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Intravaginal vitamin C supplementation in bacterial vaginosis: a systematic review

Suplementação com vitamina C intravaginal na vaginose bacteriana: uma revisão sistemática

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Abstract

Background: The aim of this review was to assess the efficacy of intravaginal vitamin C in reducing symptoms and treating Bacterial Vaginosis (BV).

Methods: In October 2023, the authors conducted a systematic review by searching for scientific publications indexed in the PubMed and Cochrane Central database. Inclusion criteria included published articles/trials that met the following conditions: the population of women with an active diagnosis or recurrent history of BV-related vaginitis, undergoing treatment or prophylaxis with vitamin C, compared to placebo or other first line/adjunctive/prophylactic measures used in BV. Exclusion criteria included non-original articles, duplicated studies and discrepancy between content of the article and the aim of this review. Of the initial 264 articles, five randomized studies were included.

Results: Concerning treatment, results showed a superiority of BV cure rates and reduction in symptomatology, using intravaginal vitamin C compared to placebo, in monotherapy or adjuvant therapy regimens. In the only study evaluating intravaginal vitamin C for prophylaxis of this condition, there was a decrease in BV recurrence after six months of intravaginal vitamin C use, with a higher likelihood of no recurrence from the fifth month. Regarding its safety, vitamin C appears to be well tolerated.

Discussion: Intra-vaginal vitamin C at a dosage of 250 mg, once a day, for six to seven days, may constitute a possible treatment regimen for BV, either as monotherapy or as adjuvant therapy.

Keywords: Ascorbic acid; Bacterial vaginosis; Intravaginal therapy; Vaginitis; Vitamin C.

Resumo

Introdução: O objetivo desta revisão consistiu em avaliar a eficácia da vitamina C intravaginal na redução dos sintomas e cura da Vaginose Bacteriana (VB).

Métodos: Os autores realizaram em outubro de 2023 uma revisão sistemática através da pesquisa de publicações científicas indexadas nas bases de dados PubMed e Cochrane Central. Os critérios de inclusão incluíram a população de mulheres com diagnóstico ativo ou história recorrente de VB, em tratamento ou profilaxia com vitamina C, em comparação com placebo ou outras medidas de primeira linha/adjuvantes/profiláticas. Excluíram-se artigos não originais, estudos duplicados e discrepância entre o conteúdo do artigo e o objetivo desta revisão. Dos 264 artigos iniciais, foram incluídos cinco estudos randomizados.

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Resultados: Relativamente ao tratamento, os resultados demonstraram superioridade nas taxas de cura da VB e redução da sintomatologia, com uso de vitamina C intravaginal em comparação com o placebo, em regimes de monoterapia ou terapia adjuvante. No único estudo que avaliou a vitamina C intravaginal profilática, houve diminuição da recorrência de VB após seis meses de tratamento com maior probabilidade de não recorrência a partir do quinto mês. Quanto à segurança, a vitamina C parece ser bem tolerada.
Discussão: A vitamina C intravaginal na dose de 250 mg, uma vez ao dia, durante seis a sete dias, pode constituir um possível regime de tratamento para VB, seja em monoterapia ou terapêutica adjuvante.

Palavras-chave: Ácido ascórbico; Vaginose bacteriana; Terapêutica intravaginal; Vaginite; Vitamina C.

INTRODUCTION

The physiological vaginal microflora primarily consists of Gram-positive bacilli from the *Lactobacillus* family. These organisms play a crucial role in maintaining a balanced environment by producing antimicrobial components such as hydrogen peroxide, bactericidal substances, and lactic acid. These components are responsible for lowering the vaginal pH (pH 3.5 – 4.5) and exerting toxic oxidative effects on anaerobic microorganisms, thereby avoiding the entry of potential infectious agents[1]. The dysregulation of this microbiota, due to decreased levels of *Lactobacillus* and consequent vaginal alkalinity, leads to a disruption of the environment, promoting dysbiosis such as Bacterial Vaginosis (BV), characterized by the replacement of *Lactobacillus* by anaerobic bacteria. The global prevalence of bacterial vaginosis in women of reproductive age in the general population is high, ranging from 23 to 29%, with racial disparities. According to geographical region, the prevalence also varies, as follows: Europe and Central Asia, 23%; East Asia and the Pacific, 24%; Latin America and the Caribbean, 24%; Middle East and North Africa, 25%; Sub-Saharan Africa, 25%; North America, 27%; South Asia, 29%. Since this is a prevalent disease, and also with concomitant high economic burden it is important to study the effectiveness of new therapeutic regimens[2].

