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Research Article

Infectious Complications after a Liver Transplant

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Abstract

Liver transplantation is a life-extending procedure for patients with end-stage liver disease (ESLD), post-transplant infections continue to be a leading cause of morbidity and mortality. Infection risk varies over time, with issues most commonly related to transplant surgery and nosocomial infections in the early post-transplant period. Because of the increased burden of immunosuppression, opportunistic infections become more common between 1 and 12 months post-transplant. As immunosuppression is reduced after 12 months, the risk of opportunistic infections decreases. Recipients are still vulnerable to community-acquired infections, and recurrent cholangitis may become an issue in those with chronic allograft dysfunction or recurrent cholestatic liver disease. This article will go over a strategy for dealing with infectious complications in the early, intermediate, and late stages following liver transplantation, with a focus on the most common infections as well as those of emerging concern.

Keywords: liver transplantation; infection; opportunistic infection; multidrug resistant organisms

Introduction

Since the 1980s, liver transplantation has been the standard of care for patients with end-stage liver disease (ESLD) [1]. Patient and graft survival have improved as surgical techniques and post-operative management have improved, particularly in terms of immunosuppression. Despite numerous advances in the field of liver transplantation, infection continues to be a leading cause of morbidity and mortality in recipients [2]. The risk of infection after liver transplantation varies over time, which is usually a reflection of the immunosuppressive burden and allograft function. The approach to infections in liver transplant recipients will be described in this review using the traditional time frame of early, intermediate, and late post-transplant infectious complications [3,4].

1 month after transplant: Because full immunosuppression does not occur within the first month, typical post-surgical and nosocomial infections frequently dominate this timeframe. These are more common in patients who have spent a significant amount of time in the hospital prior to transplant. Opportunistic infections are less likely to occur during this time unless the patient was on immunosuppression prior to transplant for an underlying autoimmune disease or was undergoing re-transplant for graft dysfunction.

Complications after surgery: Surgical site infection (SSI), one of the post-operative complications, is a common infectious problem in the early post-transplant period. The majority of centers use one or two antibacterial medications that protect against both skin and gastrointestinal pathogens, despite the fact that surgical prophylaxis regimens are not standardized across institutions. Despite this, SSI rates are high among people who have had liver transplants. While liver recipients have higher rates of deep infections like abscesses (3% vs. 15% in one study), general surgical patients typically experience more superficial wound infections [5]. According to systematic reviews of the literature, SSI affects 10–37% of recipients in total [6].

Complex surgeries performed in a clean-contaminated environment, or even a contaminated environment if the failing liver is infected at the time of transplantation, have been linked to an increased incidence. Furthermore, bile duct reconstruction is thought to be the most challenging step in a successful liver transplant [7,8]. Choledochocholedochostomy (CDCD or duct-to-duct anastomosis) and choledochojejunostomy (CDJ or Roux-en-Y) are the two alternatives. When a T-tube is removed from a CDCD reconstruction, it may become dislodged or leak, which can cause SSI [9,10]. Alternately, early ascending cholangitis can be brought on by stent dislodgement or strictures resulting from subpar surgical technique [9]. Grafts that are split or incomplete can leak right from the cut surface [11].

Host risk factors for SSI include things like diabetes, obesity, having had a liver transplant before, or having a high MELD score, while surgical risk factors include things like long operating times, a lot of transfusions needed, or Roux-en-Y biliary anastomosis [12,13]. Although bacterial pathogens are

more frequent, fungal infections, especially Candida, can also happen because these organisms frequently colonize the gastrointestinal tract. Without prophylaxis, invasive fungal infections were reported to affect 18–42% of liver transplant recipients, and they remained at 5-7% with prophylaxis [14–18]. The source of the vast majority of these cases is frequently intra-abdominal candidiasis [19,20]. Intravascular catheters or secondary seeding from an intra-abdominal source can also cause bloodstream infection. The most prevalent pathogen among these is Candida albicans [20]. Patients who received fluconazole for antifungal prophylaxis, however, run the risk of contracting azole-resistant Candida infections like C. glabrata or C. krusei [21].

Long or repeated operations, re-transplantation, high intraoperative transfusion needs, renal failure, exposure to broad-spectrum antibiotics, choledochojejunostomy, and Candida colonization are risk factors for Candida [18,22].

