Perspective

Infectious complications of liver transplantation

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Abstract: Liver transplantation is a life-prolonging procedure for patients with end-stage liver disease (ESLD); however, post-transplant infections remain a leading cause of morbidity and mortality. Infection risk varies over time with issues in the early post-transplant period most commonly being related to the transplant surgery and nosocomial infections. Opportunistic infections become more common between 1 and 12 months post-transplant, owing to the greater burden of immunosuppression. Beyond 12 months, the risk of opportunistic infections wanes as immunosuppression is reduced. Recipients continue to be at risk for community acquired infections and recurrent cholangitis may become a concern in those with chronic allograft dysfunction or recurrent cholestatic liver disease. In this article, we will review an approach to infectious complications in the early, intermediate, and late period following liver transplantation with a focus on the most common infections and those of emerging concern.

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

Received: 18 December 2017. Accepted: 29 December 2017; Published: 05 January 2018.

doi: 10.21037/amj.2017.12.10

View this article at: http://dx.doi.org/10.21037/amj.2017.12.10

Introduction

Liver transplant has become the standard of care for patients with end-stage liver disease (ESLD) since the 1980s (1). Patient and graft survival have increased with improvements in surgical techniques and post-operative management, particularly with respect to immunosuppression. However, despite the many advances in the field of liver transplantation, infection remains a leading cause of morbidity and mortality for recipients (2). The risk of infection after liver transplantation varies with time, usually a reflection of the burden of immunosuppression and allograft function. In this review, we will describe the approach to infections in liver transplant recipients using the traditional time frame of early, intermediate and late post-transplant infectious complications (3,4).

Part 1: <1-month post-transplant

Since the full extent of immunosuppression is not achieved within the first month, typical post-surgical and nosocomial infections often dominate this timeframe. These are more common in patients with significant lengths of stay in hospital before transplant. Opportunistic infections are less likely to occur in this period unless the patient was taking immunosuppression pre-transplant for underlying autoimmune disease or in the setting of re-transplant for graft dysfunction.

Surgical complications

Of the surgical complications, surgical site infection (SSI) is a frequent infectious issue in the early post-transplant period. Although surgical prophylaxis regimens are not standardized across institutions, most centers use one or two antibacterial agents that cover both skin and gastrointestinal pathogens. Despite this, liver transplant recipients have high rates of SSI. While superficial wound infections are typically more common in the general surgical patient, liver recipients have higher rates of deep infections such as abscesses (3% *vs.* 15% in one study) (5). Overall, SSI occurs in 10–37% of recipients in systematic reviews of the literature (6). Reasons for the increased incidence include

a complex surgery in a clean-contaminated space, or even contaminated space if the failing liver is infected at the time of transplantation. In addition, bile duct reconstruction is considered to be the most difficult aspect to successful liver transplantation (7,8). The two possibilities are choledochocholedochostomy (CDCD or duct-to-duct anastomosis) and choledochojejunostomy (CDJ or Roux-en-Y). If a T-tube is left in CDCD reconstruction, it can become dislodged or leak at the time of removal which then leads to SSI (9,10). Alternatively, stent dislodgement or strictures from imperfect surgical technical can cause early ascending cholangitis (9). Split or partial grafts can leak directly from the cut surface (11).

Risk factors for SSI can be divided into host risk factors—such as diabetes, obesity, prior liver transplantation or high model for end-stage liver disease (MELD) score—and surgical factors—such as prolonged surgical time, high transfusion requirements, or Roux-en-Y biliary anastomosis (12,13). Although bacterial pathogens are more common, fungal infections—particularly *Candida*—can also occur as these are common gastrointestinal colonizers. Invasive fungal infections were reported to occur in 18–42% of liver transplant recipients in the absence of prophylaxis and remain at 5–7% with prophylaxis (14-18). The overwhelming majority of these are invasive candidiasis and the source is frequently intra-abdominal (19,20). Bloodstream infection can also occur as a result of intravascular catheters or secondary seeding from an intra-abdominal source. Of these, *Candida albicans* is the most common pathogen (20). However, patients who received antifungal prophylaxis with fluconazole may develop infections with azole-resistant *Candida* such as *C. glabrata* or *C. krusei* (21). Risk factors for *Candida* include prolonged or repeat operation, re-transplantation, high intraoperative transfusion requirements, renal failure, broad spectrum antibiotic exposure, choledochojejunostomy, and *Candida* colonization (18,22).

