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ORIGINAL ARTICLE

Prostate Disease

# Chronic bacterial prostatitis and irritable bowel syndrome: effectiveness of treatment with rifaximin followed by the probiotic VSL#3

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This study was undertaken to evaluate the influence of treatment with rifaximin followed by the probiotic VSL#3 versus no treatment on the progression of chronic prostatitis toward chronic microbial prostate-vesiculitis (PV) or prostate-vesiculo-epididymitis (PVE). A total of 106 selected infertile male patients with bacteriologically cured chronic bacterial prostatitis (CBP) and irritable bowel syndrome (IBS) were randomly prescribed rifaximin (200 mg, 2 tablets bid, for 7 days monthly for 12 months) and probiotic containing multiple strains VSL#3 ( $450 \times 10^9$  CFU per day) or no treatment. Ninety-five of them (89.6%) complied with the therapeutic plan and were included in this study. Group A = “6Tx/6-”: treatment for the initial 6 and no treatment for the following 6 months ( $n = 26$ ); Group B = “12Tx”: 12 months of treatment ( $n = 22$ ); Group C = “6-/6Tx”: no treatment for the initial 6 months and treatment in the last 6 months ( $n = 23$ ); Group D = “12-”: no treatment ( $n = 24$ ). The patients of Groups A = “6Tx/6-” and B = “12Tx” had the highest frequency of chronic prostatitis (88.5% and 86.4%, respectively). In contrast, group “12-”: patients had the lowest frequency of prostatitis (33.4%). The progression of prostatitis into PV in groups “6Tx/6-” (15.5%) and “6-/6Tx” (13.6%) was lower than that found in the patients of group “12-” (45.8%). Finally, no patient of groups “6Tx/6-” and “6-/6Tx” had PVE, whereas it was diagnosed in 20.8% of group “12-” patients. Long-term treatment with rifaximin and the probiotic VSL#3 is effective in lowering the progression of prostatitis into more complicated forms of male accessory gland infections in infertile patients with bacteriologically cured CBP plus IBS.

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## INTRODUCTION

Chronic prostatitis, the true cause of many cases of cystitis and urethritis, is commonly diagnosed in a community setting and affects approximately 1 in 22 men.<sup>1</sup> In particular, chronic bacterial prostatitis (CBP) has symptoms in a continuous evolution, but it can also slowly evolve into more complicated forms without or with limited symptoms. CBP maintains a condition of lower urinary tract infection and triggers multiple disorders (high-pressure voiding, “intra-prostatic reflux” of urine, bladder neck sclerosis or obstruction, urethral stricture, detrusor sphincter dyssynergia and dysfunctional voiding)<sup>2,3</sup> with shifted retrocanalicular pathogen spread into the seminal tract, which can cause recurrent chronic vesiculitis and epididymitis. Thus, CBP can lead to infertility by damaging the ejaculatory ducts and/or causing vesiculitis and epididymitis, which may be regarded as intermediate or fully extended forms of male accessory gland infections (MAGI), respectively.<sup>4</sup>

To prevent the postinfectious complication of chronic prostatitis into prostate-vesiculitis (PV) or prostate-vesiculo-epididymitis (PVE), more careful control of the predisposing factors strongly associated with prostatitis is needed.<sup>1</sup> Along with urological causes

(anatomical urogenital tract abnormalities, history of sexually transmitted diseases, sexual behavior, and history of mechanical trauma to the lower pelvis area), prostatitis has been reported with a higher frequency in association with nonurological conditions, such as gastrointestinal (GI) disturbances, compromised immune system due to other chronic illnesses, and/or medications, and certain psychiatric conditions (anxiety and mood disorders).<sup>1,5</sup>

Among the predisposing GI disorders leading to prostatitis, a growing role is attributed to irritable bowel syndrome (IBS), a symptom complex in the absence of any biochemical or pathological structural abnormalities diagnosed on the basis of the Rome III criteria.<sup>6</sup> Similar to another study,<sup>7</sup> recently, we observed the simultaneous presence of prostatitis syndromes and IBS in 30.2% and 31.8% of patients screened by andrologists and gastroenterologists, respectively.<sup>8</sup> These patients also had an increased prevalence of CBP and noninflammatory prostatitis.<sup>6</sup> Furthermore, we found that patients with CBP and IBS had a significantly higher frequency (82%) of MAGI compared with patients with CBP alone.<sup>9</sup>

