Atopobium vaginae: a literature review on findings and potential clinical implications

Andrea Mariano[1], Angelo Salzo[1], Valentina Felice[2], Massimiliano Scutellà[2]

[1]Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso; [2]Complex Operating Unit of Laboratory Medicine, Civil Hospital "A. Cardarelli", Campobasso, Italy

Summary

Atopobium vaginae is an anaerobic Gram-positive bacterium. It is recognized as a causal agent of bacterial vaginosis onset and occasionally associated to gynaecologic-obstetric complications (including pelvic inflammatory disease, endometritis, tubo-ovarian abscesses and preterm delivery with neonatal consequences). Additionally, bacteraemia and invasive infections have rarely been reported. The scientific and technological progress allowed an accurate and rapid identification of *Atopobium vaginae* supporting diagnosis and clinic interventions. In this article, literature has been deeply examined to report the state-of-the-art on *Atopobium vaginae*, which might be useful in clinical scenarios.

Correspondence: Andrea Mariano, Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Via Francesco De Sanctis 1, 86100 Campobasso, Italy.
E-mail: a.mariano989@gmail.com

Key words: *Atopobium vaginae*, bacterial vaginosis, bacteraemia, invasive infection, 16S rRNA gene sequencing, MALDI TOF-MS.

Acknowledgements: the authors thank Ms. Diana Isabel Fanelli for helping in the linguistic review.

Contributions: AM as corresponding author contributed to literature search, data collection and interpretation, to prepare tables and writing the article; all the other authors contributed equally to the drafting.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received for publication: 20 December 2018.
Revision received: 11 April 2019.
Accepted for publication: 11 April 2019.

Microbiologia Medica 2019; 34:8014
doi:10.4081/mm.2019.8014

Introduction

Atopobium vaginae (*A. vaginae*) is an anaerobic Gram-positive bacterium which is part of the genus *Atopobium*. This genus was introduced by Collins and Wallbanks in 1992 to reclassify formerly identified *Lactobacillus minutus*, *Lactobacillus rimae* and *Streptococcus parvulus* bacteria, demonstrating their linkage by the 16S ribosomal RNA(16S rRNA) gene sequencing (9). *A. vaginae,* described in 1999 (45), and *Atopobium deltae* in 2014, both validated by the same abovementioned method, were subsequently added to this genus. Further studies on *A. vaginae* included: bacterium identification, possible physiologic functions, its role in bacterial vaginosis (BV) onset, relationships with *Gardnerella vaginalis* (*G. vaginalis*), gynecologic-obstetric implications, its pathogenetic activities in invasive infections and an adequate prophylactic and antibiotic treatment.

The purpose of this article is to give an overview on *A. vaginae* by critically evaluating recent emerged studies in different fields, also emphasizing its clinical relevance, common traits and generally recognized characteristics, due to the availability of multiple strains.

Background and clinical relevance

A. vaginae was firstly described by Rodriguez Jovita as a Gram-positive elliptical or rod-shaped coccus bacterium, which occurs singly, in pairs or in short chains, non-mobile, asporigenous and non-capsulated, which measures approximately 0.6-0,9 µm, forming small clear colonies similar to tiny pinheads, in cultures on Columbia blood agar at 37°C. Although being described as a facultative anaerobic bacterium (45), it was subsequently classified as a strict anaerobe (15,19). The production of lactic acid (common feature of the genus *Atopobium)* (5,14,23,45), led to assimilate *A. vaginae* function to the lactobacilli one as a component of the physiological vaginal ecosystem, which prevents the growth of undesirable microorganisms. A further biochemical characterization (analytical profile index, API), allowed the discrimination of two enzymes exclusively expressed by *A. vaginae*: histidine arylamidase and serine arylamidase (with a profile partially common to *A. deltae*, as subsequently tested, and far from other members of the genus *Atopobium*) (10,45) (Table 1).

