

# Clinical challenges in diagnosis and treatment of recurrent vulvovaginal candidiasis

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## Abstract

Vulvovaginal candidiasis is a common infection associated most often with the overgrowth of the fungal species *Candida albicans*. Although most women will have at least one episode of vulvovaginal candidiasis in their lifetime, some will experience recurrent infections. Recurrent vulvovaginal candidiasis can significantly impact quality of life, causing both physical and psychological symptoms, and poses a substantial financial burden for women and the health care system. Acute vulvovaginal candidiasis infections are often diagnosed symptomatically by clinicians or self-diagnosed by patients themselves; this can result in over- and underdiagnosis, as well as misdiagnosis, and has the potential to lead to ineffective treatment and incomplete infection resolution. Clinical diagnosis should include confirmatory laboratory tests, including microscopy and fungal culture, especially in women with a history of recurrent vulvovaginal candidiasis, who are more likely than women with vulvovaginal candidiasis to be infected with less-common *Candida* species or with azole-resistant strains. With proper diagnosis, most acute vulvovaginal candidiasis episodes can be successfully treated; however, women with recurrent vulvovaginal candidiasis may require long-term maintenance therapy. US-based guidelines recommend  $\leq 6$  months of maintenance fluconazole treatment, but infection recurs in up to 50% of women treated. There are currently no US Food and Drug Administration–approved treatments for recurrent vulvovaginal candidiasis; however, several promising treatments for recurrent vulvovaginal candidiasis are in development.

## Keywords

Recurrent vulvovaginal candidiasis, *Candida*, antifungals, diagnosis, treatment, guidelines

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## Introduction

Vulvovaginal candidiasis (VVC) is a fungal infection characterized by inflammation of the vulval and vaginal epithelium. Up to 75% of women will have at least one episode of VVC in their lifetime, most often during their reproductive years.<sup>1,2</sup> Recurrent vulvovaginal candidiasis (RVVC) is defined as  $\geq 3$  symptomatic acute episodes of VVC within a 12-month span.<sup>3</sup> *Candida albicans* has been confirmed responsible in 85%–95% of VVC infections and in the majority of RVVC infections as well.<sup>3</sup> Although only 9% of women with VVC are estimated to have RVVC,<sup>2,4</sup> a large systematic review in 2018 estimated the worldwide annual prevalence of RVVC at 138 million women, and this number is projected to increase to nearly 158 million women by 2030.<sup>2</sup>

The objective of this literature review is to expand clinical knowledge on the status of and challenges in diagnosis and management of RVVC for health care professionals in the United States; searches in major databases including PubMed and Cochrane Library were conducted using the search terms: “recurrent vulvovaginal candidiasis; treatment

recurrent vulvovaginal candidiasis (and/or RVVC); diagnosis recurrent vulvovaginal candidiasis (and/or RVVC); and management recurrent vulvovaginal candidiasis (and/or RVVC).”

## Burden of RVVC

Although most women report a duration of RVVC of 1–2 years, some women have recurrent infections for 4–5 years, or even for decades.<sup>3</sup> In addition to the discomfort of and limitations due to symptoms, women with RVVC report significantly reduced quality of life<sup>2</sup> and debilitating

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negative psychosocial effects.<sup>5</sup> Women with RVVC have reported increased stress and decreased self-esteem and confidence<sup>2</sup> and are more likely to suffer from clinical depression.<sup>6</sup> In qualitative interviews, women with RVVC reported high levels of anxiety and fear regarding social interactions and dating and avoidance of sexual activity.<sup>6</sup>

RVVC also imposes a substantial economic burden: these same women rated managing out-of-pocket costs for doctor visits and treatment as one of the top burdens of the disease.<sup>6</sup> In the United States, the total annual insurer and out-of-pocket costs for outpatient VVC treatment was estimated at US\$368 million for 2017<sup>7</sup>; the estimated annual economic impact of RVVC in the United States in 2010 from lost work hours was US\$1 billion.<sup>2,4,8</sup>