Diagnosis of this disease can be made based on Amsel criteria, which implies the presence of three of the following four signs: thin, homogeneous, non-irritating, white-grey vaginal discharge; vaginal pH > 4.5; fishy odor after application of 10% potassium hydroxide drops – positive amine test (whiff test); observation of clue cells upon fresh microscopic examination[3]. The Amsel criteria have been criticized because the assessment of the appearance of the discharge and the odour can be subjective and difficult to standardize, and therefore subject to misdiagnosis[4]. In addition, the use of the Amsel criteria also has low sensitivity when compared to the diagnosis of BV based on Gram staining or molecular tests. Diagnosis based on Gram stain has been widely accepted, especially in research studies. Gram-stained vaginal smears can also be interpreted repeatedly and by more than one evaluator, thus increasing the reliability of the diagnosis with this method. The most widely used classification method based on gram staining is the Nugent index[5].

Treatment of this condition typically involves antibiotics, such as topical and/or oral formulations of clindamycin or metronidazole[1,6-8].

Despite the wide use of antibiotics, there is a high recurrence rate, particularly within the first year following infection. It is believed that this may be due to the production and persistence of predominantly anaerobic biofilms, even after successful initial treatment[7-9]. Therefore, alternative therapeutic approaches, such as supplements, have been under investigation to enhance treatment efficacy and reduce the use of antibiotics, thus minimizing long-term resistance. Some studies have highlighted the benefits of *Lactobacillus* probiotics, lactic acid gel[9], or antiseptics such as chlorhexidine or polyhexamethylene biguanide in the treatment of BV[10].

More recently, there has been a growing interest regarding the role of ascorbic acid, as decreased levels of vitamin C have been observed in the vaginal fluid of women diagnosed with vaginitis[11]. Other studies have demonstrated that acidification of the environment, through the application of vaginal tablets containing

TABLE I. SEARCH STRATEGY IMPLEMENTED BY THE AUTHORS.

Database	Search builder	Mesh terms	Search strategy
MEDLINE	PubMed Advanced Search Builder	Vitamin C, vaginitis	All fields: vitamin C AND vaginitis
Cochrane Central	Cochrane Library Advanced Search	Vitamin C, vaginitis	All text: vitamin C AND vaginitis

250 mg of ascorbic acid[12,13], had a positive impact on normalizing initially abnormal vaginal microflora[13]. Therefore, it can be hypothesized that vitamin C may be beneficial in the treatment of BV.

Given the rationale outlined, the authors aim to investigate whether there is scientific evidence supporting the use of intravaginal vitamin C in the management of BV.

METHODOLOGY

The authors conducted a systematic review by searching for indexed scientific publications in PubMed and Cochrane Central Library databases. The aforementioned research was conducted on October 30, 2023, and the related Medical Subject Headings (MeSH) terms used were "vitamin C" and "vaginitis". No temporal filter was applied. Table I outlines the research process on the databases.

In order to address the aforementioned question, based on the PICO (Population, Intervention, Control, Outcome) acronym, articles written in English, Portuguese and Spanish, involving a population of women with an active diagnosis or recurrent history of BV-related vaginitis (Population), undergoing treatment or prophylaxis with vitamin C (Intervention) versus placebo or other first line/adjunctive/prophylactic measures used in BV (Control), were included to assess any potential efficacy of vitamin C in reducing symptoms/healing of BV (Outcome). Duplicated studies, articles of opinion, case reports or other reviews were excluded. Discrepancy between content of the article and the aim of this review was also considered an exclusion criterion.

All titles and abstracts were stored in the Google Sheets® platform and subsequently analyzed by two independent groups, each consisting of two authors of this study. After the initial screening, the same process was repeated for the full-text reading of the papers. Any discrepancies between the two groups during this process would be reviewed by the supervising author of the study, however, it was not necessary to reach this phase, as there was 100% agreement. This study enabled the authors to identify 264 articles, with five publications being included for discussion in this review. The steps of article selection are illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart in Figure 1.

