Prevention of Fungal and Hepatitis Virus Infections in Liver Transplantation

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Invasive fungal infections, especially those caused by *Candida albicans,* and recurrence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection after transplantation are common complications in orthotopic liver transplant (OLT) recipients. *Candida* species account for >50% of all invasive fungal infections, which occur in 10%–15% of OLT recipients. The epidemiology and pathogenesis of invasive fungal infections are unique to each type of organism. Fluconazole is effective and safe in the prevention of *Candida* infection after OLT. Preventive measures against *Aspergillus* or *Cryptococcus* remain ill defined. Both HBV and HCV recur almost universally after OLT in infected individuals. The natural course of HBV and HCV, leading to end-stage liver damage, is accelerated. In OLT patients, administration of immunoglobulin with high titers against HBV, alone and/or in combination with lamivudine, immediately after transplantation reduces the recurrence of HBV. The combination of interferon and ribavirin is mildly effective in OLT patients who have evidence of recurrent hepatitis, and additional alternatives are being evaluated.

This article will address 2 of the most serious infectious complications that have a presentation and/or incidence that is somehow unique to liver transplantation: invasive fungal infections and hepatitis virus infection. Infections caused by other organisms, such as cytomegalovirus (CMV) infection, Epstein-Barr virus infection, or *Pneumocystis carinii* pneumonia (PCP), are discussed in separate articles within this issue, because their features are common to many types of solid-organ transplantations. As is the case for many of the infectious complications that follow solid-organ transplantation, there is a paucity of well-designed randomized placebo-controlled trials that would allow us to conclude that a specific regimen is of benefit in preventing invasive fungal infections or recurrence of hepatitis B or C virus (HBV or HCV) infection after liver transplantation. This is in contrast to the large body of anecdotal studies that propose the use of a specific preventive approach. Fortunately, there is adequate information about the epidemiology of these infectious complications, which will help to identify patients at risk for these infectious complications.

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INVASIVE FUNGAL INFECTIONS

The incidence and mortality rate seen with invasive fungal infections were very high until the early 1980s [1–3]. As many as 42% of patients developed invasive fungal infection, and the mortality rate was as high as 60% [2]. With improvements in the technical aspects of transplant surgery and the appreciation of specific risk factors that predispose these patients to severe fungal infections (table 1), the incidence has been reduced to 8%–15%, but the mortality rate remains high [3]. Compared with heart, lung, or heart-lung transplant recipients, in whom the incidence of *Aspergillus* infection is higher than that of *Candida,* more than one-half of the invasive fungal infections seen in liver transplant recipients are caused by *Candida* organisms. The rest are caused mainly by *Aspergillus, Cryptococcus,* dimorphic fungi, and other opportunistic fungi [3].

Table 1. Risk factors for invasive fungal infection in liver transplant recipients.

Candida species	*Aspergillus* species	*Cryptococcus* species
Prolonged and complicated liver transplantation surgery and repeated intra-abdominal surgery after transplantation	Fulminant hepatitis as indication for liver transplantation	Severe immunosuppression
Prolonged use of broad-spectrum antibacterial therapy	Severe immunosuppression	Cytomegalovirus disease
Critically ill patient (prolonged periods of dialysis, intensive care unit, intubation, etc.)	Cytomegalovirus disease	
Cytomegalovirus disease		

