FUNGAL GASTROINTESTINAL TRACT INFECTIONS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – December 2023

To the CHI Original Fungal Gastrointestinal Infections - Issued March 2020

Contents

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Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
BID	Twice Per Day
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
EACS	European AIDS Clinical Society
EMA	European Medicines Agency
FDA	Food and Drug Administration
GI	Gastrointestinal
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
IDF	CHI Drug Formulary
IDSA	Infectious Diseases Society of America
IU	International Unit
IV	Intravenous
MIC	Minimum Inhibitory Concentration
MSF	Médecins Sans Frontières (Doctors Without Borders)
N/A	Not Applicable or Not Available
NHS	National Health Service
OD	Every Day
OPC	Oropharyngeal Candidiasis
PE	Prescribing Edit
PO	Per Os (by mouth)
QD	Once Per Day
QDS	To Be Taken Four Times a Day
QID	Four Times a Day
RCT	Randomized Controlled Trial
SFDA	Saudi Food and Drug Authority

Executive Summary

Fungal gastrointestinal (GI) tract infections are a fungal (yeast) infection that can manifest in various parts of the GI tract, including the mouth and throat. These types of infections may arise due to yeast overgrowth in the gut, exposure to contaminated food and water, or as part of disseminated invasive fungal infections originating from other body sites. Signs and symptoms of gastrointestinal fungal infections include diarrhea, vomiting, melena, hemorrhage, abdominal pain, and fever, and are often similar regardless of the type of fungus involved[1].

Candida species are the most common culprits for mucosal infections, although instances of mold infections are on the rise. Diagnosing serious invasive mold infections poses challenges as symptoms often lack specificity[1].

Fungal GI tract infections may include Candida spp. infections (oral mild–moderate candidiasis, oral severe candidiasis, esophageal candidiasis, fluconazole-refractory candidiasis) and other fungal infections like Mucormycosis, Aspergillosis, Cryptococcosis, Histoplasmosis, Blastomycosis, and Coccidioidomycosis. Anti-fungal therapy is the mainstay of treatment of all these infections.[2].

Oropharyngeal candidiasis (oral candidiasis) is an alternative term for thrush affecting the mouth or throat. Individuals may experience the formation of white, elevated, cottage cheese-like lesions on the tongue and cheeks, leading to potential irritation, mouth pain, and redness[3].

The severity of the condition is contingent upon underlying risk factors, such as diabetes or immunosuppression, and can manifest as colonization, localized infection, fungemia, or evolve into aggressive and potentially life-threatening GI tract infections. Timely identification, immediate initiation of antifungal treatment, and, in some cases, surgical intervention is crucial for potentially life-saving outcomes[1].

This report will focus mainly on the superficial mucous membrane infection: oral candidiasis. The oral carriage of candida organisms is reported to be 30–45% in the general healthy adult population[4]. A study conducted in Saudi Arabia revealed that oral Candida was isolated from 73.1% in individuals chewing betel quid with tobacco, 72.4% in individuals chewing betel quid without tobacco and 61% of non-chewers[5].

Candida infections significantly increases the total hospital charges and cost of hospitalization ($6,000-29,000 and $3,000-22,000, respectively), and length of stay (3-13 days)[6].

CHI issued Fungal Gastrointestinal Infections clinical guidance after thorough review of renowned international and national clinical guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Fungal Gastrointestinal Infections clinical guidance and seeks to offer guidance for the effective management of Oral Candidiasis. It provides an **update on the Fungal Gastrointestinal Infections Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of new references that are added to the report** such as the Oral and oropharyngeal candidiasis - MSF medical guidelines **2023**, the Oropharyngeal and Esophagitis Candidiasis – EACS European AIDS Clinical Society **2023**, the Oral Candidiasis – NHS Lanarkshire **2021,** the Nottinghamshire Area Prescribing Committee Oral Candidiasis Guidelines **2023**, the Use and efficacy of mouthwashes in elderly patients: A systematic review of randomized clinical trials **2022**, and the Comparative Efficacy and Safety of Anti-fungal Agents in the Prophylaxis of Oropharyngeal Candidiasis among HIV-Infected Adults: A Systematic Review and Network Meta-Analysis **2022.**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that it is recommended to add **Isavuconazonium sulfate** to the CHI formulary. Moreover, there have been **no withdrawals** of drugs on the CHI formulary, for the management of Fungal Gastrointestinal Infections. However, there have been **updates** regarding certain previously mentioned drugs in terms of drug information and prescribing edits since March 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the therapeutic management of Oral Candidiasis.

Below is a table summarizing the major changes based on the different Oral Candidiasis treatment guidelines used to issue this report:

Table 1. General Recommendations for the Management of Oropharyngeal and Esophageal Candidiasis

Management of Oral Candidiasis		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
Candidiasis		
Treatment options for mild to moderate oral and oropharyngeal candidiasis includes Miconazole oral gel or Nystatin	Not graded	MSF medical guidelines 2023[7]

oral suspension. The same options apply for the prevention of oral candidiasis, which is recommended for HIV and immunosuppressed patients. An alternative treatment option could be amphotericin B oral suspension.		EACS Guidelines 2023[8] NHS Lanarkshire 2021[9]
A treatment option for moderate to severe oral candidiasis and esophageal candidiasis would be Fluconazole PO	Not graded	MSF medical guidelines 2023[7]
Topical azoles are more effective than topical nystatin. Fluconazole is indicated in extensive/severe candidiasis; if HIV or immunosuppression, use 100mg dose.	Not graded	NHS Lanarkshire 2021[9]
Treatment duration of oral candidiasis is 7 to 14 days and 14 to 21 days for oropharyngeal candidiasis	Not graded	MSF medical guidelines 2023[7] EACS Guidelines 2023[8]
Fluconazole PO is recommended as secondary prophylaxis for children and adults. This is indicated only for frequent and severe recurrences in HIV and immunocompromised patients.	Not graded	MSF medical guidelines 2023[7]
Treatment options for esophagitis include Fluconazole PO. Consider Posaconazole PO or Voriconazole PO or Caspofungin and other Echinocandins IV. Amphotericin B deoxycholate 0.3 to 0.7 mg/kg per day may also be used in patients with nonresponsive candida esophagitis (as a third line therapy to the above-mentioned medications), but it has serious medication side effects, and clinicians should avoid routine use. In cases of refractory disease, treat according to resistance testing.	Not graded	EACS Guidelines 2023[8] Diagnosis and Treatment of Esophageal Candidiasis 2019[10]
Itraconazole was found to be not effective in preventing the occurrence of OPC, while	Moderate recommendation	A Systematic Review and

fluconazole, on the other hand, was able to achieve a reduction in OPC episodes when compared to placebo. Fluconazole higher than itraconazole in terms of safety. Fluconazole has been known to be less likely to cause hepatotoxicity and to have better tolerability when compared to itraconazole.		Network Meta-Analysis 2022[10]
Fluconazole (50 mg daily, 100 mg daily, or 150 m weekly) is beneficial in the prevention of OPC in HIV-infected adults. However, the use of fluconazole as secondary prophylaxis should be weighed against the cost, possible drug–drug interactions, and drug resistance, which may arise from the routine use of fluconazole as secondary prophylaxis. It was also reported that there was a significantly lower rate of mycological relapse among those who received fluconazole prophylaxis.	Not graded	A Systematic Review and Network Meta-Analysis 2022[10]
Though many studies suggest 'HAART' to be effective in reducing the prevalence of opportunistic infections (including OPC), several other reports have shown that patients with poor compliance to these medications have thrice the risk of developing any opportunistic infection in comparison to those with good compliance, and hence, patient compliance to HAART can be considered as the chief determining factor regarding opportunistic infections.	Not graded	A Systematic Review and Network Meta-Analysis 2022[10]
Studies reported that weekly and daily doses of fluconazole as secondary prophylaxis did not have any significant impact on resistance, fluconazole as secondary prophylaxis does not increase the risk of developing resistant strains, and that OPC relapses were less compared to	Not graded	A Systematic Review and Network Meta-Analysis 2022[10]