SSIs in liver transplant recipients can manifest in a variety of ways, from asymptomatic patients with abnormal lab results to those exhibiting fever, erythema at the incision site, abdominal pain, or septic shock symptoms. These might be comparable to patients who have biliary tract problems and early cholangitis. Imaging of the transplanted organ as well as laboratory testing and peripheral cultures are necessary for diagnosis. In most situations, source control is essential for effective infection eradication. This is becoming more crucial as antimicrobial resistance rises, which is important for liver transplant recipients in particular. In a recent US study, it was discovered that MDROs were responsible for 67% and 53% of recipients' superficial and deep SSIs, respectively [5].

In most cases, source control is critical to successful infection eradication. This is becoming increasingly important as antimicrobial resistance rises, which is especially important for liver transplant recipients. A recent US study found that multi-drug resistant organisms (MDROs) caused 67% and 53% of superficial and deep SSIs in recipients, respectively [5]. Another study discovered that 75-85% of Klebsiella pneumoniae and E. coli isolates from surgical sites were multidrug resistant, with nearly half of the Klebsiella spp. resistant to carbapenem and 96% resistant to vancomycin (VRE) [23].

Azole-resistant candida is to be expected in patients who have been exposed to azoles. If possible, infected collections within the abdomen are best managed through drainage (either surgical or radiology). Infected intravascular devices should be removed as well, especially if they are infected with candidemia or other resistant organisms [24]. The selection of antimicrobial agents should be based on the success of source control and should be tailored to the strain and susceptibilities over time. If antifungal therapy is required, clinicians should keep in mind that azoles interact with calcineurin inhibitors. Echinocandins may be preferred, especially early on while susceptibilities are being assessed [24].

Other infections related to health care: Following SSI, a number of other health-care associated infections are common in the early post-transplant period. Hospital-acquired pneumonia, urinary tract infection, Clostridium difficile, and catheter-associated infections are examples. Although a variety of pathogens can cause these, bacterial infections are the most common in the first two months [25-27]. Gram-positive organisms were found to be the most common cause of bacteremia in the first month (79 % of episodes) in one study, with the primary source usually being the abdomen or a catheter [28].

Gram-negative organisms were more likely to be found late after transplantation; when they did appear early, they came from the abdomen or the urine. Prolonged hospital stays, acute liver failure, high bilirubin, long surgical times, and acute rejection are all risk factors for bacteremia [29-31]. Another well-known early complication is pneumonia, which has an incidence rate of 7-46% [32]. It is linked to increased length of stay and mortality, especially when multidrug resistant pathogens are isolated [33-35].

The prevalence of multidrug resistant strains has increased in recent years in all patients, but it is especially concerning in liver transplant recipients. ESLD patients are more likely to be colonized and infected with MDROs due to increased contact with the health care system and frequent antibiotic exposure [36,37]. Global rates of multidrug resistant gram-negative bacilli in liver transplant recipients have exceeded 50%, while the rate of VRE colonization post-transplantation has been estimated to be around 18% [38-40]. Infection with these organisms causes significant morbidity and mortality in post-operative recipients. In liver recipients, mortality rates for infection with carbapenem-resistant Klebsiella pneumoniae ranged from 33-80%, with infection being the most common cause of death [41,42].

In some studies, VRE colonization has been linked to both VRE infection, which can be difficult to treat due to a lack of effective antibiotics, and increased mortality [43-45]. Therapy for any of these organisms is limited and risks significant side effects as well as the development of additional resistance. Aminoglycosides or colistin, which are commonly used to treat carbapenem-resistant organisms, can cause renal failure or hearing loss, whereas linezolid, one option for VRE, has been linked to cytopenia and neuropathy [46,47]. Daptomycin exposure, another treatment option for VRE, increases the risk of resistance, which is associated with increased mortality [45].

Donor-derived infections can be transmitted through infected tissue or through systemic infection of the donor during organ procurement. Donor infectious work-up may be less than ideal due to the urgency and time constraints between organ procurement and transplantation. Donor testing currently relies on donor next of kin history, as well as serology, culture, and nucleic acid testing (NAT). Unfortunately, despite novel diagnostic testing such as NAT, infections may still be missed, particularly for donors during the window period for detection of viral infections such as HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) [48].

