Management of Infections in Liver Transplantation Setting

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INTRODUCTION

• Liver transplantation (LT) is the treatment of choice for decompensated cirrhosis, small hepatocellular carcinomas, or acute liver failure
• The success of LT has meant that there is a growing cohort of recipients with increasing number of long term survivors
• These long-term survivors are at risk of morbidity and mortality

Lucey et al ,Liver Transpl. 2014
Introduction

• Infection is the most common cause of in-hospital mortality after LT, accounting for 62.5% of all causes.

• The burden of infectious diseases is clearly attributable to the dysfunction of defensive mechanisms of the host, both as result of:
  
  Cirrhosis
  
  Immunosuppressive agents

Kaido et al, Liver Transpl. 2009

Feltracco et al, World J Hepatol. 2011
AGENDA

• Pre transplant work up
  ✓ Active infections
  ✓ Preventable infections
  ✓ Latent infections

• Post transplant management of infections other than HCV, HBV and HIV
  ✓ Bacterial infections
  ✓ Viral infections CMV
  ✓ Fungal infections
Pre Transplant work up

• Evaluation of the infectious risk is essential, aiming to:

1. Prevent or reduce the risk of infection-related drop out from the waiting list

2. Minimize the negative impact on the outcome after LT

• Therefore identification, control, and eradication of either bacterial, viral, fungal, or parasitic infections is crucial before LT
Pre LT Work up allows us to identify:

- **Active infections** that would require therapy prior to transplantation
- **Preventable infections** that need vaccinations to reduce the risk of de novo infections after transplant
- **Latent infections** that can reactivate after transplantation
Pre Transplant work up

• Due to hepatocellular dysfunction, cirrhotic patients are at increased risk of infections, including spontaneous bacterial peritonitis, cholangitis, pneumonias, urinary tract infections, and catheter-related bloodstream infections.

• *Active infection* needs to be adequately treated before LT can be attempted

Fischer and Lu, Am J Transplant. 2013
Pre Transplant work up

• As part of transplant evaluation, vaccination for a variety of preventable diseases, should be undertaken, especially as live vaccines are contraindicated post-LT

• Although vaccination responses in some patients awaiting LT are suboptimal, antibody responses are usually even more attenuated when vaccines are administered later

Evaluation for Liver Transplantation in Adults: Practice Guideline by AASLD and AST Hepatology 2013
Pre Transplant work up

• For these reasons, primary immunizations should be given before transplantation, and as early as possible during the course of disease
• Transplant candidates to be immunized against HAV and HBV, varicella, Pneumocococcus, influenza and tetanus

Pre Transplant work up

• The infectious screening in liver transplant recipients should be graduated in different levels
• **Level 1** in all candidates to LT
• **Level 2** only in patients eligible to LT at the time of listing
• **Level 3** in patients with risk factors or from geographic area endemic for specific infections

Fagiuoli et al, Journal of Hepatology 2014
Pre Transplant work up

- Level 1 in all candidates to LT
Pre Transplant work up

1– Hepatitis B virus (HBV) serology: HBsAg, HBcAb, HBsAb
   - if HBsAg + HBeAg/HBe Ab; HBV-DNA, Hepatitis D virus (HDV) IgG
2 – Hepatitis C virus (HCV) Ab if positive, HCV-RNA
3 – Hepatitis A virus (HAV) Ab IgG
4 – Human immunodeficiency virus (HIV) 1 and 2 Abs
5 – Chest X-ray
Pre Transplant work up

• Level 2 only in patients eligible to LT at the time of listing
Pre Transplant work up

- Mycobacterium tuberculosis: history + Tuberculin skin test + Interferon-Gamma Release Assays
- Cytomegalovirus, Epstein Barr virus
- Human herpes virus 8
- Varicella zoster virus, Herpes simplex virus 1, Herpes simplex virus 2
- Urine culture, parasitological exam and stool culture
- Staphylococcus aureus nasal/axillary swab
- Dental X-ray or dental scan

Fagiuoli et al, Journal of Hepatology 2014
Pre Transplant work up

Tuberculosis:
• A relative risk of 4.3 for the development of symptomatic TB when skin test was positive instead of negative
• Reactivated latent tuberculosis represent the majority of post-transplant cases of active TB
• The identification of patients with LTBI is recommended before LT to apply for prophylaxis

Torre-Cisneros et al  Clin Infect Dis 2009
Holty and Sista, Curr Opin Org Transpl 2009
Pre Transplant work up

Tuberculosis:

Who should be considered for prophylaxis?
When to start?
Which schedule?
Pre Transplant work up

Who?

✓ PPD-Mantoux ≥ 5 mm after 48–72 h and + IGRAs
✓ Recent close exposure to person with active TB
✓ PPD-Mantoux <5 mm and IGRAs positive
✓ PPD-Mantoux ≥ 10 mm and IGRAs negative

Which?

✓ Isoniazid 5 mg/kg/d,(max 300), pyridoxine for 6-9 m.

When?