placebo.		
Aspergillosis		
Voriconazole, Posaconazole, and Liposomal amphotericin B are treatment options for aspergillosis	Not graded	Fungal Infections of the Gastrointestinal Tract[2]
Isavuconazonium sulfate is an azole antifungal indicated for use in the treatment of invasive aspergillosis and invasive mucormycosis for patients 18 years of age and older.	Not graded	FDA 2015 approval[11]
Mucormycosis		
Liposomal amphotericin B, Isavuconazonium sulfate, and posaconazole are treatment options for Mucormycosis	Not graded	Fungal Infections of the Gastrointestinal Tract [2]
Cryptococcosis		
Liposomal amphotericin B + flucytosine, and Fluconazole are treatment options for Cryptococcosis	Not graded	Fungal Infections of the Gastrointestinal Tract [2]
Histoplasmosis and Blastomycosis		
Itraconazole and amphotericin B are treatment options for both Histoplasmosis and Blastomycosis.	Not graded	Fungal Infections of the Gastrointestinal Tract [2]
Coccidioidomycosis		
Itraconazole, Fluconazole, and Liposomal amphotericin B are treatment options for Coccidioidomycosis	Not graded	Fungal Infections of the Gastrointestinal Tract [2]
Terbinafine is the safest oral antifungal. Low-dose fluconazole (up to 150 mg) may be used; however, higher doses are not recommended. Itraconazole, ketoconazole, and griseofulvin may be best avoided due to lack of reliable human data. The potential	Not graded	Common Antifungal Drugs in Pregnancy: Risks and Precautions[12]

maternal complications with oral azoles are spontaneous abortions, and the reported fetal malformations include musculoskeletal, congenital heart anomalies, and eye defects. All topical agents can be safely used in pregnancy and are the preferred 1st line treatment in mild cases.		
All echinocandins have embryo toxic potential and should be used in pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.	Not graded	Lexicomp 2023[13] Echinocandins: A ray of hope in antifungal drug therapy[14]
Both oral stomatitis and angular cheilitis resulting from fungal infections are managed using the same treatment approach as oral candidiasis.	Not graded	Oral Stomatitis Cleveland Clinic 2021[15] Angular Cheilitis Cleveland Clinic 2021[16]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Fungal Gastrointestinal Infections clinical and therapeutic management.** Additionally, **appendices** are provided for treatment algorithms and further information on the topic.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Fungal Gastrointestinal Infections report, while the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the March 2020 CHI Fungal Gastrointestinal Infections Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1.1 **Infectious Diseases Society of America** (IDSA) Clinical Practice Guideline for the Management of Candidiasis (**2016**)	Not available

1.1.1 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Management of Candidiasis (2016)

*Please refer to **section 1.1 and 1.2** of the previous Fungal Gastrointestinal Infections CHI report for the recommendations published by IDSA for the management of both oropharyngeal and esophageal candidiasis.*

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Fungal Gastrointestinal Infections report, along with their recommendations.

Table 3. List of Additional References

Additional References
Medecins Sans Frontieres (MSF) Clinical Guidelines on Oral and Oropharyngeal Candidiasis (**2023**)
European AIDS Clinical Society (EACS) Oropharyngeal and Esophagitis Candidiasis (**2023**)
National Health Services (NHS) Lanarkshire Primary Care Guidance on Oral Candidiasis (**2021**)
National Health Services (NHS) Nottinghamshire Area Prescribing Committee Guideline on Oral Candidiasis (**2023**)
Comparative Efficacy and Safety of Anti-fungal Agents in the Prophylaxis of Oropharyngeal Candidiasis among HIV-Infected Adults: A Systematic Review and Network Meta-Analysis (*Life*, **2022**)
Review Article: Fungal Infections of the Gastrointestinal Tract (*Gastroenterol Clin N Am*, **2021**)

1.2.1 Médecins Sans Frontières (MSF) Clinical Guidelines on Oral and Oropharyngeal Candidiasis (2023)

The below non-graded recommendations are published by the MSF medical guidelines 2023 for the management of oral and oropharyngeal candidiasis[7]:

Treatment

- Nystatin oral suspension for 7 days
    - Children and adults: 400 000 IU daily, i.e. 1 ml of the oral suspension (100 000 IU) 4 times daily

  or

- Miconazole oral gel for 7 days
    - Children 6 months to 2 years: 1.25 ml 4 times daily
    - Children over 2 years and adults: 2.5 ml 4 times daily
- Apply the oral suspension of nystatin or the oral gel of miconazole between meals; keep in the mouth for 2 to 3 minutes, then swallow. In young children, apply to the tongue and inside of each cheek.

Prevention of opportunistic infections for patients with HIV

- Mild oral candidiasis
    - Nystatin PO:
        - Children and adults: 100 000 IU (= 1 ml) 4 times daily
    - Or Miconazole oral gel
        - Children 6 months-2 years: 1.25 ml 4 times daily
        - Children over 2 years and adults: 2.5 ml 4 times daily

➔ The treatment lasts 7 to 14 days.

- Moderate to severe oral candidiasis and esophageal candidiasis
    - Fluconazole PO
        - Children: 3 to 6 mg/kg once daily
        - Adults: 50 to 200 mg once daily up to 400 mg daily if necessary

➔ The treatment lasts 7 to 14 days for oral candidiasis and 14 to 21 days for esophageal candidiasis.

- Candidiasis is an indication for prophylaxis with co-trimoxazole.
- Fluconazole PO as secondary prophylaxis
    - Children: 3 to 6 mg/kg once daily
    - Adults: 100 to 200 mg once daily
- Only for frequent and severe recurrences

1.2.2 European AIDS Clinical Society (EACS) Oropharyngeal and Esophagitis Candidiasis (2023)

In October 2023, the EACS published clinical guidelines on the management of HIV/AID, which included a section on the management of oropharyngeal and esophagitis candidiasis[8]. Tables 4 and 5 summarize the recommended treatment regimens.

Table 4. Oropharyngeal Candidiasis Treatment Recommendations (EACS 2023 Guidelines)

Drug/dose	Comments
Fluconazole 150-200 mg qd po	Once or until improvement (5-7 days)
Nystatin 3-6 lozenges at 400000 units (approx. 4-6 mL of oral suspension)/day	7-14 days
OR **amphotericin B** oral suspension 1-2 g bid - qid	7-14 days

Table 5. Esophagitis Treatment Recommendations (EACS 2023 Guidelines)

Drug/dose	Comments
Fluconazole 400 mg qd po OR 400 mg loading dose, then 200 mg qd po	3 days 10-14 days
Consider **Posaconazole** 400 mg bid po OR **Voriconazole** 200 mg bid po OR **Caspofungin** as 70 mg iv on day 1, then 50 mg qd; other **echinocandins**	In cases of refractory disease, treat according to resistance testing. Adapt **posaconazole** and **voriconazole** dose according to MICs of candida and drug trough levels

➔ Micafungin dosing regimen[13]:

- Oropharyngeal, refractory disease (alternative agent) (off-label use):
    - Note: Reserve for fluconazole-refractory disease in patients who require IV therapy (eg, severe disease)
    - IV: 100 mg once daily. Transition to an oral antifungal once patient tolerates oral intake if susceptibility allows; total antifungal duration is 14 to 28 days
- Esophageal, refractory disease (alternative agent):

- Note: Reserve for fluconazole-refractory disease in patients who require IV therapy (eg, severe disease)
- IV: 150 mg once daily. Transition to an oral antifungal once patient tolerates oral intake if susceptibility allows; total antifungal duration is 14 to 28 days

➔ Anidulafungin dosing regimen[13]:

- Oropharyngeal, refractory disease (alternative therapy) (off-label use):
  - Note: Reserve for fluconazole-refractory disease in patients who require IV therapy (eg, severe disease)
  - IV: 200 mg on day 1, then 100 mg once daily. Transition to an oral antifungal once patient tolerates oral intake if susceptibility allows; total antifungal duration is 14 to 28 days
- Esophageal, refractory disease (alternative agent):
  - Note: Reserve for fluconazole-refractory disease in patients who require IV therapy (eg, severe disease)
  - IV: 200 mg once daily. Transition to an oral antifungal once patient tolerates oral intake if susceptibility allows; total antifungal duration is 14 to 28 days.

1.2.3 National Health Services (NHS) Lanarkshire Primary Care Guidance on Oral Candidiasis (2021)

Topical azoles are more effective than topical nystatin. Oral candidiasis is rare in immunocompetent adults; consider undiagnosed risk factors including HIV. Fluconazole is used if extensive/severe candidiasis. If HIV or immunosuppression, use 100mg dose. Table 6 summarized the recommended treatment regimens[9].

Table 6. Treatment Recommendations for Oral Candidiasis (NHS Lanarkshire, 2021)

Drug details	Dose	Duration
Miconazole **oral gel**	20mg/mL QDS	7 days or until 2 days after symptoms
If Miconazole not tolerated: Nystatin **suspension**	100,000 units/mL QDS	7 days or until 2 days after symptoms
Fluconazole **oral tablets**	50mg OD or 100mg OD	7 days further 7 days if persistent

1.2.4 National Health Services (NHS) Nottinghamshire Area Prescribing Committee Guideline on Oral Candidiasis (2023)

As part of the antimicrobial prescribing guidelines for primary care, NHS Nottinghamshire included a short guideline on the management of oral candidiasis. The main recommendations are summarized below[17]:

- Treatment - Children and adults:
    - If infection is mild and localized:
        - → Prescribe topical antifungal – topical azoles are more effective than topical nystatin.
    - If infection is extensive or severe consider:
        - → Prescribing oral fluconazole for a maximum of 14 days (>16 years) or seek specialist advice.
        - → For children, seek pediatrician specialist advice if inadequate response after 14 days of topical treatment.

