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REVIEW

Combined systemic (fluconazole) and topical (metronidazole + clotrimazole) therapy for a new approach to the treatment and prophylaxis of recurrent candidiasis

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ABSTRACT

Recurrent vulvovaginal candidiasis (RVVC) is an important pathological and infectious condition that can greatly impact a woman's health and quality of life. Clinical and epidemiological studies show that different types of therapies are able to eliminate the signs and symptoms of mycotic vaginitis in the acute phase, but so far none of these has proved able to significantly reduce the risk of long-term recurrence. In this review, based on the available literature and original data from a preliminary *in-vitro* microbiological study on the compatibility between fluconazole, clotrimazole and metronidazole a new therapeutic approach to RVVC is discussed and presented. The treatment proposed is a combined scheme using both systemic antimicrobial drug therapy with oral fluconazole 200 mg and topical drug therapy using the association metronidazole 500 mg and clotrimazole 100 mg (vaginal ovules) with adjuvant oral probiotic therapy. In detail, at the time of diagnosis in the acute symptom phase, we propose the following treatment scheme: fluconazole 200 mg on day 1, 4, 11, 26, then 1 dose/month for 3 months at the end of the menstrual cycle; plus metronidazole/clotrimazole ovules 1/day for 6 days the first week, then 1 ovule/day for 3 days the week before the menstrual cycle for 3 months; plus probiotic 1 dose/day for 10 days for 3 months starting from the second month to the end of the menstrual cycle. This scheme aims to address the recurrent infection aggressively from the outset by attempting not only to treat acute symptoms, but also to prevent a new event by countering many of the potential risk factors of recurrence, such as the intestinal Candida reservoir, the mycotic biorhythm, the formation of biofilm, the phenotype switching and the presence of infections complicated by the presence of *C. non albicans* or *G. Vaginalis*, without interfering, but rather favoring the restoration of the vaginal lactobacillus species. Future clinical studies will be useful to confirm the proposed scheme.

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KEY WORDS: Fluconazole; Metronidazole; Clotrimazole; Probiotics; Candidiasis.

Vulvovaginal candidiasis (VVC) is an infection generally caused by *Candida albicans* and less frequently supported by other species of *Candida* non-*albicans*, such as *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*.[1] It is estimated that about 75% of women will suffer from at least one episode of vaginal candidiasis in their lifetime, and that 40-45% will have two or more episodes.[2]

Typical symptoms include vaginal itching and pain, dyspareunia, dysuria and the presence

of leucorrhea. In addition, VVC can also be associated with increased susceptibility to human immunodeficiency virus (HIV) infection and, especially if untreated, can contribute to the onset of complications such as pelvic inflammatory disease, infertility, miscarriage and menstrual disorders.[1] For these reasons, the prevention and timely treatment of VVC, especially among risk groups and in relapsing patients, are essential if complications are to be avoided.

Recurrent vulvovaginal candidiasis (RVVC) is considered to be present in its acute form with a frequency of more than 4 episodes/year per patient; it is an important pathological and infectious condition with a strong impact on the health and quality of life of women.[3]

RVVCs generally last 2 to 5 years, but they can go on even longer. A prevalence of up to 6 to 9% is currently calculated in the female population, with an increase in menopausal women as a result of hormone replacement therapy.[3, 4] The available therapies recommended by the International Centers for Disease Control and Prevention (CDC) guidelines for the treatment of candidiasis are effective and include oral antifungals such as fluconazole or topical therapies like clotrimazole depending on the level of complication of the infection.[5]

Nevertheless, clinical and epidemiological studies show that different types of therapies can eliminate signs and symptoms of acute mycotic vaginitis, but none of them are able to significantly reduce the risk of long-term recurrences.[3, 6-9] For these reasons, the problem of how to deal with RVVCs effectively remains open.

In this review, based on the available literature and original data from a preliminary *in-vitro* microbiological study on the compatibility between fluconazole, clotrimazole and metronidazole a new therapeutic approach to RVVC is discussed and presented.

Our proposal was to use a combined therapy using systemic fluconazole and topical treatment with metronidazole and clotrimazole and the probiotic adjuvant therapy, to contrast the recurrent infection right from the start in an aggressive way by treating acute symptoms, and preventing a new event by attacking many of the potential recurrence risk factors.