Although the pathophysiology of IBS is complex and multifactorial, patients with CBP and IBS represent a clinical model of mechanisms

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underlying both these conditions. These include primitive pathogenetic factor (intestinal dysbiosis) or secondary pathogenetic mechanisms due to modified commensal gut flora related to antibiotic therapy for treatment of CBP, which in turn may lead to mucosal inflammation. The comprehension of the interaction between the dysbiotic microbiota and the host will probably lead to the development of a more integrated multidisciplinary treatment.<sup>10</sup> Accordingly, probiotics are among the pharmacological agents approved for the treatment of IBS, although their clinical efficacy on IBS is still controversial.<sup>11</sup> Indeed, 34 out of 42 trials examining lactic acid bacteria (LAB) effectiveness in patients with IBS showed beneficial effects in at least one of the endpoints or symptoms examined<sup>12</sup> or an association with the stabilization of intestinal microbiota.<sup>13</sup> In contrast, two other studies with LAB did not report any benefit.<sup>14,15</sup> Controversies on effectiveness of probiotics in patients with IBS may be in part explained by an imbalance between commensal and pathogen bacteria inhabiting the human gut. This may cause a small intestine overgrowth of the intestinal commensal microflora and/or a relative overgrowth of pathogen enterobacteria. In a recent pilot study, treatment with rifaximin (550 mg 3 times daily for 10 days), a gut-directed antibiotic, was found efficacious in reducing both GI score and symptoms in patients with chronic prostatitis type III and IBS.<sup>16</sup>

Therefore, we thought to contribute to this topic with this study conducted on infertile patients with clinical history of CBP and IBS bacteriologically cured after 1–3 intermittent courses of antibiotics and/or nonsteroidal antiinflammatory (NSAI) compounds, to evaluate the influence of treatment with rifaximin and the probiotic combination VSL#3 on the progression of chronic prostatitis into PV or PVE.

## MATERIALS AND METHODS

### Patient selection

During the period of year between January 2011 and January 2013, 106 selected infertile male outpatients (median age: 31 years, range: 19–46 years), consecutively recruited from the Andrology and Endocrinology Unit Clinic, Policlinic University of Catania (Catania, Italy), with a confirmed diagnosis of CBP and IBS (Rome III criteria) were enrolled in this study. A simple “10-point” objective questionnaire based on the Rome III IBS module was used.<sup>17,18</sup> Primary infertility was defined as lack of conception after at least 12 months of unprotected intercourse: the mean infertility duration was 17 months (range: 12–42 months). Eleven patients did not comply with the treatment and therefore, were excluded from the study.

The diagnosis of CBP and IBS was made 6–26 months before the patients were included in this study. At the moment when the diagnoses of CBP and IBS were made, all patients had an increased number of leukocytes (>10 HPF) in the expressed prostatic secretion (EPS) and a positive sperm culture (with CFU > 10<sup>5</sup> ml<sup>-1</sup>). All of them were a continuation of a previous study, in which they had been treated with antibiotics and found bacteriologically cured (in terms of complete bacterial eradication) after 1–3 intermittent courses of antibiotics and/or NSAI compounds. Then they were randomly prescribed a nonabsorbable antibiotic and probiotics or no treatment until the next checkup. When the patients returned for the subsequent follow-up visit, a complete gastroenterological and andrological history was once again taken and a physical examination was performed. Each of the 95 patients enrolled, including the 6 who had become fertile, underwent didymo-epididymal and prostate-vesicular transrectal ultrasound scans and sperm culture.

We defined CBP and progression into PV or PVE, when these patients, during the 6- and 12-month follow-up visits, fulfilled the following conditions:

- CBP was defined in presence of an increased numbers of leucocytes (>10 HPF) in the EPS and a positive sperm culture (with CFU > 10<sup>5</sup> ml<sup>-1</sup>). This CBP was a localized prostatic infection since it was characterized by the absence of ultrasound signs considered indicative of progression, in terms of extension into more sexual accessory glands (seminal vesicles and epididymites). Therefore, this condition was considered clinically as prostatitis stable compared with pretreatment phase with antibiotics. Standard bacteriological methods were used to quantify and identify all organisms, in one aliquot from each sample (derived from EPS or semen) cultured aerobically and anaerobically after diluting the samples (1:2) in saline solution, according to previously published methods.<sup>19,20</sup>
- Instead, progression into PV or PVE was located and verified when they showed clinical signs (palpation of tender prostate at the physical examination) and ultrasound findings considered indicative of PV or PVE, as previously described.<sup>21</sup>
- This combination of multiple ultrasound findings at the level of the seminal vesicle or epididymis had not been observed before, at the time of first diagnosis.
- Sperm cultures with significant bacteriospermia (>10<sup>5</sup> CFU ml<sup>-1</sup>). The cutoff value of > 10<sup>5</sup> CFU ml<sup>-1</sup>, much higher than the value mentioned in the WHO semen manual<sup>22</sup> was selected due to its recently reported strong association with ultrasound abnormalities.<sup>21</sup>
- They had a diarrhea-predominant IBS, since they had loose, mushy, or water stools in the last 3 months with no hard or lumpy stools ([question 9 = 0] and [question 10 > 0]).<sup>17,18</sup>
- The patients declared a regular compliance with the treatment assigned to them.

Exclusion criteria were constipation-predominant IBS (according to the definition in the Rome II criteria),<sup>23</sup> a history of inflammatory bowel disease, diabetes mellitus, unstable thyroid disease, or renal or hepatic disease.

### Study design and treatments

Patients were prescribed treatment with rifaximin, a nonabsorbable antibiotic (200 mg, 2 tablets bid) (Normix®, Alpha Wassermann, Alanno, PE, Italy) for 7 days a month for 6 or 12 months followed by probiotic combination VSL#3 (450 × 10<sup>9</sup> CFU per day, 1 small envelope) (VSL#3®, Ferring SpA, Milan, Italy) (Table 1).

The probiotic VSL#3 is a mixture of eight different species of Gram-positive bacteria, namely *Streptococcus salivarius* subsp.

**Table 1: Study design**

Groups	Previous therapy	Bacteriological eradication	Treatment assigned at the moment of the microbiological eradication	
			The initial 6 months	The second 6 months
“6Tx/6-” (n=26)	1–3 courses	Yes	Rifaximin (200 mg, 2 tablets bid for 7 days a month) and VSL#3 (450×10 <sup>9</sup> CFU per day)	No treatment
“6-/6Tx” (n=23)	1–3 courses	Yes	No treatment	Rifaximin (200 mg, 2 tablets bid for 7 days a month) and VSL#3 (450×10 <sup>9</sup> CFU per day)
“12Tx” (n=22)	1–3 courses	Yes	Rifaximin (200 mg, 2 tablets bid for 7 days a month) and VSL#3 (450×10 <sup>9</sup> CFU per day) for 12 months	
“12-” (n=24)	1–3 courses	Yes	No treatment for 12 months – out	

CFU: colony forming unit

*thermophilus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Bifidobacteria longum*, *Bifidobacteria infantis*, and *Bifidobacteria breve*. The probiotic combination VSL#3 was chosen because it has many interesting properties (antiinflammatory and antioxidant capacity as well as the potential improvement of IBS. In particular, therapeutic trials show the potential benefit of VSL#3 on symptoms in IBS) both *in vitro* and *in vivo* that may account for its clinical efficacy.<sup>11</sup>

All patients were randomly divided into four groups that were assigned to four different therapeutic schemes. Group A = “6Tx/6-”: these patients received the above indicated treatment for the initial 6 months (*n* = 26); group B = “12Tx”: these patients were treated consecutively for all 12 months (*n* = 22); group C = “6-/6Tx”: these patients were treated for the second 6 months (*n* = 23); and group D “12-”: these patients did not receive any treatment (*n* = 24). Randomization was achieved by a computer-generated list. The first random set of numbers was assigned to group “6Tx/6-”; the second random set of numbers was assigned to group “12Tx”, the third random set of numbers was assigned to group “6-/6Tx”; and finally the fourth random set of numbers was assigned to group “12-”.

This study subjects were informed of the risks and requirements for the study. The protocol was approved by the internal Institutional Review Board and an informed written consent was taken from each man.

**Statistical analysis**

Results are shown as percentages throughout the study. At 6 months, comparison between groups “6Tx/6-” and “6-/6Tx” was computed by Fisher’s exact test. At 12 months, the four groups were compared through an ordinal logistic model (proportional-odds) because of the ordinal nature of the independent variable. *P* < 0.05 was considered to be statistically different.