Table 7. Oral and Topical Treatment Options for Oral Candidiasis (NHS Nottinghamshire Area Prescribing Committee, 2023)

Drug	Dosage	Duration	Comments
First Choice			
Miconazole oral gel 20mg/g (24mg/ml) **(Off label when used in children younger than 4 months)**	Neonate: 1ml two to four times a day Child 1-23 months: 1.25ml four times a day after meals Child 2-17 years: 2.5ml four times a day after meals Adult: 2.5ml four times a day after meals	Treatment should be continued for at least 7 days after the symptoms have cleared and for no longer than 14 days maximum.	Do not prescribe if taking a statin or withhold statin. Be aware of drug interaction with warfarin (MHRA) and sulphonylureas.
If first choice ineffective or contraindicated			
Nystatin oral suspension 100,00units/ml	Children and adults: 1 ml (100,000 units) four times a day.	7 days and continued for 48 hours after symptoms have resolved.	
For severe/extensive, unresponsive symptoms (after topical treatment has been tried			

Fluconazole	Adults > 16 years: 50mg once daily Immunocompromised: Adults >16 years: 50-100mg once daily	7–14 days (max. 14 days except in severely immunocompromised)	Not recommended in pregnancy

1.2.5 Comparative Efficacy and Safety of Anti-fungal Agents in the Prophylaxis of Oropharyngeal Candidiasis among HIV-Infected Adults: A Systematic Review and Network Meta-Analysis (*Life*, 2022)

This systematic review and network meta-analysis study aimed at comparing the efficacy and safety of antifungal agents used in the prevention of oropharyngeal candidiasis among HIV-infected adults[10]. The recommendations are outlined below:

- Oropharyngeal candidiasis (OPC) has been suggested as a valuable biomarker for HIV disease progression owing to antiretroviral therapy (HAART) failure as the prevalence of OPC directly correlates with the HIV viral load. Within the HIV population, the use of antifungal interventions often helps in reducing clinical symptoms, thereby delivering a transient clinical response by reducing the number of fungi in the affected area. However, complete eradication of the Candida spp. can be challenging, and as the HIV infection proceeds, the patients tend to experience more relapses and shorter disease-free intervals. Therefore, for HIV patients with frequent occurrences of OPC, secondary prophylaxis may be beneficial; however, there is concern regarding the issue of azole resistance secondary to long-term exposure to fluconazole
- The authors present a pooled data incorporating trials with fluconazole and itraconazole compared to placebo. On analysis, itraconazole was found to be not effective in preventing the occurrence of OPC, while fluconazole, on the other hand, was able to achieve a 55% relative risk reduction in OPC episodes when compared to placebo. The overall quality of evidence according to GRADE for this comparison was found to be moderate.
- Studies were also done to evaluate the efficacy of fluconazole in reducing the number of relapses of OPC:
    - The patients who received fluconazole prophylaxis had significantly had fewer relapses of OPC compared to those who did not receive it ($p < 0.01$), and there was no difference in terms of the number of relapses between the two doses of fluconazole (50 or 100 mg). Thus, the study suggested that low-dose fluconazole, 50 mg once a day, could prevent OPC recurrence and be beneficial to HIV-infected patients who are in the advance stages.

    - Another study evaluated the efficacy of fluconazole 100 mg daily and the results reported no cases of OPC relapse in the arm that received fluconazole as compared to placebo (sample size was small)
    - Weekly fluconazole dosing regimens have been studied to see whether they may be beneficial as secondary prophylaxis for OPC. According to a mentioned study that evaluated the benefits of fluconazole at a dose of 150 mg weekly compared to placebo, the authors reported that the majority of those in the weekly fluconazole arm were free of OPC relapse for the study duration of 24 weeks, while all the patients in the placebo group had relapsed. The study also reported that there was a significantly lower rate of mycological relapse among those who received fluconazole prophylaxis compared to those in the placebo group ($p = 0.004$)
- In a trial, where the time to the primary endpoint, defined as the third OPC relapse, it was shown that it was significantly longer among patients who received weekly fluconazole prophylaxis compared to that in those who received placebo ($p = <0.0001$)
- Guidelines have not recommended any primary and secondary prophylaxis for mucosal candidiasis; however, studies have suggested that appropriate antiretroviral therapy can prevent the occurrence of OPC as well. Further studies are needed.
- A concern of whether to prescribe antifungals for prophylaxis could be the emergence of azole resistance. Studies analyzed the development of resistance to fluconazole among patients and reported that weekly and daily doses of fluconazole as secondary prophylaxis did not have any significant impact on resistance, fluconazole as secondary prophylaxis does not increase the risk of developing resistant strains, and that OPC relapses were less compared to placebo.
- Evidence with regards to azole resistance in the literature is conflicting as two studies linked the presence of azole-resistant strains of C. albicans among HIV patients with low CD4 cell count with prolonged prior exposure to fluconazole, while other RCTs have shown no significant differences in terms of the emergence of azole resistance when fluconazole was given continuously as prophylaxis as compared to intermittent dosing.
- The analysis for the safety profile of antifungal agents used in preventing OPC in this study ranked fluconazole higher than itraconazole. Fluconazole has been known to be less likely to cause hepatotoxicity and to have better tolerability when compared to itraconazole.

- Limitations in the literature include no new studies are available in the literature with newer drugs such as posaconazole and echinocandins, which are reported to have a better safety profile than the older antifungal agents.
- Though many studies suggest 'HAART' to be effective in reducing the prevalence of opportunistic infections (including OPC), several other reports have shown that patients with poor compliance to these medications have thrice the risk of developing any opportunistic infection in comparison to those with good compliance, and hence, patient compliance to HAART can be considered as the chief determining factor regarding opportunistic infections.
- There was also a lack of RCTs examining OPC prevention in children, hence, the results of this study were confined to HIV-infected adults.
- The findings from this network meta-analyses show that fluconazole is beneficial in the prevention of OPC in HIV-infected adults. However, the use of fluconazole as secondary prophylaxis should be weighed against the cost, possible drug–drug interactions, and drug resistance, which may arise from the routine use of fluconazole as secondary prophylaxis.
- Further studies should be conducted to identify the optimal parameters for the use of antifungals for the prevention of OPC. High-quality trials are needed to compare fluconazole with relevant new comparators' prevention as well as other outcomes, including adverse effects and quality of life.
- Future work should also focus on the cost-effectiveness of use of antifungals for the prevention of OPC.

1.2.6 Review Article: Fungal Infections of the Gastrointestinal Tract (*Gastroenterol Clin N Am*, 2021)

This article published by Chao and Vazquez in 2021 provides a comprehensive review on the various types of fungal GI tract infections, their risk factors, as well as treatment options. Findings are summarized in tables 8 and 9[2].

Table 8. Fungal Infections of the Gastrointestinal Tract and Risk Factors

Disease state	Risk factors
Candidiasis	Antimicrobial therapy Age Radiation therapy Corticosteroids Neutropenia HIV/AIDS

	Immunosuppressive therapy Chronic mucocutaneous candidiasis
Zygomycosis	Neutropenia Malnutrition Diabetes Acidosis Corticosteroids Malignancy Solid organ and stem cell transplants
Aspergillosis	Neutropenia HIV/AIDS Chronic liver disease Immunosuppressive therapy Solid organ and stem cell transplants
Histoplasmosis	Residing in endemic area HIV/AIDS Tumor necrosis factor blockers
Blastomycosis	Residing in endemic area HIV/AIDS
Coccidioidomycosis	Residing in endemic area HIV/AIDS Age >50 Immunosuppressive therapy Tumor necrosis factor blockers

Table 9. Gastrointestinal Infections and Appropriate Antifungal Therapy

Disease State	Antifungal Therapy	Dosing regimen[13]
Candidiasis		
Oral mild–moderate	Nystatin Clotrimazole troches Miconazole mucoadhesive tablets Fluconazole tablets	Please refer to above references
Oral severe	Fluconazole Itraconazole	Please refer to above references