### Factors contributing to recurrence in RVVC

Although still not fully understood, multiple factors are thought to contribute to the pathogenesis of RVVC. *Candida* is a commensal organism in the vaginal area in many women, following migration from the lower gastrointestinal tract. This colonization can remain harmonious and asymptomatic for years. *Candida* overgrowth, however, can trigger a symptomatic infection.<sup>3</sup> *Candida* overgrowth in the vaginal epithelium can be influenced by behavioral factors, such as sexual activity, use of sponge/intrauterine device, and oral contraceptives or hormone replacement therapy.<sup>3</sup> Alterations in health status and immune protective defenses, including type 1 diabetes and HIV, have also been shown to be potential contributing factors.<sup>3</sup> In approximately 20%–30% of women, no predisposing factors have been identified.<sup>9</sup>

Research is ongoing into genetic and immune-related host factors that may contribute to the development or duration of RVVC. The epithelium of the vagina acts as the first barrier to foreign organisms.<sup>9</sup> When an RVVC infection occurs, patterns on *Candida*, referred to as pathogen-associated molecular patterns, are recognized by Toll-like receptors (TLRs) on innate immune cells, triggering intracellular signals from the epithelial cells of the vagina.<sup>10</sup> These signals stimulate a proinflammatory cytokine response that recruits immune cells, such as phagocytes and T cells, to eradicate the fungus.<sup>9</sup> Genetic mutations, including polymorphisms in TLR2 and mannose-binding lectin 2, that may increase susceptibility to VVC infection have been observed in women with RVVC.<sup>9</sup> Women with RVVC may also have a genetic-based hyperinflammatory response to *Candida* colonization and invasion, though more research is needed in this area.<sup>9</sup>

Recurrence can also result from developed resistance to antifungal treatment, usually due to prolonged or repeated use of a single agent.<sup>11</sup> Given the increased accessibility of over-the-counter (OTC) antifungal therapy, some strains of *Candida* that were previously susceptible have become resistant,<sup>12</sup> and women infected with resistant strains may not achieve symptom remission because of the limited

number of treatment options effective against azole-resistant *Candida* species.<sup>13</sup>

### Clinical challenges in diagnosis of RVVC

The substantial psychosocial and economic burdens faced by women with RVVC, and the increasing prevalence and mycologic complexity of vulvovaginal fungal infection, make prompt, accurate, and comprehensive testing for and diagnosis of acute VVC and RVVC critical to formulating informed clinical strategies.

