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# Postoperative Infectious Complications of Abdominal Solid Organ Transplantation

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There is a rapidly growing population of immunocompromised organ transplant recipients. These patients are at risk of a large variety of infections that have significant consequences on mortality, graft dysfunction, and graft loss. The diagnosis and treatment of these infections are facilitated by an understanding of the preoperative, perioperative, and postoperative risk factors; the typical pathogens; and their characteristic time of presentation. On the basis of these factors, we put forth an algorithm for diagnosing and treating suspected infections in solid organ transplant recipients.

**Keywords:** infection; kidney transplantation; liver transplantation; pancreas transplantation; postoperative complications

## Introduction

Although the number of people with end-stage organ disease requiring transplantation increases annually, the number of solid organ transplantations performed is limited by the availability of donated organs. According to the US Organ Procurement and Transplantation Network (OPTN) data, in 2006, a total of 28,920 organs were transplanted in the United States.[1] However, on October 1, 2007, 96 768 people were still on the waiting list for an organ. The vast majority of patients awaiting organ transplantation are in need of a kidney or liver transplant. Fortunately, as advances in surgical techniques, perioperative care, and immunosuppressive therapies improve, transplantation has become more successful and organ recipients are surviving longer. The most recent average 1-year patient survival for all abdominal solid organ transplants is approximately 93%; at 5 years, patient survival is approximately 80%.[1] Therefore, there is a growing population of high-risk immunocompromised organ recipients that require ongoing care.

After transplantation, organ recipients are at a significant risk of bacterial, fungal, and viral infections (Tables 1 and 2). Infections in this patient population have increased morbidity and mortality and unique infectious risks compared to immunocompetent intensive care unit (ICU) patients. Several studies of patients receiving transplanted abdominal organs demonstrate the importance of postoperative infection in transplant recipients. A recent retrospective review of 385 adult-to-adult living donor liver transplantations demonstrated that the most common early complication, seen in 32% of recipients, was infection.[19] Furthermore, infection after orthotopic liver transplantation (OLT) was an independent predictor of mortality[20] and a prolonged hospital stay.[21]

In a study of 66 patients undergoing simultaneous pancreas and kidney transplants (SPK), every

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Table 1. Common Infections in Solid Organ Transplant Recipients

| |
|---|
| Bacterial |
| Gram-positive cocci: *Enterococcus, Staphylococcus, Streptococus, Escherichia* |
| Gram-negative rods: *Pseudomonas, Klebsiella, Serratia, Clostridium difficile* |
| Drug-resistant bacterial |
| Methicillin-resistant *Staphylcoccus aureus* (MRSA) |
| Vancomycin-resistant *Enterococcus faecium* (VRE) |
| MDR *Pseudomonas aeroginosa* |
| ESBL producing *Klebsiella pneumoniae* and *Escherichia coli* |
| Fungal |
| *Candida* species |
| *Aspergillus fumigatus* |
| *Pneumocystis carinii* |
| Viral |
| Cryptococcus neoformans |
| CMV |
| HSV |
| VZV |
| HHV-6 |
| Polyomaviruses (BKV, JCV) |
| Adenovirus |

NOTES: BKV = BK virus; CMV = cytomegalovirus; ESBL = extended-spectrum b-lactamase; HHV-6 = human herpesvirus 6; HSV = herpes simplex virus; JCV = JC virus; MDR = multiply drug resistant; VZV = varicella zoster virus.

Table 2. Incidence (%) of Infectious Disease in Solid Organ Transplant Recipients[a]

| Organism | Liver | Kidney | Pancreas[b] |
|---|---|---|---|
| Bacteria | 33-49 | 12-86 | 35-81 |
| Fungi/mold | 1-42 | 2-20 | 4-38 |
| Viruses | 5-39 | 38-50 | 6-16 |

NOTES: PAK = pancreas after kidney; PTA = pancreas transplant alone; SPK = simultaneous pancreas and kidney transplant.

[a] References: 2-18.

[b] Includes SPK, PAK, and PTA.

patient had at least 1 infection after surgery.[22] In another study of 478 renal transplant patients, 65% had an infection in the first 6 months.[2] Infections can have a direct impact on graft survival. Postoperative infections are reported to be responsible for 3% to 18% of pancreatic graft loss.[3,23,24] Renal graft loss is associated with early acute bacterial allograft pyelonephritis, for which cytomegalovirus (CMV) infection is considered a risk factor.[25] Similarly, liver graft survival appears to be lower in patients who experience surgical site infections (SSIs).[21]

Recipients of abdominal organs are often admitted to a generalized surgical or medical-surgical ICU in the immediate postoperative period. In addition, patients are frequently readmitted to the ICU with the presumed diagnosis of sepsis. The goal of this review is to describe the commonly seen infectious complications for abdominal solid organ transplant recipients and the standard prophylactic, diagnostic, and treatment measures.

Postoperative infections in transplant recipients can be divided into 3 time periods based on the types of infections likely to develop: first month posttransplantation, 1 to 6 months posttransplantation, and more than 6 months posttransplantation.[26] This facilitates the diagnosis and treatment of specific pathogens and should drive empiric therapy (Figure 1).