	Posaconazole	
Esophageal candidiasis	Fluconazole Itraconazole Voriconazole Posaconazole	Please refer to above references
Fluconazole-refractory candidiasis	Posaconazole Caspofungin Micafungin Anidulafungin Amphotericin B deoxycholate Liposomal amphotericin B	Please refer to above references
Mucormycosis	Liposomal amphotericin B	IV: 5 to 10 mg/kg once daily. Note: 10 mg/kg once daily recommended for patients with CNS disease or solid organ transplant recipients. Treatment duration is typically weeks to months depending on response and host immunosuppression
	Isavuconazonium sulfate	IV, Oral: Initial: 372 mg (isavuconazole 200 mg) every 8 hours for 6 doses; Maintenance: 372 mg (isavuconazole 200 mg) once daily. Start maintenance dose 12 to 24 hours after the last loading dose.
	Posaconazole	Mucormycosis, salvage and step-down therapy (off-label use): Note: For use after amphotericin B. Prompt surgical debridement is often needed to achieve clinical cure. Oral: Note: Tablet preferred to IR suspension; some experts do not use IR suspension for mucormycosis because of

		suboptimal bioavailability. Delayed-release tablet: 300 mg twice daily for 2 doses, then 300 mg once daily. IR suspension: 200 mg 4 times daily or 400 mg twice daily. IV: 300 mg twice daily for 2 doses, then 300 mg once daily. Duration: Varies based on clinical and radiologic response and patient immune status; several months are often warranted, with some patients requiring lifelong therapy.
Aspergillosis	Voriconazole	Duration: ≥6 months; some patients require prolonged, potentially lifelong therapy. Invasive (including disseminated and extrapulmonary): Note: For severe or progressive infection, some experts use as part of a combination antifungal regimen. IV: 6 mg/kg twice daily for 2 doses, then 4 mg/kg twice daily. Note: Once a patient is able to tolerate oral administration, consider transition to oral formulation. Oral: 200 to 300 mg twice daily or weight-based dosing (3 to 4 mg/kg twice daily). Duration: Minimum of 6 to 12 weeks, depending on degree/duration of

		immunosuppression, disease site, and response to therapy; immunosuppressed patients may require more prolonged treatment
	Isavuconazonium sulfate	IV, Oral: Initial: 372 mg (isavuconazole 200 mg) every 8 hours for 6 doses; Maintenance: 372 mg (isavuconazole 200 mg) once daily. Start maintenance dose 12 to 24 hours after the last loading dose. Duration of therapy: Minimum of 6 to 12 weeks, although duration is highly dependent on degree/duration of immunosuppression, disease site, and evidence of disease improvement
	Posaconazole	Chronic cavitary pulmonary (alternative agent): Oral: Note: Some experts prefer the tablet over the IR suspension. Delayed-release tablet: 300 mg twice daily for 2 doses, then 300 mg once daily. IR suspension (off-label use): 200 mg 3 times daily or 400 mg twice daily. IV: 300 mg twice daily for 2 doses, then 300 mg once daily. Note: Some experts reserve IV therapy for severely ill patients. Duration: ≥6 months; some patients require prolonged, potentially lifelong therapy.

		Invasive (including disseminated and extrapulmonary) (alternative agent for patients who are refractory to or intolerant of first-line agents): Oral: Note: Tablet preferred to IR suspension. Delayed-release tablet: 300 mg twice daily for 2 doses, then 300 mg once daily. IR suspension (off-label use): 200 mg 3 times daily or 200 mg 4 times daily during hospitalization, then 400 mg twice daily as an outpatient. IV: 300 mg twice daily for 2 doses, then 300 mg once daily. Duration: Minimum of 6 to 12 weeks; total duration depends on degree/duration of immunosuppression, disease site, and response to therapy; immunosuppressed patients may require more prolonged treatment.
	Liposomal amphotericin B	IV: 3 to 5 mg/kg once daily; doses up to 7.5 mg/kg once daily have been recommended for CNS infection. Minimum duration of treatment is 6 to 12 weeks and depends on site of infection, extent of disease and level/duration of immunosuppression. Note: Guidelines recommend amphotericin B lipid formulations be considered for invasive aspergillosis only

		when triazoles, specifically voriconazole, are contraindicated or not tolerated.
Cryptococcosis	Liposomal amphotericin B + flucytosine	**Liposomal amphotericin B:** Induction therapy: IV: 3 to 4 mg/kg once daily with flucytosine (preferred) or fluconazole, or without a concomitant agent, for 2 weeks, followed by consolidation and maintenance therapy with fluconazole **Flucytosine:** Cryptococcal meningitis, disseminated disease, or severe pulmonary infection: Note: Where available, IV formulation may be used in place of oral therapy. Oral: Induction: 25 mg/kg/dose 4 times daily, as part of an appropriate combination regimen. Duration of induction therapy is ≥2 weeks, but should be extended in patients with evidence of neurological complications; for cerebral cryptococcomas, recommended duration is ≥6 weeks. Induction therapy is followed by consolidation and maintenance therapy with fluconazole
	Fluconazole	**Cryptococcosis, pulmonary infection (off-label use):** Mild to moderate symptoms (if severe pneumonia, treat

		like CNS infection): Immunocompetent or immunocompromised patients without diffuse pulmonary infiltrates or disseminated infection: Oral: 400 mg once daily for 6 to 12 months; for patients with HIV, some experts recommend 400 to 800 mg once daily for 10 weeks, followed by 200 mg once daily for a total of 6 months in combination with effective antiretroviral therapy). Chronic suppressive therapy may be warranted for patients with ongoing immunosuppression
Histoplasmosis	Itraconazole	Treatment: Note: Oral itraconazole may be used as initial therapy for mild to moderate disease or step-down therapy after amphotericin B for more severe infection: IV [International product]: 200 mg twice daily for 2 days, then 200 mg daily for up to 12 days. Consider oral maintenance therapy for the remainder of the regimen. Oral: Solution or capsule (100 mg): Loading dose: 200 mg 3 times daily for 3 days. Maintenance dose: Mild to moderate disease in immunocompetent patients: 200 mg once to twice daily; some experts favor 200 mg

		twice daily. Moderately severe to severe or disseminated disease and immunocompromised patients: 200 mg twice daily. CNS infection: 200 mg 2 to 3 times daily; some experts favor 200 mg 3 times daily for patients with HIV and CNS infection. Capsule (65 mg): 130 mg once daily; if no improvement or if there is evidence of progressive fungal infection, increase dose in 65 mg increments to a maximum of 260 mg/day (doses >130 mg/day should be given in 2 divided doses). May give a loading dose of 130 mg 3 times daily for the first 3 days of therapy. Capsule (50 mg [International product]): 100 mg once or twice daily. Duration: 6 to 12 weeks for mild to moderate pulmonary infection and ≥12 weeks for moderately severe to severe pulmonary infection; ≥12 months for immunocompromised patients and/or patients with CNS, chronic cavitary pulmonary, or disseminated infection. Long-term suppression therapy (secondary prophylaxis) in select immunocompromised patients: Solution or capsule

		(100 mg): 200 mg once to twice daily. Prophylaxis, primary prophylaxis in patients with HIV (off-label use): Note: Not routinely given; some experts recommend primary prophylaxis in patients with CD4 count <150 cells/mm3 and increased risk due to occupational exposure or residence in a hyperendemic area. Oral: Solution or capsule (100 mg): 200 mg once daily.
	Liposomal amphotericin B	Acute pulmonary disease, moderately severe to severe: Induction therapy: IV: 3 to 5 mg/kg once daily for 1 to 2 weeks, followed by itraconazole maintenance therapy. Disseminated disease, moderately severe to severe: Induction therapy: IV: 3 mg/kg once daily for 1 to 2 weeks (patients without HIV) or at least 2 weeks (patients with HIV), followed by itraconazole maintenance therapy.
Blastomycosis	Itraconazole	Note: For initial treatment of mild to moderate disease or step-down therapy after amphotericin B for more severe infection: Oral: Solution or capsule (100 mg): Loading dose: 200 mg 3 times daily for 3 days.

		Maintenance dose: Mild to moderate disease in immunocompetent patients: 200 mg once to twice daily. Moderately severe to severe disease and immunocompromised patients: 200 mg twice daily. CNS infection (alternative agent): 200 mg 2 to 3 times daily. Capsule (65 mg): 130 mg once daily; if no improvement or if there is evidence of progressive fungal infection, increase dose in 65 mg increments to a maximum of 260 mg/day (doses >130 mg/day should be given in 2 divided doses). May give a loading dose of 130 mg 3 times daily for the first 3 days of therapy. Duration: 6 to 12 months; ≥12 months is recommended for patients with moderately severe to severe disseminated infection, osteoarticular or CNS infection, and for all immunocompromised patients
	Liposomal amphotericin B	7.5 mg/kg/day is appropriate for patients with pulmonary blastomycosis who are receiving extracorporeal membrane oxygenation.[18]
Coccidioidomycosis	Itraconazole	Soft tissue infection (not associated with bone infection): Oral: Solution or

		capsule (100 mg): 200 mg twice daily for at least 6 to 12 months
	Fluconazole	Soft tissue infection (not associated with bone infection) TREATMENT: Oral: 400 mg once daily; some experts give up to 800 mg once daily; duration is for ≥6 to 12 months
	Liposomal amphotericin B	Coccidioidomycosis in patients with HIV (off-label use): Non-CNS infection, severe (ie, diffuse pulmonary or severely ill with extrathoracic, disseminated disease): IV: 3 to 5 mg/kg once daily until clinical improvement, then initiate triazole therapy (eg, fluconazole or itraconazole).