**RESULTS**

The patients of groups “6Tx/6-” and “12Tx” had the highest frequency of chronic prostatitis (88.5% and 86.4%, respectively). In contrast, group “12-” patients had the lowest frequency of prostatitis (33.4%). Furthermore, the progression of prostatitis into PV in groups “6Tx/6-” (15.5%) and “6-/6Tx” (13.6%) was lower than that found in the patients of group “12-” (45.8%). Finally, no patient of groups “6Tx/6-” and “6-/6Tx” had PVE, considered the most complicated forms of MAGI, whereas it was diagnosed in 20.8% of group “12-” patients. In particular, at 6 months, patients of groups “6Tx/6-” and “6-/6Tx” showed a significant difference of progression into PV and PVE (*P* = 0.03) (Figure 1). At 12 months, the ordinal logistic model showed that the odds of progressing into PVE, as opposed to progressing

into PV or staying in the prostatitis status (equivalent to the odds of progressing into PVE or PV, as opposed to staying in the prostatitis status) are 2.16 (confidence interval 95% =1.44–3.25, *P* = 0.0002), for each one-unit increase of treatment from that of group “12Tx” to “6Tx/6-”, from group “6Tx/6-” to “6-/6Tx” and from group “6-/6Tx” to “12-”), meaning that the risk of progression increased significantly with less treatment (Figure 2).

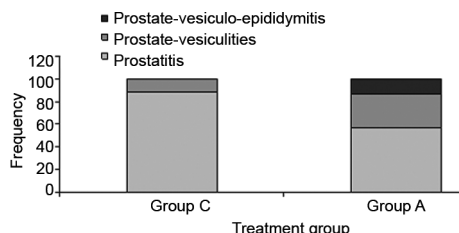
**Microbial findings at the follow-up**

Microbial infection was considered to be significant when the bacteriospermia was > 10<sup>5</sup> CFU ml<sup>-1</sup>. Overall, the treatment with rifaximin and VSL#3 was beneficial in terms of lowering the frequency of bacteriospermia when it was started immediately after the initial germ eradication rather than 6 months later. Indeed, patients of group “6Tx/6-” had the lowest frequency of positive sperm culture compared with patients of group “6-/6Tx” who received the treatment during the last 6 months of observation. The highest frequency was found in patients who were not prescribed any treatment and conversely, the lowest frequency was found among patients of group “12Tx” who received the treatment for all 12 months (Table 2).

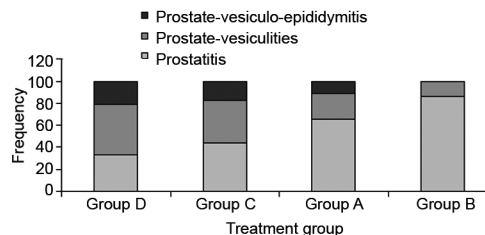
**DISCUSSION**

A growing number of studies have focused on the concomitant presence of prostatitis syndromes and IBS.<sup>7,8,16</sup> When these dual clinical conditions occur, prostatitis syndromes are present with an increased prevalence of CBP and noninflammatory prostatitis.<sup>8</sup> Furthermore, we found that patients with CBP and IBS had a significantly higher frequency (82%) of MAGI compared to patients with CBP alone.<sup>9</sup> These findings suggest that treatments aimed at reducing the evolution of prostatitis into more complicated forms of MAGI are needed. Some studies have highlighted that the treatment of one of the two syndromes also improves the other. In particular, after effective treatment of chronic prostatitis, IBS improves in 78.8% of the cases;<sup>7</sup> as well, treatment with rifaximin (550 mg 3 times daily for 10 days) was found efficacious in reducing CPSI score and GI symptoms in 16 patients with chronic prostatitis type III plus IBS.<sup>16</sup>

Probiotics are among the pharmacological agents approved for the treatment of IBS and there is a general agreement that probiotics decrease global IBS symptoms.<sup>24–26</sup> The mechanisms, the rationale, and the current evidence for the efficacy of probiotics, including *Lactobacilli*, *Bifidobacteria*, and VSL#3, for the treatment of IBS have been addressed.<sup>11</sup> The mechanisms influenced by probiotics include immune function, motility, and the intraluminal milieu. Probiotics may suppress the low-grade inflammation associated with IBS or



**Figure 1:** Frequency of prostatitis, prostate-vesiculitis, and prostate-vesiculo-epididymitis in bacteriologically cured infertile patients with chronic bacterial prostatitis and irritable bowel syndrome who were treated with rifaximin and VSL#3. Treatment groups at 6 months: second 6 out of 12 months of treatment (group C = “6-/6Tx”, *n* = 23); initial 6 months of treatment (group A = “6Tx/6-”, *n* = 26).