RVVC risk factors

A recent review by Sobel describes the pathophysiology underlying RVVC.[3] In this study, risk factors of various nature emerge, some of them unmodifiable (*e.g.* genetic), others external (diabetes, HIV, use of antibiotics, steroids, hormone replacement therapy), behavioral (sexual habits), or microbiological.[3] This last could be potentially contrasted pharmacologically.

The microbiological risk factors include the formation of mycotic biofilm, fed by the vaginal or intestinal *Candida* reservoir, which forms an impenetrable protection and in which *Candida* grows before reaching a condition allowing it to pass from the quiescent form of spore to the pathogenic form of hypha through phenotype switching.[10, 11] Another important risk factor is represented by the fact that recurrent candidiasis are often characterized by mixed etiology where, in addition to *Candida albicans*, other species of *Candida non albicans* such as *Candida glabrata* or bacterial vaginosis may be present, and these must therefore be managed.[3, 12]

Furthermore, in a recent study conducted on 467 women that investigated the composition of vulvovaginal microbiota, it was observed that the group of patients with RVVC presented a changed microbiota with significant reduction in lactobacillus (40% *vs.* 95%) and with a prevalence of *Gardnerella vaginalis* (37% *vs.* 1%) compared to a group of female controls.[13]

The role of fluconazole

Fluconazole is a triazole antifungal used successfully for years in the treatment of vaginal candidiasis.[5] It acts antifungally with respect to most common *Candida* species such as *C. albicans, C. parapsilosis, C. tropicalis*, while *C. glabrata* shows a wide range of sensitivity to fluconazole and *C. krusei* is resistant.[14]

The main mechanism of action of fluconazole derives from its ability to block the biosynthesis of *Candida* ergosterol by inhibiting alpha-demethylase.[14] This action determines the accumulation of sterol precursors by the fungus with the consequent formation of a plasma membrane with altered structure and functions.[15] The action

of fluconazole is dose dependent and therefore increases with an increasing dosage.[16]

The drug is mostly absorbed (>90% bioavailability) systemically, it has a long plasma half-life (over 30 hours), low protein binding (12%) and is distributed rapidly in tissue fluids.[17] Pharmacokinetic studies show that a single oral dose of 150 mg of fluconazole results in a peak concentration in vaginal secretions 8 to 24 hours later, and fluconazole persists in the vagina in higher concentrations than MIC for most strains of *C. albicans* for at least 3 days.[18] Finally, it should be remembered that oral fluconazole can act against the fungi not only at vaginal, but also at intestinal level;[19] since the intestine can be a *Candida* reservoir, the action of fluconazole in this area could reduce one of the most important recurrence risk factors.

All these data are important because they tell us that by increasing the dosage of oral fluconazole it is possible to significantly increase the drug's bioavailability and also allow us to calculate the frequency of drug administration adequately so as to effectively counteract *Candida*'s mycotic biorhythm.

In fact, the increase in the dosage of fluconazole from 150 mg to 200 mg together with a less frequent administration of the drug improves the therapeutic result as is shown by comparing the RCT Study by Sobel *et al.*[6] and that of the ReCiDiF Trial by Donders *et al.*[7] In the first case, a randomized placebo-controlled study conducted on 387 women with RVVC treated with 150 mg fluconazole at days 1, 3, 7, followed by weekly administration for 6 months, and a follow-up period with no treatment, showed an incidence of relapses of 10% in the first 6 months, but with a relapse of about 60% after one year.[6] The figure improved when patients were treated with fluconazole 200 mg on days 1, 3, 5, then 200 mg weekly for 2 months, 200 mg biweekly for 4 months, 200 mg monthtly for 6 months. In this case the incidence of recurrences was 10% at 6 months and 20% after one year.[7] An excellent result but one that did not give the certainty of completely eliminating the risk of recurrences.