## Risk Factors

### Invasive Procedures/Surgical Intervention

In the first month after transplantation, the sources of infection are primarily nosocomial secondary to the surgical technique or technical complications.[3] There are risks of SSIs, intraabdominal abscesses, and infected hematomas. In liver transplantation, surgical complications such as biliary leaks can lead to subsequent infections including peritonitis, cholangitis, and hepatic abscesses. The risk of fungal infections after OLT increases with renal failure, transfusions, retransplantation, relaparotomy, and creation of a Roux-en-Y biliary duct anastomosis.[3]

Surgical site infections of the soft tissue are usually diagnosed clinically by the presence of erythema, tenderness, purulence, and crepitus around the wound.[27] Often, superficial SSIs can be treated with antibiotics only; however, any rapidly progressing soft tissue infection requires prompt surgical treatment. Gram-positive organisms are usually the source of superficial SSIs, but necrotizing infections are often polymicrobial. Surgical site infections involving deeper tissue structures are more difficult to recognize. Diagnostic procedures include culturing and Gram staining of any fluid from the wound or drains, an ultrasound or a computed tomographic (CT) scan to localize the possible fluid collections, and a possible relaparotomy. Laparotomies are associated with an increased mortality but are often necessary in critically ill patients, especially those with

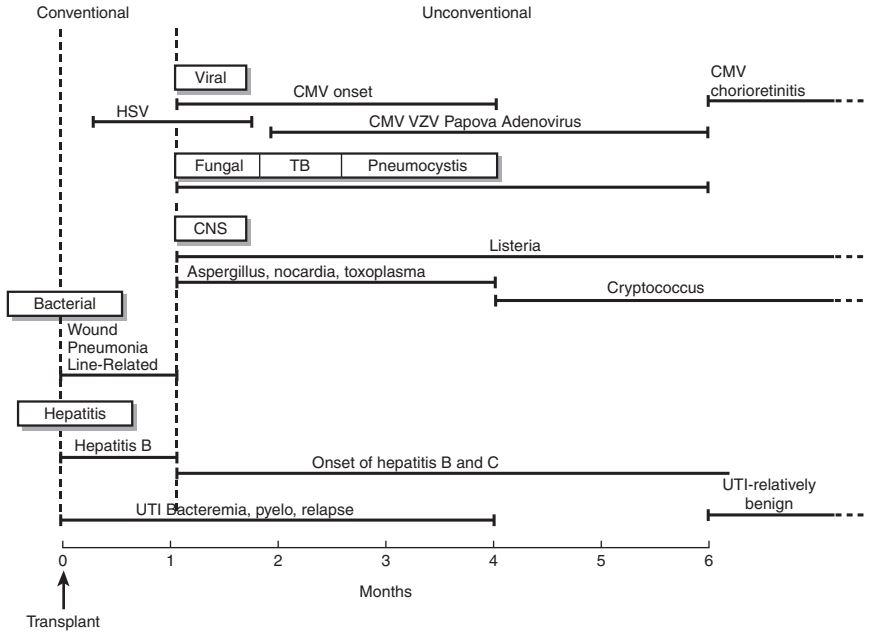


**Figure 1.** Timetable of infection following organ transplantation. Adapted from *Clinical Approach to Infection in the Compromised Host*. 4th ed. In: Rubin RH and Young LS, eds. New York: Kluwer Academic/Plenum Publishers; 2002 and from *Am J Transplant*.[26] 2004;4:6-9. CMV, cytomegalovirus; CNS, central nervous system; HSV, herpes simplex virus; TB, tuberculosis; UTI, urinary tract infections; VZV, varicella zoster virus.

sepsis and multiorgan failure.[20] Computed tomography–guided drains successfully treat 80% of abdominal abscesses in general surgical patients.[28]

Intraabdominal abscesses in OLT are often near the biliary tract, especially if a Roux-en-Y choledochojejunostomy was used for the biliary reconstruction. The renal transplant patients are at risk of perigraft hematomas and urinary leaks that serve as niduses for intraabdominal infections.[4] After a SPK, the risk of an intraabdominal SSI may be slightly increased if pancreatic exocrine secretions are drained enterically rather than drained via the pancreatic duct anastomosis to the bladder.[29]

Renal allograft recipients with high serum creatinine, urinary fistulae or leaks, and a prolonged urinary bladder catheterization have a higher risk of wound infections.[30] Additionally, kidney transplant recipients with a peritoneal dialysis catheter present prior to transplantation may have an increased risk of intraabdominal, bloodstream, and wound infections.[30,31]

Frequently, transplant patients require extensive postoperative critical care with prolonged intubation and indwelling central venous and urinary catheters. These devices are significant risk factors for ventilator-associated pneumonia (VAP), catheter-related bloodstream infections (CRBSIs), and urinary tract infections (UTIs), respectively.[20,3,32,5] Comorbidities such as diabetes and persistent renal dysfunction increase susceptibility to infections. For example, renal failure incurs a 15- to 21-fold increased risk of invasive fungal infection.[3] Pneumonia accounts for 41% of febrile episodes in the ICU in the first 7 days postoperatively; the risk of CRBSI increases 3-fold after the first week.[3]

## Immunosuppression

Postoperative immunosuppressive medications prescribed to prevent graft rejection are monitored closely. Dosing must be carefully titrated high enough to prevent acute rejection, but not so high that the recipient develops serious infections or toxic side effects. Multiple immunosuppressant mechanisms exist. Corticosteroids have anti-inflammatory effects, inhibit cytokine gene transcription, and significantly impair macrophage-mediated and polymononuclear neutrophil–mediated cell killing, the essential components of host immunity.[6] Tacrolimus and cyclosporine specifically inhibit T-cell activation.

Table 3. Incidence (%) of CMV Infection by Donor and Recipient Status[a,b]

| Donor Status | Organ Recipient Status | | | | | |
|---|---|---|---|---|---|---|
| | Liver | | Kidney | | Pancreas/Kidney | |
| | Sero+ | Sero− | Sero+ | Sero− | Sero+ | Sero− |
| Sero+ | 32 | 85 | 9 | 46 | 37 | 52 |
| Sero− | | 4 | | | 40 | 11 |

NOTE: CMV = cytomegalovirus.
[a] References: 12, 35, 36.
[b] Cells with empty entries are those studies that did not distinguish between D+ and D−; percentage listed for the seropositive donor applies to both D+ and D−.

