Indicators of Bacterial Vaginosis: A Systematic Literature Review

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KEYWORDS
Bacterial Vaginosis Diagnosis, Probiotics in BV Management, Amsel Criteria and Nugent Score.

ABSTRACT
Bacterial Vaginosis (BV) is a common vaginal infection with a prevalence of 23-29%. Accurate diagnosis and appropriate treatment are important to prevent complications. Antibiotic treatment often faces recurrence and resistance. This study aims to identify and explore indicators of BV diagnosis based on scientific literature in relation to the use of probiotics in the management of Bacterial Vaginosis, providing a comprehensive understanding of the methods and criteria for BV diagnosis. Systematic literature review was conducted through a comprehensive search and 1405 articles were obtained from the Scopus and Web of Science databases (2019-2024). Articles were selected based on inclusion and exclusion criteria, assessed for quality using MMAT, and 27 articles were extracted using NVivo. Thematic analysis was conducted to identify indicators of BV diagnosis. Various indicators were used in the diagnosis of BV, including Amsel criteria, Nugent score, vaginal pH, clinical symptoms, pro-inflammatory cytokines, clue cells, predominance of anaerobic bacteria, increased specific pathogenic bacteria, decreased Lactobacillary grade, and increased exfoliation of vaginal epithelium. Amsel criteria and Nugent score are most commonly used. Findings highlight the importance of using validated indicators to improve the accuracy of BV diagnosis. The implication is the need for standardization and optimization of diagnosis by utilizing a combination of indicators. Standardization of diagnosis based on valid indicators can aid appropriate treatment and prevention of complications. This study contributes to a comprehensive review of BV diagnosis indicators. Standardization of indicators and development of more accurate and efficient diagnostic approaches can improve vaginal health and quality of life for women. Further research is needed to strengthen the findings and explore potential new biomarkers as well as the integration of multi-omics and machine learning approaches.

1. Introduction

Bacterial Vaginosis (BV) is a common vaginal infection in women of childbearing age, with prevalence ranging from 23% to 29%. [1]. BV is characterized by an imbalance of the vaginal microbiota, where there is a decrease in the number of beneficial Lactobacillus and an increase in the growth of anaerobic bacteria [2], [3]. This condition is often accompanied by symptoms such as vaginal discharge, unpleasant odor, and discomfort in the genital area. [4].

Although BV is a common condition, accurate diagnosis and appropriate treatment are essential. Studies have shown that BV increases the risk of pregnancy complications, such as preterm birth, premature rupture of membranes, and postpartum infection. [5], [6]. In addition, BV is also associated with an increased risk of transmission of sexually transmitted infections, including [6], [7]. Therefore, the identification of appropriate indicators for the diagnosis of BV is of great importance in efforts to prevent and manage related complications.

Current treatment of BV generally relies on the use of antibiotics, such as metronidazole and clindamycin [8], [9]. However, this approach often faces the challenge of high recurrence rates, ranging from 30% to 50% within 3-6 months after treatment. [10], [11]. In addition, the use of antibiotics can also disrupt the healthy balance of the vaginal microbiota and increase the risk of antimicrobial resistance [1], [8]. [1], [8].

The side effects and limitations of antibiotic treatment have prompted research to explore alternative approaches to BV. One promising strategy is the use of probiotics, particularly Lactobacillus strains, to restore and maintain a balanced vaginal microbiota. [6], [10]. Several studies have shown that probiotic supplementation, either orally or intravaginally, can improve the healing rate of BV, reduce symptoms, and prevent recurrence [12], [13]. [12], [13].

However, the effectiveness of probiotics in BV treatment still requires further research. Some of the challenges include the variety of probiotic strains used, optimal dosage, duration of treatment, as well as the underlying mechanism of action. [7], [14]. In addition, there are still limitations in determining the most suitable indicators

to assess the success of BV treatment using probiotics. [15].

Based on the phenomena, problems, and previous research, there is a need to further examine the indicators used in the diagnosis of BV. Therefore, the research questions posed in this systematic literature review are: What are the indicators used in the diagnosis of Bacterial Vaginosis (BV) according to the existing literature?