Quality assessment

After the mentioned screening, the authors assessed the five included articles, described as randomized clinical trials, regarding the quality of their methodology. To do so, auxiliary tools for assessing the quality of randomized clinical trials were used, such as from Critical Appraisal Skills Programme, Joanna Briggs Institute or National Heart, Lung and Blood Institute. The compilation of quality appraisal scores for each study is presented in Table II. The authors established a score threshold of 50% or more for each article, across all tools, as the criteria for final inclusion in the results and discussion.

RESULTS

All five studies used intravaginal vitamin C at a dosage of 250 mg and studied premenopausal adult women with BV, with only two including adolescents[14,15].

Regarding short-term treatment of BV, when compared with placebo, vaginal application of vitamin C resulted in higher cure rates after one to two weeks, as well as reduction in signs and symptoms such as malodor, pH and clue cells. However, statistical significance could not be proven for the improvement of vaginal itching[15,16]. When compared to a first-line treatment like topical metronidazole, vitamin C did not demonstrate statistically significant superiority overall, except for the reduction of clue cells in the first week

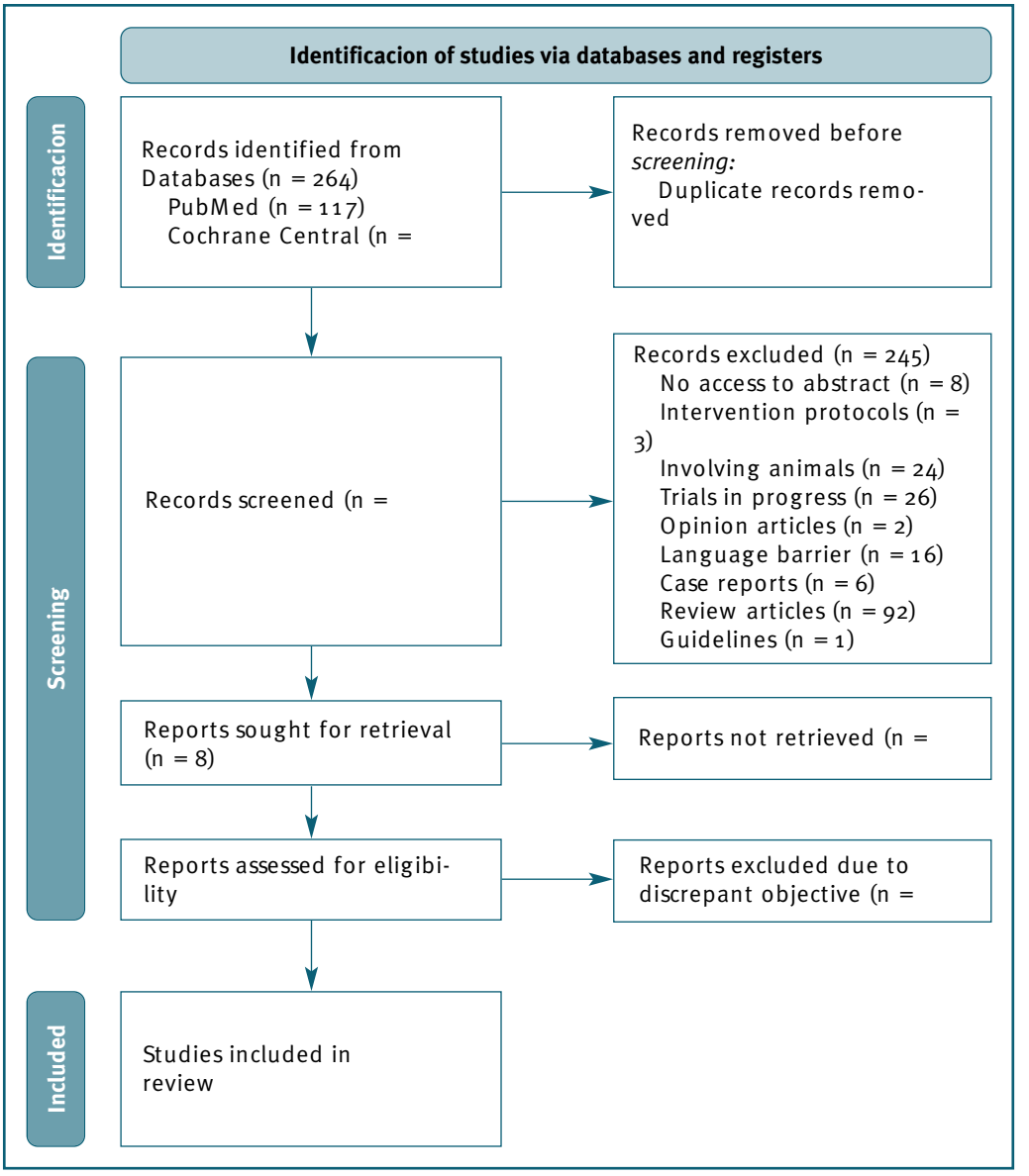

FIGURE 1. Flowchart according to PRISMA diagram regarding selection process of identified articles from databases.

MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

after treatment initiation. Despite the aforementioned, there was improvement in various parameters assessed with the use of vitamin C, including better BV cure rates when compared to metronidazole[14].

In the only study comparing vitamin C to placebo as adjunct to antibiotic therapy, significantly better results were observed for vitamin C group regarding the absence of BV and improvement in the parameters of Amsel and Nugent criteria. There was also an improvement in initial complaints reported by patients, such as itching and abdominal pain, one month after the start of treatment[17].

With respect to its prophylactic use, there was a reduction in recurrence of this condition after six months of prophylaxis, with a higher likelihood of no recurrence from the fifth month[18].

TABLE II. COMPILATION OF METHODOLOGICAL QUALITY SCORES ACROSS DIFFERENT ASSESSMENT TOOLS.

Study	CASP Randomized Controlled Trial Checklist score	JBI Critical Appraisal Tool for Randomized Clinical Trials score	NHLBI Quality Assessment of Controlled Intervention Studies score