A. vaginae isolation from a healthy woman vaginal flora, in Göteborg (Sweden), suggested that it is a normal saprophyte of healthy vaginal flora (5,45), with the possibility of becoming predominant in favourable conditions, such as a decrease in normal lactobacillary flora (45). This hypothesis was supported by the metabolic features of the genus *Atopobium*, which prefers habitats

rich in proteins that are used as an energy source (14,27,29). This scenario usually occurs in postmenopausal women, who present a reduction of vaginal epithelial cells glycogen production (1,4,6,7), with a possible shift of vaginal microbiota from lactobacilli to other species. Indeed, subjects on hormone therapy have a lower incidence of *A. vaginae* (5); in fact, it has also been demonstrated that the use of vaginal estriol can lead to a recovery of the normal lactobacilli flora, with a reduced risk of infections (5,44).

However, this hypothesis is not supported by the coexistence of this bacterium with *G. vaginalis* in BV (55).

Indeed, evidence suggests a direct relationship between the reduction of lactobacillary bacteria and the increase of *A. vaginae* and *G. vaginalis* in BV (2). These two species appeared specific for BV, with *A. vaginae* being more recurrent than *G. vaginalis*. (2,18,48). Furthermore, it should be noted that these two bacteria may be present with a low bacterial load in healthy women vagina without complications (20). In fact, vaginal microbiota is not a static structure (43). The cervicovaginal microflora of women is variable, according to their ethnicity, age and pregnancy status (17,46,57). BV is associated with high counts of *G. vaginalis* and/or the presence of a polymicrobial biofilm containing *G. vaginalis* (25,26,40,49,50,51,54). The strong adherence and the biofilm-forming capacities to vaginal epithelium suggests that *G. vaginalis* might be an initiator of the vaginal colonization, subsequently favouring adhesion of other species (21,32,50), one of them being *A. vaginae* (5,15). Furthermore, several molecular studies have indicated a probable role of *A. vaginae* in BV (5,34,56) and in the establishment of a biofilm together with *G. vaginalis* (50,51). Considering its presence in 80-90% of cases of relapse (2) and the in-vitro metronidazole resistance of some strains (12), *A. vaginae* could be relevant in BV recurrence after standard treatment with metronidazole. Although the Nugent score is the laboratory BV detection gold standard (38), its sensitivity could be compromised by interobserver variability in the vaginal smears grading (34,55).

Several studies have proposed a molecular diagnosis of BV, targeting a combination of BV-related bacteria in a polymerase chain reaction (PCR), after an evaluation of the threshold concentrations of these bacteria (30,34). Others suggested the fluorescence *in situ* hybridization (FISH), to study the biofilm structure and composition. The labelling of the cells with a fluorescent probe tailored for *A. vaginae* (21) together with a probe for *G. vaginalis* (31) and a universal bacterial probe (41) allows to investigate the composition of vaginal biofilm in BV (22). Although further studies are needed to explain the biofilm role and the bacterial implication in BV, there are strong indications towards the relevance of *A. vaginae* and its symbiosis with *G. vaginalis* in the biofilm pathogenic activities leading to BV onset (22).

In addition to the emphasized role in BV (2,15,22,34,39), *A. vaginae* has been associated with a higher risk of preterm births (3,35,37).

However, invasive infections caused by *A. vaginae*, including bacteraemia until today have been reported in only seven patients (8,11,19,24,28,33,58). Although rare, these cases demonstrated the pathogenetic potential of this bacterium, especially after invasive medical-diagnostic procedures (Table 2).

Diagnosis and treatment

An accurate and rapid identification of *A. vaginae* is necessary to support the diagnosis and guide clinic interventions and treatments with the best outcomes for patients. Samples and methods used for *A. vaginae* detection are various, depending on the nature of the infection and its presentation. In studies carried out on BV and vaginal microflora, samples usually consist in vaginal swabs or vaginal lavage fluid (15,45), while in bacteraemia and invasive infections there are different specimens, for example blood, swabs or organic material from the infection site (8,11,19,24,28,33,58).