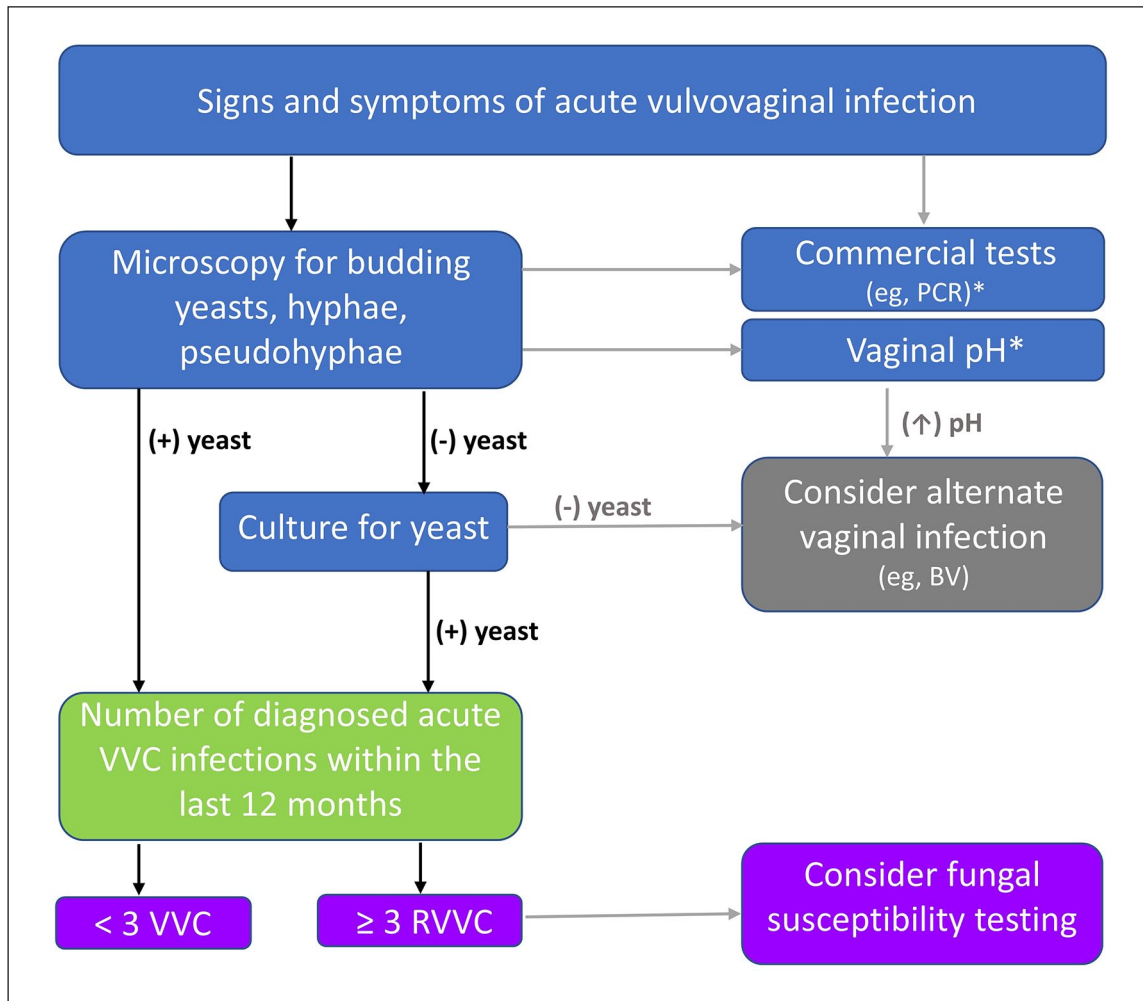
### Diagnosis of RVVC

Because *Candida* is a common vaginal commensal that can be found in the absence of infection, its presence is not diagnostic in itself.<sup>6</sup> Acute VVC is defined as signs and symptoms of inflammation, with the presence of *Candida* species and the absence of other infectious etiologies—except in cases of coinfection.<sup>14</sup> Signs and symptoms of vaginal infection include dysuria and vulvar pruritus, pain, swelling, and redness, and may vary from patient to patient.<sup>15</sup> These symptoms are largely nonspecific and should not be used in isolation for clinical diagnosis of VVC,<sup>1</sup> as this can result in under- and overdiagnosis, as well as misdiagnosis.<sup>3</sup> Other considerations can aid in diagnosing VVC. For example, vaginal pH is usually normal in VVC. Elevated pH suggests an alternate diagnosis,<sup>3</sup> bearing in mind that VVC can co-occur with other vaginal infections such as bacterial vaginosis, which generally presents with elevated pH.<sup>1,3</sup>

Although the most common causative pathogen in VVC is *C. albicans*,<sup>3</sup> the prevalence of infection with non-albicans *Candida* (NAC) species is increasing. Widespread use of broad-spectrum antibiotics coupled with increased availability of OTC and prescription antimycotic medications has fueled this shift.<sup>12</sup> NAC species have been reported to be causative in approximately 10% of cases, with some studies citing up to 45% of VVC cases.<sup>12</sup> *Candida glabrata* is the second-most prevalent *Candida* species in vulvovaginitis<sup>8</sup>; risk factors for infection with *C. glabrata* include having type 2 diabetes, being postmenopausal, and being older.<sup>1,3</sup> Symptoms of *C. albicans* and NAC infections are generally not clinically distinguishable,<sup>1</sup> but diagnostic and treatment considerations differ.<sup>8</sup>

Diagnosis of VVC (Figure 1) should include microscopy of vaginal discharge, a fungal culture, or other tests such as polymerase chain reaction (PCR) to identify the presence and species of yeast(s).<sup>15</sup> Microscopy of vaginal discharge by wet preparation (saline, 10% potassium hydroxide) for the presence of budding yeasts, pseudohyphae, or hyphae is a commonly used, rapid method to confirm a suspected VVC infection.<sup>15</sup> Limitations of microscopy include low (40%–70%) sensitivity<sup>3</sup> and less ability to identify certain species, such as *C. glabrata*, because they do not form hyphae or pseudohyphae.<sup>15</sup>