Zahra A et al., 2010[14]	69.2%	69.2%	57.1%
Petersen EE et al., 2011[15]	76.9%	69.2%	71.4%
Petersen EE et al., 2004[16]	61.5%	69.2%	64.3%
Mohammad-Alizadeh S et al., 2017[17]	100%	100%	100%
Krasnopolsky VN et al., 2013[18]	84.6%	69.2%	64.3%

CASP: Critical Appraisal Skills Programme; JBI: Joanna Briggs Institute; NHLBI: National Heart, Lung and Blood Institute.

Concerning safety of vitamin C, some adverse effects were evident in the studies analyzed, such as itching, burning sensation, irritation, candidiasis, or pain[14-18].

Table III provides a compilation of the most important points regarding the publications included in this subsection.

DISCUSSION

The results presented suggest a potential benefit of using 250 mg of intra-vaginal vitamin C in non-pregnant premenopausal women, as the main option or adjuvant treatment and prophylaxis of BV, as well as in controlling most of its characteristic symptoms and signs.

Regarding treatment of a BV episode, the application of intravaginal vitamin C, either as monotherapy or in conjunction with another treatment, once a day, for six to seven days seems to be clinically useful, with a good cure rate after one to two weeks, also supported at the microscopic level by a significant reduction in clue cells, which are highly characteristic of anaerobic presence, such as *Gardnerella vaginalis.* This effectiveness may be explained by the notable decrease in pH, consistent in the majority of the analyzed studies, and subsequent normalization of the previously alkaline vaginal environment, which promotes adversity to the anaerobic infectious agents, causative of BV[19]. It's worth noting that the majority of studies compared vitamin C with placebo, with only one study comparing it with metronidazole. In the latter, similar efficacy was observed in both treatments, leading the authors to suggest that vitamin C may be a treatment option for BV[17]. However, further studies comparing vitamin C to other first-line therapeutic options in BV are needed to corroborate this assertion.

Concerning prophylaxis of BV, the prolonged use of 250 mg of vitamin C, for six consecutive days per month, after each menstruation, seems promising in reducing the recurrence of BV episodes, especially if prophylaxis is maintained for at least five months. Only the investigation carried out by Krasnopolsky VN *et al.* addressed the theme of vitamin C prophylaxis in BV[18], so further studies need to be carried out in this area to corroborate the above. At the same time, it would be important to compare vitamin C with other prophylactic methods, such as probiotics[20].