Inhibition of these inflammatory pathways can also mask typical signs of infection such as fever, pain, and erythema from developing, thereby, delaying their diagnosis and treatment.[24] In addition, patients with recent episodes of graft rejection are at higher risk of acquiring infections because these episodes are usually treated with increases in immunosuppressive dosing, steroid pulses, and additional immunosuppressants.[2]

## Infected Donors

The transplant community has increased the use of extended criteria donors (ECDs, donors who are not ideal due to medical illness or age) to reduce mortality in patients on the organ waiting list. Some of these ECDs have documented infections that may be transferable to the recipient. Donors are screened for hepatitis B and C, CMV, Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) and cultured extensively for bacteria. Diagnostic radiological tests are also reviewed for the evidence of infection.[33] However, the results of these studies are often not available at the time of organ procurement and transplantation, so a thorough history and physical is necessary. A retrospective review from a single-state organ procurement organization found that 7.5% of organ donors had positive blood cultures and 4.5% had positive urine cultures. Of the 36 contaminated organs that were transplanted at that institution, only 3 (8%) developed infections caused by organisms found in the donor.[34] All had been on broad-spectrum antibiotics that were then tailored to the organism once culture data were available.

The *American Journal of Transplantation* guidelines state that there is no need to treat a recipient who receives an organ from a donor with a localized, nonbacteremic infection outside the target organ.[33] The only exception to this is the organ donor with meningitis, in which case the recipient should be treated appropriately with antibiotics.[33] Recipients who receive organs from bacteremic donors require appropriate antimicrobial therapy based on the isolated organism. A longer duration of therapy, in the range of 2 weeks posttransplantation, is recommended for particularly virulent organisms such as *Staphylococcusaureus* and *Pseudomonas aeroginosa* because there have been documented cases of mycotic aneurysms at the vascular anastomoses caused by these organisms.[33] This therapy should narrowly focus on the isolated organism to reduce the risk of selecting for those with multidrug resistance.

In general, any active invasive fungal infection is a contraindication to organ donation. Transmission of some of the dormant endemic mycoses, especially histoplasmosis and coccidiomycosis, has been reported. However, reactivation of these diseases is much more common than transmission via transplantation.[33]

The viruses that are of particular interest in donor organs are hepatitis B, hepatitis C, CMV, EBV, and the herpes viruses. Human immunodeficiency virus infection is currently a contraindication to donation at most centers. Cytomegalovirus serologic status of both the donor and recipient is important in determining prophylaxis and treatment regimens. Although it is not contraindicated to transplant a CMV seropositive donor (D+) into a seronegative recipient (R−), the risk of developing CMV is very high (Table 3).[37]Epstein-Barr virus seronegative recipients who receive a seropositive graft are at the highest risk of posttransplant lymphoproliferative disease

(PTLD). This is a special concern in the pediatric patients who are less likely to have been exposed to EBV.

Hepatitis B viral serology of the organ of donation is important in determining the risk of transmission.[38] Grafts from donors that have hepatitis B virus (HBV) core antibody (HBcAb+) may be appropriate for transplantation, but donors with HBV surface antigen (HBsAg+) have active HBV infection and are at high risk of transmitting HBV to the recipient. Hepatocytes harbor HBV; therefore, liver transplantation carries a higher risk of transmission than kidney or pancreas transplantation. Ideally, HBcAb+ liver grafts should only be transplanted into recipients with hepatitis B cirrhosis who are committed to perioperative hepatitis B treatment already; however, with the increasing severity of the organ shortage, these organs are being successfully given to nonhepatitis B recipients. These recipients are treated with hepatitis B antiviral medications such as lamivudine to prevent reactivation of the virus.

The risk of hepatitis C virus (HCV) transmission is highest if there is a high viral load as determined by HCV-RNA polymerase chain reaction (PCR) quantification, but this test result may not be available at the time of transplantation. The use of organs from HCV-positive donors varies and is dependent on urgency and institutional policy.

Rare, but noteworthy, transmission of the rabies virus and West Nile Virus has been reported.[39,40] A subclinical rabies infection in 1 donor led to the death of 4 organ recipients. A donor with West Nile Virus was believed to have been infected by contaminated blood products prior to brain death. Only 1 of the 4 graft recipients died as a result of West Nile encephalitis. Testing for West Nile Virus is available but time-consuming and routine screening is not universally recommended for organ donors.[33]

## Bacterial Infections

Bacteria are the most common pathogen in patients after solid organ transplantation frequently causing UTIs, pneumonia, and bacteremia. Because of routine perioperative antibiotic usage, usually with a first- or second-generation cephalosporin, the trend over the last 20 years has been an increased incidence of infections due to gram-negative bacilli and drug-resistant gram-positive cocci.[3,41-43]

### Gram-negative Bacilli

Many of the virulent gram-negative bacilli have become multiple drug resistant (MDR) or capable of producing extended-spectrum β-lactamases (ESBL). Drug-resistant *P aeroginosa* and *Enterobacter* were seen in a study of liver transplant recipients.[42] In this study, MDR bacteria caused 63% of all infections. Notably, 63% of the *P aeroginosa* species were resistant to carbapenems. Risk factors for imipenem-resistant *P aeroginosa* infection are transplantation and imipenem use.[41]

Gastrointestinal tract colonization, use of broad-spectrum antibiotics, and an extended ICU length of stay are the risk factors for ESBL organisms.[43] *Klebsiella pneumoniae* and, to a far lesser extent, *Escherichia coli*, are associated with the production of ESBL that can hydrolyze β-lactam antibiotics. In 1 report, 28% of *K pneumoniae* isolated from blood cultures of OLT patients were ESBL producing.[3] However, there is a marked center-to-center and regional variation in ESBL rates.

### Gram-positive Cocci

At many centers, gram-positive cocci, specifically staphylococci and enterococci, are the predominant pathogens. Drug resistance in these organisms is also common. Methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE) are estimated to be the foremost cause of bacterial infections at many institutions.[3,44] In a Centers for Disease Control and Prevention (CDC) survey, approximately 25% to 35% of staphylococci infections were due to MRSA. Deep-seated MRSA infection, as opposed to MRSA CRBSI, is associated with high mortality in liver transplant patients.[3] Additionally, eradication of colonization has been shown to decrease MRSA infection.[41] However, recolonization rates are high, so this practice is best used immediately prior to an anticipated surgery and may not be possible prior to transplantation.