Fungal culture is considered as the reference standard for the diagnosis of VVC and should be undertaken for women



**Figure 1.** Diagnosis of VVC and RVVC.<sup>1,15–17</sup>

displaying symptoms suspicious for VVC infection but with negative microscopy and normal vaginal pH.<sup>15</sup> Commercial tests, such as PCR, are increasingly being utilized, as they often have faster turnaround than culture<sup>16</sup>; however, many PCR tests are not US Food and Drug Administration (FDA) approved. Clinicians choosing PCR for diagnosis should be familiar with the performance characteristics of the specific test being utilized.<sup>15</sup>

VVC is classified as uncomplicated or complicated.<sup>14</sup> Uncomplicated VVC is defined by the presence of all of the following: mild-to-moderate symptoms, *C. albicans* as likely causative species, no immunocompromising comorbidity, and sporadic or infrequent episodes.<sup>15</sup> VVC is classified as complicated if any of the following apply: severe symptoms; NAC as causative species; concomitant underlying immunodeficiency, immunocompromising condition, immunosuppressive therapy, diabetes, or pregnancy; or recurrent episodes of active infection, that is, RVVC.<sup>14,15</sup>

RVVC is diagnosed when a woman has had  $\geq 3$  symptomatic acute VVC episodes in a 12-month span (Figure 1),

with symptom-free periods between episodes.<sup>3</sup> In women with a history of RVVC (identified by their medical history or medical record), new symptomatic episodes should not be diagnosed empirically. A diagnostic workup, including fungal culture, should be performed to confirm the diagnosis and identify the causative species, including less-common species, such as *C. glabrata*. *C. glabrata* and other NAC species are reported in 10%–20% of women with RVVC.<sup>15</sup>

Testing to determine whether isolates are susceptible or resistant to a variety of antifungal agents should also be performed in women with RVVC, to inform antimycotic agent treatment selection and duration of the treatment.<sup>12</sup> Development of azole-resistant infection may be suspected in women who do not respond to standard treatment regimens or who experience breakthrough symptoms despite compliant long-term fluconazole maintenance therapy.<sup>11</sup> Although breakthrough infections are still relatively rare (usually  $< 5\%$  of patients), *in vitro* susceptibility testing can be useful in selecting subsequent treatment.<sup>11,18</sup>

## Self-diagnosis of VVC and RVVC

Although not guidelines recommended,<sup>16</sup> women who have symptoms associated with VVC may skip consultation with a doctor and instead self-diagnose and self-treat with OTC preparations.<sup>3</sup> Studies have shown, however, that women often base self-diagnosis on nonspecific symptoms and without a full understanding of the variety of vaginal conditions that can cause similar symptoms.<sup>6</sup> Even in women who previously had a clinically diagnosed acute VVC infection, only one-third correctly self-diagnosed a subsequent VVC infection.<sup>6</sup> Women who reported having self-diagnosed an infection were less likely to report symptom relief compared with women who were diagnosed by a physician: 57% versus 84%, respectively.<sup>19</sup> In women who have chosen to self-diagnose, clinical evaluation and testing is recommended if symptoms persist or recur in less than 2 months.<sup>15</sup>

## Clinical challenges in therapeutic management of RVVC

The Infectious Diseases Society of America, US Centers for Disease Control and Prevention, and American College of Obstetricians and Gynecologists have all published treatment guidelines for VVC and RVVC.<sup>15–17</sup> There is a variety of prescription and OTC agents, both topical and oral, that can be used to treat uncomplicated acute VVC (Supplemental Appendix 1). Mycologic cure<sup>16</sup> and symptom relief are achieved in 90% of women with uncomplicated acute VVC who complete their therapeutic regimen.<sup>15</sup> Choice of therapeutic regimen for uncomplicated VVC can be individualized based on patient preference, convenience, cost, and history of response or adverse reaction to previous treatment.<sup>16</sup>

Treatment recommendations for RVVC are shown in Table 1. The treatment regimen is dependent on causative yeast(s)/*Candida* species present, and azole susceptibility of cultured strains.<sup>17</sup> As there are no FDA-approved medications for RVVC, recommended treatments for acute VVC episodes in women with RVVC generally include 7–14 days of induction therapy with a topical or oral agent followed by weekly maintenance treatment for 6 months.<sup>17</sup> Topical azole antifungals, widely used to treat VVC, are used less commonly in RVVC.<sup>17,20</sup>