Liver transplant recipients with SSIs can present in a variety of ways from an asymptomatic patient with laboratory abnormalities to symptoms of fever, erythema at the incision site, or abdominal pain to septic shock. These may be similar to patients with early cholangitis from biliary tract issues. Diagnosis not only requires laboratory work and peripheral cultures, but also imaging of the transplanted organ.

Source control is vital to successful eradication of infection in most cases. This is becoming more important with increases in antimicrobial resistance, which is particularly relevant for liver transplant recipients. One recent US study found that 67% and 53% of superficial and deep SSIs in recipients were caused by multi-drug resistant organisms (MDROs) (5). Another found that 75–85% of *Klebsiella pneumoniae* and *E. coli* isolates from surgical sites were multidrug resistant, of which nearly half of the *Klebsiella* spp. were carbapenem resistant and 96% of the *Enterococcus faecium* were vancomycin resistant (VRE) (23). In patients with azole exposure, azole-resistant candida would be expected. Infected collections within the abdomen are best managed via drainage (either surgical or via radiology) if possible. Infected intravascular devices should also be removed, particularly with candidemia or other resistant organisms (24). The choice of antimicrobial agents should be targeted to the strain and susceptibilities with duration based on the success of source control. If antifungal therapy is needed, clinicians need to remember that the azoles interact with calcineurin inhibitors. Echinocandins may be preferred, especially early on while awaiting susceptibilities (24).

Other health-care associated infections

After SSI, there are a number of other health-care associated infections that are also common in the early post-transplant period. These include hospital-acquired pneumonia, urinary tract infection, *Clostridium difficile* and catheter associated infections. Although these can be caused by a number of different pathogens, bacterial infections are the most common in the first 2 months (25-27). Gram-positive organisms were found in one study to be the most common cause of bacteremia in the first month (83% of episodes) with the primary source usually identified as either the abdomen or a catheter (28). Gram-negative organisms were more likely to be seen late post-transplant; when they presented early, the source was either the abdomen or the urine. Risk factors for bacteremia include prolonged hospital stays, acute liver failure, high bilirubin, prolonged surgical times, and acute rejection (29-31). Pneumonia is another well-known early complication with incidence rates of 5–48% (32). It is associated with increased length of stay and mortality, particularly if multidrug resistant pathogens are isolated (33-35).

The incidence of multidrug resistant strains has been on the rise in recent years for all patients; however, this is of particular concern for liver transplant patients. Due to increased contact with the health care system and frequent antibiotic exposure, ESLD patients are at increased risk of

colonization and infection with MDROs (36,37). World-wide rates of multidrug resistant gram-negative bacilli in liver transplant recipients have reached over 50% while the rate of colonization with VRE post-transplantation has been found to be approximately 16% (38-40). Infection with these organisms poses significant morbidity and mortality to recipients in the post-operative period. Mortality rates for infection with carbapenem-resistant *Klebsiella pneumoniae* have ranged from 35–71% in liver recipients, most directly attributable to infection (41,42). VRE colonization has been associated with both VRE infection, which can be difficult to treat given limited effective antibiotics, and increased mortality in some studies (43-45). Therapy for any of these organisms is limited and risks both considerable side effects and the development of further resistance. Aminoglycosides or colistin—commonly used for carbapenem resistant organisms—can lead to renal failure or hearing loss while linezolid—one option for VRE—is associated with cytopenia and neuropathy (46,47). Daptomycin exposure—another option for VRE—risks resistance, which is again associated with increased mortality (45).

Donor derived

Donor derived infections may be transmitted via infected tissue or systemic infection of the donor at the time of organ procurement. As a result of the urgency and time limitations between organ procurement and transplantation, donor infectious work-up may be less than ideal. At present, donor testing relies on any history gained from donor next of kin as well as serology, culture and nucleic acid testing (NAT). Unfortunately, despite novel diagnostic testing like NAT, infections may still be missed particularly for donors within the window period for detection of viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) (48). Although certain donor infections such as active sepsis may preclude organ donation, there is a shortage of available organs compared to candidates on the wait list and waitlist mortality remains high (2). As a result, more marginal donors such as those who are actively infected (e.g., bacteremia) or those at increased infectious risk from HIV, HBV and HCV are being used (48). There are also more donors at risk, not only from changes in the definitions of these donors and awareness of transplantation, but also as a result of a recent epidemic of opioid overdose deaths (49). These factors increase the risk of donor derived infection in recipients (50).

