Spanish cohort reported a three-month overall mortality rate of 58 percent in liver transplant recipients with invasive aspergillosis [124].

As noted above, the American Society of Transplantation Infectious Diseases Community of Practice guidelines recommend targeted prophylaxis in high-risk patients: those undergoing retransplantation, those on renal replacement therapy at time of transplant or within seven days of transplantation, and those requiring reoperation involving the abdomen or chest [76]. (See "Epidemiology and clinical manifestations of invasive aspergillosis" and "Treatment and prevention of invasive aspergillosis".)

Other opportunistic pathogens — Infection due to *Nocardia*, *Listeria*, *Cryptococcus*, and *M. tuberculosis* can be seen during this time period. The risk for tuberculosis among solid organ

transplant recipients is much higher than that of the general population, and the post-transplant incidence worldwide ranges from 0.3 to 15 percent, depending upon the country [130]. The disease is presumed to be largely related to reactivation of latent infection, although new infections may also occur in transplant recipients residing in endemic countries.

Tuberculosis can have serious consequences when it occurs in the post-transplant setting. Disseminated infection is not uncommon in transplant recipients and is associated with a high mortality rate. (See "Tuberculosis in solid organ transplant candidates and recipients".)

After six months — Opportunistic infections are uncommon beyond six months post-transplant in patients who have good graft function since immunosuppression has generally been tapered to a maintenance regimen. These patients usually develop the same types of community-acquired infections seen in the general population [9] though manifestations may be more severe [10]. Transplant recipients may be more susceptible to some pathogens such as *Legionella* [131] and may experience more severe manifestations of certain infections such as West Nile virus infection [132].

On the other hand, patients with impaired graft function or those receiving higher levels of immunosuppressive medications are at risk for the infections typically encountered during the period of one to six months after transplant. One of these is *Cryptococcus neoformans*, which usually causes meningitis. (See "Clinical manifestations and diagnosis of Cryptococcus neoformans meningoencephalitis in patients without HIV".)

Patients on chronic immunosuppression often initially have only subtle findings of infection due to attenuation of inflammatory responses by immunosuppressants, but this may be followed by a precipitous decline in status and severe manifestations of infection. Respiratory infections due to pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* can be life-threatening if not promptly treated. Patients who have chronic rejection are also more susceptible to chronic viral infections, possibly from the increased immunosuppressive regimens.

- **Herpes viruses** − Chronic or recurrent viral infections including those due to EBV, CMV, hepatitis B (HBV), hepatitis C (HCV), and potentially human herpesviruses 6 and 7 also can lead to complications in the late post-transplant period. As an example, CMV infection can be persistent or occur following prophylaxis discontinuation or following treatment for allograft rejection, with manifestations as described above. In addition, the immunomodulatory effects of CMV and other viruses may increase the risk of opportunistic infections such as *P. jirovecii* (formerly *P. carinii*) pneumonia (PCP) and

invasive aspergillosis. As mentioned above, CMV infection has also been associated with ductopenic rejection [117].

- **Viral hepatitides** − Chronic viral infections can also produce damage to the liver allograft (HBV and HCV) or cause secondary tumors during this period, including post-transplant lymphoproliferative disease due to EBV and hepatocellular carcinoma due to HBV or HCV [44]. Hepatitis E virus (HEV) can also cause chronic hepatitis in liver transplant recipients and should be considered in patients with unexplained liver enzyme elevations [133]. (See "Epidemiology and risk factors for hepatocellular carcinoma" and "Hepatitis E virus infection".)

- **Endemic fungi** − The endemic fungi, including *Histoplasma capsulatum* (most often occurring in the Ohio River Valley), *Coccidioides immitis* (most often occurring in the southwestern United States), and *Blastomyces dermatitidis* (most often occurring in the central and southeastern United States), may also be seen in the late post-transplant period. In two series, the median time from transplant to symptoms from histoplasmosis was approximately 11 months [134,135]. Endemic fungal infections may represent reactivation of disease or new infection. Listeriosis has been noted in patients on chronic immunosuppression. It is usually associated with meningitis but can also cause hepatitis and bacteremia. Transmission of *Listeria* is usually through contaminated dairy products. The stable low incidence of *Listeria* can be partially attributed to some protection from trimethoprim-sulfamethoxazole prophylaxis for PCP [136]. (See "Clinical manifestations and diagnosis of Listeria monocytogenes infection" and "Treatment and prevention of Listeria monocytogenes infection".)

