



Infections in Liver Transplant Patients and the Influence of Infectious Diseases Specialists on the Entire Process

Karaciğer Nakil Hastalarında Enfeksiyonlar ve Enfeksiyon Hastalıkları Uzmanlarının Sürece Etkisi

Yaşar Bayındır¹, Reem S. Almaghrabi², Kenan Moral³

¹Department of Infectious Diseases and Clinical Microbiology, Güven Hospital, Ankara, Türkiye

²Department of Transplant Infectious Diseases, King Faisal Specialist Hospital and Research Center, Organ Transplant Center of Excellence, Riyadh, Saudi Arabia

³Department of Gastroenterology and Hepatology, Gazi University Faculty of Medicine, Ankara, Türkiye

Abstract

Liver transplantation is the most advanced and effective life-saving treatment for end-stage liver diseases. Despite medical advances, infections remain the leading cause of morbidity and mortality after transplantation. Infections vary according to the post-transplant timeline and net immunosuppression status, but environmental exposures and other factors also play a role. Infectious diseases specialists, along with all the members of the transplant team, play a key role in the management of infections. It is recommended that infectious diseases specialists are trained and become experienced in this area.

Keywords: Infections; Liver transplantation; Transplant infection specialist

Liver transplantation is a unique and promising option for patients with acute liver failure or end-stage liver diseases, including hepatocellular carcinoma, who meet criteria.^[1,2] The number of centers performing living and cadaveric liver transplantation has been increasing worldwide, organ donation is supported with campaigns and legislation is constantly updated in countries.^[3] Despite advancements in surgical techniques and immunosuppressive management, infectious complications are still a common cause of morbidity and

mortality in liver transplant recipients.^[4] Specific factors, such as preoperative clinical conditions and recurrent infections, postoperative surgical complications, and immunosuppressive state of the patients, increase the risk of infection.^[5] Experienced Infectious diseases specialists and advanced microbiology laboratory plays a critical role in the management of infections, but multidisciplinary contribution of the entire transplant team is important. This article discusses the general management rationale of infections and the role of the specialists.

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Correspondence: Yaşar Bayındır, M.D. Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü, Güven Hastanesi, Ankara, Türkiye

E-mail: yasar.bayindir@guven.com.tr **Submitted:** 12.01.2025 **Revised:** 15.01.2025 **Accepted:** 30.01.2025



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The aim of this article was to review the current perspective on infections in liver transplant patients. For this purpose, the keywords “liver transplantation, common infections, infection management, infectious diseases and clinical microbiology specialists” were searched on PubMed and Web of Science databases between 1998-2024. Those suitable for our purpose were selected from the literature. Principle management of infections, and the role of infectious diseases specialists in transplant centers were reviewed.

Epidemiology

Due to the nature of liver transplants and immunosuppression, infections remain the leading cause of mortality. A cohort study involving all solid organ transplant patients revealed that 55 percent of 577 liver transplant recipients developed an infection within 12 months post-transplantation. The breakdown of these infections was as follows: 59 percent bacterial, 33 percent viral, and 8 percent fungal. The mortality rate attributed to infections during the post-transplant period can reach as high as 42%.^[1] A post-mortem examination based on autopsies revealed that infections were responsible for the deaths of 64% of 321 patients who had undergone liver transplantation.^[4] Several factors contribute to a higher risk of infections in liver transplant patients. These include a pre-transplant Model for End Stage Liver Disease-Sodium (MELD-Na) score exceeding 30, the necessity for renal replacement therapy post-transplantation, subsequent surgeries or transplants, and extended stays in intensive care units.^[2] Consequently, infections emerge as the primary cause of mortality among liver transplant recipients within the first year following the procedure, although infection rates vary across different medical centers.^[5]

Liver Transplant Recipient-Specific Features

The management of infections in transplant recipients is typically divided into three timeframes: the first month, one to six months, and beyond six months post-transplantation.^[6,7] The nature and causative agents of infections often vary across these periods. Due to immunosuppression, infection symptoms can be subtle and challenging to diagnose and treat.^[5] Fever-inducing non-infectious conditions, such as allograft rejection, medication side effects, or thrombosis, may resemble infections.^[8] The required use of immunosuppressants can lead to significant drug interactions with antimicrobials, a factor that must be considered in patient care. Infections in liver transplant recipients may be more severe, and progress faster

compared to those in individuals with normal immune function. Thus, prompt and appropriate treatment is crucial for reducing morbidity and mortality.^[5,7]