Donor derived infection can be divided into expected and unexpected transmissions. Expected transmission occurs in the case of a cytomegalovirus (CMV) seropositive liver transplant going into a CMV seronegative recipient. Strategies to mitigate this transmission such as prophylaxis or monitoring can be implemented. However, unexpected transmissions are more difficult to detect. They often manifest within the first month post-transplantation but certain infections [e.g., tuberculosis (TB)] can present years after transplantation complicating the assessment (50).

Of donor derived infections, liver transplant recipients most commonly receive expected transmissions from donors with CMV, HBV or HCV as this is accepted practice. In terms of HBV, these are typically donors with negative HBV surface antigen and DNA tests, but positive HBV core antibody test results (indicating cleared HBV). In the setting of immunosuppression, these recipients remain at risk of reactivation throughout their life as HBV DNA remains latent in the liver despite clearance of the infection (51). For HCV, it has been standard up until now to transplant HCV-positive livers from donors with minimal evidence of liver fibrosis into HCV-positive liver transplant recipients (52). There is much interest in the era of the new direct acting antivirals about the possibility of using these organs for HCV-negative recipients (53). Further discussion about HBV and HCV can be found in other articles in this issue.

Beyond these expected transmissions, unexpected transmission can occur. These can be of common infections (e.g., MRSA, multidrug resistant gram-negatives) or more unusual pathogens such as *Cryptococcus*, lymphocytic choriomeningitis virus, or microsporidium (54-57). Clinicians should remain vigilant to the possibility of this event, particularly for patients with unusual clinical symptoms or persistent fever without a source identified from routine clinical testing. Testing and therapy needs to be individualized depending on the clinical circumstances.

Part 2: 1–12 months post-transplant

The risk of opportunistic infections is highest in the first year after transplant, particularly between months 1–6 as the recipient is tapered down on their immunosuppression to a stable maintenance regimen. This was the period in which the classic opportunistic infections, including *Pneumocystis jirovecii*, CMV, and herpes simplex virus (HSV) were recognized to occur (4). With both improved recognition and advances in diagnostics or prophylactic therapy, these pathogens occur later or atypically in the

current era of transplantation. In addition, new pathogens—such as *C. difficile* or MDROs—have taken their place (3,58). Complications from HBV and HCV can also occur within this time period. Further information about complications of viral hepatitis can be found in other articles in this issue.

CMV

Despite medical advances, CMV is still the most common virus to occur after liver transplantation with significant impact on the morbidity and mortality of recipients (59). The risk is highest for those recipients who acquire infection at the time of transplantation from their donor (CMV D+/R–) because of the lack of existing cell-mediated immunity necessary to control the infection plus the implications of acquiring an infection in the setting of immunosuppression. This risk is followed second by CMV R+ patients; CMV D–/R– have the lowest risk as they must acquire the infection from new exposures in the post-transplantation period. The estimated incidence of CMV disease in the first 12 months after transplant ranges from 44–65% for the highest risk group (D+/R–) to 8–19% for the R+ recipients to 1–2% for the lowest risk group (D–/R–) (60,61). Prophylaxis reduces this incidence but does not eliminate it at 12–30% and 3–4% for high and moderate risk populations, respectively (60). Immunosuppression, particularly lymphocyte-depleting agents, viral co-infections, and allograft rejection also increase risk for CMV disease (62).

CMV has both direct and indirect effects on a patient's post-transplant course (63). Direct effects refer to the clinical symptoms and signs caused by CMV. Of these, CMV syndrome is the most common in the liver transplant population. It is characterized by fever and myelosuppression and affects 60% of CMV disease post liver transplant (64). Tissue-invasive disease usually affects the gastrointestinal tract (CMV esophagitis, gastritis, colitis). In addition, the allograft is particularly susceptible and liver transplant recipients can develop CMV hepatitis which is less common in transplant recipients of other organs (65). This can be difficult to differentiate from acute allograft rejection without pathological analysis (60). The indirect effects of CMV refer to those changes in the host that occur as a result of the viral replication; these include immunomodulation leading to increased immunosuppression, oncogenesis or allograft injury. In liver recipients, CMV may give rise to 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 (60). CMV infection is an independent predictor of mortality post liver transplant, with one study quoting a 5-fold increased risk of all-cause mortality and an 11-fold increased risk of infection-related mortality (66).