✓ Before LT whenever feasible and tolerated
✓ Post LT as soon as a patient’s liver function has stabilized

Fagiuoli et al, Journal of Hepatology 2014
Pre Transplant work up

- **Level 3** in patients with risk factors or from geographic area endemic for specific infections
Pre Transplant work up

- Vancomycin-resistant Enterococcus (VRE) and multidrugresistant (MDR) Gram (negative) rectal swab
- Serology for: Histoplasma, Coccidiomycosis, Trypanosome, Schistosoma, Leishmanina
- Malaria blood test
- Human T cell lymphotropic viruses (HTLV) 1–2 IgG
• Pre transplant work up
• Post transplant work up

Prophylactic measures

Management of active infections

✓ Bacterial
✓ CMV
✓ Fungal
Post Transplant work up

• Prophylactic measures post LT
  General measures
  ✓ Strict hand hygiene practices and contact precautions among all medical personnel
  ✓ Limiting invasive devices such as urinary catheters for a minimum period of time
  ✓ Discourage prolonged use of broad-spectrum antibiotics without evidence of an active infection

Hernandez et al, Gastroenterology and Hepatology 2015
Post Transplant work up

• Prophylactic measures post LT

Specific measures

✓ Prophylactic antibiotics should be given cefotaxime and ampicillin or piperacillin-tazobactam not exceeding 48-72 h.

✓ Cotrimoxazole (TMP-SMX) is the drug of choice for its activity against Pneumocystis jiroveci, Nocardia spp., Toxoplasma gondii and Listeria spp.

Bratzler et al, Am J Health Syst Pharm 2013
Post Transplant work up

Management of active infections

• There are three consecutive and often overlapping periods after LT that are associated with specific types of infections

✓ Early post-LT infections (first month)
✓ Intermediate period (from 2 to 6 months)
✓ Late post-LT infections (>6 months)

Romero et al, World J Hepatol 2011
Post Transplant work up

Early post-LT infections (first month):

- Risk factors
  - Surgical procedures
  - Prolonged hospitalization
  - Indwelling vascular and urinary catheterization
- Types of infections (mostly bacterial)
  - Surgical site
  - The abdominal cavity
Post Transplant work up

Early post-LT infections

• **Surgical infections** (wound infections, peritonitis) can lead to intra-abdominal infections

• Once **intra-abdominal infection** is suspected the diagnosis is based on radiographic imaging (CT scan or ultrasound) and cultures

• Treatment is based on combination of surgical debridement and empiric or targeted (culture based) antimicrobial therapy
Post Transplant work up

Intermediate period (2-12 months)

Risk factors

✓ Over-immunosuppression and allograft rejection,
✓ Repeated biliary tract manipulations

Type of infection

• Opportunistic pathogens (mostly)
✓ Herpes viruses (especially CMV, herpes zoster and simplex, and EBV),
✓ Fungi (including Aspergillus and Cryptococcus)
Post Transplant work up

- **CMV**
  - CMV remains the most significant opportunistic pathogen and produces diverse clinical manifestations and significant morbidity and mortality
  - The most common clinical syndromes include viremia, bone marrow suppression, and involvement of the gastrointestinal tract and liver

Razonable et al, Liver Transpl 2010
Post Transplant work up

CMV

Prophylaxis

High-risk recipients (donor-positive/recipient-negative) should receive prophylaxis with ganciclovir or valganciclovir for a minimum of 3 months after transplantation
Post Transplant work up

- **CMV** (Diagnosis)
  - Serology has no role in post-LT CMV disease
  - Cultures (blood and urine) are of limited utility for CMV disease management
  - CMV pp65 antigenemia (semi-quantitative test) and CMV viral load are acceptable options for diagnosis, preemptive therapy and monitoring response to therapy
Post Transplant work up

- **CMV** (treatment)
  - Recipients are symptomatic, have a tissue injury, or have persistent or increasing viremia.
  - Reduction of immunosuppression
  - Intravenous ganciclovir (5 mg/kg bid) or oral valganciclovir (900 mg bid) minimum 2 weeks
  - Treatment should be continued to complete the resolution of all symptoms and viremia
  - The optimal duration is uncertain

Lucey et al, Liver transpl. 2013
Post Transplant work up

- **Fungal Infections**
  - Risk factors:
    - Preoperative fungal colonization
    - Massive transfusion requirements
    - Choledochojejunostomy
    - Reoperation or retransplantation
    - Renal replacement therapy
    - Extended intervals of ICU immediately before LT

Eschenauer et al, Liver Transpl. 2009
Post Transplant work up

- **Fungal infections** (Diagnosis)
  - Blood cultures are most helpful for the diagnosis of Candida bloodstream infections
  - Aspergillus is especially difficult to diagnose with noninvasive testing. The sensitivity and specificity of galactomannan in either blood or BAL from LT recipients are variable
  - Cryptococcal antigen testing of CSF or blood is most helpful for the diagnosis of Cryptococcus
Post Transplant work up

- Fungal infections (treatment)
  - Candida
    - Fluconazoles (e.g., fluconazole, itraconazole, voriconazole)
    - Echinocandin (e.g., caspofungin, micafungin)
  - Aspergillus
    - Triazoles (voriconazole) is the drug of choice
Post Transplant work up

- **Late post-LT infections** (>6 months)
  - Minimal immunosuppression
  - Usual community acquired infections
    - FLU, LRTI, UTI
Conclusion

- Pre LT work up
  - Infectious disease screening, immunization and prophylactic antimicrobials
- Post LT work up
  - Early diagnosis and treatment of infections are crucial
  - The intensity of immunosuppression
  - Attention should be paid to potential drug interactions with antimicrobial therapies
THANK YOU