Although less common, vancomycin-resistant enterococcus (VRE) infections are often associated with bacteremia and have few therapeutic options. Although enterococci are not generally considered virulent organisms, VRE infections after transplantation can be severe.[3] The usual sites of infection for these bacteria are the bloodstream, surgical wounds, abdomen, and biliary tree. Risk factors for developing VRE include extended-spectrum cephalosporin

antibiotic use, ICU admission, renal insufficiency, exposure to other colonized or infected patients, and prolonged hospitalization.[45] Reports show a colonization rate between 11% and 63% after liver or kidney transplantation, with infection rates varying between 1% and 16%.[41]

## Less Common Bacterial Infection

Less common infectious agents include *Legionella, Clostridium difficile*, and *Nocardia*. *Legionella* pneumonia should be suspected if there is an alveolar infiltrate and, occasionally, a cavitary lesion that is unresponsive to aminoglycoside or β-lactam antibiotics. In kidney recipients, such *Legionella*-associated pneumonias often coincide with graft rejection.[30] The most sensitive test for *Legionella pneumophilia* is the urinary antigen test, but this test only detects the serotype 1 antigen of *L pneumophilia* and none of the non-*pneumophilia* species. Culture and direct fluorescent antibody testing of sputum or bronchoalveolar lavage (BAL) samples for *Legionella* may be of use. If *Legionella* pneumonia is suspected, treatment with azithromycin or fluoroquinolones should not be delayed because there is a high associated mortality in transplant patients.[30,46]

*Clostridium difficile* may cause significant colitis, resulting in diarrhea and abdominal discomfort. *Clostridium difficile* colitis is probably not increased in transplant recipients compared to other hospitalized patients.[47] In transplant patients, it usually occurs early in the postoperative course but may relapse. Unlike immunocompetent patients, transplant patients may have more severe symptoms or extraintestinal disease. The disease is toxin mediated and strongly associated with antibiotic use. Patients with persistent diarrhea should have *C difficile* testing.

*Nocardia* is an opportunistic infection of the immunosuppressed patients. This gram-positive aerobic branching rod is a ubiquitous environmental organism that usually infects via inhalation into the lungs. In addition to immunosuppression, the risk factors for *Nocardia* infection are CMV disease, graft rejection, and profound hypogammaglobulinemia.[30] Nocardiosis is rarely seen early in the transplantation period because many patients are placed on trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for *Pneumocystis carinii*. Pulmonary nocardiosis presents with irregular, nodular lesions in the lungs that may cavitate or with diffuse infiltrates and pleural effusions. Once pulmonary nocardiosis is confirmed by sputum or BAL culture, extrapulmonary involvement, especially brain abscesses and meningitis, must be investigated. Sulfonamides are the treatment of choice for nocardiosis.[48]

*Urinary Tract Infection*. After kidney transplantation, the incidence of an UTI is 35% to 79%[30]; after SPK it is 14% to 89%.[22,7,49] Bacterial pathogens in these populations include enterococci, staphylococci, P aeroginosa, and enteric gram-negative bacteria. Renal transplantation requires bladder catheterization and can predispose patients to developing a symptomatic infection within the first 3 weeks postoperatively.[30] One should consider treating UTIs in transplant patients even if fewer than 100 000 colonies per milliliter are cultured, especially if there is a single organism. Early UTI can ascend to cause acute graft pyelonephritis (AGPN) and spread to the bloodstream. Acute graft pyelonephritis occurred in 13% of kidney recipients in 1 cohort study of 187 patients and the only identified risk factor was CMV infection.[25] Acute graft pyelonephritis within the first 3 months of transplantation was also a significant predictor of poor graft outcome. The prompt removal of the indwelling bladder catheters is the best prevention for UTI, but antimicrobial prophylaxis with TMP-SMX or a quinolone has also been shown to decrease UTI rates.[30]

Simultaneous pancreas and kidney transplant confers a higher rate of UTI than kidney transplant alone.[30,8] Among the different types of pancreas transplantation procedures, all have UTI rates greater than 40%.[9] The exocrine output of pancreatic transplants can be surgically drained to the bladder or the small bowel. Some studies[7,50] have found that the risk of UTI after SPK is not significantly different between bladder and enteric exocrine drainage. Other studies[49,51-54] have found decreased UTI rates with enteric drainage. Gram-positive organisms may be slightly more prevalent in patients with bladder-drained grafts, but gram-negative organisms were much more likely in the enteric-drained grafts.[7] Enteric drainage has become popular and has resulted in fewer infectious complications and improved patient survival. Enteric drainage may, however, increase the risk of intraabdominal infections,[29] but this has not been seen consistently.

### Bacteremia

Perioperative bacteremia has been seen in 6.2% of SPK patients and 3.5% to 4.8% of lone kidney recipients.[2,55] A study of SPK recipients found that most bacteremic episodes (57%) developed from a urinary tract source in the initial postoperative period. Catheter-related bloodstream infections accounted for only 11% of all bacteremic episodes in SPK patients.[2] In comparison, a study of liver transplant recipients showed that the sources of bacteremia were most likely from intravascular catheters (29%), pneumonias (18%), and biliary sources (18%).[24] A total of 65% of positive blood cultures were either MRSA or *P aeruginosa*.