Diagnosis of CMV infection has improved dramatically in recent years. Serology is only useful for determining risk pre-transplant. Post-transplantation, viral load detection has become the standard of care as it is faster and more sensitive than traditional viral culture (67). Options include polymerase chain reaction (PCR) or CMV pp65 antigenemia. Quantitative real-time PCR assays are now widely available and have become the first choice for viral detection (68). Some centers still rely on the older semi-quantitative pp65 antigenemia test which uses a fluorescently labeled monoclonal antibody to the pp65 protein of CMV found in peripheral blood polymorphonuclear leukocytes (69). The two correlate with each other, and either are acceptable for monitoring (70). Diagnosis of CMV tissue invasive disease is made via histopathology with the finding of either viral inclusion bodies or detection of viral antigens using immunohistochemistry (67). PCR of tissue is possible but positive results may not always indicate tissue injury (67).

CMV disease occurring after liver transplantation is treated with intravenous (IV) ganciclovir or valganciclovir. A multi-centre study demonstrated non-inferiority between oral valganciclovir and IV ganciclovir treatment for non-severe CMV disease (71). However, IV ganciclovir remains the treatment of choice for severe or life-threatening CMV disease or in patients with limited gastrointestinal absorption (64). Duration of treatment is continued until the clinical symptoms have resolved and patients have at least two negative CMV PCR results 1 week apart (67).

There are two approaches to prevention of CMV disease after liver transplantation—preemptive therapy and antiviral prophylaxis (64). Antiviral prophylaxis involves the use of ganciclovir or valganciclovir, typically for 3 months (64). Landmark studies of ganciclovir (both IV and oral) have shown that prophylaxis is effective in reducing the risk of CMV infection and disease from 60–80% compared to placebo (72,73). Similarly, valganciclovir—the prodrug of ganciclovir with better bioavailability—was also shown to be effective when compared to oral ganciclovir in a heterogenous group of transplant recipients (74). However, when broken down by organ group, there was a higher rate of CMV disease for liver transplant recipients in the oral

valganciclovir group (19% *vs.* 12% for oral ganciclovir) and the drug did not obtain FDA approval for this indication. Despite this, it is still the most commonly used drug post-liver transplant (75).

The aim of preemptive therapy is to detect CMV viremia before clinical disease manifests. This has become more feasible as diagnostic testing has improved. Patients are monitored with weekly CMV surveillance, typically using PCR, for at least 12 weeks post-transplant. If a significant level of replicating virus is detected, IV ganciclovir or valganciclovir is started at treatment dose until a negative viral load is achieved. Preemptive therapy has been shown to reduce CMV disease by 70% (76-78). Although both strategies can be used, prophylaxis has typically been preferred for the highest risk patients (D+/R–) with individual centers deciding on how to manage those at intermediate risk (67). The issue with prophylaxis is that is it does not prevent late-onset CMV (59).

Pneumocystis jirovecii pneumonia (PJP)

PJP is a ubiquitous fungus that causes acute lung injury in immunocompromised hosts (79). Mechanisms for acquisition and transmission of this infection are still being investigated although we now understand asymptomatic colonization is possible even within the immunocompromised host and person-to-person transmission can occur (80,81). A recent review found that the incidence in liver transplant recipients ranged from 1–11% in large studies of patients not on prophylaxis and 0–2% in patients on prophylaxis (82). Unfortunately, the mortality rate for patients who develop infection is high from 7–88%.

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

Presentation can vary in the liver transplant recipient. It was classically described in patients with HIV as a febrile respiratory illness with symptoms of dry cough and dyspnea progressing over several weeks (86). However, transplant patients are more likely to have acute presentations with symptom evolution over 1–2 days and an absence of fever (83). Similarly, chest radiographs may or may not show the typical bilateral interstitial infiltrates with characteristic reticular or granular opacities that are seen in patients with HIV.