A further step forward could derive from the use of fluconazole with an interval that better counters the "mycotic biorhythm of Candida," namely that also combats vegetative forms and not only the hyphal form of *Candida,* with a longer interval between one dose and another to promote patient compliance.[8, 20, 21]

For this purpose, a preliminary study demonstrated the efficacy of oral fluconazole at a dose of 200 mg on days 1, 4, 11 and 26 and 200 mg/month for the following 3 months in reducing the symptoms of chronic recurrent vulvovaginitis and without recurrence after six months follow-up.[22]

The role of the topical association metronidazole + clotrimazole

Clotrimazole is an imidazole drug that is particularly effective in the topical treatment of candidiasis where it has been used for some time and is recommended for the treatment of uncomplicated vulvovaginitis.[5] Clotrimazole has a molecular antifungal action that mainly prevents the synthesis of ergosterol with a well-known, broad spectrum antifungal action not only on *C. albicans* but also on *C. krusei, C. glabrata, C parapsilosis* and *C. tropicalis*.[23, 24]

Metronidazole is a broad-spectrum nitroimidazole derived drug with antiprotozoal and antimicrobial action, used effectively in clinical practice both orally and topically and recommended for topical treatment in bacterial vulvovaginosis.[5] Metronidazole has a direct trichomonicidal effect and is active on Gram-positive anaerobic and Gram-negative anaerobic cocci, with a marked action on *Gardnerella vaginalis* where it is more than 80% effective.[23, 25, 26]

The topical association of metronidazole and clotrimazole in patients with VVC has been successfully tested in a number of studies. In previous study conducted on patients with vaginal fungal and bacterial mixed infection, treated with 1 ovule of metronidazole 500 mg + clotrimazole 100 mg/day for 6 days, the clinical efficacy of the treatment and the antimicrobial activity of the individual active ingredients and their association on isolated and collected strains was evaluated.[24] Clotrimazole has been shown to be active against fungi assayed both alone and in association with metronidazole. Both clotrimazole and metronidazole proved inactive against Gram-positive and Gram-negative aerobic bacteria; on the contrary,

both were active against *G. vaginalis* with an improvement in the minimum inhibitory concentrations when combined. The study also demonstrated the complete inactivity of the association metronidazole and clotrimazole towards the lactobacilli (*L. rhamnosus, L. acidophilus, L. plantarum*). In all patients studied, the lack of growth of isolated pathogens was observed, both at the first examination after therapy and at follow-up after 30 days with the restoration of the physiological vaginal lactobacillus level.[24]

In a previous study conducted on 33 women with RVVC, the effectiveness of the treatment of the topical association metronidazole 500 mg + clotrimazole 100 mg formulated in ovules in the treatment of the acute phase and in the prevention of recurrences was evaluated. Treatment of the acute phase was 1 ovule/day for 6 days; in the following months in the event of symptom improvement, but persistence of microbiological positivity and hence the presence of *Candida*, the patient was subjected to a cycle of prophylactic therapy using 1 ovule/day for 3 days in the week before the menstrual cycle. Two months after this treatment, 81.8% of the cases showed a clear reduction or complete resolution of symptoms. In patients who improved and underwent subsequent prophylactic treatment, microbiological eradication, clinical resolution and absence of recurrences were observed at 6-month follow-up.[27]

Finally, in support of the rationale for the topical action of the association metronidazole and clotrimazole in RVVC, more recently we have also shown that the association metronidazole/clotrimazole at a concentration of 64/320 µg/mL was capable of inhibiting *Candida*'s "phenotype switching."[28]

The role of probiotics

Given the importance of vaginal microbiota and lactobacilli, particularly in the defense of the organism against vulvovaginal infections, the use of probiotics as adjuvants to antimicrobial drug therapy has long been studied both *in vitro* and *in vivo*.

For example, a recent *in-vitro* study showed that *L. rhamnosus* was able to reduce the virulence of various isolated strains of *C.albicans* by interfering with the formation of the spore germ tube and increasing *Candida's* sensitivity to various antimycotics, including fluconazole.[29] Another *in-vitro* study showed that *L. rhamnosus* and *L. reuteri* were able to reduce the growth of *C. albicans* and the expression of mycotic genes involved in *Candida's* resistance to fluconazole.[30]

From the clinical standpoint, a recent Cochrane review analyzed 10 RCTs and concluded that compared to conventional treatment, the use of probiotics as adjuvant therapy in VVCs may increase the rate of clinical recovery and short-term mycological eradication and decrease the rate of recurrence at one month, although failing to achieve a higher frequency of long-term clinical or mycological treatment.[31]

The proposed therapeutic scheme

With regard to the above, our proposed therapy involves a combined approach with the association oral fluconazole + topical metronidazole/clotrimazole + oral probiotics, as shown in Table I.