The purpose of this Systematic Literature Review (SLR) study is to identify and explore the indicators used in the diagnosis of Bacterial Vaginosis (BV) based on available scientific literature, so as to provide a comprehensive understanding of the methods and criteria for diagnosis of BV that have been established in previous studies.

This research has implications for the standardization and optimization of Bacterial Vaginosis (BV) diagnosis using validated indicators based on scientific literature. The results of the study can serve as a reference for health practitioners in accurately diagnosing BV and improving the quality of treatment of patients with symptoms associated with BV.

2. Research Method

This systematic literature review was conducted through several structured and systematic steps. These steps include: determining a clear and specific research question, developing a review protocol that includes objectives, inclusion and exclusion criteria, search strategy, and data analysis methods, conducting a comprehensive literature search using relevant databases, study selection based on inclusion and exclusion criteria, data extraction to collect important information from selected studies, assessment of study quality using appropriate assessment tools, data synthesis to integrate findings from various studies, transparent and complete reporting of results, discussion and conclusions that include implications and limitations of the review, and publication of review results in relevant scientific journals. [16], [17], [18].

The research questions in this systematic literature review were formulated using the PICO (Population, Intervention, Comparison, Outcome) framework. The population studied was women with Bacterial Vaginosis (BV), the intervention evaluated was the use of probiotics, the comparison used was placebo or no intervention, and the outcomes measured were indicators used in the diagnosis of BV.

The article identification process was carried out using the Scopus and Web of Science databases. The keywords used for the search in Scopus were "TITLE-ABS-KEY (("Vaginosis" OR "Bacterial Vaginosis" OR "BV") AND "Probiotic")", while for Web of Science was "("Vaginosis" OR "Bacterial Vaginosis" OR "BV") AND "Probiotic") (Topic)". The search was limited to articles published in 2019-2024.

The article screening process uses inclusion criteria which include English language articles, research article types, published in 2019-2024. Review articles, proceeding papers, and book chapters were excluded from the screening process. Article selection was carried out in two stages, namely selection based on title and abstract, and selection based on full text.

The study quality assessment was conducted using the Mixed Methods Appraisal Tool (MMAT). The MMAT is a validated tool for assessing the methodological quality of studies of various designs, including qualitative, quantitative and mixed methods studies. The tool includes screening questions and items corresponding to five methodological domains: qualitative research, randomized controlled trials (RCTs), non-randomized studies (NRS), quantitative descriptive studies, and mixed methods studies (MMS). [19], [20].

Data from articles that passed the quality selection were extracted using NVivo software. Each article was coded in-vivo and grouped by research focus, i.e. BV indicators. The coding results in each focus were grouped based on similarities in meaning, and these groups became sub-codes of each focus. NVivo is widely used in systematic literature reviews for qualitative coding and analysis, ensuring systematic and reproducible results [21], [22], [23].

3. Result and Discussion

The number of publications related to the use of probiotics in the treatment of Bacterial Vaginosis from 2014 to 2024 has increased overall from year to year. The highest point was in 2021 which reached 127 articles. Although there are fluctuations, such as a decrease in 2015 and 2018, the number of publications still shows an upward trend. After reaching its peak in 2021, the number of publications experienced a slight decline, but remained at a fairly high level until 2023. In 2024, although the data is not yet complete, there were already 76

publications, indicating that research interest in this field continues. Despite fluctuations in some years, the publication trend remains upward, reflecting the growing recognition of the importance of the vaginal microbiome and its potential modulation through probiotics as a promising treatment strategy. While research interest continues, more studies are needed to understand the effectiveness, optimal dosage, most beneficial strains, and factors that influence the success of probiotic therapy in treating Bacterial Vaginosis.