PJP can be diagnosed based on immunofluorescent staining or PCR of pulmonary samples. Diagnosis is most sensitive if both bronchoalveolar lavage (BAL) and transbronchial biopsies are taken or multiple respiratory samples are obtained (87). The burden of organisms is lower in non-HIV patients than HIV patients and this diagnosis can be difficult to make (88).

Liver transplant recipients who are suspected to have PJP should be started on TMP-SMX as soon as possible. If confirmed, the optimal duration of TMP-SMX is extrapolated from HIV patients where 21 days is typically used (89). Adjunctive corticosteroids are recommended for moderate to severe PJP (PaO_2 <70 mmHg on room air) within 72 hours of initiating antimicrobial therapy (83). Regimensgenerally include prednisone 40–60 mg twice daily for 5–7 days followed by a taper afterword.

Aspergillosis

Aspergillus species occurs in 1–9% of recipients (90). Risk factors include re-transplantation, steroid-resistant rejection, renal failure, CMV, prolonged broad-spectrum antibiotic exposure and diabetes (13,91,92). Compared with candidiasis, aspergillosis usually occurs later post-transplant, although 75% of cases occur within 6 months (93). Infection is acquired through respiratory inhalation of spores leading to pulmonary infection. Extrapulmonary dissemination can extend to any organ.

Diagnosis of invasive aspergillosis is challenging. Initial CT chest is recommended when pulmonary aspergillosis is suspected to look for nodular or cavitating lesions. Bronchoscopy with BAL and transbronchial biopsy, if possible, is performed for patients with suspicion of invasive pulmonary aspergillosis. The gold standard is a tissue biopsy with evidence of invasion by hyphae. Serum and BAL galactomannan can be used as adjuncts (90).

Azoles are the preferred treatment option for most

patients, but monitoring for drug interactions, especially with calcineurin inhibitors, is required. Voriconazole has the most evidence but other options include posaconazole or isavuconazole (94,95). Amphotericin B is reserved for patients in whom azoles cannot be used. Treatment duration is typically 6–12 weeks depending on disease severity, need for continued immunosuppression, and clinical and radiographic response (95). Unfortunately, mortality is reported in 33–100% of recipients depending on the era in which the infection occurred; moreover, liver transplant recipients appear to have worse outcomes than other organ groups (90,93).

Coccidioidomycosis

Of the three dimorphic fungi—*Coccidioides* species, *Blastomyces dermatitidis*, *and Histoplasma capsulatum*—*Coccidioides* are the only ones of significance in the transplant setting. *Blastomyces* and *Histoplasma* infection post-transplantation are rare, even in endemic areas (96). *Coccidioides* species are found in the desert soils of Southern California, Arizona, Mexico, and parts of Central and South America. Inhalation of even a single spore can lead to infection. The incidence in liver transplant recipients ranges from 0.59–3% (97,98). The biggest risk factors are living in an endemic area, prior coccidioidomycosis or positive coccidioidal serologic tests at transplantation (99,100). Donor transmission has also been reported (101-103).

Clinical presentation of coccidioidomycosis ranges from asymptomatic to disseminated disease, the latter being more likely in transplant patients (99). Pulmonary coccidioidomycosis presents with fevers, chills, night sweats, cough, and dyspnea while dissemination can involve the central nervous system (CNS), bone and joints or the skin (96). It also frequently involves the graft (98,104). There are no characteristic radiographic findings and suspicion should remain high for recipients in endemic areas (99).

Diagnosis is made by isolating *Coccidioides* in bodily fluids or tissues via culture or histopathology. At room temperature, *Coccidioides* assumes a highly infectious form, so it is important to alert laboratory personnel for proper handling of the specimen if *Coccidioides* is suspected. Serologic testing is available, however, its sensitivity can be reduced in the setting of immunosuppression (99).

Treatment of mild to moderate coccidioidomycosis involves oral fluconazole or itraconazole (105). For severe or disseminated infection, liposomal amphotericin B is preferred with the exception of CNS disease. CNS coccidioidomycosis may be treated with high dose oral fluconazole (105). Lifelong therapy is recommended to prevent relapse (96,105). Universal fluconazole prophylaxis for 1 year has been recommended for new liver transplant recipients who reside in an endemic area without evidence of *Coccidioides* exposure pre-transplant; 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

The World Health Organization estimates one-third of the world's population is infected with *Mycobacterium tuberculosis* (106). Most of these infections are latent, with risk of reactivation and active disease in the setting of immunosuppression post-transplantation. The biggest risk factor for acquisition of disease is country of origin as TB is endemic in many regions of the world (107). Risk factors for reactivation include concomitant infection such as CMV, allograft rejection or dysfunction, and renal failure (108). The estimated incidence in liver transplant recipients is approximately 500 cases per 100,000 recipients per year with a prevalence of 1.3% (109,110). Most of these infections occurred in the first year post-transplantation, typically between months 3–12, similar to other transplant populations (110). Only a small minority of these are felt to be donor-derived with the majority arising from reactivation of previous infection in the recipient (109).