- **COVID-19** − SARS-CoV-2, the cause of coronavirus disease 2019 (COVID-19), can lead to severe respiratory infection in liver transplant recipients as well as liver dysfunction [137]. Liver donors and recipients are tested for COVID-19 prior to transplantation [138]. (See "COVID-19: Issues related to solid organ transplantation".)

  A French national registry study of 104 liver transplant recipients who contracted SARS-CoV-2 reported an overall 30-day mortality rate of 20 percent and a mortality rate of 28 percent in patients requiring hospitalization. Age was associated with mortality when adjusting for other factors [17]. An international multicenter registry study compared the outcomes of SARS-CoV-2 infection between 151 liver transplant recipients and 627 patients without a liver transplant [139]. In a propensity score-matched analysis adjusting for comorbidities, liver transplantation was not associated with a higher rate of SARS-CoV-2-related mortality and there were no liver-related deaths in the transplant group. Liver transplant recipients had a higher rate of mechanical ventilation.

Liver transplant recipients have low rates of anti-nucleocapsid and antispike immunoglobulin (Ig)G antibodies one year after SARS-CoV-2 infection, significantly lower than a nontransplant control population [140]. The neutralizing antibody response to the Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine was measured 10 to 20 days after the second dose of the vaccine in 80 liver transplant recipients and compared with 25 healthy controls [141]. Only 47.5 percent of liver transplant recipients developed protective levels of SARS-CoV-2 S1/S2 IgG antibodies and mean titers were about one-half the levels of the control group. Older age and immunosuppression including receipt of high-dose prednisone within 12 months, mycophenolate, and triple drug immunosuppression were associated with failure to achieve a protective antibody response.

Liver transplant recipients should be counseled about taking precautions against contracting COVID-19 and liver transplant candidates and recipients should be vaccinated against SARS-CoV-2. (See "COVID-19: Issues related to solid organ transplantation" and "Society guideline links: COVID-19 – Solid organ transplantation".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Infections in solid organ transplant recipients" and "Society guideline links: COVID-19 – Index of guideline topics".)

SUMMARY AND RECOMMENDATIONS

- **Infection as a major cause of morbidity** − Despite advances in liver transplantation, morbidity and mortality due to infectious complications remains a major problem. In many centers, infection is the most frequent cause of death following liver transplantation even though deaths related to infectious diseases in nontransplant settings have steadily decreased. (See 'Epidemiology' above.)

- **Identification of risk factors before transplantation** − Identification of risk factors for infection before transplantation permits the optimal use of strategies for preventing infections in the post-transplant setting. However, there is no single test that can accurately predict a patient's risk of infection after transplantation. (See 'Risk factors' above.)

- **Key preventive measures** − In addition to screening potential liver donors and recipients for infection, there are several approaches to the prevention of infections in liver

transplant patients. These include vaccination, the administration of prophylactic antimicrobials to patients at increased risk for specific infections, pre-emptive therapy, targeted prophylaxis, and educated avoidance. (See 'Prevention' above.)

- **Antibacterial and PCP prophylaxis** − We recommend that trimethoprim-sulfamethoxazole (TMP-SMX) be administered after liver transplantation to reduce the risk of *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia (PCP). It is generally administered for 6 to 12 months. In addition to preventing PCP, TMP-SMX also helps prevent infections with organisms including *Listeria monocytogenes*, *Nocardia asteroides*, *Toxoplasma gondii*, and many common urinary, respiratory, and gastrointestinal bacterial pathogens. However, the optimal dosing for prevention of infections other than PCP is unclear. (See 'Antibacterial prophylaxis' above and 'Pneumocystis prophylaxis' above.)

- **CMV prophylaxis or pre-emptive therapy** − Cytomegalovirus (CMV) remains the most important viral infection in liver transplant recipients. Ganciclovir and valganciclovir have been incorporated into strategies designed to prevent CMV disease in patients at risk of CMV reactivation. (See 'Prevention of herpes virus infections' above.)

  - We recommend either universal prophylaxis or pre-emptive monitoring with CMV polymerase chain reaction or antigenemia in all CMV donor-seropositive/recipient-seronegative (D+/R-) and R+ solid organ transplant recipients. The choice of drug and duration of prophylaxis vary among transplant centers, but most centers use antiviral CMV prophylaxis for three to six months after transplant and during intensification of immunosuppression for rejection. (See 'Prevention of herpes virus infections' above.)