A landmark RVVC treatment study using an induction regimen of fluconazole (three 150 mg doses at 72 h intervals) followed by weekly maintenance doses of 150 mg of fluconazole for 6 months was shown to reduce symptoms and recurrences.<sup>21</sup> An alternative maintenance regimen of 200 mg doses of fluconazole weekly for 2 months, then every 2 weeks for 4 months, followed by once-monthly 200 mg doses for another 6 months has also been assessed.<sup>22,23</sup> Maintenance therapy for RVVC is rarely curative; it is intended to suppress rather than eradicate the causative yeast.<sup>24</sup> Although symptom resolution is achieved in ~90% of women with RVVC who undergo ≥6 months of

maintenance therapy,<sup>16,21,22</sup> up to 50% will have a recurrence after the termination of maintenance therapy.<sup>13</sup>

Long-term use of fluconazole has risks, including an FDA pregnancy warning.<sup>25</sup> Repeated use of fluconazole also increases risk for the development of resistant strains.<sup>13,18,26</sup> Treating azole-resistant vaginitis constitutes a major clinical challenge for providers, given the current paucity of alternative antimycotic agents.<sup>11</sup> Suggested regimens for azole-resistant *Candida* RVVC include induction and maintenance with boric acid vaginal suppositories or capsules, nystatin vaginal suppository induction therapy, amphotericin B vaginal cream or suppositories, or flucytosine cream.<sup>3</sup>

Treatment of NAC-species RVVC can also be clinically challenging. Treatment failure on standard recommended regimens is common, as some NAC strains are inherently resistant to the azole drug class, have acquired resistance mechanisms,<sup>8</sup> or have low susceptibility to commonly used antifungal agents,<sup>27</sup> all of which complicates therapeutic management of NAC-species RVVC.<sup>8</sup> Alternative treatment options are limited because, as with azole-resistant strains, the current armamentarium of antifungal agents active against NAC strains is limited.<sup>12</sup> Suggested therapeutic options for *C. glabrata* RVVC include induction and maintenance with boric acid or nystatin vaginal suppository regimens,<sup>3</sup> as mentioned above for azole-resistant RVVC.<sup>3</sup> Topical flucytosine may also be considered, although cost may be prohibitive for some patients.<sup>16</sup>

The use of adjuvant probiotic supplements for the treatment of VVC and RVVC is still being investigated to determine clinical benefit. A 2017 Cochrane review of randomized controlled trials (RCTs) using probiotics in addition to conventional antifungal treatment regimens for VVC in non-pregnant women showed increased short-term clinical and mycological cure rates and a reduced short-term relapse rate.<sup>28</sup> Trials of women with RVVC were not included in this meta-analysis, however, and the evidence level was considered low/very low.<sup>28</sup> Findings from ongoing and future RCTs with standardized methodologies, larger sample sizes, and longer follow-up periods are needed to determine the true benefit of adjuvant probiotics for treatment of VVC or RVVC.<sup>28</sup> Probiotics are not currently recommended in any US-based treatment recommendations or guidelines.

## Treatment innovations for RVVC

More-effective and safer therapeutic options are critically needed to ease the physical symptoms and psychosocial burden of RVVC and provide additional treatment options for resistant-strain and NAC-species infections. Several promising therapeutic options are on the horizon.

Oteseconazole (previously VT-1161, Mycovia Pharmaceuticals, Inc., Durham, North Carolina) is a novel oral agent recently approved by the FDA for RVVC.<sup>29</sup> It has demonstrated potent antifungal activity against clinical isolates of *Candida* species, including those with reduced