Candida Species Infection

Background and epidemiology. *Candida* species infections account for >50% of invasive fungal infections in liver transplantation [1–6]. *Candida albicans* is the most frequent species isolated, followed by *Candida glabrata* and *Candida tropicalis* [1–7]. The site of infection is usually restricted to the intra-abdominal cavity and not infrequently is the source of bloodstream infection. In addition, and like in any other type of solid-organ transplant recipient, line sepsis caused by *Candida* can be occasionally observed. Candida infections usually present as intra-abdominal abscesses, recurrent cholangitis due to biliary strictures, and peritonitis, all of which can be accompanied by fungemia [5]. The pathogenesis of *Candida* species infections in liver transplantation suggests that the source is the lumen of the gastrointestinal tract [8]. Conditions that favor supercolonization or overgrowth of *Candida* in the gut ultimately favor translocation of the fungus to the extraluminal areas, subsequent intra-abdominal infection, and further dissemination. If *Candida* overgrowth is present at the time of the transplant surgical procedure in which the intralumen of the duodenum is exposed, intra-abdominal spill can occur at that time. Likewise, reoperation due to factors such as recurrent intra-abdominal bleeding and hepatic artery thrombosis will also favor extra gut dissemination. *Candida* overgrowth in the lumen of the gastrointestinal tract is secondary to changes in the bacterial flora. It has been clearly established that the presence of anaerobic bacteria in the gut conveys a protective effect as it neutralizes the overgrowth of *Candida* [8]. This has been the basis for the use of selective bowel decontamination regimens, the main goal of which is to maintain a healthy anaerobic flora [8–11]. In fact, all the risk factors identified in multiple epidemiological studies addressing the predisposition for invasive fungal infection with *Candida* species highlight this underlying pathogenesis [4–6]. In addition, some selective bowel decontamination regimens have included oral amphotericin preparations to further enhance the elimination of *Candida* from the bowel. The clinical effectiveness of this technique in reducing systemic *Candida* infection (beyond the potential beneficial effect of selective bowel contamination), however, remains unknown. Finally, CMV disease [12] is also an independent risk factor.

Preventive measures. Two randomized controlled studies have shown the efficacy of oral fluconazole in the prevention of invasive fungal infection caused by *Candida* species [7, 13]. In one study, fluconazole administered at a dosage of 100 mg per os q.d. for the first 4 weeks after liver transplantation reduced colonization and superficial infection, and a trend toward reduction of invasive fungal infection was seen. Most important, when fluconazole was administered at this dose, it was well tolerated and safe, and did not interfere with cyclosporine levels [13]. A second, larger study published years later demonstrated that fluconazole administered at a dosage of 400 mg per os q.d. for 100 days significantly reduces the incidence of colonization, superficial infection, and invasive fungal infection caused by *Candida.* More important, it reduces the mortality rate associated with invasive fungal infection [7]. When used at this higher dose, there was significant interference with cyclosporine and with cyclosporine-associated side effects such as CNS manifestations. An important aspect of these 2 trials is that there was no significant increase of fluconazole-resistant *Candida* organisms, compared with the control or placebo arm, and, as expected, *C. glabrata* and *Candida krusei* were not prevented by fluconazole. An additional randomized control study demonstrates that lipid-associated amphotericin B, when administered during the first 5 days after liver transplantation at a dose of 1 mg/kg, is also effective in reducing *Candida* infections during the first months after liver transplantation [14]. It is interesting to note that no reduction in *Aspergillus* infection was seen in this study, although the number of end points used to assess the efficacy of treatment was very low. Recommendations regarding the prevention of invasive fungal infection are outlined in table 2.

Whether preemptive use of these agents is of value remains to be proven. Many centers have elected to administer fluconazole prophylaxis only to those patients who, at the time of transplantation, are identified to be at high risk based on the risk factors presented in table 1 or thereafter if specific risk factors develop after liver transplantation, such as prolonged antibacterial therapy or intubation. Because CMV disease is a clear risk factor for all types of invasive fungal infection [12], effective prophylaxis of patients at high risk for CMV disease, such as those who are CMV D+/R− (donor positive, recipient

Table 2. Potential prevention strategies for invasive fungal infections in liver transplant recipients and recommendations.