Although certain donor infections, such as active sepsis, may preclude organ donation, there are fewer available organs than candidates on the waiting list, and waitlist mortality remains high [2]. As a result, more marginal donors are being used, such as those who are actively infected (e.g., bacteremia) or at high infectious risk from HIV, HBV, and HCV [48]. There are also more donors at risk, not only as a result of changes in donor definitions and transplant awareness, but also as a result of the recent opioid overdose epidemic [49]. These factors increase recipients' risk of donor-derived infection [50].

Donor-derived infection can be classified as expected or unexpected. Transmission is expected when a cytomegalovirus (CMV) seropositive liver transplant is given to a CMV seronegative recipient. Prophylaxis and monitoring are two strategies for mitigating this transmission. Unexpected transmissions, on the other hand, are more difficult to detect. They frequently appear within the first month after transplantation, but certain infections, such as tuberculosis (TB), can appear years later, complicating the assessment [50].

As is standard practice, liver transplant recipients most commonly receive expected transmissions from donors infected with CMV, HBV, or HCV. In terms of HBV, these are donors who have negative HBV surface antigen and DNA tests but positive HBV core antibody test results (indicating cleared HBV). In the context of immunosuppression, these recipients are at risk of reactivation for the rest of their lives because HBV DNA remains latent in the liver despite infection clearance [51]. Until now, transplanting HCV-positive livers from donors with minimal evidence of liver fibrosis into HCV-positive liver transplant recipients has been standard practice [52].

The possibility of using these organs for HCV-negative recipients has sparked considerable interest in the era of new direct acting antivirals [53]. Other articles in this issue discuss HBV and HCV in greater detail. Unexpected transmissions can occur in addition to these expected transmissions.

These can be common infections (e.g., MRSA, multidrug resistant gram-negatives) or pathogens that are more unusual (e.g., Cryptococcus, lymphocytic choriomeningitis virus, or microsporidium [54-57]. Clinicians

should be on the lookout for this occurrence, especially in patients who have unusual clinical symptoms or persistent fever without a source identified through routine clinical testing. Individualized testing and therapy are required based on clinical circumstances.

1 to 12 months after transplant: The risk of opportunistic infections is highest in the first year after transplant, especially between months 1-6 as the recipient's immunosuppression is tapered down to a stable maintenance regimen. This was the time when classic opportunistic infections like Pneumocystis jirovecii, CMV, and herpes simplex virus (HSV) were discovered [4]. These pathogens appear later or atypically in the current era of transplantation due to improved recognition and advances in diagnostics or prophylactic therapy. In addition, new pathogens, such as C. difficile or MDROs, have replaced them [3,58]. HBV and HCV complications can also occur during this time period. Other articles in this issue contain more information on viral hepatitis complications.

CMV: Despite medical advances, CMV remains the most common virus to occur after liver transplantation, having a significant impact on recipient morbidity and mortality (59). The risk is greatest for recipients who acquire infection from their donor at the time of transplantation (CMV D+/R), due to a lack of existing cell-mediated immunity required to control the infection, as well as the implications of acquiring an infection in the context of immunosuppression. This risk is followed by CMV R+ patients; CMV D/R patients have the lowest risk because the infection must be acquired from new exposures during the post-transplantation period.

This risk is followed by CMV R+ patients; CMV D/R patients have the lowest risk because the infection must be acquired from new exposures during the post-transplantation period. In the first 12 months after transplant, the estimated incidence of CMV disease ranges from 44-65% for the highest risk group (D+/R) to 8-19% for R+ recipients to 1-2% for the lowest risk group (D/R) [60,61]. Prophylaxis reduces but does not eliminate this incidence, with rates of 12-30% and 3-4% for high and moderate risk populations, respectively [60]. Immunosuppression, especially lymphocyte depleting agents, viral co-infections, and allograft rejection all increase the risk of CMV disease [62].

CMV affects a patient's post-transplant course in both direct and indirect ways [63]. The clinical symptoms and signs caused by CMV are referred to as direct effects. CMV syndrome is the most common among these in the liver transplant population. It causes fever and myelosuppression and affects 60% of CMV disease after liver transplantation [64]. Tissue-invasive disease is most commonly associated with the gastrointestinal tract (CMV esophagitis, gastritis, colitis). Furthermore, the allograft is particularly vulnerable, and liver transplant recipients can develop CMV hepatitis, which is less common in other organ transplant recipients [65]. Without pathological analysis, this can be difficult to distinguish from acute allograft rejection [60].