**Table 1.** Recommended treatment regimens for RVVC.

Classification	Treatment regimens for RVVC	Source/citation
RVVC caused by azole-susceptible <i>Candida</i> species (other than <i>C. glabrata</i> or <i>Candida krusei</i> )	Induction: Treat for acute VVC infection Maintenance: Weekly doses of topical or oral azole antifungal <ul style="list-style-type: none"> <li>• Clotrimazole 500 mg topical (weekly)</li> <li>• Clotrimazole 200 mg topical (twice weekly)</li> <li>• Fluconazole 150 mg orally (weekly for 6 months)</li> </ul> Induction: <ul style="list-style-type: none"> <li>• Topical antifungal (7–14 days)</li> <li>• Oral fluconazole 100, 150, or 200 mg orally (one every third day, for a total of three doses)</li> </ul> Maintenance: <ul style="list-style-type: none"> <li>• Oral fluconazole 100, 150, or 200 mg (weekly for 6 months)</li> <li>• Topical antifungal (intermittent use)</li> </ul> Induction: Topical antifungal therapy or oral fluconazole for 10–14 days Maintenance: Fluconazole 150 mg weekly for 6 months	ACOG <sup>16</sup>  CDC <sup>15</sup>  IDSA <sup>17</sup>
RVVC caused by azole-resistant <i>Candida</i> species	Induction: <ul style="list-style-type: none"> <li>• Boric acid vaginal suppository or capsule 600 mg (daily for 14 days)</li> <li>• Nystatin 100,000-unit suppository (daily for 14 days)</li> <li>• Amphotericin B vaginal cream/suppositories 5%–10% (nightly for 14 days)</li> <li>• Flucytosine cream 5 g (nightly for 14 days)</li> <li>• Combination of amphotericin B and flucytosine</li> </ul> Maintenance: Maintenance regimen for nystatin should be considered	Sobel <sup>3</sup> and ACOG <sup>16</sup>
RVVC caused by <i>C. glabrata</i>	Induction: <ul style="list-style-type: none"> <li>• Boric acid vaginal suppository or capsule 600 mg (daily for 14 days)</li> <li>• Nystatin 100,000-unit suppository (daily for 14 days)</li> </ul> Maintenance: Maintenance regimen for nystatin should be considered	Sobel <sup>3</sup>
RVVC caused by <i>C. krusei</i>	Any of the above regimens EXCEPT fluconazole	Sobel <sup>3</sup>

Abbreviations: ACOG: American College of Obstetricians and Gynecologists; CDC: US Centers for Disease Control and Prevention; IDSA: Infectious Diseases Society of America; RVVC: recurrent vulvovaginal candidiasis; VVC: vulvovaginal candidiasis.

susceptibility to standard azole agents.<sup>30</sup> In Phase 3 clinical trials (CL-011 (NCT03562156) and CL-012 (NCT03561701), oteseconazole was shown to be highly efficacious in preventing recurrence of acute VVC episodes in women with RVVC, even women with azole-resistant *C. albicans* or *C. glabrata* infections.<sup>31</sup>

Ibrexafungerp (formerly SCY-078; SCYNEXIS Inc., Jersey City, New Jersey) is an oral 1,3- $\beta$ -D-glucan synthase inhibitor<sup>32</sup> that is FDA approved to treat acute VVC.<sup>33</sup> A Phase 3 study (NCT04029116) is underway to evaluate the efficacy of oral ibrexafungerp in preventing recurrent VVC episodes in participants with RVVC.<sup>34</sup>

A fungal immunotherapeutic vaccine (NDV-3A, NovaDigm Therapeutics, Grand Forks, North Dakota) was evaluated in a Phase 2 double-blind placebo-controlled clinical trial (NCT01926028).<sup>35</sup> In a post hoc analysis, NDV-3A significantly reduced the frequency of symptomatic VVC episodes in women younger than 40 years with RVVC.<sup>34</sup>

## Conclusion

This review provides an overview of the burden and potential risk factors for RVVC and best practices for diagnosing acute VVC and RVVC. Treatment of RVVC has inherent

clinical challenges because of the complexity of its pathophysiology and the increasing number of NAC-species and azole-resistant infections. Due to differences in diagnostic and management guidelines for RVVC internationally, this review focused on US-based guidelines and US FDA-approved treatments.

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## Author contributions

C.M.N. and M.G.M. were involved in the conception of the work, were involved in drafting and revising the article for intellectual content, approved the final version for publication, and agreed to be accountable for all aspects of the work. Mycovia Pharmaceuticals, Inc. was not involved in the development of this article.

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### Supplemental material

Supplemental material for this article is available online.

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