  - In patients who do not receive CMV prophylaxis, we recommend that an antiviral with activity against herpes simplex virus and varicella-zoster virus (acyclovir, valacyclovir, famciclovir) be given during at least the first month after transplantation and during periods of intensified immunosuppression (treatment of graft rejection). Prophylaxis can also be considered for other "stresses" (eg, concomitant infection or surgery). (See 'Prophylactic and pre-emptive CMV therapy' above.)

- **Prevention of fungal infections** − *Candida* is the predominant fungal infection encountered after liver transplantation, with a shift toward infection due to non-albicans *Candida* spp. *Aspergillus* is also a predominant pathogen in patients with certain risk factors. While antifungal prophylaxis is commonly used in liver transplant recipients, the optimal patient population, dose, and duration of prophylaxis remain to be defined. (See 'Prevention of fungal infections' above.)

- **Time course of infections** − The risk of infection and types of infections differ based upon the time after transplantation, although, with changes in immunosuppressive agents over time and the institution of prophylaxis for various infections, the timeline of infection has been altered to some extent. Nevertheless, most postoperative infections can be grouped into three major periods: transplant to one month, one month to six months, and after six months. (See 'Time course of infections' above.)

  - **Early post-transplantation** − Infections occurring immediately following transplantation are similar to those seen in immunocompetent hosts following surgery, such as wound infections, pneumonia, and infections resulting from technical issues. (See 'Transplant to one month' above.)

  - **One to six months post-transplantation** − Opportunistic infections tend to occur one to six months after transplant due to the cumulative effect of relatively high-dose immunosuppression. (See 'One to six months' above.)

  - **Late post-transplantation** − Opportunistic infections are uncommon beyond six months post-transplant in patients who have good graft function since immunosuppression has generally been tapered. These patients usually develop the same types of community-acquired infections seen in the general population (although at an increased rate and, in some cases, with greater severity). An exception is certain viral infections; CMV infection may occur in the setting of recently discontinued CMV prophylaxis, and hepatitis B and hepatitis C infections can cause complications during this period. (See 'After six months' above.)

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Topic 4588 Version 47.0

GRAPHICS

The pretransplant laboratory evaluation for solid organ transplant candidates

	Everyone	Vaccinate if seronegative or not vaccinated	With epidemiologic risk factors
Pathogen			
Cytomegalovirus	X		
Epstein Barr Virus	X		
Varicella	X	X	
HIV (HIV-1 and -2 immunoassay)*	X		
Hepatitis B virus (HBsAg, HBsAb, HBcAb)*¶	X	X	
Hepatitis C virus*¶	X		
Treponema pallidum (Venereal Disease Research Laboratory or rapid plasma reagin)	X		
Tuberculosis (screening skin test or interferon-gamma release assay for tuberculosis$^{\Delta}$)	X		
Mumps, measles, and rubella	X	X	
Toxoplasma gondii (heart transplant candidates)	X		
Coccidioides antibody			X
Histoplasma antibody			X
Blastomyces antibody			X
Strongyloides stercoralis serology$^{\diamond}$			X
Trypanosoma cruzi (Chagas disease)			X
Leishmania spp (visceral disease only, may cross react with *T. cruzi*)			X
Schistosoma spp (cystoscopy may be useful in renal transplant candidates)			X
HTLV1 and 2 (suboptimal screening platforms in low-prevalence areas)			X

Hepatitis A serology		X	X
SARS-CoV-2 (COVID-19) NAAT[§]		X	
Other tests			
Chest radiograph, urinalysis	X		
Stool exam for ova and parasites			X

Refer to UpToDate content for detail on vaccination schedules and treatment of infections identified during screening.

HBsAg: hepatitis B surface antigen; HBsAb: hepatitis B surface antibody; HBcAb: hepatitis B core antibody; HTLV: human T-lymphotropic virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; NAAT: nucleic acid amplification testing.

* Repeat as close as possible to time of transplant (at least within one week of transplant) and repeat for recipients of organs from donors with increased risk for transmission of infection. Refer to the UpToDate topic on screening and diagnostic testing for HIV infection for the preferred approach.

¶ For individuals with known infection or at increased risk for infection (based on risk factors detected in the medical and/or social history), quantitative nucleic acid testing should also be performed.

Δ Refer to the UpToDate topic on tuberculosis in solid organ transplant candidates for the preferred approach.

◇ Strongyloides stercoralis: Empiric therapy (ivermectin × 2 doses) is often used in place of serologic testing for appropriate epidemiologic history.

