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Committee Approvals/Dates:
Antimicrobial Use Subcommittee: December 2019
Pharmacy and Therapeutics Committee: December 2019
Introduction
Invasive fungal infections (IFIs) have been associated with increased mortality, length of hospital stay and overall cost. 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, UWCH 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.

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

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

Target Population: Adult patients who have received a liver transplant

Definitions
- IFI: Invasive fungal infection

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: (UW Health Strong Recommendation, Moderate Quality of Evidence)
   - 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-jejunalostomy
   - 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
     (UW Health Conditional Recommendation, Low Quality of Evidence)
   - Hospital admission seven days or longer prior to liver transplant
     (UW Health Conditional Recommendation, Low Quality of Evidence)
   - ICU admission within seven days prior to transplant
     (UW Health Conditional Recommendation, Low Quality of Evidence)
   - Receipt of a living donor liver transplantation
     (UW Health Conditional Recommendation, Very Low Quality of Evidence)
   1.2. A prospective observational trial found fluconazole prophylaxis was an independent risk factor for IFI. Analysis indicates that most of this effect was attributable to increased Aspergillus infections in patients receiving fluconazole instead of amphotericin or an echinocandin.
   1.2.1. A retrospective study evaluating the use of a fungal prophylaxis protocol utilizing static dosing of fluconazole (400 mg daily for 14 days) demonstrated significantly decreased risk of IFI after liver transplant without adversely altering fungal epidemiology and may have a positive impact on allograft and patient survival.
   1.3. Expert opinion from the American Society of Transplantation indicates that fluconazole remains the preferred prophylaxis agent of choice in most settings based on lower cost, ease of administration enterally, and continued efficacy.
   1.4. It is unclear if multiple risk factors are additive.
2. Patients who do not qualify as high risk should not receive antifungal prophylaxis to reduce unnecessary antifungal exposure.\(^4,12,20,22\) (UW Health Strong Recommendation, Moderate Quality of Evidence)

3. Ordering of prophylaxis for high-risk liver transplant recipients
   3.1. All high-risk patients should receive targeted antifungal prophylaxis post-transplant.\(^20\) (UW Health Strong Recommendation, Low Quality of Evidence)
   3.2. Fluconazole at a dose of 400 mg by mouth daily is recommended prophylaxis.\(^4,6,8,11,13,14,20,23,24\) (UW Health Strong Recommendation, Moderate Quality of Evidence)
   
   3.2.1. Fluconazole dose adjustment for renal dysfunction is not indicated due to low risk of toxicity and wide therapeutic index. (UW Health Conditional Recommendation, Low Quality of Evidence)
   
   3.2.2. An alternative regimen is probably indicated for patients with prior isolation of a fluconazole-resistant Candida isolate. (UW Health Conditional Recommendation, Low Quality of Evidence)
   
   3.2.3. 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. (UW Health Conditional Recommendation, Low Quality of Evidence)
   
   3.2.4. 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.\(^2,5,6,8,11,13-15,25,26\) (UW Health Strong Recommendation, Low Quality of Evidence)
   
   3.3. Fourteen days of prophylaxis duration of therapy may be reasonable. (UW Health Conditional Recommendation, Low Quality of Evidence)
   
   3.3.1. Extension of antifungal prophylaxis beyond fourteen days may be considered if risk factors persist (e.g. ongoing biliary leak). (UW Health Conditional Recommendation, Low Quality of Evidence)
   
   3.3.2. If the patient is discharged from the transplant encounter prior to fourteen days of systemic prophylaxis, fluconazole should be continued for the course entirety unless otherwise specified by the attending transplant surgeon. (UW Health Conditional Recommendation, Low Quality of Evidence)
   
   3.4. While fluconazole resistance is rising in Candida species, the rate of fluconazole-resistant Candida albicans at UWHC is low (below 5%).\(^25\)

4. Alternative to fluconazole
   4.1. 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.\(^8,10,13,25\) (UW Health Conditional Recommendation, Moderate Quality of Evidence)
   
   4.2. In the case of a fluconazole allergy or intolerance, micafungin 100 mg IV daily is recommended.\(^8,13,25\)
   
   Micafungin demonstrated non-inferiority to fluconazole in an open-label, randomized trial with respect to prevention of post-transplant IFI and occurrence of adverse events.\(^27\) (UW Health Conditional Recommendation, Moderate Quality of Evidence)
   
   4.3. Liposomal amphotericin B has been studied for the prevention of IFIs after liver transplantation.\(^22,28\) 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.\(^16\) (UW Health Strong Recommendation, Moderate Quality of Evidence)

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This 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.
Methodology
Developmental Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence
The following criteria were used by the guideline authors and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:
- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 1995 to 2019

Search Terms:
- “invasive fungal infection prophylaxis AND liver transplant”

Methods to Select the Evidence
Literature included for review were those in English language and of any study design, including review articles.

Methods Used to Formulate the Recommendation
The workgroup members created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Internally developed recommendations were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).
Figure 1. GRADE Methodology adapted by UW Health

Rating Scheme for the Strength of the Evidence/Recommendations:

<table>
<thead>
<tr>
<th>GRADE Rating of Evidence</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>GRADE Ratings for Recommendations For or Against Practice</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong (S)</td>
<td>Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)</td>
</tr>
<tr>
<td>Conditional (C)</td>
<td>May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)</td>
</tr>
</tbody>
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Cost Analysis: None performed

Recognition of Potential Health Care Disparities: None identified
Collateral Tools & Resources
The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics
• Identification of high-risk liver transplant recipients
• Initiation of antifungal prophylaxis in high-risk patients
• Incidence of invasive fungal infections after transplant

Protocols
• Liver Transplant Antifungal Prophylaxis Delegation Protocol [123]
References