## Fungal Infections

Fungal infections can be seen early in the postoperative course, in particular, in patients who remain critically ill or have poor organ function after transplantation. The most common fungal infections posttransplantation are candidiasis and aspergillosis. Others include *P carinii* pneumonia (PCP), *Histoplasma, Cryptococcus*, and the ubiquitous fungi (*Rhizopus* and *Mucor* species).[10] Of the solid abdominal organs, liver transplant recipients have the highest incidence of invasive fungal infection (4%-42%), followed by pancreas and SPK recipients (6%-38%), and renal transplant recipients (0%-20%).[56] Although fungal infections are less common than bacterial infections, the morbidity and mortality tend to be higher. Patients with aspergillosis have an especially high mortality rate of 80% to 100%.[23]

### Prophylaxis

At most transplant centers, liver, kidney, and pancreas recipients receive prophylaxis against invasive candidiasis. The drug of choice is fluconazole because of its low side effect profile.[11,57] However, fluconazole inhibits the metabolism of calcineurin inhibitors; therefore, lower doses of the calcineurin inhibitors are usually required to reach therapeutic serum levels in patients on both medications. Prophylaxis against aspergillosis has mainly been advocated only in high-risk liver transplant patients. Because of their low toxicity profile, the triazole antifungals have become first-line therapy for aspergillosis prophylaxis over the more toxic amphotericin B preparations.

Itraconazole, a triazole antifungal with broader coverage and greater potency than fluconazole, has been tested in liver recipients, but the use of this drug for prophylaxis against fungal infections is unknown.[58] It has in vitro activity against *Aspergillus* and *Candida* species, but efficacy has only been shown in trials for *Candida*.[56] Voriconazole became available in 2002 and because of its broad spectrum, minimal drug interactions, and few side effects, it has become a popular choice against fungi. However, prophylactic voriconazole has not been studied in the transplant recipient. The newest triazole antifungal, posaconazole, has not been evaluated in the solid organ transplant recipient. Studies in neutropenic cancer patients and stem cell transplant patients showed equality or superiority of posaconazole over voriconazole and fluconazole as a prophylactic medication.[59,60]

Prophylaxis against *P carinii* with TMP-SMX is efficacious and almost universal after abdominal solid organ transplantation.[10] For patients with a sulfa allergy, inhaled pentamidine or oral dapsone may be substituted.

### *Candida*

*Candida* infection in all solid organ transplant recipients develops early in the postoperative course, often within the first 2 months after surgery. *Candida* species are responsible for the majority of early fungal infections. Diabetes and hyperglycemia are known risk factors for candidiasis.

The most common species of *Candida* observed in transplant recipients include *Candida albicans, Candida glabrata*, and *Candida tropicalis*, although other infectious species exist. Infections are usually derived from endogenous flora and donor transmission is very rare. *Candida* may cause mucocutaneous infections, wound infections, gastrointestinal or genital-urinary tract infections, peritonitis, endocarditis, candidemia, catheter or foreign body infection, brain abscesses, osteomyelitis, and pneumonia. Disseminated disease may lead to shock that is unresponsive to antifungal therapy.[56] Candidal CRBSI commonly leads to systemic candidiasis. Visceral infection rarely leads to a systemic infection; however, visceral seeding is common after candidemia.[10] In the renal graft recipient, the urinary tract is the

most common site of candidal infection. In pancreas recipients, candidal infections of the wound, urinary tract, bloodstream, and peritoneum are seen.[10]

Fungal staining and cultures of urine and blood facilitate the diagnosis of an invasive or systemic candidiasis. Interpretation of respiratory cultures is problematic because there can be candidal colonization of the upper gastrointestinal tract. If respiratory cultures are evaluated, a quantitative sample is recommended to differentiate from benign colonization. Occasionally, invasive procedures may be needed to sample fluid collections, cerebrospinal fluid (CSF), or grafted organs to diagnose fungal infection. Because the susceptibility to azole antifungals varies, speciation and susceptibility testing should be performed after *Candida* has been isolated.[56]

Asymptomatic candiduria can be treated without antifungal therapy by removing the indwelling bladder catheter. Treatment of documented candidemia requires removal of venous catheters and an antifungal agent. In the acutely ill patient, treatment of suspected candidiasis should begin prior to the documentation of infection and antifungal resistance should be anticipated. Limited mucocutaneous candidiasis is best treated with an oral wash of nystatin or azole antifungals.

Numerous *Candida* species exhibit resistance to fluconazole, notably *C glabrata* and *Candida krusei*. An echinocandin antifungal, caspofungin, has broader anticandidal coverage than fluconazole and is as effective as the amphotericin preparations with less toxicity.[61] The introduction of caspofungin and voriconazole, which has efficacy against many fluconazole-resistant *Candida* species, has decreased the need for amphotericin B in candidiasis. However, amphotericin B, possibly combined with flucytosine, is the "gold standard" for fungal therapy and may be required for resistant cases.[11] Similar to the treatment algorithm for bacterial infections, antifungal treatment should be modified or discontinued depending on the final culture results. Candidemia also warrants ophthalmic evaluation for retinal candidiasis.

## *Aspergillus*

In liver recipients, aspergillosis tends to occur early, usually within the first month of transplantation and is seen in patients who remained critically ill in the ICU after graft transplantation.[62] Aspergillosis usually develops later in renal graft recipients, often after the patient has been discharged and may come from exposure in the community. Many of the other risk factors for candidiasis and aspergillosis are the same: prolonged operative time, relaparotomy and retransplantation, high transfusion requirements, Roux-en-Y biliary anastomosis, renal failure, prolonged antibiotic use, and rejection. Risk factors for early *Aspergillus* infection are graft dysfunction, fulminant hepatic failure (liver recipients), CMV infection, and excessive immunosuppression.[6,10,56,62] Immunomodulatory viruses, specifically CMV and human herpes viruses (HHV-6), have been shown to inhibit lymphocyte function and increase the incidence of invasive fungal infections.

