Management of Infections in Liver Transplantation Setting

Moataz Seyam
Prof. Hepatology and Gastroenterology
Theodor Bilharz Research Institute

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 Transplant work up

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, Pneumococcus, influenza and tetanus

EASL Clinical Practice Guidelines: Liver transplantation J Hepatol (2015)

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, Leishmania
- ✓ – 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

Sato et al, Liver Transpl. 2016

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 tarnspl.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 (eg.fluconazole, Itraconazole, voriconazole

Echinocandin (eg, 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