CMV's indirect effects are those that occur in the host as a result of viral replication, such as immunomodulation leading to increased immunosuppression, oncogenesis, or allograft injury. CMV can cause bacterial or fungal superinfection, Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorder, acute or chronic allograft rejection, and vanishing bile duct syndrome or ductopenic rejection in liver recipients [60]. CMV infection is an independent predictor of mortality after liver transplantation, with one study reporting a 5-fold increase in all-cause mortality and an 11-fold increase in infection-related mortality [66].

CMV infection diagnosis has greatly improved in recent years. Serology is only useful for assessing risk prior to transplant. Viral load detection after transplantation has become the standard of care because it is faster and more sensitive than traditional viral culture [67]. Polymerase chain reaction (PCR) or CMV pp65 antigenemia are two options. Quantitative real-time PCR assays are now widely available and have replaced traditional methods for detecting viruses [68]. Some hospitals continue to use the older semi-quantitative pp65 antigenemia test, which employs a fluorescently labeled monoclonal antibody to the CMV pp65 protein found in peripheral blood polymorphonuclear leukocytes [69].

Both correlate with one another, and either is suitable for monitoring [70]. Histopathology is used to diagnose CMV tissue invasive disease, and either viral inclusion bodies or viral antigens are detected using immunohistochemistry [67]. Tissue PCR is a possibility, but positive results do not always indicate tissue injury [67]. CMV disease that develops after a liver transplant is treated with IV ganciclovir or valganciclovir.

A multi-center study found no difference in efficacy between oral valganciclovir and intravenous ganciclovir treatment for non-severe CMV disease [71].

However, IV ganciclovir remains the treatment of choice for patients with severe or life-threatening CMV disease, as well as those with limited gastrointestinal absorption [64]. Treatment is continued until clinical symptoms resolve and patients have at least two negative CMV PCR results one week apart [67]. Preventing CMV disease after liver transplantation involves two approaches: preventive therapy and antiviral prophylaxis [64]. Antiviral prophylaxis entails taking ganciclovir or valganciclovir for three months [64].

Ganciclovir (both IV and oral) prophylaxis has been shown in landmark studies to reduce the risk of CMV infection and disease by 60-80% compared to placebo [72,73]. Similarly, valganciclovir, a prodrug of ganciclovir with improved bioavailability, was shown to be more effective than oral ganciclovir in a diverse group of transplant recipients [74]. However, when the data was broken down by organ group, there was a higher rate of CMV disease in the oral valganciclovir group (19% vs. 12% for oral ganciclovir), and the drug was not approved by the FDA for this indication. Despite this, it remains the most commonly used drug following a liver transplant [75].

Preventive therapy seeks to detect CMV viremia before clinical disease manifests. As diagnostic testing has improved, this has become more feasible. For at least 12 weeks after transplant, patients are subjected to weekly CMV surveillance, typically via PCR. If a significant level of replicating virus is detected, IV ganciclovir or valganciclovir is started at the recommended treatment dose and continued until a negative viral load is achieved. CMV disease can be reduced by 70% with preventive therapy [76-78]. Although both strategies can be used, prophylaxis has traditionally been preferred for the most vulnerable patients (D+/R), with individual centers deciding how to manage those at intermediate risk [67]. The problem with prophylaxis is that it does not protect against late-onset CMV [59].

Pneumocystis jirovecii pneumonia (PJP) is a type of pneumonia caused by Pneumocystis jirov PJP is a common fungus that causes acute lung injury in immunocompromised individuals [79]. The mechanisms of infection acquisition and transmission are still being studied, but we now know that asymptomatic colonization is possible even in immunocompromised hosts, and person-to-person transmission can occur [80,81]. According to a recent review, the incidence in liver transplant recipients ranged from 1-11% in large studies of patients not receiving prophylaxis to 0-2% in patients receiving prophylaxis [82]. Unfortunately, the mortality rate for patients who become infected ranges between 7-88%.

The burden of immunosuppression, particularly steroid dose and induction with lymphocyte-depleting agents or alemtuzumab, is the major risk factor for PJP in liver transplant recipients [83]. Comorbidities such as allograft rejection (which frequently results in increased immunosuppression), neutropenia, low CD4 counts, and concurrent infections, specifically CMV, are also linked to an increased risk [83,84]. Although most infections occur within the first few months of transplantation, late infections have occurred due to outbreaks among liver transplant units [82,85]. Trimethoprim-sulfamethoxazole (TMP-SMX) is the preferred treatment and prophylactic agent [86]. TMP-SMX prophylaxis is generally recommended for 6 to 12 months after transplantation in centers with rejection rates greater than 3-5%, with additional prophylaxis given during treatment [83].