Different laboratory methods need to be considered. The Gram stain with the Nugent scoring is a BV diagnostic method, which is simple, inexpensive, and well suited to resource-limited settings, but it might present problems related to subjective interpretations. Additionally, the composition profile of the vaginal microbiota resulting from vaginal swab could be inaccurate (6,36,38).

The classical culture method on plate resulted difficult to apply, although fundamental to prove the bacterium presence, considering *A. vaginae* a strict anaerobic microorganism (15,19). This problem has been partially solved by the introduction of automatic systems, with a reduction in manipulation and sample collection (blood and infected liquid material) directly in anaerobic bottles.

Table 1. Differential biochemical features among members of the genus *Atopobium*.

Biochemical features	*A. deltae*	*A. fossor*	*A. minutum*	*A. parvulum*	*A. rimae*	*A. vaginae*
Acidification of D-mannose	P	P	P	P	P	N
Alanine arylamidase	P	ND	N	P	N	N
Arginine dihydrolase	P	ND	P	N	N	P
Arginine arylamidase	P	ND	P	P	N	P
Histidinearylamidase	P	ND	N	N	N	P
b-Galactosidase	N	ND	N	P	N	N
Leucine arylamidase	P	ND	N	P	N	P
Proline arylamidase	P	ND	P	N	N	P
Pyroglutamic acid arylamidase	N	ND	V	P	P	N
Glycinearylamidase	P	ND	N	P	N	P
Serine arylamidase	P	ND	N	N	N	P
Tyrosinearylamidase	P	ND	N	P	N	N
Phenylalaninearylamidase	P	ND	ND	ND	ND	WP or N
Aesculinhydrolysis	N	ND	ND	P	ND	N

Data from Cools *et al.* 2014 (10). N, negative; P, positive; V, variable; WP, weakly positive; ND, not determined.

However, this diagnostic technique is time-dependent and limiting in urgencies (56).

Upon the last technological and database progresses, the Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) may be a good compromise in precision, processing time and samples preparation, with the only limit in equipment costs. Indeed, its use helps in the diagnosis of almost all the invasive cases of infection caused by *A. vaginae* (11,24,33,58).

Lastly, the 16S rRNA gene sequencing could be considered a useful alternative method for a rapid and accurate bacterium detection (8) and applicable upon different matrices, as demonstrated by several cases reported in literature (8,11,19,24,28,33,58). Indeed, PCR assays methods are considered sensitive and specific diagnostic tools, as they can provide additional information on microbial species presence and load in a semi-quantitative and rapid manner (13,15,18,30).

Regarding *A. vaginae* antimicrobial susceptibility, limited data are available. Initially, it had been proved to be resistant to metronidazole (18), with the recommendation to treat the bacterium-supported BV with clindamycin. Recently, despite these results, a metronidazole sensible strain has been isolated (47). In this regard, the study that best characterizes *A. vaginae* antimicrobial susceptibility was carried out by De Backer et al. (12), who studied nine reference bacterial strains. Data reported in literature indicate that penicillin and clindamycin are effective agents (sensitivity generally conserved), while the combination amoxicillin-clavulanic acid is the recommended therapy in most cases of invasive infections reported so far (11) (Table 2). Further studies have been carried out in order

Table 2. Summary of *Atopobium vaginae* invasive infections cases reported in literature

