

Review Article

Gardnerella vaginalis as a cause of septicemia and bacteremia: A systematic review

Khadijeh Ahmadi¹, Omid Poursmaeil², Alireza Mohammadzadeh³, Fatemeh Nemati Shahri⁴, Maryam Afzali⁵, Jalil Moshari⁶, Abolfazl Sharifi⁴, Jalal Mardaneh^{3*}

¹Abadan University of Medical Sciences, Abadan, Iran.

²Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

³Department of Microbiology, School of Medicine, Infectious Diseases Research Center, Gonabad University of Medical Sciences, Gonabad, Iran.

⁴Infectious Diseases Research Center, Gonabad University of Medical Sciences, Gonabad, Iran.

⁵Innovative Medical Research Center and Department of Microbiology, Mashhad Branch Islamic Azad University, Mashhad, Iran..

⁶Department of Pediatrics, School of Medicine, Gonabad University of Medical Sciences, Gonabad, Iran.

Abstract. *Gardnerella vaginalis* is a facultative anaerobic gram-negative bacterium that can be sexually transmitted and usually causes genital infections such as vaginitis. This microorganism is an opportunistic pathogen and in addition to genital infections, it can also cause invasive infections. We searched various English articles published between January 1980 and October 2021 in the database Medline, EMBASE, Web of Science, Google Scholar, PubMed, Scopus, Research Gate. Data were extracted based on the characteristics and quality of the study. We studied 20 case report articles of bacteremia and sepsis caused by *Gardnerella vaginalis* from different parts of the body. Cases included men and women with different clinical conditions in different age groups. This factor may not be considered because the microbiological diagnosis of *Gardnerella vaginalis* is difficult and is not detected by routine culture media. Most of the cases reported in these articles were treatable. In conclusion, physicians should consider the association of this bacterium with invasive infections such as bacteremia and sepsis. The use of specific culture media and new microbiological methods can quickly identify this microorganism and show its role in invasive and systemic infections more clearly.

Keywords: *Gardnerella vaginalis*; septicemia; bacteremia; systematic review

Introduction

Gardnerella vaginalis is a variable gram bacillus, facultative anaerobe, non-spore-forming, non-motile, non-capsulated, urease, catalase, and oxidase negative, it was first introduced by Leopold in 1953 and was named *Haemophilus vaginalis*, then changed to *Corynebacterium vaginale* in honor of Herman Gardner and later to *Gardnerella vaginalis* [1, 2]. Although this bacterium is considered as commensals of vaginal flora, it can also be considered as a pathogen of the genital tract of women. *G. vaginalis* factor virulence is not well identified. The hemolysin and sialidase produced by this bacterium cause mucosal invasion and tissue damage, and its teichoic acids can also cause inflammatory responses [3, 4]. *G. vaginalis* is commonly associated with bacterial vaginosis (BV) in women, but also in cases of gestational sepsis, endometritis and septic abortion [5, 6], bacteremia after

vaginal myomectomy, vertebral osteomyelitis, prostate adenoma [7], asymptomatic bacteremia, urinary tract infection, septic emboli, urethritis, endocarditis has also been reported [8]. *G. vaginalis* is also associated with maternal and neonatal sepsis [9]. Although these are rare, physicians should consider *G. vaginalis* as a potential pathogen when treating these types of infections. This study is to update the knowledge about the relationship between *G. vaginalis* isolated from human and septic samples. In recent years, no comprehensive study of septicemia and bacteremia caused by *G. vaginalis* in patients has been performed. In this study, a systematic review was performed to update the knowledge about the relationship between *G. vaginalis* isolated from human specimens and the incidence of sepsis and bacteremia.

*Corresponding author: Dr. Jalal Mardaneh
(jalalmardaneh@yahoo.com)

Materials and Methods

Research databases

In this systematic review study, we searched for articles in English in electronic databases (Medline, EMBASE, Web of Science, Google Scholar, PubMed, Scopus, Research Gate. "*Gardnerella*" or "*Gardnerella vaginalis*" or "septicemia" or "bacteremia" and "sepsis" were used as search strategies. All studies available on the internet as of October 2021 focusing on septicemia/bacteremia caused by *Gardnerella vaginalis* groups of different patients were considered for the study.

Study selection

Inclusion criteria included studies conducted between January 1980 and October 2021 and included only cases of sepsis and bacteremia caused by *Gardnerella vaginalis*. Studies performed outside the mentioned period and other infections caused by *Gardnerella vaginalis* and septicemia and bacteremia caused by other bacteria were considered as exclusion criteria.