Airborne *Aspergillus* spores are ubiquitous in the environment. Therefore, in the organ transplant recipients, invasive aspergillosis usually presents in the lungs, but it can also present in the central nervous system (CNS) up to 50% of the time.[6] Pulmonary sequelae include hemoptysis and empyemas. The radiologic findings of pulmonary aspergillosis include nodules that can be cavitary, pulmonary effusions, and lobar infiltrates. A high-resolution chest CT should be performed if there is any clinical suspicion.[56,63] Cavitation with a "halo" sign may occur early, and branching mucoid impactions characterize bronchopulmonary aspergillosis.[64]

Central nervous system lesions may be suspected if there are mental status changes, seizures, or focal neurological deficits. Central nervous system aspergillosis should be evaluated with gadolinium-enhanced magnetic resonance imaging (MRI) to search for single or multiple ring-enhancing lesions and surrounding edema.[56,63] Aspergillomas can also be seen in the renal pelvis or sinuses.[56] Because of its angiotropic characteristics, the presence of any *Aspergillus* species at a single site necessitates evaluation for occult disseminated disease.

The accurate diagnosis of aspergillosis is difficult because it is difficult to culture *Aspergillus* from blood samples even when there is an invasive disease. The galactomannan antigen assay has been found to be moderately sensitive but highly specific for invasive aspergillosis.[63,65] However, there is a high rate of false-positive galactomannan assays in patients taking amoxicillin and piperacillin and in patients infected with other fungi.[66] Combining the galactomannan assay with an assay that detects a fungal cell wall polysaccharide called (1→3)-β-D-glucan (BG) completely eliminates these false

positives.[67] More recently, PCR detection of *Aspergillus* DNA has been evaluated, but the incidence of false positives has been high and there is currently no standardization.[56,63]

Voriconazole is superior to amphotericin B and has become the treatment of choice for invasive aspergillosis.[68] Side effects are minimal but include reversible vision changes, skin reactions, and hepatic function abnormalities.[10] Alternatives to voriconazole are caspofungin, itraconazole, and amphotericin B.

In addition to medical therapy, early surgical intervention is indicated for the successful treatment of aspergillomas and soft tissue, musculoskeletal, and nonvascular anastomotic site *Aspergillus* infections.[56]

### *Pneumocystis*

*Pneumocystis* is prevalent between the first and sixth months posttransplantation. *Pneumocystis carinii* reactivation in the immunosuppressed patient after solid organ transplantation results in a pneumonia characterized by a dry, subacute cough, fever, severe hypoxemia, bilateral patchy, diffuse infiltrates on chest radiograph, and an increased risk of pneumothorax. It is associated with episodes of rejection, increased immunosuppression, and CMV infection.[69] The definitive diagnosis is dependent on the demonstration of organisms in lung tissue or respiratory secretions obtained from induced sputum, tracheal aspirates, or BAL. Trimethoprim-sulfamethoxazole is a highly efficacious treatment. High-dose steroids may be useful in the acutely ill patient with hypoxemia.[69] Alternatives to TMP-SMX for patients who are intolerant include pentamidine, dapsone, and atovaquone.

### Other Fungi and Molds

*Cryptococcus* and endemic fungal infections develop 4 to 6 months posttransplantation. *Cryptococcus* species may cause CNS, pulmonary, cutaneous, or other clinical disease, usually greater than 6 months after transplantation.[56] Exposure to birds with the disease can lead to spore inhalation; although pneumonia may not develop despite disseminated disease. Testing for serum cryptococcal antigen confirms the diagnosis.[10] Endemic fungi such as *Coccidiodes* and *Histoplasma* can also cause pneumonia or disseminated disease. Azoles, extended-spectrum triazoles, and amphotericin preparations are all active against these fungi.

Dematiaceous (dark-pigmented) fungi, zygomycoses, and hyaline molds rarely lead to infection in the transplant patient. These dematiaceous fungi can be systemic and invasive or limited to skin and soft tissue infections.[6] Zygomycoses (*Rhizopus, Cunninghamella*, and *Mucor* species) usually occur as a rhinocerebral form. Hyaline mold infection, specifically *Fusarium* species, which is common in bone marrow transplant recipients, is very uncommon and usually well localized in solid organ transplant patients.[6] The triazole antifungals are the drugs of choice for the dematiaceous fungi. Surgical debridement and amphotericin are the treatments for zygomycoses and hyaline molds.[70]

## Viral Infections

### Cytomegalovirus

The incidence of CMV seropositivity in the community is high. Cytomegalovirus is the most common perioperative viral infection in transplant patients and infers a high morbidity. The highest risk of acquiring CMV disease is in the seronegative recipient who receives an organ from a seropositive donor, commonly notated as D+/R−. Infection rates in this group range from 80% to 90%[35] (Table 3). D−/R− liver transplant patients have less than 5% risk of CMV disease if CMV negative blood products are used.[35] One study of OLT patients found that variables associated with CMV infection in seropositive recipients (R+) were Hispanic race, seropositive donors, and hepatocellular carcinoma.[35]

Cytomegalovirus disease presents either as a "viral syndrome" with fever and malaise or as tissue-invasive disease such as pneumonitis, colitis, or hepatitis.[37] Cytomegalovirus infection of the allograft is also common due to an altered local immune response. Although evaluation of CMV antibodies is useful to determine seroconversion in R− patients after transplantation, an antigenemia assay is used to determine disease in the R+ patient. A peripheral blood sample is tested for infected cells by detection of the pp65 antigen. This method has a higher sensitivity and specificity than culture-based tests.[37] Cytomegalovirus PCR testing may be done to determine the quantitative viral load.

Cytomegalovirus appears to have an immunomodulatory effect by altering the cytokine activity and the configuration of T-lymphocyte subsets.[71]

Consistent with this finding is that CMV infection is a significant risk factor for other infections, including bacteremia, fungal disease, and EBV-related PTLD. Additionally, an association between acute and chronic organ rejection and CMV has been delineated.[8,36,12] Cytomegalovirus disease has been documented both before and after episodes of acute rejection. Acute rejection followed by antilymphocyte therapy has an especially high incidence of CMV disease in renal allograft recipients.[8] The risk of renal allograft loss due to acute rejection is highest in the D+/R− group. However, if the graft is not lost, the graft function as determined by the creatinine clearance is similar to the other groups.[36] Animal studies have indicated that CMV disease may increase chronic allograft nephropathy, but human studies have not yet supported this.