**Figure 2:** Frequency of prostatitis, prostate-vesiculitis, and prostate-vesiculo-epididymitis in bacteriologically cured infertile patients with chronic bacterial prostatitis and irritable bowel syndrome who were prescribed rifaximin and VSL#3. Treatment groups at 12 months, following scheme: group A = “6Tx/6-” initial 6 months of treatment (*n* = 26); group B “12Tx”: 12 consecutively months of treatment (*n* = 22); group C = “6-/6Tx”: second 6 out of 12 months of treatment (*n* = 23); and group D = “12-”: no treatment (*n* = 24).



**Table 2: Number and percentage (in parentheses) of patients with bacteriologically cured CBP who had a positive sperm culture after treatment with rifaximin (200 mg, 2 tablets bid for 7 days a month) and VSL#3 (450×10<sup>9</sup> CFU per day)**

	Groups					
	"6Tx/6-" (n=26)		"12Tx" (n=22)	"6-/6Tx" (n=23)		"12-" (n=24)
Follow-up (months of examination)	6 <sup>th</sup>	12 <sup>th</sup>	12 <sup>th</sup>	6 <sup>th</sup>	12 <sup>th</sup>	12 <sup>th</sup>
Positive (CFU>10 <sup>5</sup> ml <sup>-1</sup> ) sperm culture (%)						
All patients	4 (15.4)	10 (38.5)	3 (13.6)	11 (47.8)	13 (56.5)	16 (66.7)
Patients with prostatitis	1 (3.8)	1 (3.8)	0 (0)	1 (4.3)	0 (0)	2 (8.3)
Patients with PV	3 (11.5)	6 (23.1)	3 (13.6)	7 (30.4)	9 (39.1)	9 (37.5)
Patients with PVE	0 (0)	3 (11.5)	0 (0)	3 (13.0)	4 (17.4)	5 (20.8)

CBP: chronic bacterial prostatitis; CFU: colony forming unit; PV: prostate-vesiculitis; PVE: prostate-vesiculo-epididymitis

restore normal local immune function. However, the clinical effect of probiotics on IBS is still controversial.<sup>11</sup> Indeed, 34 out of 42 trials examining the efficacy of LAB in patients with IBS reported beneficial effects in at least one of the endpoints or symptoms examined,<sup>12</sup> or an association with the stabilization of the intestinal microbiota.<sup>13</sup> The results of other studies are difficult to compare because of the differences in study design and probiotic dose and strain.<sup>27</sup> Several of these studies have been conducted with either *Lactobacilli* or *Bifidobacteria*.<sup>28</sup> One of the probiotic products studied with success in this disorder is VSL#3,<sup>29</sup> a product that combines both bacterial strains. Two separate placebo-controlled studies reported improvement in bloating, flatulence, and colonic transit in response to the probiotic cocktail VSL#3, which comprises eight different bacterial strains including *Lactobacilli* and *Bifidobacteria*.<sup>29,30</sup> An increase in the peripheral antiinflammatory (IL-10) and pro-inflammatory (IL-12) cytokine ratio was associated with probiotic administration and symptom improvement.<sup>31</sup> In contrast, two other studies with *Lactobacillus* did not report any benefit.<sup>14,15</sup>

In this study, performed on a selected group of patients with a clinical history positive for IBS and CBP cured with antibiotics and resulting in a bacteriological eradication, we evaluated the protective role of long-term treatment with rifaximin and VSL#3 on the evolution of prostatitis toward more complicated forms of MAGI. In these patients, the therapeutic rationale was to achieve a better balance of the intestinal microflora to interrupt the mechanism (s) able to involve, in the long run, also the seminal vesicles and the epididymis.

