

Vulvovaginal Candida Infections & Boric Acid Treatments

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AFTER COMPLETING THIS ACTIVITY, PHARMACISTS SHOULD BE ABLE TO:

1. List the different pathogens that commonly cause vulvovaginal candidiasis
2. List the treatment options for vulvovaginal candidiasis
3. Describe methods used in the preparation of compounded boric acid treatments

The 2016 Standards addressed by this activity include: 1.4, 1.5, 2.1, 2.2, 2.3, 3.1, 3.3, 3.4.

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Vulvovaginal candida (VVC) infections are common in women, with Candida albicans the most common species responsible. This article discusses treatment approaches to vaginal thrush, with special emphasis on treatment of the most common atypical candida species isolated in VVC, Candida glabrata.

Introduction

Vulvovaginal candida (VVC) infections are a common health problem for women, which cause significant morbidity, with over 75% of women affected at least once throughout their lifetime.^{1,2} Approximately 40-50% of women will experience a second VVC infection.⁶ These infections can affect both the physical and emotional health of women.² In Western countries studies have shown that candida and bacteria are the most common causes of vaginal infections.^{5,6} Candida are a family of yeasts which inhabit the human gastrointestinal and genital tract.⁷ VVC infections occur when there is an overgrowth of candida within the vulvovaginal area.³ *Candida albicans* is the most common species responsible for VVC infections.^{1,2,3} However, atypical candida species are isolated in approximately 5% of

patients with *Candida glabrata* the most common atypical species.³ There are a variety of medical conditions, medications and lifestyle factors which have been shown to increase the risk of developing a VVC infection.^{8,16} These include:^{8,16}

- Diabetes
- Immunosuppressant medications
- Pregnancy
- Broad spectrum antibiotic use
- Skin conditions including vulval psoriasis
- Tight synthetic clothing

VVC infections are most commonly diagnosed through symptoms however a swab should be taken to determine the species of candida.³ Symptoms of VVC infections include:⁸

Common symptoms

- Itch (the most common)
- Discharge that is often thick,

white, and odourless (similar to cottage cheese), however can be watery or smooth. The amount of discharge is variable and may be negligible.

Less common symptoms

- Soreness
- Swelling and redness
- Burning
- Vulvar dysuria
- Dyspareunia (painful sexual intercourse)

VVC infections are classified as uncomplicated or complicated.⁸

Uncomplicated infections are more than likely due to *C. albicans*, they present sporadically with infrequent episodes (≤ 3 per 12 months), with mild-to moderate symptoms.⁸

Complicated infections classified as those which are infected with other *Candida* species, present with severe symptoms, recurrent episodes (≥ 4 per 12 months), and in patients with co-conditions including pregnancy, uncontrolled diabetes, and immunosuppression.⁸

Misdiagnosis is a common occurrence when patients present with vaginal symptoms.⁸ As per the Therapeutic Guidelines, a swab should be taken before starting any treatment, to isolate and determine the *Candida* species responsible for the VVC infection, and confirm the diagnosis.³ Pharmacists should encourage patients to consult with their doctor

if complication is suspected. Women with recurrent thrush must be referred to a doctor. This is of particular importance as *C. glabrata* seems to develop resistance to many drug classes, including the azole antifungals, although the mechanism of why resistance develops is not well understood²². This means that treatment with over the counter (OTC) antifungals is unlikely to treat a VVC infection caused by *C. glabrata*, and patients presenting with recurrent infections could potentially have an infection caused by *C. glabrata* which they are ineffectively treating with OTC antifungals.

Treatments are available over the counter (OTC) as Pharmacist

Treatment approach for vaginal thrush: a summary

Gather patient information

- Consider:
- A. Symptoms
 - B. Medical and lifestyle history
 - C. Patient characteristics

Assess patient needs

- Consider: D. The need to refer

Recommend treatment

- Consider: E. Goals of treatment
F. Treatment options

Provide counselling supported by written information

- Consider: G. How to use the medicine
H. Adverse effects
I. Prevention
J. Follow-up
K. Additional information
K. Additional information

Refer if necessary

- First time symptoms, symptoms that have not previously been diagnosed by a doctor or symptoms suggestive of a cause other than vulvovaginal candidiasis
- Recurrent episodes (≥ 4 /year) or persistent symptoms
- Symptoms that have not responded to appropriate therapy
- Abnormal vaginal bleeding
- Pelvic or abdominal pain
- Systemic symptoms (e.g. fever, malaise)
- Discharge that has an unusual colour/odour
- Vaginal/vulval sores or blisters
- History suggestive of a sexually transmissible infection or sexual assault
- Allergy to thrush treatments
- Dyspareunia
- Use of immunosuppressants
- Urinary symptoms (e.g. pain/burning on urination, frequency, urgency)
- Recent birth, miscarriage or abortion
- Presence of an intrauterine device (IUD)
- Medical conditions – diabetes, HIV infection
- Age < 16 or > 60 years