Section 2.0 Drug Therapy

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

2.1.1 Isavuconazole (Isavuconazonium Sulfate)

In 2015, the FDA granted approval for isavuconazole for the management of patients 18 years of age and older with invasive aspergillosis and invasive mucormycosis[11]. Approval was based on results from two phase III clinical trials known as SECURE and VITAL.

In the SECURE study, 516 patients with invasive aspergillosis or other filamentous fungi were enrolled. The randomised, double-blind, active-control study evaluated the overall safety profile of isavuconazole in comparison with voriconazole, another triazole antifungal drug. Patients treated with isavuconazole demonstrated non-inferiority to voriconazole on the primary endpoint of all-cause mortality at day 42. The all-cause mortality reported in the isavuconazole treatment group was 18.6%, while it was 20.2% in the voriconazole treatment group. Adverse events found in the isavuconazole -administered patients during the clinical study included nausea, vomiting, diarrhea, headache, elevated liver chemistry tests and hypokalemia. Some patients also reported constipation, dyspnea, cough, peripheral oedema, and back pain[19].

The VITAL study was an open-label non-comparative study intended to evaluate the safety and efficacy profile of isavuconazole in patients with invasive mucormycosis. It enrolled a subpopulation of 37 patients with invasive mucormycosis. Results of the trial demonstrated that all-cause mortality in patients treated with isavuconazole was 38%. The efficacy of the drug for the treatment of invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials[20].

It is recommended as capsules for oral use or injection for intravenous use.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Table 10 below details drug information related to isavuconazole[13].

Table 10. Isavuconazole Drug Information

SCIENTIFIC NAME Isavuconazole	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Indicated in adults for whom amphotericin B is inappropriate.
MHRA	Yes
PMDA	Yes, approved for Cryptococcosis (pulmonary cryptococcosis, disseminated cryptococcosis [including cryptococcal meningitis]), as well.
Indication (ICD-10)	Invasive Aspergillosis (B44. 0) and Mucormycosis (B46. 5)
Drug Class	Antifungal
Drug Sub-class	Azole derivative
ATC Code	J02AC
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion and Capsule, hard
Route of Administration	IV Use, oral use
Dose (Adult) [DDD]	**Aspergillosis and Mucormycosis, invasive:** IV, Oral: Initial: 372 mg (isavuconazole 200 mg) every 8 hours for 6 doses; Maintenance: 372 mg (isavuconazole 200 mg) once daily. Start maintenance dose 12 to 24 hours after the last loading dose. Duration of therapy: Minimum of 6 to 12 weeks, although duration is highly dependent on degree/duration of immunosuppression, disease site, and evidence of disease improvement.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	**Aspergillosis, invasive:** Adolescents ≥18 years: IV, Oral: Initial

	(loading doses): 372 mg isavuconazonium sulfate every 8 hours for 6 doses; maintenance (begin 12 to 24 hours after last loading dose): 372 mg isavuconazonium sulfate every 24 hours. Minimum duration is 6 to 12 weeks; duration should be individualized depending on degree and duration of immunosuppression, disease site, and evidence of improvement. **Mucormycosis, invasive (salvage treatment):** Adolescents ≥13 years weighing ≥40 kg: Limited data available in ages <18 years: IV, Oral: Initial (loading doses): 372 mg isavuconazonium sulfate every 8 hours for 6 doses; maintenance (begin 12 to 24 hours after last loading dose): 372 mg isavuconazonium sulfate every 24 hours. Treatment duration is highly individualized depending on degree and duration of immunosuppression, disease site, clinical resolution, and improvement on imaging studies; typically weeks to months or longer.
Maximum Daily Dose Pediatrics	Children and Adolescents <18 years: Very limited data available. Maximum dose: 372 mg isavuconazonium sulfate per loading and maintenance dose
Adjustment	**Older Adult** Refer to adult dosing. **Altered Kidney Function: Adult and pediatric** The renal dosing recommendations are based upon the best available evidence and clinical expertise. No dosage adjustment is necessary for any degree of kidney dysfunction. **Hepatic Impairment: Adult and pediatric**

	Mild or moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary. Severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.
Prescribing edits*	MD, PA, PE, AGE, QL
AGE (Age Edit):	It is approved for patients 18 years of age and older
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Isavuconazonium sulfate treatment should only be initiated by an infectious disease specialist
PA (Prior Authorization):	Isavuconazonium sulfate is indicated for patients 18 years of age and older with invasive aspergillosis and invasive mucormycosis. It is recommended as capsules for oral use or injection for intravenous use. Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly. It has a specific dosage regimen: IV, Oral: Initial: 372 mg (isavuconazole 200 mg) every 8 hours for 6 doses; Maintenance: 372 mg (isavuconazole 200 mg) once daily. Start maintenance dose 12 to 24 hours after the last loading dose. Duration of therapy: Minimum of 6 to 12 weeks, although duration is highly

	dependent on degree/duration of immunosuppression, disease site, and evidence of disease improvement. This drug is recommended to be prescribed by an infectious disease specialist.
QL (Quantity Limit):	Children and Adolescents <18 years: Very limited data available. Maximum dose: 372 mg isavuconazonium sulfate per loading and maintenance dose
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	It has a specific dosage regimen for adults and pediatric population as described above.
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common (frequency: >10%)** >10%: **Cardiovascular**: Peripheral edema (15%) **Endocrine & metabolic**: Hypokalemia (19%) **Gastrointestinal**: Abdominal pain (17%), constipation (14%), diarrhea (24%), nausea (28%), vomiting (25%) **Hepatic**: Increased liver enzymes (17%) **Nervous system**: Fatigue (11%), headache (17%), insomnia (11%) **Respiratory**: Dyspnea (17%)
Drug Interactions	**Category X** interactions: - Aprepitant - Asunaprevir - Bilastine - Bosutinib - Budesonide (Topical) - CYP3A4 Inducers (Strong) - CYP3A4 Inhibitors (Strong) - Dofetilide - Domperidone - DOXOrubicin (Conventional)

	- Elacestrant - Eletriptan - Flibanserin - Fosaprepitant - Fusidic Acid (Systemic) - Infigratinib - Itraconazole - Ivabradine - Lemborexant - Lomitapide - Lonafarnib - Methysergide - Mizolastine - Neratinib - Nisoldipine - Orelabrutinib - Pacritinib - PAZOPanib - Pimozide - Saccharomyces boulardii - Sertindole - Simeprevir - Sirolimus (Protein Bound) - St John's Wort - Topotecan - VinCRIStine (Liposomal)
Special Population	N/A
Pregnancy	Evaluate pregnancy status prior to use; patients who could become pregnant should use effective contraception during therapy and for 28 days after the last isavuconazonium sulfate dose. Based on data from animal reproduction studies, in utero exposure to isavuconazonium sulfate may cause fetal harm.
Lactation	It is not known if isavuconazonium sulfate is present breast milk. The manufacturer recommends

	breastfeeding be discontinued during maternal isavuconazonium sulfate therapy.
Contraindications	Hypersensitivity to isavuconazonium sulfate (e.g., isavuconazole) or any component of the formulation; concurrent use of strong CYP3A4 inhibitors (e.g., ketoconazole, high-dose ritonavir [400 mg every 12 hours]); concurrent use of strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's wort, long-acting barbiturates); familial short QT syndrome. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Canadian labeling: Additional contraindications (not in US labeling): Concurrent use of moderate CYP3A4/5 inducers (e.g., efavirenz, etravirine)
Monitoring Requirements	Hypersensitivity reactions with initial doses, LFTs (e.g. AST, ALT, alkaline phosphatase, total bilirubin) at baseline and periodically during therapy. Infusion-related reactions (e.g. hypotension, dyspnea, chills, dizziness, paresthesias, hypoesthesia) during IV infusion. Routine therapeutic drug monitoring is not recommended; consider assessing serum drug concentrations if there is concern for toxicity, therapeutic failure, or possibility of impaired drug absorption
Precautions	**Hepatic effects**: Severe reactions (hepatic failure [including fatalities], hepatitis, and cholestasis) have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy). Other reactions (elevations in AST, ALT, alkaline phosphatase, and total bilirubin) have