Data extraction

The authors of the present study independently extracted the important variables of all the studies that included the inclusion criteria. Information about the first author, study area, year of study, gender, age and clinical condition of the patient, source of sample isolation, antibiotic prescribed by a physician, physician's final diagnosis, treatment outcome, and microbial infection were recorded. To ensure the accuracy of the entered information, data extraction was performed at least twice and also predefined forms were used.

Assessment of study quality

The Joanna Briggs Institute (JBI) Critical Evaluation Checklist (Table 1) was used for the quality assessment of studies. JBI consists of eight key questions:

1. Were the patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?
4. Were diagnostic tests or assessment methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?

The assessment was carried out by two reviewers separately and each of the above questions was answered as yes, Unclear, not applicable, or no, the disagreements between reviewers were resolved by consensus.

Results

After removing duplicate studies and irrelevant articles, a total of 20 articles were obtained using keywords from the database, as shown in supplementary data; TableS1.

Twenty case report articles matched the inclusion criteria of the present study (supplementary data; FigureS1). The most important inclusion criteria were septicemia and bacteremia caused by *Gardnerella vaginalis*. The information reviewed in the articles included: authors, year of publication, project location, age and sex, medical history, source of isolation, method of diagnosis, final diagnosis, treatment, and outcome. All data are shown in supplementary data; TableS1.

Quality appraisal

The overall quality of the cases was good to moderate.

Demographic and epidemiological characteristics

A total of 20 patients with bacteremia or sepsis caused by *Gardnerella vaginalis* were studied alone or in combination with other bacteria. The mean age of patients was 38 years (range 2-77) and 50% of patients were female. In total, 65% (13/20) of patients had one or more underlying diseases. The details of each are described in supplementary data; TableS1.

Methods of diagnosis

Gardnerella vaginalis was isolated from blood samples in 18 cases (90%) of patients and was isolated to a lesser extent than urine and pleural fluid culture and tracheal aspiration samples.

The final diagnosis

The final diagnosis was septicemia and bacteremia in most patients and was reported in only two cases pulmonary edema and Pyelonephritis due to *Gardnerella vaginalis*.

Treatment and outcome

Of the 20 patients studied, 8 (40%) were treated with metronidazole. Of these, two patients received only metronidazole, while others received it in combination with other antibiotics. Four patients (20%) used vancomycin, all four of which were combined with other antibiotics. The other antibiotics used are shown in supplementary data; TableS1. Overall, only one in 10 patients with the underlying disease died, and the other patients responded well to treatment and survived.

Polymicrobial infections

In 15% (3/20) of patients, other bacteria are isolated in addition to *Gardnerella vaginalis*.

Discussion

Gardnerella vaginalis is a gram-dependent coccobacillus that is part of the natural flora of some women's reproductive tract but can also be considered a local pathogen. In women, the microorganism is usually associated with vaginal infections, but can also cause significant systemic disease. Asymptomatic men can also be considered a reservoir for this microorganism. *Gardnerella* affects different age groups and factors such as immuno-

TABLE 1
REPORTED CASES AND THEIR QUALITY APPRAISAL

Authors/year	Patient demographics	patient's history	clinical condition of the patient	diagnostic tests or assessment methods and result	treatment	post-intervention clinical condition	adverse events (harms) or unanticipated events
Datsomor E et al ¹⁰ 2021	YES	YES	YES	YES	YES	YES	Unclear
Alfraji N et al ¹¹ 2020	YES	YES	YES	YES	YES	YES	YES
Taillandier P ¹² 2020	YES	YES	YES	YES	YES	YES	NO
Murray Let al ¹³ 2019	YES	YES	YES	YES	YES	YES	YES
Bhatia P et al ¹⁴ 2018	YES	YES	YES	YES	YES	YES	Unclear
Pritchard H et al ¹⁵ 2018	YES	YES	YES	YES	YES	YES	YES
Saikali P et al ¹⁶ 2016	YES	YES	YES	YES	YES	YES	NO
Babics A. et al ¹⁷ 2015	YES	YES	YES	YES	YES	YES	YES
McCool R. et al ¹⁸ 2012	YES	YES	YES	YES	YES	YES	YES
Yoon HJ et al ¹⁹ 2010	YES	YES	YES	YES	YES	YES	YES
Philippe R et al ²⁰ 2008	YES	YES	YES	YES	YES	Unclear	Unclear
Agostini et al ⁵ 2003	YES	YES	YES	YES	YES	YES	YES
Amaya RA et al ²¹ 2002	YES	YES	YES	YES	YES	YES	YES
Florez C et Al ²² 1994	YES	YES	YES	YES	YES	Unclear	NO
Denoyel G et al ⁷ 1990	YES	YES	YES	YES	YES	YES	YES
Legrand J et al ²³ 1989	YES	YES	YES	Not applicable	Not applicable	Not applicable	Not applicable
Wilson JA et al. ²⁴ 1989	YES	YES	YES	YES	YES	YES	Unclear
DeBrucker P. et al ²⁵ 1986	YES	YES	YES	YES	YES	YES	Unclear
Leonard J et al. ²⁶ 1984	YES	YES	YES	YES	YES	Unclear	Unclear