Cytomegalovirus disease in the posttransplant patient is managed either by universal prophylaxis or by frequent surveillance testing for viral replication. For universal prophylaxis, all patients are given antiviral medications in the immediate postoperative period. Valganciclovir or ganciclovir are the drugs of choice; acyclovir has poorer efficacy than either.[37] Valacyclovir has been evaluated in kidney recipients as a prophylactic medication with good results and fewer episodes of biopsy-proven rejection. The duration of prophylaxis has not been standardized, but many centers have continued prophylactic antivirals for 100 days after transplantation. Even less clear is the role of intravenous immunoglobulin (IVIG) or CMV hyperimmune globulin (CMVIG) as a preventative measure. In the preemptive approach of CMV prevention, patients are treated with antiviral medications only after the surveillance tests are positive for CMV infection but prior to the onset of CMV disease. Ganciclovir or valganciclovir are the recommended medications, but once again, the optimal length of treatment has not been clearly defined. The continued evaluation of CMV DNA by PCR or CMV antigenemia may be useful in guiding the length of therapy.

After CMV disease has been diagnosed, intravenous ganciclovir, valganciclovir, or foscarnet are the preferred treatments. The usual duration of treatment is 2 weeks, but length should be guided by PCR and antigenemia assays until no virus can be detected.[37] The benefit of CMVIG with ganciclovir is unclear in the treatment of established CMV disease.

## Herpes Viruses

Early viral infection is frequently due to reactivation of herpes simplex virus (HSV) infection; however, prophylactic acyclovir or ganciclovir has decreased the incidence.[4,72]

Herpes viruses include HSV-1,HSV-2, varicella zoster virus (VZV), and the HHV-6, -7, and -8. Cytomegalovirus is also classified as a herpes virus (HHV-5) and has 66% DNA homology with HHV-6.[13,14] Herpes simplex virus-1,HSV-2, and VZV all cause characteristic skin lesions and are quite prevalent in the United States general population.[73] The diagnosis of HSV infection is usually clinically based when skin or mucus membranes are involved, but atypical visceral or invasive disease may require laboratory investigation. Viral culture or direct fluorescent-antibody (DFA) assays of specimens are used for diagnosis. Effective prevention of disease due to HSV or VZV is possible with oral acyclovir. However, if a patient is being given universal prophylaxis for CMV, no additional antiviral medication is necessary to prevent HSV and VZV.[73] Prospective organ recipients should be vaccinated prior to transplantation if they are shown to be seronegative for VZV; however, it is a live viral vaccine and should not be given after transplantation when the patient is immunosuppressed.

Human herpes virus-6 infection in the transplant recipient has been linked to increased fungal infections,[74] mental status changes of unidentified etiology,[74] increased mortality at greater than 90 days,[74] worsened fibrosis score with HCV recurrence,[15] biopsy-proven hepatic allograft rejection,[13] and CMV coinfection.[14] Human herpes virus-6 viremia occurred at a median of 20 days at a rate of 32% of liver transplant recipients in 1 study.[13] As with CMV, ganciclovir, valganciclovir, and foscarnet are effective antiviral medications against HHV-6. Current guidelines do not recommend routine prophylaxis.[73]

## Less Common Viral Infections

The abdominal solid organ transplant recipient is at a low-to-moderate risk of developing PTLD, ranging from 1% to 12%. However, a primary EBV infection after transplantation is a strong risk factor for developing PTLD.[75] High viral loads of EBV often predate