Candida species	*Aspergillus* species	*Cryptococcus* species
Fluconazole, 100–400 mg per os q.d. for 4–8 weeks after transplantation (A-I)	Lipid-associated amphotericin B, 1 mg/kg, or intraconazole (iv or per os) before and after (4 weeks) liver transplantation in patients with acute fulminant hepatitis (C-III)	Prevention of cytomegalovirus disease (C-III)
Lipid-associated amphotericin B, 1 mg/kg for 5 days after transplantation (B-I)	Microbiological surveillance and antifungal preemptive treatment in immunocompromised individuals (C-III)	High index of suspicion in severely immunocompromised individuals (C-III)
Prevention of cytomegalovirus disease (B-I)	Prevention of cytomegalovirus disease (C-III)	
Selective bowel decontamination (B-III)		
Targeted therapy with fluconazole based on presence of risk factors (C-III)		

NOTE. For risk factors, see table 1.

negative), has been shown to reduce significantly the incidence of invasive *Candida* infection in the absence of specific anti-*Candida* prophylaxis [15].

Aspergillus Species Infection

Background and epidemiology. *Aspergillus* species infection is relatively uncommon in liver transplant recipients, compared with the higher frequency observed in lung transplant recipients. It can account for up to one-quarter of all fungal infections, and its overall incidence ranges between 2% and 6% among all liver transplant recipients [3]. Compared with that of *Candida* infection, the temporal presentation of *Aspergillus* infection after orthotopic liver transplantation is later (within the second month), and the mortality rate is extremely high, especially when *Aspergillus fumigatus* is present. Unlike *Candida, Aspergillus* is acquired via the respiratory tract, and therefore either a very high inoculum, as is the case with exposure of transplant recipients to construction sites or soil removal, or a very significant level of immunosuppression in previously colonized individuals favors the development of invasive fungal *Aspergillus* infections. Conditions that cause severe immunosuppression (especially of T cell and phagocytic function) in liver transplant recipients favor the development of invasive *Aspergillus* infection in exposed individuals [3, 5, 16] (table 1).

Preventive measures. Unfortunately, there are no trials documenting that *Aspergillus* infection can be effectively prevented after liver transplantation. Because the incidence of this infection after liver transplantation is relatively small, and without considering point-source outbreaks, a preemptive approach to prevention seems more logical. Unfortunately, except for patients who have acute fulminant liver failure before transplantation, patients at risk (e.g., those who are severely immunocompromised) are difficult to identify. One practical approach that remains to be proven effective is administration of systemic antifungal prophylaxis with agents that have anti-*Aspergillus* activity (such as amphotericin B or intraconazole, iv or per os) to patients with acute liver failure. This strategy could be started on admission to the intensive care unit and continued after transplantation for a total of 3–4 weeks, the duration being based on the fact that *Aspergillus* infection is noted after 4 weeks after OLT [5]. Voriconazole, which should be available in the near future, could also be an alternative. For severely immunocompromised patients, such as those receiving multiple courses of steroid boluses and anti–T cell receptor–antibody therapy, we recommend that there be an enhanced level of suspicion for the development of this fungal infection and that the search for the infection be prompt and aggressive. Whether surveillance sputum cultures to detect *Aspergillus* colonization have any positive predictive value in liver transplant recipients is unknown [16].

Cryptococcus Species Infection

Background and epidemiology. The incidence of *Cryptococcus neoformans* infection can be even higher than that of *Aspergillus* infection in liver transplant recipients; *C. neoformans* is the second most common pathogen causing invasive fungal infection at some liver transplant centers. As is the case with *Cryptococcus* infection in other immunocompromised patients, the liver transplant patients at risk are those who have a severe level of immunosuppression that is secondary to antirejection therapy and is contributed to by the immunosuppressive state conferred by high levels of CMV replication. In fact, CMV can have an impact not only on the risk for *Cryptococcus* infection, but also on the risk for *Aspergillus* and *Candida* infection [5, 12]. Thus, it is not surprising to observe that patients who are at very high risk for CMV disease, which implies a significant level of CMV replication (as is seen in patients who are CMV D+/R−) are also the ones who develop infections with the 3 organisms mentioned above. The clinical presentation can be subtle and, in many cases, without CNS manifestations. Dissemination is common and usually fatal [5, 17].

Preventive measures. Except for the importance of maintaining a high index of suspicion for development of this type of fungal infection in severely immunocompromised liver

Table 3. Preventive measures for hepatitis virus recurrence in liver transplant recipients.