The presentation of the liver transplant recipient can vary. In HIV patients, it was traditionally described as a febrile respiratory illness with symptoms of dry cough and dyspnea that progressed over several weeks [86]. Transplant patients, on the other hand, are more likely to have acute

presentations with symptom evolution over 1-2 days and no fever [83]. Similarly, chest radiographs may or may not show the typical bilateral interstitial infiltrates with reticular or granular opacities seen in HIV patients.

Immunofluorescent staining or PCR of pulmonary samples can be used to diagnose PJP. When both bronchoalveolar lavage (BAL) and transbronchial biopsies are obtained, or multiple respiratory samples are obtained, the diagnosis is most sensitive [87]. Non-HIV patients have a lower burden of organisms than HIV patients, making this diagnosis difficult [88]. TMP-SMX should be started as soon as possible in liver transplant recipients suspected of having PJP. If confirmed, the optimal TMP-SMX duration is extrapolated from HIV patients, where 21 days is commonly used [89].

Adjunctive corticosteroids should be given within 72 hours of starting antimicrobial therapy for moderate to severe PJP (PaO2 70 mmHg on room air) [83]. Prednisone 40-60 mg twice daily for 5-7 days, followed by a taper, is the most common regimen.

Aspergillosis Aspergillus species are found in 1-9% [90] of recipients. Re-transplantation, steroid-resistant rejection, renal failure, CMV, prolonged broad-spectrum antibiotic exposure, and diabetes are all risk factors [13,91,92]. Aspergillosis occurs later after transplantation than candidiasis, but 75% of cases occur within 6 months [93]. Infection is acquired through spore inhalation, which results in pulmonary infection. Extrapulmonary spread can affect any organ.

Invasive aspergillosis is difficult to diagnose. When pulmonary aspergillosis is suspected, a CT chest is recommended to look for nodular or cavitating lesions. If invasive pulmonary aspergillosis is suspected, bronchoscopy with BAL and transbronchial biopsy are performed. A tissue biopsy with evidence of hyphae invasion is the gold standard. As an adjunct, serum and BAL galactomannan can be used [90].

Azoles are the preferred treatment option for the majority of patients, but drug interactions, particularly with calcineurin inhibitors, must be monitored. The most evidence supports voriconazole, but other options include posaconazole and isavuconazole [94,95]. Amphotericin B is reserved for patients who cannot be treated with azoles. The duration of treatment is typically 6-12 weeks, depending on the severity of the disease, the need for continued immunosuppression, and the clinical and radiographic response [95]. Unfortunately, mortality has been reported in 33-100% of recipients depending on the era of infection; additionally, liver transplant recipients appear to have worse outcomes than other organ groups [90,93].

Coccidioidomycosis: Coccidioides species, Blastomyces dermatitidis, and Histoplasma capsulatum are the only dimorphic fungi of significance in transplant settings. Even in endemic areas, Blastomyces and Histoplasma infections after transplantation are uncommon [96]. Desert soils in Southern California, Arizona, Mexico, and parts of Central and South America are home to Coccidioides species. Even a single spore inhaled can cause infection. In liver transplant recipients, the incidence ranges from 0.59 to 3% [97,98]. Living in an endemic area, prior coccidioidomycosis, or positive coccidioidal serologic tests at transplantation are the most significant risk factors [99,100]. Donor transmission has been reported as well [101-103].

Coccidioidomycosis can present as asymptomatic to disseminated disease, with the latter being more common in transplant patients [99]. Fever, chills, night sweats, cough, and dyspnea are common symptoms of pulmonary coccidioidomycosis, and dissemination can affect the central nervous system (CNS), bone and joints, or the skin [96]. It is also frequently associated with the graft [98,104]. There are no distinguishing radiographic findings, and recipients in endemic areas should be treated with caution [99].

Coccidioides in bodily fluids or tissues are isolated for diagnosis using culture or histopathology. Coccidioides assumes a highly infectious form at room temperature, so it is critical to notify laboratory personnel for proper specimen handling if Coccidioides is suspected. Serologic testing is available, but its sensitivity can be reduced in immunocompromised patients [99]. Fluconazole or itraconazole [105], taken orally, is used to treat mild to moderate coccidioidomycosis. With the exception of CNS disease, liposomal amphotericin B is preferred for severe or disseminated infection. Coccidioidomycosis of the CNS can be treated with high-dose oral fluconazole [105].