In detail, at the time of diagnosis in the acute symptom phase, we propose the following treatment scheme: fluconazole 200 mg on day 1, 4,

TABLE I.—*Therapeutic scheme proposed for the treatment of RVVCs.*

	Topical therapy (vaginal ovules): metronidazole 500 mg + clotrimazole 100 mg	Systemic therapy (oral): fluconazole 200 mg	Systemic therapy (oral): probiotic
1st month	Day 1, 2, 3, 4, 5, 6	Day 1, 4, 11, 26	
2nd month	1/day evening for 3 days, lst week precycle	1/month end of cycle	1/day in the morning for 10 days at end of cycle immediately after fluconazole
3rd month	1/day evening for 3 days, lst week precycle	1/month end of cycle	1/day in the morning for 10 days at end of cycle immediately after fluconazole
4th month	1/day evening for 3 days, lst week precycle	1/month end of cycle	1/day in the morning for 10 days at end of cycle immediately after fluconazole

Day 1 is the day of the diagnosis of the infection carried out after gynecological examination (signs and symptoms, acute phase of recurrence) and microbiological confirmation.
Probiotic*: L. rhamnosus* and/or *L. reuteri* and/or *L. acidophilus* and/or *L. fermentum*.

11, 26, then 1 dose of fluconazole/month for 3 months at the end of the cycle; plus metronidazole/clotrimazole ovules 1/day in the evening for 6 days the first week, then 1 ovule/day in the evening for 3 days the week before the menstrual cycle for 3 months; plus Probiotic 1 dose/day in the morning for 10 days for 3 months starting from the second month to the end of the menstrual cycle just after fluconazole. In the event of an irregular cycle one month after the previous administration.

For the choice of probiotic, we suggest a lactobacillus among those with the most scientific literature to support the treatment of candidiasis such as *L. rhamnosus, L. reuteri, L. acidophilus, L. fermentum*.[31] The decision to start using probiotics from the second month after the beginning of treatment is justified by the fact that in the acute phase the presence of active *Candida* infection would counteract the colonization of lactobacilli in the vaginal environment.

Fluconazole compatibility on the vaginal microbiota

In the proposed formulation, as the non-interference of metronidazole and clotrimazole on the vaginal ecosystem had already been verified,[24] it was necessary to confirm that fluconazole also did not interfere with the homeostasis of the vaginal microbiota.

For this purpose, 20 strains of vaginal lactobacilli, recently isolated (from vaginal swabs of healthy women) and belonging to the collection of the Section of Microbiology of the Department of Biomedical and Biotechnological Sciences (University of Catania), were tested *in vitro* with the Minimum Inhibiting Concentration (MIC) method against various concentrations of fluconazole.

As can be seen in Table II, all tested strains proved resistant to fluconazole, with MIC values higher than the maximum limit of the tested range. Only one standard strain (*L. casei ATCC 393*) had a MIC of 64 µg/mL, but considering that pharmacokinetics data show that fluconazole reaches vaginal concentrations of 2 ug/mL, there are no problems of interference with lactobacilli.[18]

TABLE II.—*MIC (µg/mL) of fluconazole with respect to* Lactobacillus spp.

Lactobacillus species	FLU[a] MIC (µg/mL)
L. delbrueckii 012/050	>64
L. delbrueckii 032/050	>64
L. plantarum 008/050	>64
L. plantarum 042/050	>64
L. paracasei 019/050	>64
L. paracasei 028/050	>64
L. crispatus 005/050	>64
L. crispatus 026/050	>64
L. acidophilus 007/050	>64
L. acidophilus 015/050	>64
L. acidophilus 022/050	>64
L. acidophilus 023/050	>64
L. acidophilus 027/050	>64
L. rhamnosus 004/050	>64
L. rhamnosus 006/050	>64
L. rhamnsous 011/050	>64
L. rhamnosus 014/050	>64
L. rhamnosus 021/050	>64
L. acidophilus ATCC 4356	>64
L. casei ATCC 393	64

[a]FLU: fluconazole - range (64-0.125 µg/mL).