A comprehensive assessment of patients helps determine their overall immunosuppression status. Various factors can compromise this state, including the dosage, type, and duration of immunosuppressive medications, the presence of catheters or parenteral nutrition, conditions like diabetes or hemodialysis, certain metabolic disorders, immunomodulating viral infections such as *cytomegalovirus* (CMV), graft failure, and other concurrent health issues.^[5,7,9]

Preoperative Evaluation of the Liver Transplant Candidates

Preoperative evaluation and screening for the presence of active, latent, and chronic infections is crucial for the management and preventive strategies after transplantation.

Preoperative evaluation usually consists of the following sections:

1. Routine screening of donor and recipients for certain infections
2. Active infection in the donors
3. Active infection in the recipients
4. Latent infection in donor or recipient
5. Multidrug resistant bacterial colonization
6. Preoperative vaccination for vaccine preventable diseases

Each center should prepare their protocols according to their own capabilities and current guideline recommendations.^[10-12]

Common Infections According to Timeline

The type, causative agent and frequency of infection after transplantation may vary according to prophylaxis strategies, the timeline after transplantation and the net state of immunosuppression.^[5] The common infections according to the timeline are shown in Table 1 (Table 1).

Infections in First Month

Infections that develop rapidly in the first month after transplantation are generally like those in immunocompetent patients. Most infections in the first month are caused by bacteria. As nosocomial infections, surgical site infections, central catheter related blood stream infections, urinary catheter related infections, healthcare associated pneumonia are the most common

Table 1. Common infections according to the timeline following liver transplantation^[5-7]

0–1 month	1–6 month	>6 month
Nosocomial / technical (Donor / recipient derived infections)	Activation of latent infections, relapsed, residual, opportunistic infections	Community acquired infections
Nosocomial infections	With PJP and antiviral (CMV, HBV) prophylaxis	Community acquired pneumonia
Pneumonia	BK polyomavirus nephropathy (common in kidney transplantation)	Urinary tract infections
Line infection	<i>Clostridium difficile</i> colitis	<i>Aspergillus</i>
Wound infection	HCV	Atypical molds
Intraabdominal infections (anastomotic leaks/ ischemia, stenosis)	Adenovirus, influenza and others	<i>Mucor</i> species
Antimicrobial resistant species	<i>Cryptococcus neoformans</i>	<i>Nocardia</i>
MRSA	<i>Mycobacterium tuberculosis</i>	<i>Rhodococcus</i> species
VRE		
Multi/pan drug resistant bacteria		
<i>Clostridium difficile</i> colitis	Anastomotic complications Without prophylaxis add	Late viral infections
Donor-derived infections (uncommon)	<i>Pneumocystis jirovecii</i>	CMV (colitis/retinitis)
Hepatitis viruses	Herpes viruses (HCV, VZV, CMV, EBV)	Hepatitis (HBV, HCV)
HSV	HBV	HSV encephalitis
LCMV	<i>Listeria</i>	Community acquired (influenza, SARS CoV-2, west Nile virus)
Rabies	<i>Nocardia</i>	JC polyomavirus (PML)
West Nile	<i>Toxoplasma</i>	Skin cancer
Recipient-derived infections (colonization)	<i>Strongyloides</i>	Lymphoma (PTLD)
<i>Aspergillus</i>	<i>Leishmania</i>	
<i>Pseudomonas</i> and other resistant bacteria	<i>Trypanosoma cruzi</i>	

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HSV: Herpes simplex virus; LCMV: Lymphocytic choriomeningitis; MRSA: Methicillin-resistant *Staphylococcus aureus*; PJP: *Pneumocystis jirovecii* pneumonia; PML: Progressive multifocal leukoencephalopathy; PTLD: Posttransplant lymphoproliferative disorder; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; VRE: Vancomycin-resistant enterococcus; VZV: Varicella-zoster virus.