As for the safety of intra-vaginal vitamin C use, it can be used relatively safely, as there is a low frequency of adverse effects, with itching and burning sensation being the most frequent, and candidiasis occurring less frequently. In the study by Zahra et al, adverse effects were observed in 3 of 30 patients (10%) under treatment with vitamin C and in 4 of 30 patients (13.3%) under treatment with metronidazole, with no statistically significant difference observed[17]. In the study by Peterson et al, which compares the effectiveness of vitamin C with placebo, 2 patients out of 50 in the active group had candida superinfection as adverse effects and 2 patients out of 50 in the placebo group reported itching and cystitis, respectively, once again there were no significant differences between the groups regarding adverse effects[16].However, it is important to note that the severity of symptoms was not observed, nor is there a direct causality between vitamin C intake and the occurrence of each of these symptoms, so further studies are needed in this regard.

TABLE III. MAIN CHARACTERISTICS AND FINDINGS OF THE STUDIES INCLUDED AFTER QUALITY ASSESSMENT.

Study	Study focus	Population	Intervention	Control	Primary outcomes	Statistically significant secundary outcomes	Safety/Side effects
Zahra A et al., 2010*[14]	Main treatment	Non-pregnant women aged between 15 and 45 years with confirmed diagnosis of Bacterial Vaginosis by Amsel criteria (n=60)	Vaginal tablets containing 250 mg of vitamin C, once a day, for six days	5 g of metronidazole vaginal gel 0.75%, once a day, for five days	Absence of Bacterial Vaginosis one week after beginning of treatment (76,7% for vitamin C versus 80% for metronidazole gel group, respectively, not significant between groups)	Clue cells < 20% of total cells in gram stain one and two weeks after treatment initiation (p=0.02 and p=0.9, respectively)	Increased vaginal discharge and heartburn (10%)
Petersen EE et al., 2011[15]	Main treatment	Women between the ages of 16 and 65 years old, with confirmed active diagnosis of Bacterial Vaginosis (n=227)	Vaginal tablets containing 250 mg of vitamin C, once a day, for six days	Vaginal tablets of placebo, once a day, for six days	Absence of at least three out of four characteristic symptoms for Bacterial Vaginosis: discharge, malodor, pH > 4.5 and clue cells after treatment (p<0.001)	Absence of clue cells in microscopic analysis at specialized center after treatment (p<0.0001); Absence of the following findings after treatment, in patients with at least three out of four characteristic symptoms: discharge, malodor, pH > 4.5 and clue cells (p<0.001 for each variable)	Itching (5%); Burning sensation (3.5%); Pain (1.4%); Increased discharge (1.4%); Feeling of foreign body in the vagina (0.7%); Insomnia (0.7%)

(*continue*)

*studies mentioning statistical significance with a p-value < 0.05.

TABLE III. MAIN CHARACTERISTICS AND FINDINGS OF THE STUDIES INCLUDED AFTER QUALITY ASSESSMENT. *(CONTINUED)*

Study	Study focus	Population	Intervention	Control	Primary outcomes	Statistically significant secundary outcomes	Safety/Side effects
Petersen EE et al., 2004[16]	Main treatment	Women aged > 18 years and premenopausal, with confirmed active diagnosis of Bacterial Vaginosis (n=100)	Vaginal tablets containing 250 mg of vitamin C, once a day, for six days	Vaginal tablets of placebo, once a day, for six days	Absence of Bacterial Vaginosis in the first and second week after therapy discontinuation (p=0.02 and p=0.06, respectively)	Absence or decrease of the following findings, one and two weeks after therapy discontinuation: malodor, pH > 4.7, clue cells and bacteria and increase in Lactobacilli	Candidiasis (2%)
Mohammad-Alizadeh S et al., 2017*[17]	Adjuvant treatment	Non-pregnant and non-lactating women aged between 18 and 45 years, with diagnosis of Bacterial Vaginosis based on Amsel and Nugent scoring system, being monogamous of husband (n=160)	Vaginal tablets containing 250 mg of vitamin C, once a day + 500 mg of oral metronidazole tablets, twice a day, for seven days	Vaginal tablets of placebo, once a day + 500 mg of oral metronidazole tablets, twice a day, for seven days	Absence of the following findings, 10 and 30 days after treatment initiation: Bacterial Vaginosis criteria, homogeneous discharge, positive Whiff test, pH > 4.5 and clue cells (p<0.001 for each variable)	Absence of the following initial complaints, 10 and 30 days after treatment initiation: smelly discharge, itching and abdominal pain	Vaginal irritation and itching (13.9%); Treatment satisfaction in 75.6% of patients in intervention group versus 84.8% in control group