§ All transplant candidates should be screened for SARS-CoV-2 (sensitive nucleic acid assay) during pandemic and deferred if positive and if feasible. Transplant candidates with ongoing respiratory illness or radiographic pulmonary infiltrates should generally be deferred. SARS-CoV-2 antibody screening assays are highly variable and probably not useful for routine screening; may be useful in demonstrating immune response to prior infection.

Graphic 59792 Version 16.0

Vaccinations for solid organ transplant (SOT) candidates and recipients

Vaccine type	Vaccine target	Indications
Nonlive (inactivated, killed, subunit, or recombinant)	Pneumococcal vaccines	All SOT candidates and recipients not previously vaccinated. Vaccine formulation of choice depends on age, national guidelines, and availability.*
	Seasonal influenza virus	Annually for all patients ≥6 months old.¶
	Hepatitis B virus	All SOT candidates and recipients who are nonimmune based on serologic testing (eg, HBsAb-negative patients).
	Hepatitis A virus	If not previously vaccinated: ▪ All adult liver transplant candidates and recipients ▪ All pediatric SOT candidates and recipients ▪ At-risk adult nonliver transplant recipients (eg, travel to or residence in an endemic area)
	Meningococcus	At-risk patients who have not been previously vaccinated, including those treated with eculizumab and those with impaired splenic function.
	Haemophilus influenzae	At-risk patients ≥5 years old who have not been previously vaccinated, including those with impaired splenic function. Children <5 years old should be vaccinated according to the routine schedule.
	Human papillomavirus	All SOT candidates and recipients not previously vaccinated who meet age-based indications for vaccination.
	Tetanus, diphtheria, pertussis (DTaP, Tdap) or tetanus, diphtheria (Td)	All SOT candidates and recipients per guidelines for healthy persons (eg, per routine for children).
	Recombinant zoster vaccine (RZV)	SOT candidates and recipients aged ≥19 years old.
	COVID-19 vaccines[Δ]	All SOT candidates and recipients. Choice of vaccine depends on age, national guidelines, and availability.
Live, attenuated[◇]	Zoster vaccine, live (ZVL)	SOT candidates aged >50 years old. NOTE: RZV is preferred, when available, over ZVL. **(ZVL contraindicated post-transplantation).**
	Varicella vaccine	Nonimmune SOT candidates prior to transplantation; can be given as early as 6 months of age in children.

		Contraindicated post-transplantation and/or for immunosuppressed patients.[§]
	Measles, mumps, rubella	SOT candidates who have not been previously vaccinated and/or lack evidence of measles, mumps, or rubella immunity (ie, IgG seronegative); can be given as early as 6 months of age in children. **Contraindicated post-transplantation and/or for immunosuppressed patients.**[§]
	Rotavirus	Per usual guidelines for infants prior to transplantation; not indicated for older children and adults. **Contraindicated post-transplantation and/or for immunosuppressed patients.**

As part of the pretransplant evaluation, we review each patient's vaccination history and ensure that the above vaccinations have been received when appropriate. For maximal protection, vaccinations should be given pretransplantation and prior to the start of immunosuppressive therapy. This increases the likelihood of developing a protective immune response and allows for administration of any needed live vaccines, which should be given at least 4 weeks prior to transplantation and are generally contraindicated once immunosuppressive therapy has started.

For complete information on timing of vaccine administration and vaccine schedules, refer to the UpToDate topic on vaccinations in solid organ transplantation. For more detailed description of at-risk populations, refer to the UpToDate topics regarding each vaccine.

HBsAb: hepatitis B virus surface antibody; COVID-19: coronavirus disease 2019; IgG: immunoglobulin G.

* In the United States, children <2 years old should receive the pneumococcal conjugate vaccine (PCV) series, children ≥2 years old should receive both the PCV series and 23-valent pneumococcal polysaccharide vaccine (PPSV23), and adults should receive either 20-valent PCV (PCV20) alone or 15-valent PCV (PCV15) followed by PPSV23 at least 8 weeks later. Dosing intervals and schedule may vary if either one of these vaccines has been given previously. Other national guideline recommendations may vary in regard to vaccine selection.

¶ For adults, we prefer the high-dose influenza vaccine as it augments immune response and does not appear to increase the risk of rejection. However, using the standard dose is also acceptable and preferred for children.

Δ Refer to the UpToDate content on COVID-19 vaccines in SOT patients for additional information.