Relapse prevention requires lifelong therapy [96,105]. For new liver transplant recipients who live in an endemic area and have no evidence of Coccidioides exposure prior to transplant, universal fluconazole prophylaxis for one year is recommended; longer durations (including lifelong) are recommended for recipients with positive serology, a history of prior infection, or who receive organs from donors with active or previous infection [96,100].

TB: According to the World Health Organization, one-third of the global population is infected with Mycobacterium tuberculosis [106]. The majority of these infections are dormant, with the risk of reactivation and active disease in the context of immunosuppression following transplantation. Because tuberculosis is endemic in many parts of the world, the country of origin is the most important risk factor for disease acquisition [107]. Concomitant infection, such as CMV, allograft rejection or dysfunction, and renal failure are all risk factors for reactivation [108].

In liver transplant recipients, the estimated incidence is 500 cases per 100,000 recipients per year, with a prevalence of 1.3% [109,110]. The majority of these infections occurred within the first year of transplantation, usually between months 3 and 12, as in other transplant populations [110]. Only a small percentage are thought to be donor-derived, with the vast majority resulting from reactivation of previous infection in the recipient [109].

Pre-transplant evaluation for latent TB in transplant candidates is considered standard of care; however, diagnosing latent TB in the setting of ESLD presents challenges. A comprehensive evaluation includes a risk factor assessment, a chest X-ray, and some form of TB testing. Although tuberculin skin testing with purified protein derivative (PPD) or interferon-release assays detects latent TB well in otherwise healthy adults, these tests perform less well in liver transplant candidates due to anergy caused by liver dysfunction [111,112]. Furthermore, we still lack a gold standard for diagnosis, casting doubt on the sensitivity and specificity of results and making it difficult to declare a best test to use in the pre-transplant setting for this patient population [113].

Although active tuberculosis typically manifests as a pulmonary disease, liver transplant recipients are more likely to experience disseminated symptoms. In one review of all published cases [109], approximately two-thirds of post-transplant TB was extra-pulmonary. Patients with unusual post-transplant symptoms, such as fever, night sweats, and weight loss, should be evaluated for this diagnosis, especially if they have TB risk factors. Diagnosis can be made using an acid-fast bacilli smear and mycobacterial culture, histopathological evaluation of tissue, and nucleic acid amplification [114].

Transplant candidates who are found to have latent tuberculosis are best treated prior to transplantation. To reduce neurotoxicity, the standard of care is isoniazid 5 mg/kg (maximum 300 mg per dose) daily for 9 months in conjunction with pyridoxine 25-50 mg/day, with rifampin [115] as the second line. However, hepatotoxicity is the main limiting toxicity of both drugs. As a result, liver transplant candidates are more likely to discontinue therapy or have therapy delayed until after the transplant [109,118]. This increases the risk of reactivation, and unfortunately, post-transplant completion rates are just as low due to drug side effects and drug interactions [118].

After 12 months: The risk of infection decreases as the patient's distance from the transplantation procedure increases, while other complications such as malignancy become more common [2]. If the allograft fails late in the post-transplant period, recipients are at risk for typical community-acquired infections like pneumonia and influenza, as well as complications from end-organ disease. Opportunistic infections such as aspergillosis, cryptococcosis, and PJP are less common. Patients who experience allograft rejection and require increased immunosuppression have a higher risk of infection than

those who do not; their evaluation and management should be tailored accordingly [3].

Graft degeneration: Long-term liver transplant recipients are vulnerable to a variety of hepatic complications, including recurrence of the original liver disease, late biliary leaks, biliary strictures, and late acute or chronic rejection. Unfortunately, recurrent disease is still a significant issue. Autoimmune hepatitis recurs in the graft in 20-42% of transplants, primary biliary cirrhosis recurs in 10-35% of transplants, and primary sclerosing cholangitis recurs in 9-47% of transplants [119]. Only HCV recurrence, which was once common, is likely to be reduced or eliminated given recent therapeutic advances [120,121]. Patients who develop significant graft dysfunction may redevelop ESLD symptoms, including ascites, as well as the associated infectious risks (e.g., spontaneous bacterial peritonitis).