Diagram 1. Treatment approach for vaginal thrush: A summary⁸

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Only (Schedule 3) medications.¹ Scheduling these medications as OTC, allows ease of access to treatment by patients and increases autonomy for self-diagnosis. However, there is the risk of misdiagnosis with consequential incorrect treatment choice.¹ Studies have shown that isolation swabs taken after a patient has used antifungal treatment commonly report false negatives whilst the patient is still presenting with symptoms.³

The Australian Pharmaceutical Formulary and Handbook (APF 24) lists a stepwise treatment approach for pharmacists to follow when recommending

treatment for vaginal thrush.⁸ This flow chart also outlines when the patient should be referred to their GP for diagnosis and treatment (Diagram 1.).⁸

Due to this ease of access to treatment, exact infection rate numbers are difficult to determine, as there is a lack of recording and reporting of the condition.^{1,3}

Treatment options

There is a large variety of both topical and oral treatment options available in Australia for the treatment of VVC infections.^{3, 8}

Table 1 is a combination of the

treatment options as outlined in the Therapeutic Guidelines and the APF 24.

The efficacy of the commercially available treatment options for the treatment of *C. albicans* is supported by considerable evidence. In contrast, there is a lack of studies available comparing the different treatment options, and treatment duration for treating vulvovaginal candida infections in general.³

If a patients sexual partner is presenting with symptoms they need to be referred for confirmation of infection before treatment is started.⁸ Candida

Table 1: Treatment options for Vaginal Thrush^{3,8}

ACTIVE INGREDIENT	DOSAGE FORM	STRENGTH/ CONCENTRATION	DURATION OF TREATMENT	FREQUENCY OF DOSE	ADVERSE EFFECTS	PREGNANCY AND BREASTFEEDING	TREATMENT LINE
Clotrimazole	Vaginal cream	1%	6 nights	One applicator full daily at bedtime	Burning, stinging, itching, erythema	Pregnancy Category A Safe to use in breastfeeding	First line treatment
Clotrimazole	Vaginal cream	2%	3 nights	One applicator full daily at bedtime			
Clotrimazole	Vaginal cream	10%	1 night	One applicator full daily at bedtime			
Clotrimazole	Vaginal suppository/ pessary	100mg	6 nights	One pessary daily at bedtime			
Clotrimazole	Vaginal suppository/ pessary	500mg	1 night	One pessary daily at bedtime			
Miconazole	Vaginal cream	2%	7 nights	One applicator full daily at bedtime			
Nystatin	Vaginal cream	100 000 units/5g	14 nights	One applicator full daily at bedtime	Well tolerated	Pregnancy Category A Safe to use in breastfeeding	Second line treatment. Less effective than the azoles
Fluconazole	Oral capsule	150mg	1 day	Single oral dose	Nausea, vomiting, diarrhoea, headache, dizziness, dyspepsia	Pregnancy category D Considered safe in breastfeeding	Use if topical therapy is not tolerated or woman prefers oral treatment

pathogenic species include *C. albicans*, *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis*, *C. orthopsilosis*, *C. metapsilosis*, *C. famata*, *C. lusitaniae*, *C. guilliermondii*, *C. krusei*, *C. glabrata*, *C. kefyri*, *C. norvegensis*, *C. inconspicua* and *C. lipolytica*.¹⁸ However only 5 of these species, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*, are responsible for over 90% of candida infections.¹⁸

Candida glabrata

Candida glabrata, previously named *Torulopsis glabrata*, is an atypical form of candida causing VVC infections. When *C. glabrata* is isolated, intravaginal boric acid treatment is the effective treatment of choice.^{3,4,6} Boric acid has bacteriostatic and fungistatic properties, rather than fungicidal properties, although the exact mechanism of action is unknown.^{4,10} Vaginal acidification causing cell membrane dysfunction is one theory proposed for the fungistatic properties.^{4,17} Boric acid is an inorganic acid with synonyms of boracic acid and orthoboric acid.⁴ Boric acid should not be orally ingested and there is the risk of potential toxicity if systemically absorbed.^{9,10}