(continue)

*studies mentioning statistical significance with a p-value < 0.05.

TABLE III. MAIN CHARACTERISTICS AND FINDINGS OF THE STUDIES INCLUDED AFTER QUALITY ASSESSMENT. *(CONTINUED)*

Study	Study focus	Population	Intervention	Control	Primary outcomes	Statistically significant secundary outcomes	Safety/Side effects
Krasnopolsky VN et al., 2013*[18]	Prophylaxis	Women aged between 18 and 50 years old, with a history of recurrent Bacterial Vaginosis (n=142)	Vaginal tablets containing 250 mg of vitamin C, once a day, for six consecutive days per month, over six months.	Vaginal tablets of placebo, once a day, for six consecutive days per month, over six months.	Reduction in the recurrence of Bacterial Vaginosis at three (not significant) and six months post-prophylaxis (p=0.024), with a higher likelihood of no recurrence from the fifth month (p=0.039)	Decrease in vaginal pH (p=0.032 after the fourth cycle of vitamin C)	Skin irritation/ /itching/burning sensation (4%); Candidiasis (1.4%); Bronchitis (1.4%); Acceptance and tolerability of treatment similar to placebo

*studies mentioning statistical significance with a p-value < 0.05.

This study, despite analyzing randomized double-blind clinical trials, has some limitations. Firstly, most of the database platforms encountered by the authors require payment for access, so the authors did not have the opportunity to conduct a more comprehensive search, as this study was not funded by partner entities. Secondly, regarding heterogeneity there are some points relatively population and study design that require discussion: the five studies included in this systematic review involved women of varying ages (15-65 years) and different diagnostic criteria for BV (Amsel and/or Nugent). The presence of comorbidities, such as sexually transmitted infections or other gynecological conditions, was not uniformly reported in the studies, which may have affected the response to treatment. In addition, participants' marital status and sexual activity may influence exposure to risk factors for BV and the effectiveness of interventions. The studies also differed in terms of the type of intervention (vitamin C alone, metronidazole alone, vitamin C combined with metronidazole), the dose and duration of treatment. The control groups also varied, including placebo or metronidazole alone. The primary and secondary outcomes differed between the studies, making it difficult to directly compare the results. In addition, the follow up period varied throughout studies, which may have affected the assessment of the long-term effectiveness of the interventions. Overall, the heterogeneity of the studies included in this systematic review highlights the importance of considering the population and study design when interpreting the results of clinical trials of treatment of BV. Future studies should seek to standardize the diagnostic criteria, control groups and outcomes assessed in order to facilitate comparison between different interventions. In addition, it is important to consider the heterogeneity of the population, including factors such as age, comorbidities and sexual status, when planning and interpreting the results of clinical trials.

Additionally, this study is limited to only five publications, with the most recent one dating back to 2017, indicating the need for further research in this area. It should also be noted that the

population analyzed in each of the articles did not include menopausal women, however, this aspect can be explained by the lack of data in the literature regarding ideal diagnostic criteria for BV in postmenopausal women[21]. Therefore, further studies are needed to address these limitations.

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AUTHOR CONTRIBUTIONS

João Carlos Silveira – bibliographic research and selection, writing of the article. Ana Rita Fernandes – bibliographic research and selection, writing of the article. Catarina Pisco – bibliographic research and selection, writing of the article. Francisca Pinho Rocha – bibliographic research and selection, writing of the article. Vera Soares da Costa – supervision and critical review of the article.

CONFLICT OF INTEREST

The authors declare no competing interests nor financial support for this review.

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