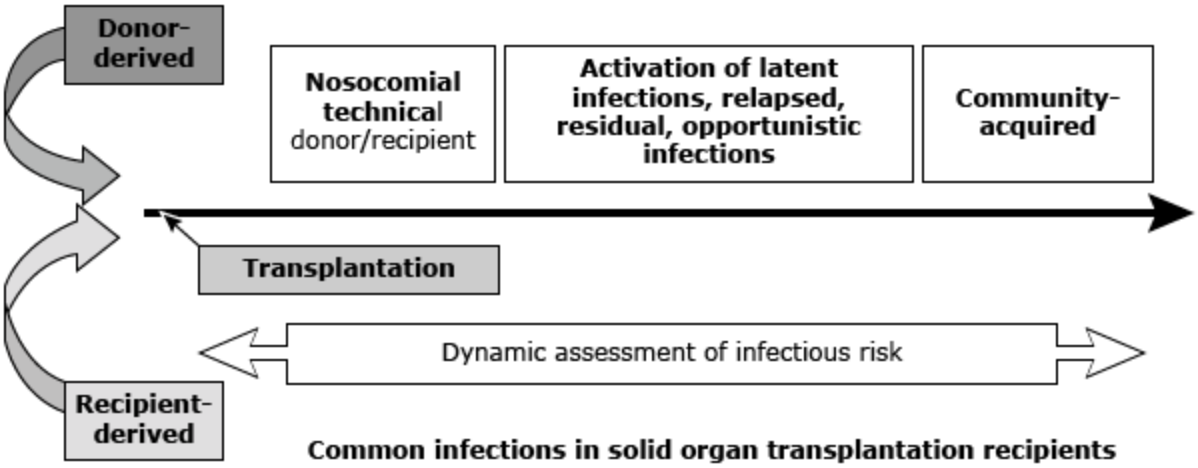
◇ Other live attenuated vaccines include the influenza nasal spray, oral typhoid, and some formulations of the Japanese encephalitis vaccine. These are typically not indicated apart from in selected circumstances (eg, travel) and/or alternative nonlive formulations are available (eg, influenza vaccines and typhoid vaccines).

§ Possible exceptions are measles- and varicella-nonimmune pediatric transplant recipients who are receiving minimal or no immunosuppression and who have had no recent allograft rejection; such

individuals may receive the varicella vaccine or measles vaccines with appropriate education and close follow-up.

Graphic 122440 Version 2.0

The timeline of infections following solid organ transplantation[1-3]



Common infections in solid organ transplantation recipients

Antimicrobial-resistant species: • MRSA • VRE • *Candida* species (non-*albicans*) Aspiration Line infection Wound infection Anastamotic leaks/ischemia *Clostridium difficile* colitis **Donor-derived (uncommon):** HSV, LCMV, rabies, West Nile **Recipient-derived (colonization):** *Aspergillus, Pseudomonas*	**With PCP and antiviral (CMV, HBV) prophylaxis:** • BK polyomavirus nephropathy • *Clostridium difficile* colitis • Hepatitis C virus • Adenovirus, influenza • *Cryptococcus neoformans* • *Mycobacterium tuberculosis* **Anastamotic complications** **Without prophylaxis add:** *Pneumocystis* Herpes viruses (HSV, VZV, CMV, EBV) Hepatitis B virus *Listeria, Nocardia, Toxoplasma, Strongyloides, Leishmania, Trypanosoma cruzi*	**Community-acquired pneumonia, urinary tract infection:** *Aspergillus*, atypical molds, *Mucor* species *Nocardia, Rhodococcus* species Late viral: • CMV (colitis/retinitis) • Hepatitis (HBV, HCV) • HSV encephalitis • Community-acquired (SARS, West Nile) • JC polyomavirus (PML), skin cancer, lymphoma (PTLD)

Common patterns of opportunistic infection are observed following solid organ transplantation based on epidemiologic exposures and the "net state of immunosuppression." The timeline is altered based on the immunosuppressive regimen and prophylactic medications. The dynamic assessment of infectious risk represents assays that will measure an individual's risk for infection due to specific pathogens or in general.

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; MRSA: methicillin-resistant *Staphylococcus aureus*; PML: progressive multifocal leukoencephalopathy; PTLD: posttransplant lymphoproliferative disorder; SARS: severe acute respiratory syndrome; VRE: vancomycin-resistant enterococcus; VZV: varicella-zoster virus.

Modified from:

1. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357:2601.

2. Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. Am J Med 1981; 70:405.

3. Fishman JA, Rubin RH. Infection in organ-transplant recipients [see comments]. N Engl J Med 1998; 338:1741.

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Graphic 58770 Version 5.0

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Conflict of interest policy

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