HBV	Hepatitis C virus
HBIg, 10,000 IU/day for 7 days immediately after transplantation and reinfusion every 3–4 weeks to achieve serum levels of HBIg >100 IU; administration for life (A-II)	Combination of IFN-α and ribavirin, once histological damage is noted in liver biopsy after transplantation (B-II)
For HBV-viremic patients, before liver transplantation (HBV e antigen and/or HBV DNA+), administration of lamivudine, 100 mg per os until viremia is resolved; continue HBIg administration as above, and, if a breakthrough occurs, start lamivudine again (B-II)	

NOTE. HBIg, immunoglobulin with high titers against HBV; HBV, hepatitis B virus.

transplant recipients, there is no agreement on how to prevent such infections. It is assumed that if a patient receives fluconazole prophylaxis to prevent *Candida* infection for the first 1–2 months after transplantation, it will have an impact on *Cryptococcus* infection. In the 2 randomized trials that examined the use of fluconazole in patients who underwent liver transplantation, there was a very low incidence or an absence of *Cryptococcal* infection, precluding evaluation of its efficacy. As is the case for other fungal infections, it is presumed that effectively preventing CMV disease will affect its incidence. Finally, it remains to be proven whether microbiological surveillance in individuals at risk (performed through the use of serum *Cryptococcus* antigen) is sensitive and thus clinically useful, as was already shown to be the case when it was used to follow up on the response to antifungal therapy.

HEPATITIS VIRUS INFECTION

Recurrent hepatitis secondary to HBV or HCV infection is a common complication after liver transplantation. Chronic viral hepatitis caused by HBV and HCV has become the most common indication for liver transplantation in many Western countries, and its significance is expected to increase as more cases of end-stage liver failure develop, especially in individuals who have unrecognized HCV infections. Although HBV infection has been declining as an indication for liver transplantation, HCV infection has been on the rise and is currently the primary cause for end-stage liver failure requiring liver transplantation in the United States. As discussed below, there are effective means to prevent HBV recurrence in liver transplant recipients, although this is not generally true for HCV (table 3).

HBV Infection

Background and epidemiology. Recurrence of HBV-induced hepatitis after liver transplantation occurs in >80% of patients who have HBV infection before liver transplantation [18–20]. The presence of active viral replication (defined as the presence of HBV e antigen (HBeAg) and/or HBV DNA) before liver transplantation predicts the incidence of recurrence and morbidity after liver transplantation. Eighty-three percent of patients in whom HBV DNA or HBeAg was detected before transplantation had recurrence of HBV infection in the allograft, as compared with the 54% who lacked these markers [20]. Coinfection with hepatitis D virus before liver transplantation somehow buffers the severity and frequency of hepatitis relapses. Recurrence of HBV-induced hepatitis is usually observed within the first 6 months after liver transplantation, with a rapid transition to chronic active hepatitis by 9–12 months and cirrhosis by 2–3 years after liver transplantation [20]. On the basis of the above, the preventive regimens that have been shown to be effective have aimed at blocking the level of HBV replication immediately before and/or after liver transplantation to avoid reinfection of the graft.

Preventive measures. Immunoglobulin with high titers against HBV (HBIg) effectively reduces the rate of HBV-induced hepatitis from 76% to 19% [18, 21]. The causes of breakthrough during immunoglobulin therapy in nonviremic patients (before transplantation) are unknown but may include low levels of immunoglobulin titers in certain preparations and the appearance of escape mutants HBV [21]. Various protocols have proposed a variety of dosing schedules of HBIg [21–23], but in general the current practice is to administer 10,000 IU/day for the first week after transplantation and thereafter at 3–4-week intervals. The goal is to achieve HBIg levels in serum that are >100 IU, although some centers consider >500 IU to be ideal. In general, the dose is ~5000 IU/month. The duration of HBIg treatment is believed to be for life, because cessation within 6–12 months after liver transplantation results in high recurrence rates. This approach incurs a cost of $5000–$15,000/year (based on the value of the US dollar in 1998). Because 30% of nonviremic (HBeAg negative or DNA negative at the time of transplantation) liver transplant recipients still develop recurrence of HBV infection in the graft despite treatment with HBIg, additional preventive measures have been sought. Preventive measures have also been contemplated for patients with HBV viremia, which until recently was considered a relative contraindication for liver transplantation in some centers.