suppression, anatomical abnormalities of the genital tract and alcoholism and diabetes, chronic diseases, etc. are considered as risk factors for this type of infection [23, 27].

In the articles studied in this study, bacteremia and septicemia caused by *Gardnerella vaginalis* in patients with diabetes, pyelonephritis, immune deficiency, chronic pelvic disease, cancer, and medical interventions including catheter endometrial ablation were reported in different age groups. According to the above, all of these cases can be considered as a risk factor for this infection. In one case, patients reported definite symptoms of inhaled bronchopneumonia with abscesses and sepsis, partly due to *Gardnerella vaginalis*, but as the patient died, it was not possible to further investigate the microorganisms in his oral cavity [23]. *Gardnerella* contains the enzymes hemolysin and sialidase. These enzymes cause hydrolysis of sialic acid on the mucosal surfaces and facilitate the penetration of bacteria into the epithelial cells of the vagina and play a role in escaping the mucosal immune system and local tissue damage. The attack causes a systemic

Inflammatory reaction. The bacterium alkalizes the environment by synthesizing biogenic amines from glycogen, reducing the activity of lactobacilli and facilitating their growth. Other factors, including sexually transmitted infections and hormonal changes can exacerbate these changes [28, 29].

Atopobium vaginae also can cause these changes, which has been isolated in one of the articles studied in this study. This bacterium can produce the enzyme vaginolysin, which is attached. And systemic infection is involved. It also can form biofilms and increase the severity of pathogenesis. Pathogenic strains show greater biofilm formation capacity, increased membrane adhesion, and toxicocytic properties, all of which invade host cells [12]. Obstetrics and gynecological procedures such as cesarean section, curettage, intrauterine device placement, vaginal hysterectomy may introduce this bacterium from the vaginal epithelium to the upper genital tract or into the bloodstream. *Gardnerella* bacteremia is more common than other invasive infections that could be due to its resistance to serum antibacterial activity [30].

In some of the articles studied in the present study, bacteremia was reported after gynecological infections, one of which was preterm delivery and spontaneous abortion [22]. In one case, women were separated from tracheal aspiration after delivery, in which case there is a hypothesis that oral aspiration of body secretions may have occurred during vaginal delivery [16, 21]. The articles showed that the most isolation was related to blood culture because blood culture vials contain an enriched broth. However, more than half of the patients were only one of the 2 positive blood cultures, which could be due to the sampling time and use of broad-spectrum antibiotics in the days before hospitalization. In addition, blood culture vials often contain sodium anticoagulant polyethanol sulfonate, which inhibits the growth of *G. vaginalis* [16]. In most of the articles studied in this study, metronidazole has been used for treatment. The rate of metronidazole release in the body is high and it has oxidative metabolism in the liver and its urinary and plasma concentration can inhibit *G. vaginalis* [8].

Conclusion

The articles reviewed in this study showed that *Gardnerella vaginalis* is also involved in extrarenal infections and can cause local and systemic infections. The bacterium does not grow in common urine culture media and is sensitive to beta-lactams and macrolides, and these two agents are commonly used in the treatment of urethritis, so they are not easily isolated by microbiologists and require specific culture media. Microbiologists should consider *G. vaginalis* gram-negative or gram-variable bacilli that grow slowly and possibly increase their isolation and identification using specific culture media. Physicians should also consider the association of this bacterium with invasive infections such as bacteremia and septicemia.

Conflict of interest

The authors declare no conflicts of interest.

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