Pre-transplant evaluation for latent TB in transplant candidates is considered standard of care, however there are challenges with diagnosing latent TB in the setting of ESLD. A comprehensive evaluation includes assessment of risk factors, a chest X-ray and some form of testing for TB exposure. Although tuberculin skin testing using purified protein derivative (PPD) or interferon-release assays perform well for detection of latent TB in otherwise healthy adults, these tests perform less well in liver transplant candidates because of anergy due to liver dysfunction (111,112). In addition, we still lack a gold standard for diagnosis leaving the sensitivity and specificity of results questionable 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 presents as a pulmonary disease, liver transplant recipients are more likely to have disseminated presentations. Approximately two-third of post-transplant TB was extra-pulmonary in one review of all the published cases (109). Patients with unusual symptoms post-transplant or explained fever, night sweats, and weight loss should be considered for this diagnosis, especially if they have risk factors for TB. Acid-fast bacilli smear and mycobacterial culture, histopathological evaluation of tissue, and nucleic acid amplification can all be used for diagnosis (114).

When a diagnosis of active TB is made post-transplant, the standard therapy is an intensive induction phase of quadruple therapy with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by continuation phase with isoniazid and rifampin alone (115). In transplant recipients, drug interactions between rifampin and calcineurin inhibitors are significant and rifabutin or another alternative may be substituted (109). Duration is tailored to the site of infection and clinical response. Resistance has become an issue in some countries leading to alterations in therapy (116). Hepatotoxicity must be closely monitored for the duration of therapy. Unfortunately, despite therapy mortality is still reported between 20% and 30% for patients with active infection (117).

Transplant candidates who are found to have latent TB are ideally treated pre-transplantation. 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 to reduce neurotoxicity with second line being rifampin (115). However, the main limiting toxicity to both drugs is hepatotoxicity. Consequently, liver transplant candidates are more likely not to complete therapy or to have therapy deferred until the post-transplant setting (109,118). This increases the risk of reactivation and unfortunately, completion rates are just as poor post-transplant due to drug side effects and drug interactions (118).

Part 3: beyond 12 months

As the patient gets farther from the transplantation procedure, the risk of infection diminishes and other complications such as malignancy become more common (2). Late in the post-transplant period, recipients are at risk for typical community-acquired infections such as community acquired pneumonia and influenza or complications from end-organ disease if they have allograft dysfunction. Less common are opportunistic infections such as aspergillosis, cryptococcosis, and PJP. In patients who experience allograft rejection requiring increased immunosuppression, their risks for infection returns to that of the immediate post-transplant period; their evaluation and management should be tailored accordingly (3).

Graft dysfunction

Long-term survivors of liver transplantation are at risk of many hepatic complications from recurrence of the original liver disease, late biliary leaks, biliary strictures, and late acute or chronic rejection. Unfortunately, recurrent disease remains a significant problem. Autoimmune hepatitis has been found to recur in the graft in 20–42% of transplants while primary biliary cirrhosis recurs in 10–35% and primary sclerosing cholangitis recurs in 9–47% of transplants (119). Only HCV recurrence, which was once universal, is likely to be reduced or eliminated given the recent improvements in therapy (120,121). Patients who develop significant graft dysfunction can again develop signs of ESLD including ascites with all the attendant infectious risks (e.g., spontaneous bacterial peritonitis). When the original disease includes the biliary tract, recurrent cholangitis becomes an issue.