There are currently no commercial products available on the market for intravaginal boric acid treatment.¹⁵ When presented with a prescription for boric acid pessaries, a pharmacist trained in complex compounding may prepare this medication extemporaneously.³ Boric acid vaginal preparations are commonly prepared compounds in Australian pharmacies. The boric acid treatment protocol for *C. glabrata* is 600 mg – 1200 mg intravaginally once daily at

bedtime for 7-14 days.^{3,4,6} The most common treatment plan being 600 mg once daily at bedtime for 14 days.^{3,4,6} Reported effectiveness of intravaginal boric acid treatment for VVC infections varies between 70-98%.^{4,6,11,16} Reported side effects include erythema, burning sensation and watery discharge, however those reported are mild and infrequent. Intravaginal boric acid is mostly well tolerated.^{4,6} There is a lack of safety data for the use of boric acid vaginal treatment in pregnant women, therefore it should be avoided where possible in pregnancy.³

A number of studies have shown effectiveness in the use of 600 mg once daily at bedtime for 5 nights, whilst the woman is menstruating, as a preventative measure for women with recurrent infections.^{6,13,14} This treatment is repeated every month for 4-6 months.^{6,13,14}

Intravaginal boric acid treatment can be compounded as either a vaginal capsule or a vaginal suppository, also known as a pessary.^{3,4} Boric acid is listed as a hazardous substance.¹² When preparing such medications, the pharmacist needs to ensure they are following correct handling procedures of hazardous substances as listed in APF 24.⁸

The following formulations can be employed when compounding either boric acid vaginal capsules or suppositories.

Formulations

APF formula for boric acid vaginal capsule⁸

Boric acid 600 mg

Method: Prepare capsules using #0 or #00 gelatin capsules

Use: Treatment of vaginal

candidiasis caused by *Candida glabrata* and other non-albicans species

Size #0 capsules have a volume of 0.68 mL and size #00 capsules have a volume of 0.91 mL. Pharmacists will need to carry out packing statistic calculations to determine the most appropriate size capsule for their preparation. These calculations will need to be repeated each time a new lot of boric acid powder is sourced by the pharmacy. If after determining these calculations, part of the capsule volume remains empty, an excipient filler is required to bring the fill up to 100%. Cellulose is an appropriate filler to choose when preparing vaginal capsule preparations.¹⁹ Capsules can be filled by hand or by using a capsule filling machine. Clear capsule shells composed of either gelatin or cellulose should be chosen to compound the boric acid into. This is to avoid the risk of staining of the skin and clothing with the dye found in coloured capsules. Patients should be counselled to wear a liner throughout treatment as leakage of the preparation can occur.

The APF 24 allows a 6 month expiry date to be placed upon powder filled capsules as long as all components have 6 months or longer expiry remaining and no component is hygroscopic or light sensitive.⁸ However, there is no guidance given to determine the expiry date to be placed on capsules which do contain hygroscopic or light sensitive components.⁸ Boric acid is a hygroscopic active pharmaceutical ingredient (API).²⁰ Boric acid vaginal capsules need to be stored below 25 degrees Celsius.⁸

Formula for boric acid vaginal suppository¹¹

Boric acid 0.600 g

Silica gel 0.025 g

Fatty acid base QS to volume

Boric acid vaginal suppositories are prepared by melting down the fatty acid base. Pharmacists will need to undertake displacement factor calculations to determine the amount of fatty acid base that will be required to prepare the suppositories. The boric acid and silica gel are homogeneously mixed into the molten base. Silica gel acts as a suspending agent for the boric acid powder to achieve a homogeneous blended mixture which is then poured into suppository shells or molds. When choosing an appropriate mold size to compound suppositories pharmacists should follow a number of rules. The age of the patient needs to be considered with smaller mold sizes, 1.3 mL and 1.7 mL, for paediatric patients. The API should not compromise more than approximately 30% of the suppository mold fill. To determine this, the pharmacist will need to undertake a number of calculations. The density of the chosen suppository base will be used to undertake these calculations. The weight of the base used to 100% fill the suppository mold will need to be determined. This weight can then determine the percentage fill of the API.

Commonly used suppository sizes include 2 mL and 2.4 mL. When incorporating powders into a suppository base a compounder cannot assume a 1 to 1 displacement of powder to base. There are three methods that can be utilized:²¹

1. Conducting a double cast process. This is the most

- accurate method although very time consuming,
2. QS to volume method which is not as accurate but also not as time consuming
 3. Average displacement, normally 0.7, which is the least accurate and also the least time consuming method.