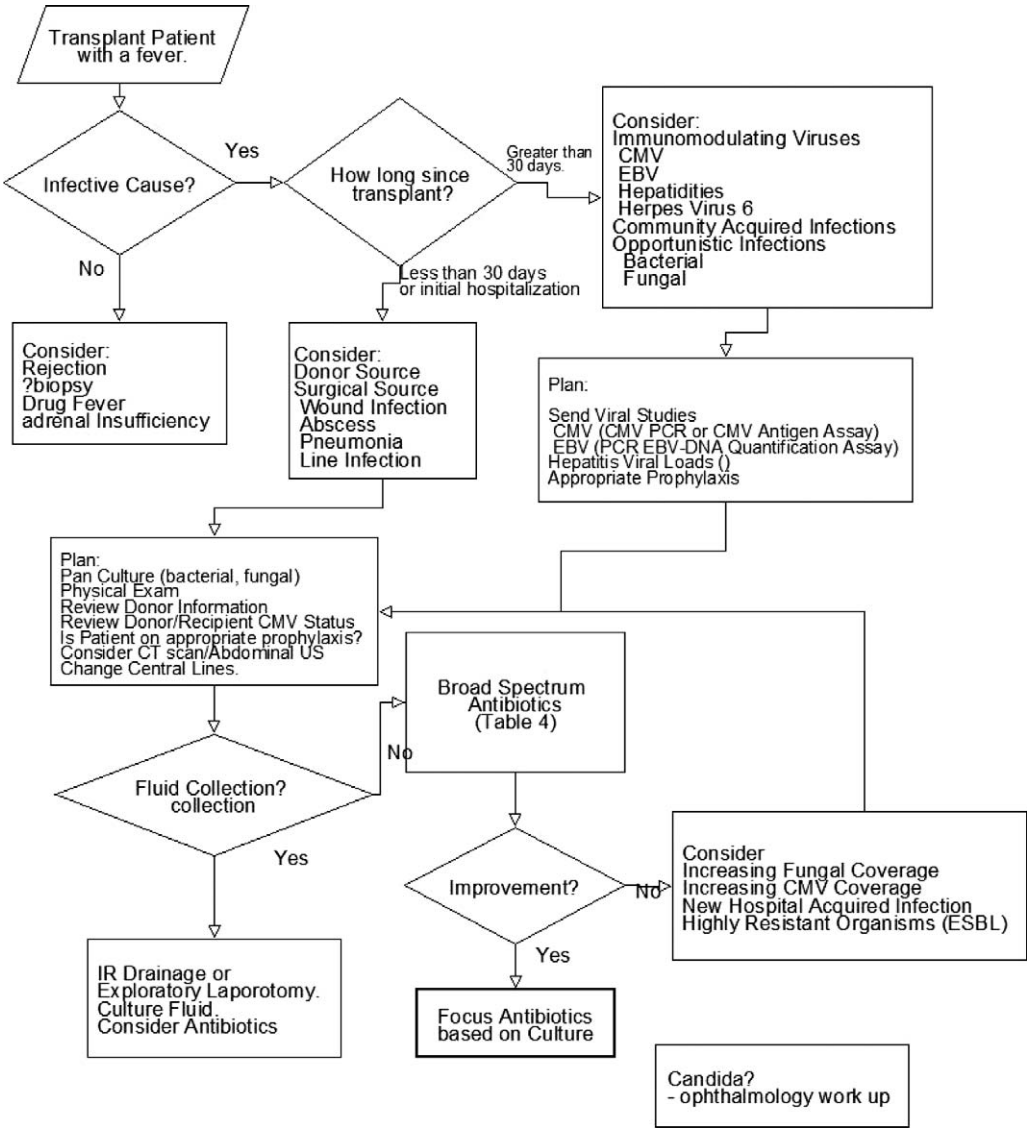


**Figure 2.** Algorithm for diagnosing and treating suspected infections in solid organ transplant recipients. EBV, Epstein-Barr virus; ESBL, extended-spectrumb-lactamases; CMV, cytomegalovirus; CT, computed tomography; Interventional Radiology, irrigation; PCR, polymerase chain reaction; US, ultrasound.

the presentation of PTLD, and prophylactic antivirals to reduce the viral load may be of benefit.[75]

BK virus (BKV) and JC virus (JCV) are widely latent polyomaviruses.[76,77] Although JCV rarely causes disease, BKV is known to cause a viral nephropathy, termed polyomavirus-associated nephropathy (PVAN), in renal allograft recipients.[78] Onset of PVAN is usually within the first year after transplantation. Polyomavirus-associated nephropathy is strongly associated with renal graft loss. A retrospective review of SPK recipients found that while 5 of 9 patients with PVAN lost renal graft function, none of the transplanted pancreases were affected.[79] Simultaneous pancreas and kidney transplant also seems to infer a greater risk of developing PVAN in the transplanted kidney than renal transplant alone.[16]

## Summary: Fever in the Posttransplant Patient

Figure 2 presents an algorithm for treating fevers in a posttransplant patient. The timely identification of preoperative and postoperative exposures to

Table 4. Initial Antibiotic Choices in Critically Ill Transplant Recipients

| |
|---|
| Vancomycin |
| Voriconazole |
| Valganciclovir (or ganciclovir) plus piperacillin/tazobactam and levofloxacin |
| OR |
| (For high institution resistance rates) meropenem |
| OR |
| (For severe penicillin allergy) aztreonam and metronidazole plus TMP-SMX if no PCP prophylaxis and pulmonary symptoms |

NOTES: PCP = Pneumocystis carinii pneumonia; TMPSMX = trimethoprim-sulfamethoxazole.

infectious pathogens is especially very important in immunocompromised transplant patients. Institutional flora and resistance patterns as well as prophylactic antimicrobial treatments affect the spectrum of potentially infectious pathogens that may be encountered. Therefore, clinicians must be aware of which bacterial pathogens are most frequent in their institution.[3,42] The trend over the last 20 years has been for the selection of gram-negative bacteria, MDR bacteria, and aspergillosis.[3,42,80]

When evaluating a fever, both infectious and noninfectious etiologies of fever must be examined. Approximately 13% of fevers in posttransplant ICU patients may have noninfectious causes, including sterile hematomas, drug reactions, and adrenal insufficiency. Acute rejection of the graft can also cause a febrile response because inflammation is a component of rejection. A febrile rejection is most likely to occur within 14 days of transplantation for OLT patients.[3]

In patients with infection, hyperthermia is more common than hypothermia; however, hypothermia portends a worse outcome. In a study of 56 OLT patients with 109 episodes of fever and infection, 5% of infected patients were hypothermic and 27% were euthermic. The mortality for the hypothermic group was 100%, compared to 20% for the hyperthermic.[3,24] The hypothermic patients primarily had pneumonias caused by *L pneumophilia*, enteric bacteria, and *Aspergillus fumigatus*.

A total of 80% of the organisms that cause fevers in the ICU after liver transplantation are bacterial (Table 2). Fungal and viral organisms accounted for 9% each. The most common locations for infection are the lungs, CRBSI, and the biliary tract.[3,24]

Infectious workup for a transplant patient should not significantly differ from other postoperative patients. Urine, blood, and sputum or pulmonary lavage samples should be cultured, central lines should be assessed, and clinicians should have a low threshold to order a CT scan or an ultrasound to assess for possible fluid collections. After the cultures are sent, broad empiric antibiotic therapy should be started (Table 4). Empiric therapy may include antifungal or antiviral medications depending on the likelihood of these infections and the patient's clinical status. After an infectious source is isolated, antibiotics should be streamlined appropriately to prevent selection of resistant organisms.

Postoperative infections after solid organ abdominal transplantation continue to be a major cause of graft dysfunction, graft loss, and mortality and should be high on the differential for any critically ill transplant patient. Rapid diagnosis is crucial and aggressive treatment is warranted. The most common early infections faced by transplant recipients are presented here. Although infectious complications will often be the cause for ICU admission, serious infection may also develop while the patient is in the ICU. The timing after transplantation, presence of risk factors, type of grafted organ, and level of immunosuppression all affect the likelihood and the type of infection. By understanding these variables, proper recognition and prompt treatment of bacterial, fungal, or viral infections in the abdominal solid organ recipient may be achieved.[17,18]

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