Recurrent cholangitis develops when the original disease affects the biliary tract. Late graft dysfunction can be caused by both acute and chronic rejection. Late acute rejection affects 7-23% of recipients, does not respond as well to pulse steroids as early acute rejection, and can result in complications such as sepsis, biliary tract abnormalities, and chronic rejection even after treatment is complete [122,123]. Chronic rejection is less common and typically involves bile duct loss; it poses a high risk of graft failure along with all of the infectious risks [123].

In 5-15% of deceased donor transplants and 28-32% of living donor transplants, biliary strictures develop [10]. They can be anastamotic or nonanastamotic, and both are more common in the late post-transplant period. Unfortunately, stricture can result in the formation of stones or sludge in the biliary tract, and patients may experience recurrent episodes of cholangitis. Patients can also develop procedure-related cholangitis because the primary therapy for stricture is typically endoscopic retrograde cholangiopancreatography with balloon dilatation or stricture stenting [10,124].

It's easy to see why, in one study of late infections after liver transplant, cholangitis was found to be the most common late infection; cholangitis was associated with primary sclerosing cholangitis and Roux-en-Y biliary anastomosis [125].

Respiratory infections: Community-acquired pneumonia affects a significant number of patients after a liver transplant [126]. In one series, it occurred in 19% of recipients diagnosed with late infection, which is nearly equal to the risk of cholangitis [125]. Streptococcus pneumoniae, Haemophilus influenzae, and atypical pathogens such as Mycoplasma pneumoniae and Chlamydophila pneumoniae are examples of common bacterial pathogens. Influenza is also a risk for liver transplant recipients. Influenza is more common in solid organ transplant recipients than in the general patient population. The most vulnerable are lung transplant recipients, but liver transplant recipients are not immune to the effects of influenza [127-129].

They are also more likely to develop complications such as myocarditis, secondary bacterial pneumonia, or acute rejection if infected [127,130]. Annual vaccination is advised to protect recipients and has been shown to be effective. However, seroconversion rates are lower than in healthy people, and new infections can occur [131-133]. Liver transplant recipients who exhibit influenza-like symptoms during the appropriate season should be tested and/or treated with antivirals. In a number of observational studies [134,135], early initiation of therapy has been associated with a lower risk of intensive care admission, mechanical ventilation, and secondary complications such as bacterial or fungal pneumonia.

Other respiratory viruses are less common in adult liver transplant recipients; this may be due to the fact that infections such as respiratory syncytial virus are mild and self-limiting [136]. Even years after transplantation, these pathogens continue to be a concern for pediatric recipients [137].

Complications from late viral infections Late CMV and herpes zoster are the most commonly reported viral complications [125]. Late-onset CMV disease has been observed in up to 26% of high-risk recipients after 2 years and 8.5% of all recipients after a median of 6.3 years [59,138]. Patients may exhibit signs of CMV syndrome or end-organ disease. The greatest risk is that the diagnosis is delayed because clinicians may be less concerned about it occurring after the initial post-transplant period. Patients should be treated in the same way as those with early-onset CMV.

Herpes zoster is a common late-after-transplant complication. The incidence estimates vary depending on how long and closely patients are followed. According to one observational study, 12% of their liver recipients developed herpes zoster after a median of 23 months [139]. Based on actuarial estimates, the 1-, 5-, and 10-year incidence rates were 3%, 14%, and 18%, respectively. Other studies [140,141] found rates as low as 1-7% after 5 years of follow-up. Most studies show mild dermatomal zoster; disseminated or visceral zoster appears to be uncommon, but recurrent zoster is well documented [139,141].

Antivirals should be administered to liver recipients who have zoster. For those with complicated or disseminated zoster, valacyclovir, acyclovir, and famciclovir are all appropriate oral agents to be combined with IV acyclovir [142]. Patients with active CMV do not require any additional treatment. Until recently, there was little to offer in terms of prevention other than life-long antiviral prophylaxis. Previously, the only herpes zoster vaccine available was a live virus vaccine, which is contraindicated in post-transplant recipients [143]. A new inactive subunit vaccine has recently been approved for prevention in healthy adults; studies on its efficacy for prevention in the post-transplant setting are eagerly anticipated [144,145].

Conclusions Despite advances in transplantation, liver transplant recipients continue to be at risk for a variety of infectious complications, as discussed in this article. Understanding the complexities of these post-transplant infections, as well as the ongoing development of preventative, diagnostic, and therapeutic interventions, aim to improve outcomes following liver transplantation.

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