In-vitro microbiological compatibility on the antifungal activity of the fluconazole, metronidazole and clotrimazole combination on *Candida albicans*

The *in-vitro* activity of fluconazole, clotrimazole and metronidazole, was evaluated for individual antimicrobials and in association with each other. 20 strains of *C.albicans* were used, recently isolated (from vaginal swabs of women diagnosed with vaginal candidiasis) and belonging to the collection of the Microbiology section of the Department of Biomedical and Biotechnological Sciences (University of Catania).

Yeast colonies grown in specific culture media were initially tested with the Germ-Tube Test (rapid identification test for *C. albicans*). Specifically, a yeast colony is diluted in 2 mL of fetal bovine serum and the tube kept at 35 °C for at least 2 hours. A drop of this suspension is then observed under a microscope (40 X): the formation of germination tubules in the fungal cells is indicative of *C. albicans*. All isolated strains, whether negative or positive to the germination test, were also identified by an enzymatic technique (API Candida, Biomerieux).

The method employed to assess antimicrobial

sensitivity was that of micro-dilutions in broth, using standardized procedures (Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST) - Clinical And Laboratory Standards Institute (CLSI).

The interaction between molecules was evaluated by means of checkerboard tests.[32]

Specifically:

• the MIC value was the concentration of substance capable of determining 50% growth inhibition compared to the positive control;

• the 3 molecules were tested with the following ranges: metronidazole: range [320-0.625 µg/mL]; clotrimazole: range [64-0.125 µg/mL]; fluconazole: range [64-0.125 µg/mL];

• the formula for calculating the FICI value is as follows:

(MIC of A in combination with B/MIC of A) +
(MIC of B in combination with A/MIC of B)

• the interpretation criteria are as follows: FICI≤0.5 synergistic effect (S); 0.5<FICI≤4.0 no effect (I); FICI >4.0 antagonism (A).

The results are shown in Table III, where:

• *in-vitro* fluconazole and clotrimazole activity is confirmed on all strains of *Candida albicans* tested;

• from the MIC values obtained with the combination FLU+CLO-MET (1:5) it may be noted that while the MIC values of Clotrimazole are identical to those obtained with the molecule on its own, the values for Fluconazole are much lower if in combination;

• from FICI values, finally, neither an antagonistic nor a synergistic effect has ever been observed.

Conclusions

Pharmacological research into the treatment of recurrent candidiasis calls for the development of more potent antimycotics, with advantages in terms of pharmacokinetics, to counter mycotic biofilm, quorum sensing, resistance phenomena, promote the vaginal inflammatory response and combat mixed infections of bacterial origin (*G. vaginalis*).[3]

On these bases we propose a new therapeutic approach to RVVCs consisting of combined

TABLE III.—In-vitro *microbiological compatibility on antifungal activity of the combination fluconazole, metronidazole and clotrimazole on* C. albicans.

Strains	MET[a]	CLO[b]	FLU[c]	FLU/CLO-MET (1:5)	FLU/MET
C. albicans 001/050	>320	0.125	0.125	0.125/0.125-0.625	0.125/0.625
C. albicans 002/050	>320	0.25	2	0.25/0.25-1.25	2/10
C. albicans 003/050	>320	0.25	1	0.25/0.25-1.25	1/5
C. albicans 004/050	>320	0.125	0.5	0.125/0.125-0.625	0.5/2.5
C. albicans 005/050	>320	0.125	0.125	0.125/0.125-0.625	0.125/0.625
C. albicans 006/050	>320	0.125	0.25	0.125/0.125-0.625	0.25/1.25
C. albicans 007/050	>320	0.125	0.125	0.125/0.125-0.625	0.125/0.625
C. albicans 008/050	>320	0.25	0.5	0.25/0.25-1.25	0.5/2.5
C. albicans 009/050	>320	0.25	2	0.25/0.25-1.25	2/10
C. albicans 010/050	>320	0.25	1	0.25/0.25-1.25	1/5
C. albicans 011/050	>320	0.25	1	0.25/0.25-1.25	1/5
C. albicans 012/050	>320	0.125	1	0.125/0.125-0.625	1/5
C. albicans 013/050	>320	0.125	0.5	0.125/0.125-0.625	0.5/2.5
C. albicans 014/050	>320	0.125	0.5	0.125/0.125-0.625	0.5/2.5
C. albicans 015/050	>320	0.125	0.125	0.125/0.125-0.625	0.125/0.625
C. albicans 016/050	>320	0.25	1	0.25/0.25-1.25	1/5
C. albicans 017/050	>320	0.125	1	0.125/0.125-0.625	1/5
C. albicans 018/050	>320	0.125	2	0.125/0.125-0.625	2/10
C. albicans 019/050	>320	0.125	0.125	0.125/0.125-0.625	0.125/0.625
C. albicans ATCC 90028	>320	0.125	0.125	0.125/0.125-0.625	0.125/0.625