To compound, the suppository base will be melted in a beaker at an appropriate temperature for the base chosen. Once this base has completely melted the boric acid and silica gel will be homogeneously incorporated. This preparation is to be poured into the suppository mold at congealing temperature. The compounder needs to ensure they wait until this point to pour the preparation. If poured too early, despite the suspending agent (silica gel), there is the risk that the API will sediment to the bottom of the mold and the suppository form incorrectly. The preparation is allowed to cool and set before dispensing to the patient.

The suppositories will need to be left to cool at room temperature before placing in the refrigerator. If the molds are placed straight into the refrigerator after pouring, there is the risk of shock cooling and the suppository crumbling. There are two different mold types to choose from, disposable and reusable. With the disposable molds, after the suppository has set, the compounder will need to seal the mold and dispense to the patient. For the reusable molds, the compounder will need to demold the suppository and wrap in foil, which is a time consuming process. Both mold choices require that the patient be counselled to remove the foil or plastic shell before inserting. As per APF 24, a 28 day expiry date

can be assigned to the vaginal suppositories, unless a stability studied formula with a longer expiry date is followed exactly.⁸ Suppositories need to be stored between 2-8 degrees Celsius unless otherwise specified by the formulation followed.⁸ As with the boric acid vaginal capsules, patients should be counselled to wear a liner whilst using this treatment, as there is the risk of leakage of the preparation from the vagina. A vaginal applicator should be provided to the patient for ease of administration.

Capsule or Suppository?

The choice between the use of a vaginal capsule or suppository is doctor and patient preference. Vaginal capsules and suppositories both have their pros and cons.

Capsules have a smaller volume than the vaginal suppositories and there is the preference to insert a smaller preparation. However, vaginal capsules pose a risk of being confused with oral capsules and there is the potential that the patient may swallow the capsule by mistake. Patients may be hesitant to use a capsule vaginally due to patient expectations that a capsule can only be taken orally. As a part of the counselling process, the pharmacist must discuss the risk of accidental oral consumption and subsequent risk of toxicity/poisoning.¹⁶ When dispensing these preparations, pharmacists should include the "Caution: Not to be taken" and "For Vaginal Use Only" labels. Vaginal capsules are reliant on moisture in the area to dissolve the capsule shell. This poses issues if the patient experiences vaginal dryness. Capsules will need to be stored

in a cool dry place below 25 degrees Celsius.

Boric acid vaginal suppositories take the compounder longer to prepare than the vaginal capsules, due to melting of the suppository base. As the fatty acid base is temperature sensitive, these preparations need to be stored in the refrigerator between 2-8 degrees Celsius in order to maintain their integrity. This is particularly pertinent during the warmer months and warmer parts of Australia. Patients can experience leakage of the fatty acid suppository base. There is anecdotal evidence that women prefer to use the fatty acid based suppository preparation over the capsules, as they found them easier to insert, soothing, and moisturizing to the area.

Conclusion

Vaginal swabs, whilst might not be considered practical, should be performed for all presenting cases of VVC infections in order to isolate the causative species of candida. This will allow the most appropriate treatment for the infection to be used as soon as possible. Pharmacists and physicians should be aware of the treatment options available to treat Candida infections, including commercially available and compounded options.

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CPD MULTIPLE CHOICE QUESTIONS

1. Which of the following is not a commercially available *candida* treatment?
 - A. Clotrimazole 2% vaginal cream
 - B. Boric acid 600 mg vaginal suppository
 - C. Clotrimazole 500 mg Vaginal suppository
 - D. Fluconazole 150 mg oral capsule
2. Vulvovaginal *candida* infections are most commonly caused by which of the following *candida* species?
 - A. *Candida tropicalis*
 - B. *Candida glabrata*
 - C. *Candida albicans*
 - D. *Candida parapsilosis*
3. Which of the following treatment regimens is most commonly used to treat *Candida glabrata*?
 - A. Intravaginal boric acid 600 mg once daily for 7 days
 - B. Intravaginal boric acid 1200 mg once daily for 14 days
 - C. Intravaginal boric acid 600 mg once nocte for 14 days
 - D. Intravaginal boric acid 1200 mg twice daily for 7 days
4. The capsule shells used in the preparation of boric acid vaginal capsules should be:
 - A. Coloured gelatin capsules
 - B. Clear gelatin capsules
 - C. Clear vegetable capsules
 - D. Coloured cellulose capsules
5. When compounding boric acid vaginal capsules, how often do packing statistics need to be repeated?
 - A. Once only
 - B. For every prescription
 - C. Once a year
 - D. With each new lot
6. Boric acid vaginal capsules can only be used to treat an existing infection.
 - A. True
 - B. False