Antifungal Prophylaxis in Liver Transplant Recipients – Adult – Inpatient Clinical Practice Guideline

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Executive Summary

Guideline Overview
This document is intended to guide clinicians in the screening of liver transplant recipients to determine their risk for invasive fungal infections and initiating antifungal prophylaxis when appropriate.

Key Practice Recommendations
1. Liver transplant patients should be evaluated for risk of postoperative invasive fungal infection. (Class I, Level C)
2. Liver transplant patients at high risk of invasive fungal infection should receive antifungal prophylaxis with either fluconazole or micafungin. (Fluconazole Class I, Level B; Micafungin Class IIb, Level C)
3. Antifungal selection based on patient and microbiological factors may be reasonable. (Class IIb, Level C)

Companion Documents
- Liver Transplant Antifungal Prophylaxis Delegation Protocol [123]

Pertinent UW Health Policies & Procedures
None

Scope
Disease/Condition: Patients undergoing liver transplantation.

Clinical Specialty: Transplant, Pharmacy

Intended Users: Transplant surgeons, physicians, physician assistants, advanced practice nurse practitioners, pharmacists

CPG Objectives:
- To guide clinicians in identifying liver transplant recipients at high risk for invasive fungal infections based on recipient risk factors.
- Selection and initiation of antifungal prophylaxis when appropriate based on these risk factors.

Target Population: Adult patients who have received a liver transplant

Interventions and Practices Considered:
This guideline provides recommendations for the identification of liver transplant recipients at high risk of developing an invasive fungal infection. It also provides recommendations on the use, dosing, and duration of antifungal prophylaxis in patients at high risk for developing an invasive fungal infection after transplant.

Major Outcomes Considered:
- Rates of invasive fungal infections after transplant
- Rates of adverse effects with antifungal medications
- Antifungal resistance rates
Guideline Metrics:
- Identification of high-risk liver transplant recipients
- Initiation of antifungal prophylaxis in high-risk patients
- Incidence of invasive fungal infections after transplant

Methodology
1. PUBMED was searched using the terms antifungal prophylaxis AND liver transplant. References from identified articles were further evaluated. Internal expert opinion was also incorporated into guideline development in cases of a lack of evidence or conflicting evidence.
2. A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology Foundation has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline (Figure 1).
Definitions

- IFI: Invasive fungal infection

Introduction

Invasive fungal infections (IFIs) have been associated with increased mortality, length of hospital stay and overall cost. Liver transplant recipients are at high risk for IFIs because of the immunosuppression required and risk factors associated with surgery. In June 2013, the United Network of Organ Sharing (UNOS) instituted the Share 35 Regional Policy, which shares organs not only with local but regional candidates with MELD scores of 35 and higher. With the advent of this policy, UWHC providers have been transplanting patients with higher MELD scores more frequently. Although these patients generally have more risk factors for IFIs, IFI prophylaxis has been non-standardized. The aim of this guideline is to standardize the process for identifying high-risk patients and prescribing appropriate antifungal prophylaxis with the goals of reducing the incidence of IFIs after transplant and minimizing the use and consequences of long-term antifungal medications used to treat IFIs.

Recommendations

1. Screening for liver transplant recipients at high risk for invasive fungal infections
   1.1. It is recommended that high-risk patients be defined as those with any of the following risk factors: (Class I, Level B)
   - Operation time greater than 10 hours in duration
   - Any repeat operation within 30 days of transplant
   - Retransplantation
   - Dialysis requirement prior to transplant
   - High intra-operative transfusion requirement during transplant surgery
     - Greater than or equal to 40 units of cellular blood products (platelets, pRBCs, plasma, cryoprecipitate)
   - History of choledocho-jejunostomy
   - Candida colonization in the peri-operative period
     - One or more cultures positive for Candida within one month of prior to transplant
     - Active treatment for Candida infection at the time of transplant
   - Physiologic MELD equal to or greater than 35 (Class I, Level C)
   - Hospital admission seven days or longer prior to liver transplant (Class IIb, Level C)
   - ICU admission within seven prior to transplant (Class IIb, Level C)

2. Ordering of prophylaxis for high-risk liver transplant recipients
   2.1. All high-risk patients should receive antifungal prophylaxis post-transplant. (Class I, Level C)
   2.2. Fluconazole at a dose of 400 mg by mouth daily is recommended prophylaxis. (Class I, Level B)
     2.2.1. Fluconazole dose adjustment for renal dysfunction is not indicated due to low risk of toxicity and wide therapeutic index. (Class IIb, Level C)
     2.2.2. An alternative regimen is probably indicated for patients with prior isolation of a fluconazole-resistant Candida isolate. (Class IIb, Level C)
     2.2.3. An alternative regimen is probably indicated for patients who have received triazole treatment dosing (fluconazole 400 mg daily for at least seven days or equivalent) within the previous 90 days. (Class IIb, Level C)
     2.2.4. If micafungin is used for this indication, it should not be considered for outpatient antibiotic therapy (OPAT) if the patient has improved rapidly and is ready for discharge before fourteen days. (Class III, Level C)
   2.3. Fourteen days of prophylaxis duration of therapy may be reasonable. (Class IIb, Level C)
     2.3.1. Extension of antifungal prophylaxis beyond fourteen days may be considered if risk factors persist (e.g. ongoing biliary leak). (Class IIb, Level C)
2.3.2. If the patient is discharged from the transplant encounter prior to fourteen days of systemic prophylaxis, discontinuation of antifungal prophylaxis may be considered at discharge. (Class IIb, Level C)

2.4. While fluconazole resistance is rising in Candida species, the rate of fluconazole-resistant Candida albicans at UWHC is low (below 5%).\(^{20}\)

3. Alternative to fluconazole

3.1. The risk of hepatic injury is low with fluconazole, with approximately 1% of fluconazole-treated patients experiencing a significant elevation in serum transaminase levels in clinical trials. Hepatic metabolism is generally not clinically significantly altered until the patient has a Child Pugh Score of C. In a patient with a Child Pugh Score of C, micafungin can be recommended.\(^{9,11,14,20,21}\) (Class IIa, Level B).

3.2. In the case of a fluconazole allergy or intolerance, micafungin 100 mg IV daily is probably recommended.\(^{9,14,20}\) (Class IIa, Level B).

3.3. Liposomal amphotericin B has been studied for the prevention of IFIs after liver transplantation.\(^{22}\) Given alternatives with comparable outcomes and the higher risk of nephrotoxicity with liposomal amphotericin B, this agent is not currently preferred for routine use as antifungal prophylaxis in liver transplant recipients.\(^{17}\) (Class III, Level B).

UW Health Implementation

Potential Benefits:
The primary benefit of implementation of this guideline is the standardization of screening for patients at high risk for developing invasive fungal infections after liver transplant and ensuring that they receive antifungal prophylaxis.

Potential Harms:
The risk of implementing this guideline and administering antifungal prophylaxis is an increase in side effects such as nausea, vomiting and headache as well as a need for close monitoring of drug interactions with immunosuppressive medications.

Qualifying Statements
There is a lack of consensus regarding various risk factors for IFIs in liver transplant recipients and various levels of evidence; therefore, these guidelines are based on current evidence and local expert opinion. The recommendations included in this guideline are subject to change with publication of additional evidence.

Implementation Plan/Tools
1. Document will be housed on U-Connect on the Guideline webpage.
2. Education on this guideline will be distributed to liver transplant surgeons and clinical pharmacists through service line meetings
3. A pharmacist delegation protocol will be created
4. Reference links to the guideline will be added to fluconazole and micafungin medication records

Disclaimer
CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
References