Gender/Age/Patient's notes	Clinical presentation	Identification method/Matrix	Treatment	Outcome	References
Female/39 years/subfertility due to endometriosis	Tubo-ovarian abscess after transvaginal puncture (left lower abdominal pain for 3 days, 2-3 months after transvaginal oocyte recovery)	16S rRNA gene sequencing/Abscess swab	Antimicrobials therapy: intravenous cefoxitin and metronidazole for 5 days and surgical intervention (hysterectomy, bilateral salpingectomy, left-sided ovariectomy, appendectomy, and adhesiolysis)	Discharged 10 days after operation and recovery	(19)
Female/33 years/caesarean section	Uterine endometritis (lower abdominal pain for 3 days, malodorous vaginal discharge)	16S rRNA gene sequencing/Intrauterine content	Antimicrobials therapy: oral amoxicillin for 4 days then intravenous meropenem for 2 days	Discharged after clinical remission with a good recovery	(58)
Female/40 years/3 vaginal deliveries, 1 spontaneous miscarriage, 1 induced abortion, 1 ectopic pregnancy with tubal removal	12 week pregnant; bloodstained vaginal discharge, fever, chills and vomiting after a chorionic villus sampling	MALDI-TOF MS and 16S rRNA gene sequencing/Blood and cervical sample	Antimicrobials therapy: intravenous cefuroxime for 4 days and then oral amoxicillin for 2 weeks and aspiration curettage or the dead foetus removal	Foetal loss and discharge 5 days after maternal recovery	(28)
Female/33 years/4 pregnancies, 1 induced abortion and 2 vaginal deliveries	39 week pregnant; spontaneous maternal bacteremia with fetal distress after onset of labor (fever, fetal distress)	16S rRNA gene sequencing/Blood	Antimicrobials therapy: intravenous and then oral amoxicillin clavulanate for 2 weeks, and emergency Lower segment caesarean section	Favourable outcome, with a healthy neonate and discharge 4 days post-partum with a good maternal recovery	(8)
Female/38 years/3 pregnancies and 2 vaginal deliveries	13 week pregnant; vaginal bleeding, fever, fatigue, and myalgia in the presence of a subchorionic hematoma	MALDI-TOF MS and 16S rRNA gene sequencing/Blood	Antimicrobials therapy: intravenous amoxicillin/clavulanic acid for 5 days, then oral amoxicillin for 3 weeks	Favourable evolution under antibiotic therapy with spontaneous resolution of the hematoma. Preterm premature rupture of membranes at week 20 with termination of pregnancy	(24)
Female/29 years/healthy primipara	39 week pregnant; spontaneous maternal bacteremia with fetal distress after onset of labor (fever, fetal distress)	MALDI-TOF MS and 16S rRNA gene sequencing/Blood	Antimicrobials therapy: intravenous amoxicillin/clavulanic acid for 3 days, then oral amoxicillin/clavulanic acid	Favourable outcome, with a healthy neonate and discharge 3 days post-partum with a good maternal recovery	(11)
Female/18 years/type 1 diabetes with erratic glycaemic control, poor dental hygiene and a previous vulval abscess self-treated with subcutaneous needles	Infective endocarditis (reported a tricuspid valve vegetation), bacteraemia, abdominal pain and haemoptysis	MALDI-TOF MS and 16S rRNA gene sequencing/Blood	Surgical excision of tricuspid valve vegetation with postoperative antimicrobials therapy: intravenous vancomycin for 4 weeks	Favourable outcome with a good recovery	(33)

to investigate a therapeutic profile valid in BV treatment (52). Despite the resistance profiles, supported by biofilm and other bacterial species (52), nifuratel has been identified as a possible solution (53), considering its effectiveness on pathogenic strains and respectfulness of lactobacillary-resident microbial flora (42,53).

Conclusions and perspectives

In conclusion, *A. vaginae* gained a relevance only in relatively recent times. With the last technological upgrades and scientific progresses, its detection and identification have become easier. This led to study and understand more about its pathogenic potential, which was unknown in the past. Firstly, considered as a normal saprophyte of the healthy vaginal flora, it is now recognized as one of the causal agents of BV and is occasionally associated to gynaecologic-obstetric complications, potentially also causing bacteraemia and invasive infections. On the basis of reported data, especially where patients referred a gynaecologic-obstetric story suggestive of bacterial infection, the presence of *A. vaginae* should be assessed during clinic evaluation and diagnostic process. Although further studies are necessary about *A. vaginae*, its role and implications result more interesting than those proposed in the past and, therefore, deserve a deeper clinical investigation.

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