Patients evaluated after 6 or 12 months of treatment with rifaximin and VSL#3 (groups "6Tx/6-" and "12Tx") had the highest frequency of prostatitis: 88.5% and 86.4%, respectively. In contrast, patients of group "12-" evaluated after 12 months of no treatment had the lowest (33.4%) frequency of stable prostatitis. Therefore, the deterioration of prostatitis in PV patients belonging to group "6Tx/6-" (n=4) and "6-/6Tx" (n=3) is less in those patients (n=12) belonging to group "12-". Finally, the deterioration in PVE, which are the most extensive pathologies of the MAGI, was present in the five patients who did not receive any therapy, whereas it was zero in the groups of patients who were prescribed rifaximin and VSL#3 for the initial 6 or for 12 months. The early initiation of this therapeutic strategy was more effective, resulting in a nonsignificant progression of prostatitis into PV or PVE in the last 6 months when the patients were not treated. Conversely, a delay of

6 months in the prescription of the treatment resulted in a significant higher frequency of both PV and PVE.

The rate of progression in more extended clinical forms of MAGI was found to be the highest in patients with no treatment (group "12-"), intermediate in patients prescribed a late treatment (group "6-/6Tx") relatively low in patients who were treated in the first 6 months of this study (group "6Tx/6-"), and the lowest in patients treated for 12 months (group "12Tx"). This paralleled the presence of a significant bacterial growth in the seminal fluid (Table 2). Although the causes of IBS remain undefined, some evidence suggests that symptoms are secondary to bacterial overgrowth in the small intestine.<sup>32,33</sup> This condition is likely to favor the onset of CBP and the progression of this uncomplicated form of MAGI into more extended ones, hence with a greater negative impact on sperm parameters.<sup>21</sup> In a recent systematic review and meta-analysis, rifaximin proved to be more effective than placebo for global symptoms and bloating in IBS patients without constipation,<sup>34,35</sup> but the exact mechanisms of action remain to be determined. The present study did not clarify whether the clinical benefits of rifaximin and VSL#3 administration result from a reduction/modification and/or new equilibrium of the intestinal colonic flora. We hypothesize the following potential explanations: (1) the effect of rifaximin, by affecting gut Gram-negative or Gram-positive enteropathogen bacteria, could reduce the bacterial products that negatively affect the host and might alter mucosal immune activation of the host;<sup>31</sup> (2) the addition of the probiotic complex VSL#3, which is a mixture of eight different species of Gram-positive bacteria, could shift the balance in favor of commensal gut bacteria; (3) in a subset of IBS patients exists a potential dysregulation in energy homeostasis (serum glucose) and liver function (serum tyrosine) that may be improved by probiotics supplementation, as suggested by a recent metabolomic study.<sup>36</sup>

The results of this study as they are preliminary and concluding remarks are awaiting confirmation from a larger case series, suggest that the administration of rifaximin and probiotics may represent an example of alternative treatment options in Andrology,<sup>37</sup> such as in patients with prostatitis syndromes and IBS. The results of this study suggest that the treatment should be prescribed immediately after eradication of the microbial component of CBP.

Although 12 months treatment of rifaximin and probiotics for patients with chronic prostatitis for the patients with bacteriologically cured CBP with antibiotics is not routine method and mainstream protocol, this regimen may represent an example of alternative treatment options in patients with chronic prostatitis and IBS, especially for the patients with reproductive demanding. In these patients, the strong inflammatory component expressed by high number of white blood cells in EPS as well as the radical oxygen species overproduction, mainly susceptible in patients with extended infection into seminal vesicles and epididymides,<sup>21</sup> might be counterbalanced and or prevented by antiinflammatory and anti-oxidative properties of probiotics recently demonstrated in critically ill-patients.<sup>38</sup>

This therapeutic strategy seems more suitable to prevent the infection of the seminal vesicles by contrasting one or more of four routes potentially involved in the pathogenesis of vesiculitis: by ascending the genito-urinary tract, by descending from the upper urinary or reproductive tract, by hematogenous spread, or by direct invasion of the glands from local sources. We believe that the clinical model of CBP and IBS, and particularly the condition of chronic prostatitis with recent microbial eradication is useful for future research aimed at defining the role of probiotics in other diagnostic categories

such as evolution or progression of CBP into chronic inflammatory prostatitis.

## AUTHOR CONTRIBUTIONS

EV and SLV are the principal investigators. AEC and RAC have performed the statistical analysis and the final revision of the manuscript; LV and RC have performed the statistical analysis and data collection.

## COMPETING INTERESTS

All authors declare no competing interests.

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