Both late acute and chronic rejection are also an issue for late graft dysfunction. Late acute rejection occurs in 7–23% of recipients, does not respond as well to pulse steroids as early acute rejection, and can lead to complications like sepsis, biliary tract abnormalities and chronic rejection even after treatment has been completed (122,123). Chronic rejection is less frequent and typically involves loss of the bile ducts; it poses a high risk for graft failure with all the infectious risks (123). Biliary strictures develop in 5–15% of deceased donor transplants and 28–32% of living donor transplants (10). They can be either anastamotic or nonanastamotic; both are more likely to occur in the late post-transplant period. Unfortunately, stricture can lead to stones or sludge forming in the biliary tract and patients may present with recurrent episodes of cholangitis. Patients can also develop procedure-related cholangitis as the primary therapy for stricture is typically endoscopic retrograde cholangiopancreatography with balloon dilatation or stenting of the stricture (10,124). It is not difficult to see why one study of late infections post-liver transplant found that cholangitis was the most common late infection; in this paper, cholangitis was associated with primary sclerosing cholangitis and Roux-en-Y biliary anastomosis (125).

Respiratory infections

Community-acquired pneumonia occurs in a significant proportion of patients late after liver transplant (126). It occurred in 19% of recipients diagnosed with late infection in one series, nearly equal to the risk of cholangitis (125). Common bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenza* and the atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. Liver transplant recipients are also at risk of influenza. Influenza occurs at higher frequency in all solid organ transplant recipients compared to the general patient population. Lung transplant recipients are at the highest risk, but liver transplant recipients are not immune to the effects of influenza (127-129). If infected, they are also more likely to get complications such as myocarditis, secondary bacterial pneumonia, or acute rejection (127,130). Yearly vaccination would be recommended to protect recipients and has been shown to be effective. However, seroconversion rates are lower than in healthy individuals and breakthrough infection can still occur (131-133). Liver transplant recipients with symptoms of influenza in the appropriate season should be tested and/or treated with antivirals. Oseltamivir is the most commonly recommended agent and early initiation of therapy has been associated with a reduced risk of intensive care admission, mechanical ventilation and secondary complications like bacterial or fungal pneumonia in a number of observational studies (134,135). Other respiratory viruses are less common in adult liver transplant recipients; the lack of information may not be due to lack of infection but rather because infections like respiratory syncytial virus are mild and self-limited (136). These pathogens remain a bigger issue for pediatric recipients, even several years out from transplantation (137).

Late viral complications

Of the viral complications, late CMV and herpes zoster are the most commonly reported (125). Late onset CMV disease has been shown to occur in up to 26% of high risk recipients at 2 years and 8.5% of all recipients at a median of 6.3 years (59,138). Patients can present with evidence of CMV syndrome or end-organ disease. The biggest risk is the diagnosis is delayed as clinicians may be less vigilant about it occurring beyond the immediate post-transplant period. Patients should be treated similarly to those with early-onset CMV.

Herpes zoster is a very common late post-transplant complication. Estimates of incidence vary depending on how long or closely patients are followed. One observational study found that 12% of their liver recipients developed herpes zoster at a median of 23 months (139). Actuarial estimates based on time from transplant had 1-, 5- and 10-year incidence rates of 3%, 14% and 18%. Other studies have found rates as low as 1–7% at approximately 5 years of follow-up (140,141). In general, most of the studies report mild dermatomal zoster; disseminated or visceral zoster appears to be rare but recurrent zoster is well documented (139,141). Liver recipients with zoster should be treated with appropriate antivirals. Valacyclovir, acyclovir and famciclovir are all appropriate oral agents with IV acyclovir for those with complicated or disseminated zoster (142). If patients have active CMV, they do not need additional therapy. Other than life-long antiviral prophylaxis, there was little to offer for prevention until lately. Previously the only vaccine against herpes zoster was a live virus vaccine which is contraindicated in post-transplant recipients (143). A new inactive subunit vaccine has just been approved for prevention in healthy adults; studies on the efficacy for prevention in the post-transplant setting are eagerly awaited (144,145).

Conclusions

Despite advances in the field of transplantation, liver transplant recipients remain at risk for a variety of infectious complications, as discussed herein. An understanding of the intricacies of these post-transplant infections, and the continued development of preventative, diagnostic and therapeutic interventions aim to provide further improvements in outcomes following liver transplantation.

Acknowledgements

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.12.10). The authors have no conflicts of interest declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2017.12.10
Cite this article as: Lin M, Mah A, Wright AJ. Infectious complications of liver transplantation. AME Med J 2018;3:5.