infections.^[7,13] Surgical complications such as bleeding, strictures and/or biliary leaks, portal vein thrombosis predisposes to infections. Moreover, unexpected or unusual symptoms may be caused by donor-derived infections during this period.^[5] Although the presence of fever and other symptoms in patients first suggests infection, it should be kept in mind that non-infectious causes may also cause fever.^[6]

If a bacterial infection is suspected, appropriate cultures should be obtained, and empirical antibiotic treatment should be initiated. Treatment is adjusted according to culture antibiogram results and response to antibacterial treatment. In recent years, the increase in multidrug-resistant bacterial infections has also attracted attention in liver transplant patients.^[13]

In the initial month following liver transplantation, *Candida* species emerge as a significant infectious complication. These fungi commonly infect the bloodstream, surgical sites, or urinary system, potentially leading to invasive or disseminated infections.^[14] Additionally, patients may develop esophagitis or infections of the skin and oral mucosa. Due to the high mortality rate associated with diagnosed or suspected disseminated candidiasis or candidemia, immediate treatment is crucial. Given the recent rise in azole-resistant non-albicans *Candida* spp. infections, empirical antifungal therapy should be guided by surveillance data.^[14,15] Viral infections are relatively rare during this period. The widespread use of CMV prophylaxis in most transplant centers has largely diminished infections caused by CMV and herpes simplex virus.^[5,16]

Table 2. Management of the infections in liver transplant patients and the role of infectious diseases specialists^[10–12,23–25]

Preoperative period	Perioperative period	Postoperative period
Evaluation and screening of candidates for infections	Surgical prophylaxis	Evaluation and follow of the recipients by clinically and laboratory tests during hospital stay
Treatment for active infections	Final evaluation last 24–48 hours	Treatment of latent/active infection
Vaccination schedule (as soon as added to the waiting list)		Vaccination
Planning for preventive strategies		After 3–6 months, if needed
CMV prophylaxis (universal prophylaxis or preemptive strategy)		After one month during the flu endemic
Hepatitis B treatment or prophylaxis		Administration of preventive strategies
PJP prophylaxis		CMV prophylaxis
Antifungal prophylaxis		Hepatitis B treatment or prophylaxis
Other (<i>Toxoplasma</i> , other Herpes viruses out of CMV, etc)		PJP prophylaxis
		Antifungal prophylaxis (for patients with risk factors)
		Other (<i>Toxoplasma</i> , other Herpes viruses out of CMV, etc.)
		Outpatient clinic follow-up and/or consultation of recipients as a member of transplantation team

CMV: Cytomegalovirus, PJP: *Pneumocystis jirovecii*.

1–6 Months After Transplantation

Opportunistic infections frequently occur during this period due to the severe suppression of the immune system. Among solid organ transplant recipients, cytomegalovirus is the most prevalent viral infection agent. When patients receive antiviral prophylaxis for CMV infections for 100 days, CMV infections may emerge later, after the prophylactic treatment has ended.^[17]

Varicella zoster virus, Epstein-Barr virus, respiratory syncytial virus, human herpesvirus 6, influenza, adenovirus, and other respiratory virus infections may manifest during this period.^[5] Diagnosis and treatment of viral infections are conducted in accordance with current recommendations.^[5,16,18–21] *Aspergillus* species represent the second most prevalent fungal infection agent following *Candida* spp. infections.^[22] While pulmonary infection is the most common, dissemination to other organs or systems can occur. Opportunistic infections, including nocardiosis, listeriosis, cryptococcosis, and tuberculosis, may manifest during this period as well.^[5,7]

After Six Months

The risk of opportunistic infections becomes comparable to that of individuals in the general population during this period, due to the reduction of immunosuppression to maintenance levels.^[6,7] However, infections may manifest with increased severity. Furthermore, patients

diagnosed with graft rejection and receiving high levels of immunosuppressive agents may be susceptible to infection by opportunistic pathogens.^[5,7]