	also been reported; these elevations are generally reversible and do not require discontinuation of therapy. Monitor liver function tests at baseline and periodically during therapy. If abnormal liver function tests develop, monitor closely for development of severe hepatic reactions. Discontinue therapy if clinical signs and symptoms of liver disease develop. **Hypersensitivity**: Anaphylactic reactions, with fatal outcome, have been reported with isavuconazonium sulfate. Discontinue isavuconazonium sulfate if a patient experiences an anaphylactic reaction. Serious hypersensitivity (eg, anaphylaxis) and severe skin reactions (e.g., Stevens-Johnson syndrome) have been reported with other azole antifungal agents. Discontinue if a severe skin reaction occurs. There is no information regarding cross-sensitivity between isavuconazonium sulfate and other azoles. Use with caution in patients with hypersensitivity reactions to other azoles. **Disease-related concerns**: Hepatic impairment: Use with caution and monitor for adverse effects in patients with severe hepatic impairment (Child-Pugh class C). **Dosage form specific issues**: **Drug particulates**: Following dilution for IV infusion, may form precipitate from the insoluble isavuconazole. Use an infusion set with an in-line filter (pore size 0.2 to 1.2 micron) for IV administration. **Infusion-related reactions**: Infusion reactions (e.g., hypotension, dizziness, chills, dyspnea, paresthesia, and

	hypoesthesia) have been reported during IV administration. Discontinue the infusion if these reactions occur.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of fungal infections treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for isavuconazole.**

Table 11. Isavuconazole HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Isavuconazole	NICE	N/A
	CADTH[21]	**October 4, 2018** **Reimburse with clinical criteria and/or conditions.** The model submitted by the manufacturer had several limitations and data-related uncertainties, some of which could be addressed by CADTH. In the CADTH base case, the ICUR for isavuconazole compared with voriconazole is likely to be significantly higher ($73,036 per QALY) than estimated by the manufacturer ($10,154 per QALY). Isavuconazole is not cost-effective compared with voriconazole at a willingness to pay of $50,000 per QALY, unless the price of isavuconazole is reduced by at least 20%. CADTH could not address some of the limitations identified, such as the quality of the evidence in the IM population and non-inclusion of surgical management in the treatment pathway; these limitations should be taken into consideration in the interpretation of the results.
	HAS[22]	**March 2016** **Favorable opinion** Isavuconazonium sulfate is an alternative to the first-line therapeutic options in the treatment of invasive

		aspergillosis, especially in patients with renal failure. It is a second-line therapeutic option in patients who cannot receive amphotericin B (refractory, intolerant or with a contraindication) in the treatment of mucormycosis. The actual benefit of this drug is substantial. This drug provides no clinical added value in the management of invasive aspergillosis and mucormycosis. Recommends inclusion on the list of reimbursable products for hospital use.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Isavuconazonium sulfate

Isavuconazonium sulfate is indicated for patients 18 years of age and older with invasive aspergillosis and invasive mucormycosis. It is recommended as capsules for oral use or injection for intravenous use.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly. It has a specific dosage regimen: IV, Oral: Initial: 372 mg (isavuconazole 200 mg) every 8 hours for 6 doses; Maintenance: 372 mg (isavuconazole 200 mg) once daily. Start maintenance dose 12 to 24 hours after the last loading dose. Duration of therapy: Minimum of 6 to 12 weeks, although duration is highly dependent on degree/duration of immunosuppression, disease site, and evidence of disease improvement. This drug is recommended to be prescribed by an infectious disease specialist. The drug has a positive recommendation from HTA bodies including CADTH and HAS.

Limitations for the use of Isavuconazonium sulfate include hepatic effects and infusion-related effects.

2.2 Modifications

Below are the modifications made to the list of Oral Candidiasis drugs since the CHI report in March 2020, reflecting the changes and updates:

Table 12. Prescribing Edits (PE) Modifications of Oral Candidiasis Drugs

Drugs	PE modifications
Amphotericin B	**ST**: Amphotericin B deoxycholate 0.3 to 0.7 mg/kg per day may also be used in patients with nonresponsive candida esophagitis (as a third line therapy to azoles and echinocandins), but it has serious medication side effects, and clinicians should avoid routine use. **MD:** This drug should be prescribed by an infectious disease specialist
Anidulafungin	**ST:** intravenous echinocandin caspofungin, micafungin or anidulafungin can be used only as second line therapy when the fungal infection was resistant to fluconazole oral or iv. **AGE:** Treatment of candidemia and other forms of Candida infections (intra-abdominal abscess and peritonitis) in adults and pediatric patients ≥ 1 month of age. **MD:** This drug should be prescribed by an infectious disease specialist
Fluconazole	**PA was removed** **ST:** fluconazole is recommended PO for moderate to severe cases. fluconazole parenteral is used for patients who cannot tolerate oral therapy
Miconazole oral gel	**ST:** recommended as first line agent for mild to moderate oropharyngeal candidiasis
Nystatin	**ST:** Nystatin oral suspension is another option for mild to moderate cases of oropharyngeal candidiasis (along with miconazole oral gel)
Voriconazole	**PA was removed** **ST:** voriconazole is used after trying fluconazole if not effective or the patient cannot tolerate fluconazole **MD:** This drug should be prescribed by an infectious disease specialist
Caspofungin	**MD:** This drug should be prescribed by an infectious disease specialist
Micafungin	**MD:** This drug should be prescribed by an infectious disease specialist

2.3 Delisting

No drugs for the management of fungal gastrointestinal tract infections have been delisted from the drug summary spreadsheet.

Section 3.0 Key Recommendations Synthesis

- Treatment and prevention options for mild to moderate oral and oropharyngeal candidiasis includes Miconazole oral gel or Nystatin oral suspension. An alternative treatment option could be amphotericin B oral suspension[7–9].
- A treatment option for moderate to severe oral candidiasis and esophageal candidiasis would be Fluconazole PO[7].
- Topical azoles more effective than topical nystatin[9].
- Fluconazole if extensive/severe candidiasis; if HIV or immunosuppression use 100mg[9].
- Treatment duration of oral candidiasis is 7 to 14 days and 14 to 21 days for and oropharyngeal[7,8].
- Fluconazole PO is recommended as secondary prophylaxis for children and adults. This is indicated only for frequent and severe recurrences[7].
- Treatment options for esophagitis include Fluconazole PO[8].
    - Consider Posaconazole PO or Voriconazole PO or Caspofungin and other Echinocandins IV.
    - In cases of refractory disease, treat according to resistance testing.
- Mouthwashes options for denture stomatitis include Chlorhexidine-based or Nystatin or other antifungal mouthwashes or garlic extract rinse. AmF–SnF2 rinse and toothpaste are also options[23].
- Itraconazole was found to be not effective in preventing the occurrence of OPC, while fluconazole, on the other hand, was able to achieve a reduction in OPC episodes when compared to placebo[10].
- Fluconazole higher than itraconazole in terms of safety. Fluconazole has been known to be less likely to cause hepatotoxicity and to have better tolerability when compared to itraconazole[10].
- Fluconazole (50 mg daily, 100 mg daily, or 150 m weekly) is beneficial in the prevention of OPC in HIV-infected adults. However, the use of fluconazole as secondary prophylaxis should be weighed against the cost, possible drug–drug interactions, and drug resistance, which may arise from the routine use of fluconazole as secondary prophylaxis[10].
- It was also reported that there was a significantly lower rate of mycological relapse among those who received fluconazole prophylaxis[10].

- Though many studies suggest 'HAART' to be effective in reducing the prevalence of opportunistic infections (including OPC), several other reports have shown that patients with poor compliance to these medications have thrice the risk of developing any opportunistic infection in comparison to those with good compliance, and hence, patient compliance to HAART can be considered as the chief determining factor regarding opportunistic infections[10].
- Studies reported that weekly and daily doses of fluconazole as secondary prophylaxis did not have any significant impact on resistance, fluconazole as secondary prophylaxis does not increase the risk of developing resistant strains, and that OPC relapses were less compared to placebo[10].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Fungal Gastrointestinal Infections report** and aims to provide recommendations to aid in the management of Oral Candidiasis. These recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Oral Candidiasis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Fungal Gastrointestinal Infections Scope

Fungal Gastrointestinal Infections Scope

Section	Rationale/Updates
Section 1.1.1 **Oral and oropharyngeal candidiasis - MSF medical guidelines 2023**[7]	Treatment: • Nystatin oral suspension for 7 days o Children and adults: 400 000 IU daily, i.e., 1 ml of the oral suspension (100 000 IU) 4 times daily or • Miconazole oral gel for 7 days o Children 6 months to 2 years: 1.25 ml 4 times daily o Children over 2 years and adults: 2.5 ml 4 times daily • Apply the oral suspension of nystatin or the oral gel of miconazole between meals; keep in the mouth for 2 to 3 minutes, then swallow. In young children, apply to the tongue and inside of each cheek. Prevention of opportunistic infections for patients with HIV: • Mild oral candidiasis o Nystatin PO: - Children and adults: 100 000 IU (= 1 ml) 4 times daily o Or Miconazole oral gel - Children 6 months-2 years: 1.25 ml 4 times daily - Children over 2 years and adults: 2.5 ml 4 times daily ➔ The treatment lasts 7 to 14 days. • Moderate to severe oral candidiasis and esophageal candidiasis o Fluconazole PO - Children: 3 to 6 mg/kg once daily - Adults: 50 to 200 mg once daily up to 400 mg daily if necessary