Metronidazole: range [320-0.625 µg/mL]; clotrimazole: range [64-0.125 µg/mL]; fluconazole: range [64-0.125 µg/mL].
MIC: substance concentration capable of determining 50% growth inhibition compared to the positive control.
[a]MET: Metronidazole; [b]CLO: Clotrimazole (CLSI M27-A3 does not show breakpoints for Clotrimazole); [c]FLU: Fluconazole (according to CLSI M27-A3, all strain was resulted sensitive); [d]FICI: Fractional Inhibitory Concentration Index; [e]Synergistic effect (S), no effect (I), antagonism (A).

therapy with high dosage (200 mg) oral fluconazole with a posology aimed at better combating the *Candida* biorhythm, in association with the topical therapy metronidazole + clotrimazole which, as a result of its wide action spectrum, has already shown it reduces *Candida*'s phenotype switching and is effective both in acute and mixed as well as in recurrent candidiasis.

In short, pending future clinical studies confirming this new therapeutic scheme, based on the literature evidences discussed so far and the new *in-vitro* microbiological data presented here, the rationale of this combined therapeutic scheme can be summarized as follows:

• metronidazole, clotrimazole and fluconazole do not interfere negatively with one another as regards their microbiological action (there is no antagonism) so they can be used in combination;

• metronidazole, clotrimazole and fluconazole are harmless to the lactobacilli and therefore do not alter the normal vaginal and intestinal microbiota (the alteration of which is recognized as a risk factor for RVVCs);

• at vaginal level clotrimazole is effective in the eradication of *Candida albicans* and *non albicans*;

• metronidazole is an added value because it acts on the bacteria responsible for bacterial vaginosis (*e.g. Gardnerella vaginalis*), often associated with candidiasis and a recognized risk factor for RVVCs;

• oral fluconazole carries out its activity by eradicating *Candida* not only at vaginal level, but also in the intestine, a well-known reservoir for *Candida* and a recognized risk factor for RVVCs;

• the combination of clotrimazole and fluconazole allows a wider spectrum of action also with respect to *Candida non albicans*, often present in RVVCs (*e.g. C. krusei* or *C. glabrata* resistant to fluconazole and sensitive to clotrimazole);

• the use of probiotics based on *Lactobacillus* spp. with proven efficacy as adjuvant therapy for the treatment and prophylaxis of Candidiasis, can be an additional aid after acute treatment with antifungal and antibacterial drug therapy, in accelerating the restoration of physiological vaginal microbiota which is protective against recurrences.

FICI[d]	EFFECT[E]	CLO/MET	FICI	Effect	FLU/CLO	FICI	Effect
1.00	I	0.125/0.625	1.00	I	0.125/0.125	2	I
1.03	I	0.25/1.25	1.00	I	0.25/0.25	1.12	I
1.01	I	0.25/2.5	1.00	I	0.25/0.25	1.25	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	1.25	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	2	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	1.5	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	2	I
1.00	I	0.25/1.25	1.00	I	0.25/0.25	1.5	I
1.03	I	0.25/1.25	1.00	I	0.25/0.25	1.12	I
1.01	I	0.25/2.5	1.00	I	0.25/0.25	1.25	I
1.01	I	0.25/2.5	1.00	I	0.25/0.25	1.25	I
1.01	I	0.125/0.625	1.00	I	0.125/0.125	1.12	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	1.25	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	1.25	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	2	I
1.01	I	0.25/2.5	1.00	I	0.25/0.25	1.25	I
1.01	I	0.125/0.625	1.00	I	0.125/0.125	1.12	I
1.03	I	0.125/0.625	1.00	I	0.125/0.125	1.06	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	2	I
1.00	I	0.125/0.625	1.00	I	0.125/0.125	2	I

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