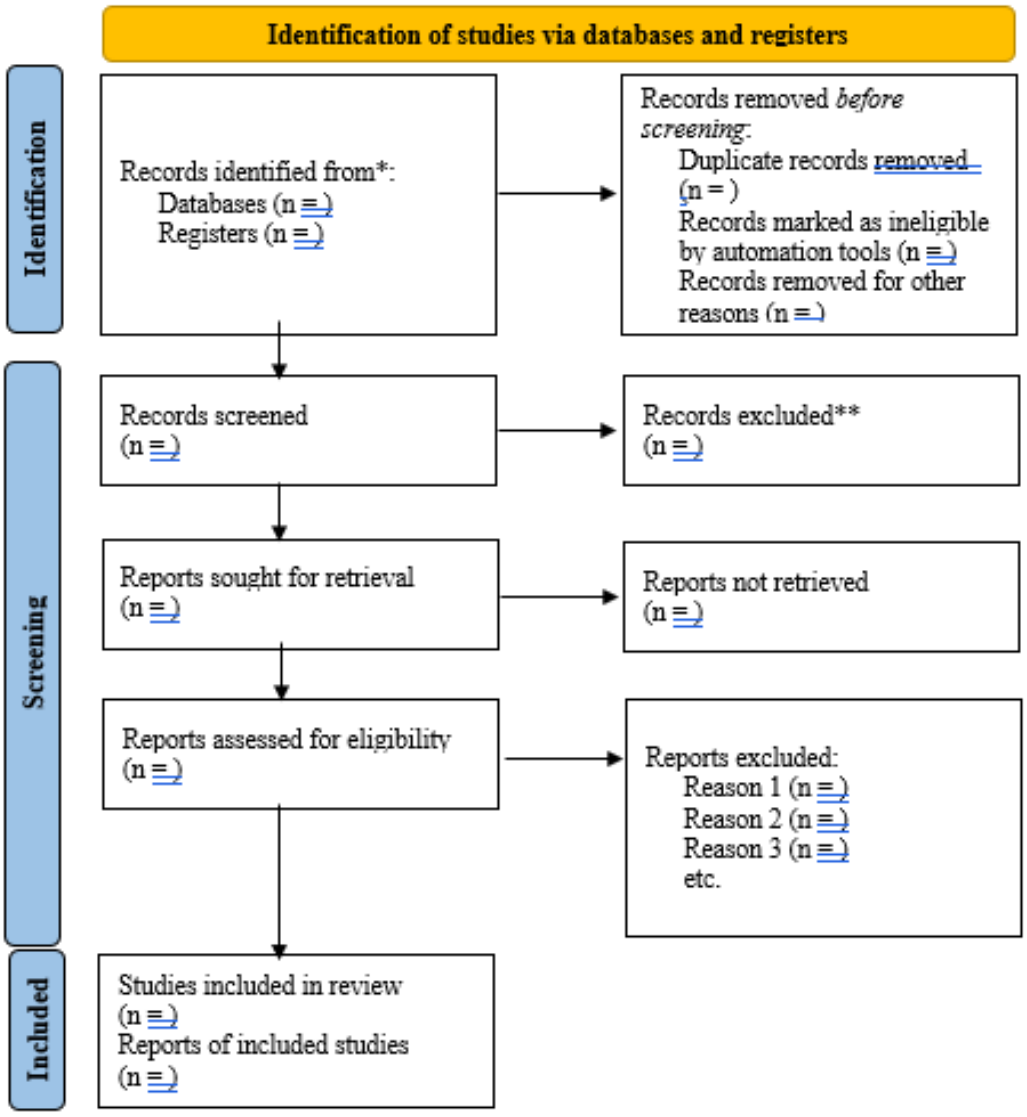

Figure 1. PRISMA Flowchart

This PRISMA flowchart illustrates the literature selection process in this systematic review on the use of probiotics for the treatment of bacterial vaginosis. At the identification stage, a total of 1405 records were obtained from searching three databases (Scopus, WoS, and PubMed), which were then filtered to 1024 records after duplicate removal. At the screening stage, 833 records were excluded for not meeting the inclusion and exclusion criteria, leaving 191 records. Of these, 32 articles could not be downloaded, so only 159 records were eligible for quality assessment.