Management of the Infections and The Role of Infectious Diseases Specialists

The management of infections commences when patients are placed on the transplant list.^[10,11] Preoperative donor and recipient candidates undergo evaluation, and active infections are diagnosed and treated. Surgical prophylaxis and other prophylactic strategies involving vaccination are planned in accordance with the guidelines and protocols of the transplant centers.^[10–12,23] Posttransplant infections should be diagnosed and treated promptly (Table 2). Although infectious disease specialists play a central role in this process, multidisciplinary management is essential, involving transplant surgeons, gastroenterologists, interventional radiologists, and microbiologists.^[5,9,24,25] This necessitates the utilization of new, rapid, and reliable diagnostic methods, including molecular microbiological tests. However, antimicrobial resistance and drug-drug interactions remain significant challenges in this field.^[1,5]

Infectious diseases specialists play a pivotal role in managing infections in liver transplant patients, significantly influencing clinical outcomes. Their expertise is essential in navigating the complexities of infections in

this immunocompromised population. Infections are a primary cause of morbidity and mortality in patients with cirrhosis and those undergoing liver transplantation, with bacterial infections occurring in 25% to 35% of patients at hospital admission or during hospitalization.^[26] The presence of infections can precipitate acute-on-chronic liver failure (ACLF), which is associated with high mortality rates, underscoring the necessity for timely and effective management.^[26] Infectious diseases specialists contribute to the early identification and treatment of infections, which is critical given that infections can alter the natural history of cirrhosis and significantly impact survival rates.^[27] Their involvement not only improves patient outcomes but also reduces the duration of hospital stays and healthcare costs.^[12] Furthermore, infectious diseases specialists are instrumental in implementing antimicrobial stewardship programs, which are vital in addressing the increasing prevalence of multidrug-resistant organisms (MDROs) in this patient population.^[28] The training of infectious diseases specialists in transplant infections should be comprehensive and tailored to the unique challenges presented by this patient population. A proposed curriculum emphasizes the importance of clinical training that includes both inpatient and outpatient care, with a focus on solid organ transplant patients.^[24] This training should encompass a minimum of one year of additional education dedicated to transplant infectious diseases, allowing fellows to gain expertise in managing infections specific to transplant recipients.^[24] The curriculum should also include exposure to various solid organ transplant types and hematopoietic stem cell transplantation, ensuring that trainees understand the epidemiology and risks associated with different infections.^[24]

Infectious diseases specialists should be trained in the use of advanced diagnostic techniques, including molecular diagnostics, to facilitate rapid identification of pathogens and appropriate treatment strategies.^[24] Moreover, the training should incorporate research components that encourage fellows to engage in clinical trials and studies focused on transplant infections, fostering a culture of inquiry and evidence-based practice. This approach not only enhances the knowledge base of infectious diseases specialists but also contributes to the advancement of the field, ultimately improving patient care in liver transplantation settings.^[24]

The integration of infectious diseases specialists into the management of infections in liver transplant patients is essential for optimizing clinical outcomes. Their expertise is crucial in recognizing the subtle presentations of

infections, as up to 46% of infections in cirrhotic patients can occur without clinical symptoms at presentation.^[29] Infectious diseases specialists utilize biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) to evaluate patients with suspected infections, as these markers can help distinguish bacterial infections from other non-infectious causes.^[26]

Collaboration between infectious diseases specialists and transplant teams is vital in developing personalized antifungal and antibacterial prophylaxis protocols tailored to the unique needs of transplant recipients.^[27] This collaboration begins with a comprehensive understanding of the patient's immunosuppressive regimen, which is essential for assessing the risk of infections, including opportunistic pathogens that may arise post-transplantation. The specialists utilize local epidemiological data to inform their decisions on prophylaxis, ensuring that the chosen antibiotics and antifungals are effective against the most prevalent organisms in the specific transplant center's patient population.^[26,28]

In conclusion, early diagnosis and treatment of infections, which may prevent the important causes of morbidity and mortality, can actually pose many challenges for liver transplant patients. The involvement of infectious diseases specialists in the care of liver transplant patients is associated with better clinical outcomes and a reduction in infection-related complications. Their role in educating the healthcare team about the complexities of infections in immunocompromised patients fosters a more comprehensive approach to patient care. By integrating their expertise with the transplant team's clinical insights, infectious diseases specialists help create a comprehensive and personalized infection prevention strategy that enhances patient outcomes in liver transplantation settings.

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