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<td>➔ The treatment lasts 7 to 14 days for oral candidiasis and 14 to 21 days for esophageal candidiasis.
• Candidiasis is an indication for prophylaxis with co-trimoxazole.
• Fluconazole PO as secondary prophylaxis
o Children: 3 to 6 mg/kg once daily
o Adults: 100 to 200 mg once daily
o Only for frequent and severe recurrences</td>
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<tr>
<td>Section 1.1.2
Oropharyngeal and Esophagitis Candidiasis – EACS European AIDS Clinical Society 2023[8]</td>
<td>• The table below showcases the Oropharyngeal candidiasis treatment recommendations by EACS:
<table>
<tr><th>Drug/dose</th><th>Comments</th></tr>
<tr><td>Fluconazole
150-200 mg qd po</td><td>Once or until improvement (5-7 days)</td></tr>
<tr><td>Nystatin
3-6 lozenges at 400000 units (aprox. 4-6 mL of oral suspension)/day</td><td>7-14 days</td></tr>
<tr><td>OR
amphotericin B
oral suspension 1-2 g bid - qid</td><td>7-14 days</td></tr>
</table>
• The table below showcases the Esophagitis treatment recommendations by EACS:
<table>
<tr><th>Drug/dose</th><th>Comments</th></tr>
<tr><td>Fluconazole
400 mg qd po
OR
400 mg loading dose, then 200 mg qd po</td><td>3 days

10-14 days</td></tr>
<tr><td>Consider
Posaconazole 400 mg bid po
OR</td><td>In cases of refractory disease, treat according to resistance testing.
Adapt posaconazole and voriconazole</td></tr>
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<tr><td></td><td>Voriconazole 200 mg bid po
OR
Caspofungin and other echinocandins as 70 mg iv qd day 1, then 50 mg qd</td><td>dose according to MIC's of candida and drug trough levels</td></tr>
<tr><td>Section 1.1.3
Oral Candidiasis – NHS Lanarkshire 2021[9]</td><td colspan="2">

Topical azoles more effective than topical nystatin. Oral candidiasis rare in immunocompetent adults; consider undiagnosed risk factors including HIV. Fluconazole if extensive/severe candidiasis; if HIV or immunosuppression use 100mg.
The table below showcases the oral candidiasis treatment recommendations by NHS Lanarkshire:

<table>
<tr><th>Drug details</th><th>Dose</th><th>Duration</th></tr>
<tr><td>Miconazole oral gel</td><td>20mg/mL QDS</td><td>7 days or until 2 days after symptoms</td></tr>
<tr><td>If Miconazole not tolerated:
Nystatin suspension</td><td>100,000 units/mL QDS</td><td>7 days or until 2 days after symptoms</td></tr>
<tr><td>Fluconazole oral tablets</td><td>50mg OD
or
100mg OD</td><td>7 days further 7 days if persistent</td></tr>
</table>
</td></tr>
<tr><td>Section 1.1.4
Comparative Efficacy and Safety of Antifungal Agents in the Prophylaxis of Oropharyngeal Candidiasis among HIV-Infected Adults: A Systematic Review and Network Meta-Analysis</td><td colspan="2">

This is another systematic review and network meta-analysis study that aimed at comparing the efficacy and safety of antifungal agents used in the prevention of oropharyngeal candidiasis among HIV-infected adults.
The recommendations are outlined below:

Oropharyngeal candidiasis (OPC) has been suggested as a valuable biomarker for HIV disease progression owing to antiretroviral therapy (HAART) failure as the prevalence of OPC directly correlates with the HIV viral load. Within the HIV population, the use of antifungal interventions often helps in reducing clinical symptoms, thereby delivering a transient clinical response by reducing the number of fungi in the affected area. However,

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2022[10]	complete eradication of the Candida spp. can be challenging, and as the HIV infection proceeds, the patients tend to experience more relapses and shorter disease-free intervals. Therefore, for HIV patients with frequent occurrences of OPC, secondary prophylaxis may be beneficial; however, there is concern regarding the issue of azole resistance secondary to long-term exposure to fluconazole. o The authors present pooled data incorporating trials with fluconazole and itraconazole compared to placebo. On analysis, itraconazole was found to be not effective in preventing the occurrence of OPC, while fluconazole, on the other hand, was able to achieve a 55% relative risk reduction in OPC episodes when compared to placebo. The overall quality of evidence according to GRADE for this comparison was found to be moderate. o Studies were also done to evaluate the efficacy of fluconazole in reducing the number of relapses of OPC: - The patients who received fluconazole prophylaxis had significantly had fewer relapses of OPC compared to those who did not receive it ($p < 0.01$), and there was no difference in terms of the number of relapses between the two doses of fluconazole (50 or 100 mg). Thus, the study suggested that low-dose fluconazole, 50 mg once a day, could prevent OPC recurrence and be beneficial to HIV-infected patients who are in the advance stages - Another study evaluated the efficacy of fluconazole 100 mg daily and the results reported no cases of OPC relapse in the arm that received fluconazole as compared to placebo (sample size was small) - Weekly fluconazole dosing regimens have been studied to see whether they may be beneficial as secondary prophylaxis for OPC. According to a mentioned study that evaluated the benefits of fluconazole at a dose of 150 mg weekly compared to placebo, the authors reported that the majority of those in the weekly fluconazole arm were free of OPC relapse for the study duration of 24 weeks, while all of the patients in the placebo group had relapsed. The study also reported that there was

	a significantly lower rate of mycological relapse among those who received fluconazole prophylaxis compared to those in the placebo group (p = 0.004) o In a trial, where the time to the primary end-point, defined as the third OPC relapse, it was shown that it was significantly longer among patients who received weekly fluconazole prophylaxis compared to that in those who received placebo (p = <0.0001) o Guidelines have not recommended any primary and secondary prophylaxis for mucosal candidiasis; however, studies have suggested that appropriate antiretroviral therapy can prevent the occurrence of OPC as well. Further studies are needed. o A concern of whether to prescribe antifungals for prophylaxis could be the emergence of azole resistance. Studies analyzed the development of resistance to fluconazole among patients and reported that weekly and daily doses of fluconazole as secondary prophylaxis did not have any significant impact on resistance, fluconazole as secondary prophylaxis does not increase the risk of developing resistant strains, and that OPC relapses were less compared to placebo. o Evidence with regards to azole resistance in the literature is conflicting as two studies linked the presence of azole-resistant strains of C. albicans among HIV patients with low CD4 cell count with prolonged prior exposure to fluconazole, while other RCTs have shown no significant differences in terms of the emergence of azole resistance when fluconazole was given continuously as prophylaxis as compared to intermittent dosing o The analysis for the safety profile of antifungal agents used in preventing OPC in this study ranked fluconazole higher than itraconazole. Fluconazole has been known to be less likely to cause hepatotoxicity and to have better tolerability when compared to itraconazole o Limitations in the literature include no new studies are available in the literature with newer drugs such as posaconazole and echinocandins, which

	are reported to have a better safety profile than the older antifungal agents o Though many studies suggest 'HAART' to be effective in reducing the prevalence of opportunistic infections (including OPC), several other reports have shown that patients with poor compliance to these medications have thrice the risk of developing any opportunistic infection in comparison to those with good compliance, and hence, patient compliance to HAART can be considered as the chief determining factor regarding opportunistic infections. o There was also a lack of RCTs examining OPC prevention in children, hence, the results of this study were confined to HIV-infected adults o The findings from this network meta-analyses show that fluconazole is beneficial in the prevention of OPC in HIV-infected adults. However, the use of fluconazole as secondary prophylaxis should be weighed against the cost, possible drug–drug interactions, and drug resistance, which may arise from the routine use of fluconazole as secondary prophylaxis. o Further studies should be conducted to identify the optimal parameters for the use of antifungals for the prevention of OPC. High-quality trials are needed to compare fluconazole with relevant new comparators' prevention as well as other outcomes, including adverse effects and quality of life. o Future work should also focus on the cost-effectiveness of use of antifungals for the prevention of OPC.
HTA Pharmacoeconomics Analysis	Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Fungal Gastrointestinal Infections:

Query	Filters	Search Details	Results
((((((((Candidiasis, Oral[MeSH Terms]) OR (Candidiases, Oral[Title/Abstract])) OR (Oral Candidiases[Title/Abstract])) OR (Oral Candidiasis[Title/Abstract])) OR (Thrush[Title/Abstract])) OR (Moniliasis, Oral[Title/Abstract])) OR (Moniliases, Oral[Title/Abstract])) OR (Oral Moniliases[Title/Abstract])) OR (Oral Moniliasis[Title/Abstract])	Guideline, in the last 5 years	("candidiasis, oral"[MeSH Terms] OR (("Candidiasis"[MeSH Terms] OR "Candidiasis"[All Fields] OR "Candidiases"[All Fields]) AND "Oral"[Title/Abstract]) OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "Oral"[All Fields]) AND "Candidiases"[Title/Abstract]) OR "oral candidiasis"[Title/Abstract] OR "Thrush"[Title/Abstract] OR "moniliasis oral"[Title/Abstract] OR (("Candidiasis"[MeSH Terms] OR "Candidiasis"[All Fields] OR "Moniliases"[All Fields]) AND "Oral"[Title/Abstract]) OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "Oral"[All Fields]) AND "Moniliases"[Title/Abstract]) OR "oral moniliasis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	1
((((((Candidiasis[MeSH Terms]) OR (Candidiases[Title/Abstract])) OR (Candida Infection[Title/Abstract])) OR (Candida Infections[Title/Abstract])) OR (Infection, Candida[Title/Abstract])) OR (Moniliasis[Title/Abstract])) OR (Moniliases[Title/Abstract])	Guideline, in the last 5 years	("candidiasis"[MeSH Terms] OR "Candidiases"[Title/Abstract] OR "candida infection"[Title/Abstract] OR "candida infections"[Title/Abstract] OR "infection candida"[Title/Abstract] OR "Moniliasis"[Title/Abstract] OR "Moniliases"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	5

Appendix D. Treatment Algorithms

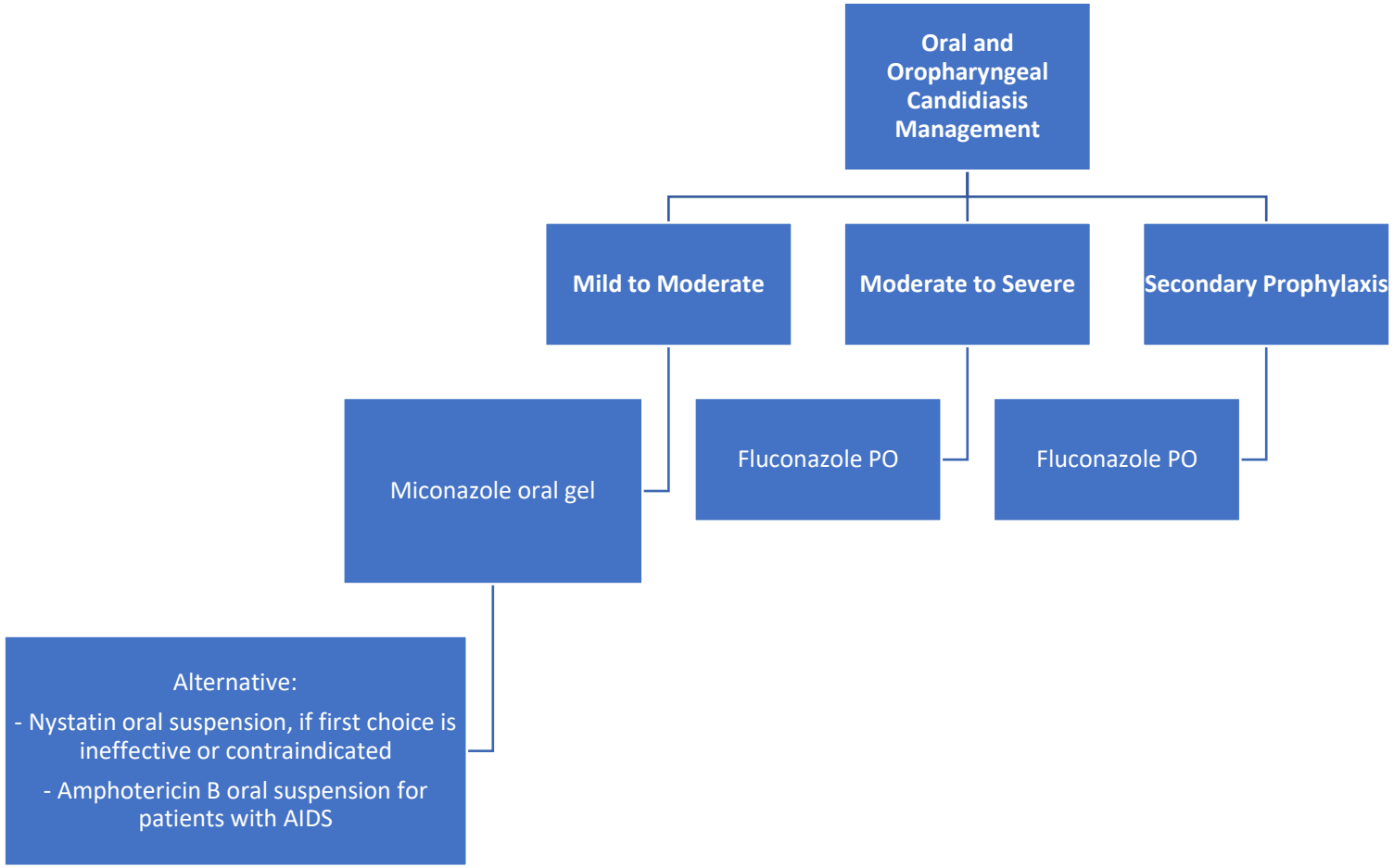

Figure 1. *Treatment algorithm for the management of oral and oropharyngeal candidiasis*

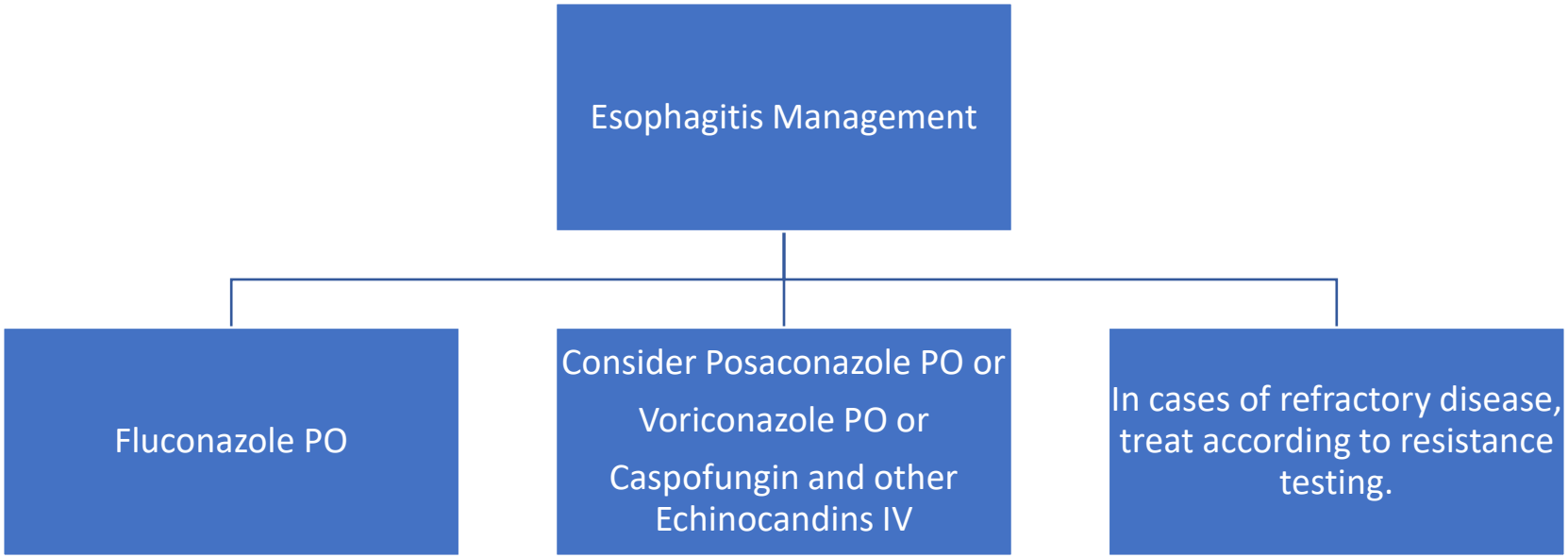

Figure 2. *Treatment algorithm for the management of esophagitis*