At the quality assessment stage, 132 out of 159 records were excluded for not meeting the predefined standards, leaving 27 high-quality articles to be processed to the data extraction stage. Although the final number of articles included may seem small, these articles have undergone a rigorous selection process and meet high quality standards. Therefore, the results of the analysis and synthesis of these 27 articles are expected to provide strong and valid evidence to support the use of probiotics as one of the therapeutic modalities for bacterial vaginosis.

Table 1: Indicators of Bacterial Vaginosis (BV) Diagnosis

Indicator	Source of Supporting Articles
Amsel criteria: (1) presence of homogeneous, thin, gray to white vaginal fluid; (2) vaginal pH > 4.5; (3) positive whiff test with addition of 10% potassium hydroxide solution; (4) presence of clue cells on wet microscopy of vaginal fluid.	[1], [4], [10], [11], [24], [25], [26], [27]
Nugent score: a scoring system based on microscopic examination of the Gram stain of vaginal smears, with a score range of 0-10 (0-3: normal, 4-6: intermediate, 7-10: BV).	[3], [4], [5], [6], [8], [10], [11], [12], [13], [15], [24], [26], [27], [28], [29], [30], [31]
Vaginal pH: elevated vaginal pH (> 4.5) as an indication of vaginal microbiota imbalance	[2], [3], [4], [6], [9], [10], [11], [12], [13], [14], [15], [28], [29], [32], [33]
Clinical symptoms: abnormal vaginal discharge, unpleasant odor, itching or irritation of the genital area	[3], [4], [6], [13], [33]
Pro-inflammatory cytokines: increased levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) in vaginal fluid	[14], [31], [32], [33]
Clue cells: presence of clue cells on wet microscopy examination of vaginal fluid	[24], [26], [27]
Predominance of anaerobic bacteria: decreased number of Lactobacillus and increased growth of anaerobic bacteria in the vaginal microbiota	[2], [12], [31]
Increased numbers of specific pathogenic bacteria: increased Gardnerella vaginalis, Mobiluncus spp., Atopobium vaginae	[6], [9]
Decreased Lactobacillary grade: a decreased Lactobacillary grade score indicating a reduced number of Lactobacillus.	[4]
Increased vaginal epithelial exfoliation: increased vaginal epithelial exfoliation associated with intermediate Nugent scores	[8]

Based on the compiled tables and uploaded files, the following is an explanation and interpretation for each group of indicators used in the diagnosis of Bacterial Vaginosis (BV):

1. Amsel criteria: Amsel criteria is one of the most commonly used clinical diagnostic methods for BV. A diagnosis of BV is made if at least three of the four Amsel criteria are met, namely the presence of homogeneous, thin, gray to white vaginal discharge; vaginal pH > 4.5; a positive whiff test with the addition of 10% potassium hydroxide solution; and the presence of clue cells on wet microscopy of vaginal fluid. [1], [4], [10], [11], [24], [25], [26], [27]. The Amsel criteria provide a simple and rapid approach to the diagnosis of BV, but have limitations in terms of subjectivity and inter-observer variability. [11].

2. Nugent Score: The Nugent score is the gold standard method for diagnosis of BV based on microscopic examination of the Gram stain of a vaginal smear. The Nugent score uses a scoring system with a range of 0-10, where a score of 0-3 is considered normal, 4-6 intermediate, and 7-10 as BV. [3], [4], [5], [6], [8], [10], [11], [12], [13], [15], [24], [26], [27], [28], [29], [30], [31]. The Nugent score provides a more objective and standardized assessment than the Amsel criteria, but requires microscopic expertise and is not always available in all clinical settings. [11], [27].

3. Vaginal pH: Elevated vaginal pH (>4.5) is one of the indicators of vaginal microbiota imbalance often found in BV. This condition is caused by a decrease in the number of Lactobacillus which plays a role in maintaining vaginal acidity through lactic acid production. [2], [3], [4], [6], [9], [10], [11], [12], [13], [14], [15], [28], [29], [32], [33]. Vaginal pH measurement is a simple and quick method to assess vaginal health, but it is not specific to BV and can be affected by other factors such as menstruation or sexual activity. [12], [15].