Lamivudine, or 3TC, is a nucleoside analogue that significantly reduces HBV replication in nontransplant HBV-infected patients; however, the possibility that lamivudine-resistant

strains will emerge during prolonged antiviral therapy is of concern (~20% after 1 year of treatment). Multiple small trials have addressed whether lamivudine could be useful in preventing recurrence of HBV infection after liver transplantation in viremic patients. Results from such trials suggest that administration of lamivudine before liver transplantation (with the aim of suppressing the viremic phase) reduces recurrence and breakthrough in the transplant patient who is placed on HBIg immediately after transplantation [24]. If HBV replication (breakthrough) is detected after transplantation while the patient is receiving HBIg, lamivudine is reintroduced. Alternately, some centers are continuing lamivudine after liver transplantation in combination with HBIg for patients who are viremic before transplantation [25], and other centers have considered reducing the dose of HBIg or not using it [26]. Famciclovir has shown some in vivo activity, but it is not highly effective. New nucleoside analogues such as adefovir, as well as some derivatives, are being considered for large multicenter trials involving patients who are not transplant recipients. Results from such studies would aid investigation of the potential use and toxicity of these drugs in patients who have undergone liver transplantation. Another issue that needs to be considered is the value of revaccinating patients to see whether boosting the HBV-specific immune response is effective in preventing HBV recurrence.

HCV Infection

Background and epidemiology. There is, unfortunately, little information about to how to avoid recurrence of HCV infection in the graft after liver transplantation. HCV RNA can be detected in as many as 90% of patients after liver transplantation, liver damage is observed in >75% of patients by 3–4 months, and as many as 25% of the patients develop cirrhosis within 5 years [27–30]. As is the case for HBV, the natural course of HCV infection and its complications are accelerated in liver transplant patients. What remains controversial is whether this affects long-term patient survival [27–30].

The risk factors that predispose to early recurrence of hepatitis after liver transplantation include the presence of HCV genotype 1B, steroid use, and treatment of acute rejection [30–32]. Although the former is controversial, reduction of the virus-specific immune surveillance is, not unexpectedly, detrimental to the control of HCV-induced damage, as shown by the increased HCV load observed in these patients' subgroups [33]. CMV may play a role as a cofactor in accelerating HCV replication and liver damage, as is seen with fungal infections, although it is less clearly documented with HCV [34]. If this were the case, effective suppression of CMV replication would have an impact on the recurrence of HCV after liver transplantation.

Preventive measures. Unfortunately, despite the relative success in management of HBV infection, the availability of compounds and/or regimens that prevent HCV recurrence and liver damage remains limited. Both interferon and ribavirin, when used as monotherapy, have been shown in anecdotal reports to be of some efficacy in reducing the level of viral replication after liver transplantation, even though they have not significantly affected the recurrence or severity of HCV hepatitis in the graft [35]. A combination of both agents in the nontransplant setting has been shown to be more effective than individual use in reducing viral replication. In the liver transplant setting, there have been reports showing reduction of HCV replication in 45%–50% of patients after 6 months of combination therapy and histological improvement, although ~15%–20% of them fail to tolerate therapy because of side effects [36, 37]. The current practice is to not give any antiviral therapy immediately after transplantation even though viral replication is detected, but to initiate antiviral combination therapy once histological recurrence is apparent in the liver graft. Studies are currently under way to test pegylated interferons, which can provide a more sustained release of interferon without causing significant side effects in combination with ribavirin in liver transplantation. Also, and after the success story of HBIg, pilot studies are being initiated to address the dose and efficacy of hyperimmune HCV immunoglobulin to prevent the recurrence of HCV infection. It is in the field of HCV infection that liver transplantation would greatly benefit from new drugs, a goal of multiple pharmaceutical and biotechnology enterprises.

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