4. Clinical symptoms: Clinical symptoms often reported by women with BV include abnormal vaginal discharge, unpleasant odor, and itching or irritation of the genital area. Although these symptoms are not specific for BV and may vary between individuals, their presence may support the diagnosis of BV along with laboratory investigations. [3], [4], [6], [13], [33]. However, it should be noted that approximately 50% of women with BV may be asymptomatic, so the diagnosis cannot rely solely on clinical symptoms. [3].

5. Pro-inflammatory cytokines: BV is associated with elevated levels of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α, in vaginal fluid. This increase in pro-inflammatory cytokines reflects an immune response to changes in the vaginal microbiota and potentially contributes to inflammatory symptoms as well as the risk of BV-related complications [14], [31], [32], [33]. Although pro-inflammatory cytokine screening may provide insight into the inflammatory status in BV, its use as a diagnostic indicator is still limited and requires further research [14], [31].

6. Clue cells: The presence of clue cells on wet microscopy examination of vaginal fluid is one of Amsel's criteria for the diagnosis of BV. Clue cells are vaginal epithelial cells that are enveloped by bacteria so that their surface looks blurred or jagged. [24], [26], [27]. The presence of clue cells reflects the disruption of the vaginal

microbiota and is an important indicator for the diagnosis of BV. [27]. However, identification of clue cells requires microscopic skills and can vary between observers. [24].

7. Dominance of anaerobic bacteria: BV is characterized by decreased numbers of Lactobacillus and increased growth of anaerobic bacteria in the vaginal microbiota. This shift in microbiota composition can be detected through microscopic examination or molecular techniques such as 16S rRNA gene sequencing [2], [12], [31]. The predominance of anaerobic bacteria reflects the disruption of vaginal ecology and plays an important role in the pathogenesis of BV [12]. However, interpretation of vaginal microbiota examination results can be complex and requires an understanding of the composition of the normal microbiota and its variation. [31].

8. Increased numbers of specific pathogenic bacteria: Some specific pathogenic bacteria, such as Gardnerella vaginalis, Mobiluncus spp. and Atopobium vaginae, are often found in increased numbers in women with BV. These increased numbers of bacteria can be detected through culture techniques or molecular examinations [6], [9]. Although the presence of specific pathogenic bacteria can support the diagnosis of BV, no single bacterial species can be used as a single diagnostic indicator for BV. [9]. Moreover, some of these bacteria can also be found in low numbers in women without BV [6].

9. Decreased Lactobacillary grade: Lactobacillary grade is a microscopic scoring system that describes the abundance of Lactobacillus in the vaginal microbiota. A decreased Lactobacillary grade score reflects a reduced number of Lactobacillus and can be an indicator of vaginal microbiota disorders, including BV [4]. Although Lactobacillary grade assessment can provide additional information on vaginal health, its use as a diagnostic indicator for BV is still limited and requires further standardization [4].

10. Increased exfoliation of the vaginal epithelium: Increased exfoliation of the vaginal epithelium has been associated with an intermediate Nugent score, reflecting disruption of the vaginal microbiota. This condition can be detected through microscopic examination and is potentially an early indicator of changes in the vaginal microbiota before progression to BV [8]. However, the clinical significance and specificity of increased vaginal epithelial exfoliation as a diagnostic indicator for BV still requires further research [8].

4. Discussion

The results of this systematic literature review show that there are various indicators used in the diagnosis of Bacterial Vaginosis (BV), including Amsel criteria, Nugent score, vaginal pH, clinical symptoms, pro-inflammatory cytokines, clue cells, predominance of anaerobic bacteria, increased numbers of specific pathogenic bacteria, decreased Lactobacillary grade, and increased vaginal epithelial exfoliation. The Amsel criteria and Nugent score are the most commonly used indicators, with the Nugent score being considered the gold standard in the diagnosis of BV [5], [10], [11]. While the Amsel criteria provide a simple and quick approach, the Nugent score provides a more objective and standardized assessment (Webb, 2021). These findings highlight the importance of using validated indicators to improve the accuracy of BV diagnosis.

The implication of these findings is the need to standardize and optimize the diagnosis of BV by utilizing validated indicators. Health practitioners can use a combination of indicators, such as the Amsel criteria and Nugent score, to improve the sensitivity and specificity of diagnosis. [24], [28]. In addition, the introduction of additional indicators, such as vaginal pH and pro-inflammatory cytokines, can provide valuable information about vaginal health status and the immune response to BV. [14], [32]. Standardization of BV diagnosis based on valid indicators may help in proper management and prevention of related complications.

The results of this study are in line with findings from previous studies highlighting the important role of Amsel criteria and Nugent score in the diagnosis of BV [10], [34], [35]. However, several studies have also pointed out the limitations of the Amsel criteria in terms of subjectivity and inter-observer variability [11], [27]. This study provides a more comprehensive picture by identifying additional indicators, such as vaginal pH, clinical symptoms, and changes in vaginal microbiota, which may complement existing diagnostic criteria. [2], [6], [9].

Although this systematic literature review provides important insights into BV indicators, there are several limitations to consider. First, heterogeneity in study design, population, and diagnosis methods may affect the comparability and generalizability of findings [27]. Secondly, most of the included studies focused on the reproductive-age female population, so the applicability of the findings to other age groups may be limited. [7].

Based on these limitations, further research is needed to address knowledge gaps and strengthen these findings.

Prospective studies with standardized designs and more diverse populations may provide stronger evidence on the validity and applicability of BV indicators. [14], [15]. In addition, further research is needed to explore potential new biomarkers, such as metabolite profiles or gene expression, that may improve the accuracy of BV diagnosis. [1], [31]. The integration of multi-omics and machine learning approaches may also open new opportunities in the development of more sensitive and specific diagnostic tools for BV. [3].

5. Conclusions

This systematic literature review identified various indicators used in the diagnosis of Bacterial Vaginosis (BV), including Amsel criteria, Nugent score, vaginal pH, clinical symptoms, pro-inflammatory cytokines, clue cells, predominance of anaerobic bacteria, increased numbers of specific pathogenic bacteria, decreased Lactobacillary grade, and increased exfoliation of vaginal epithelium. Amsel criteria and Nugent score are the most commonly used indicators, with Nugent score considered the gold standard in the diagnosis of BV. These findings highlight the importance of using validated indicators to improve the accuracy of BV diagnosis.

The implication of these findings is the need for standardization and optimization of BV diagnosis by utilizing validated indicators. Health practitioners can use a combination of indicators to improve the sensitivity and specificity of diagnosis. In addition, the introduction of additional indicators, such as vaginal pH and pro-inflammatory cytokines, may provide valuable information on vaginal health status and immune response to BV. Standardization of BV diagnosis based on valid indicators may help in proper management and prevention of associated complications.

This study makes an important contribution in comprehensively assessing the indicators used in BV diagnosis. By identifying the strengths and limitations of existing indicators, as well as exploring the potential for additional indicators, this study may help improve the accuracy and efficiency of BV diagnosis. This may ultimately lead to improved quality of care and clinical outcomes for women affected by BV.

Nonetheless, further research is needed to address existing limitations and strengthen these findings. Prospective studies with standardized designs and more diverse populations may provide stronger evidence on the validity and applicability of BV indicators. In addition, the exploration of potential new biomarkers, such as metabolite profiles or gene expression, as well as the integration of multi-omics and machine learning approaches, may open new opportunities in the development of more sensitive and specific diagnostic tools for BV.

Considering the findings and implications of this systematic literature review, improvements in the diagnosis and management of BV are expected in the future. Standardization of indicators and development of more accurate and efficient diagnostic approaches may contribute to improving vaginal health and quality of life of women globally.

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