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Sneathia: an emerging pathogen in female reproductive disease and adverse perinatal outcomes

Kevin R. Theis[a,b,†,*], **Violetta Florova**[a,c,†], **Roberto Romero**[a,d,e,f,g,h], **Andrei B. Borisov**[a,c], **Andrew D. Winters**[a,b], **Jose Galaz**[a,c], **Nardhy Gomez-Lopez**[a,b,c,*]

[a]Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, U. S. Department of Health and Human Services, Bethesda, Maryland, and Detroit, Michigan, USA

[b]Department of Biochemistry, Microbiology, and Immunology, Wayne State University School of Medicine, Detroit, Michigan, USA

[c]Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, USA

[d]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan, USA

[e]Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, Michigan, USA

[f]Center for Molecular Medicine and Genetics, Wayne State University, Detroit, Michigan, USA

[g]Detroit Medical Center, Detroit, Michigan, USA

[h]Department of Obstetrics and Gynecology, Florida International University, Miami, Florida, USA

Abstract

Sneathia is an emerging pathogen implicated in adverse reproductive and perinatal outcomes. Although scarce, emerging data suggest that vaginally residing *Sneathia* becomes pathogenic following its ascension into the upper urogenital tract, amniotic fluid, placenta, and fetal membranes. The role of *Sneathia* in women's health and disease is generally underappreciated because the cultivation of these bacteria is limited by their complex nutritional requirements, slow growth patterns, and anaerobic nature. For this reason, molecular methods are typically required for the detection and differential diagnosis of *Sneathia* infections. Here, we review the laboratory methods used for the diagnosis of *Sneathia* infections, the molecular mechanisms underlying its virulence, and its sensitivity to antibiotics. We further review the evidence of *Sneathia*'s contributions to the pathogenesis of bacterial vaginosis, chorioamnionitis, preterm prelabor rupture

[*]**Address correspondence to:** Kevin R. Theis, PhD, Department of Biochemistry, Microbiology and Immunology, Wayne State University School of Medicine, Perinatology Research Branch, NICHD/NIH/DHHS, 540 East Canfield, Michigan 48201, USA, Tel (313) 577-0877, ktheis@med.wayne.edu, Nardhy Gomez-Lopez, MSc, PhD, Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Perinatology Research Branch, NICHD/NIH/DHHS, 275 E. Hancock, Detroit, Michigan 48201, USA, Tel (313) 577-8904, ngomezlo@med.wayne.edu.

[†]These authors contributed equally to this work.

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of membranes, spontaneous preterm labor, stillbirth, maternal and neonatal sepsis, HIV infection, and cervical cancer. Collectively, growing evidence indicates that *Sneathia* represents an important yet underappreciated pathogen affecting the development and progression of several adverse clinical conditions diagnosed in pregnant and non-pregnant women, as well as in their neonates.

Keywords

preterm birth; preterm prelabor rupture of membranes (PPROM); bacterial vaginosis; vaginal biofilm; cervical cancer

Introduction

Sneathia is a genus of Gram-negative, rod-shaped, anaerobic, non-motile bacteria recently identified as an important contributor to common obstetric [1–11], neonatal [12–14] and gynecologic pathologies [15–19]. Taxonomically, *Sneathia* belongs to the family *Leptotrichiaceae*, which consists of a heterogeneous group of species with diverse metabolic and genetic characteristics [20, 21]. All members of this family are obligate or facultative anaerobes, have fermentative metabolisms, and are non-spore forming [22]. They typically reside on the mucosal surfaces of the oral cavity [23, 24], gastrointestinal tract [23–26] and the urogenital system [23, 24, 27, 28], and several species within this family are documented human pathogens [21, 24, 28, 29].

The genus *Sneathia* is closely related to that of *Leptotrichia*. Indeed, *Sneathia* species were initially classified within the genus *Leptotrichia* [12]. These two genera share several common properties, such as close 16S rRNA gene sequence similarity and the production of lactic acid [30]. However, compared to *Leptotrichia, Sneathia* is more fastidious, requires culture media with serum or blood for growth, and, with respect to enzymatic reactions, *Sneathia* produces β-glucuronidase but not α-glucosidase or β-glucosidase [30]. Based in part on these differences, *Sneathia* was re-classified as a separate genus in 2001 [30].

At present, the genus *Sneathia* includes two species (*S. amnii* and *S. sanguinegens*), which can be found in the oral cavity [25, 31], gastrointestinal tract [25, 26], and the cervix and/or vagina [27, 28, 32, 33]. In a large cohort study of 736 women, *Sneathia* was found in 43.3% of vaginal specimens [28]: 76% of the detected *Sneathia* 16S rRNA gene sequences were from *S. amnii*, 18% were from *S. sanguinegens*, and 6% were from the genus *Sneathia* but could not be assigned to either of these established species [28]. Based on several other reports, *Sneathia* is present in the cervico-vaginal microbiome of 10–100% of non-pregnant [27, 33–37] and pregnant [8, 9] women, with a mean relative abundance of 1–21% [8, 28, 33, 36].

There are indications that *Sneathia* is a constituent of a non-optimal vaginal microbiome. For instance, *Sneathia* is posited to be involved in the pathogenesis of bacterial vaginosis [34, 35, 38–42], spontaneous preterm birth [i.e. spontaneous preterm labor and preterm prelabor rupture of membranes (PPROM)] [1–5, 7–10, 43–46], chorioamnionitis [6, 11, 47], stillbirth [48, 49], sexually transmitted diseases [50, 51], and other severe pregnancy complications [13, 52] (see Figure 1). *Sneathia* species are more often present in the vaginal

samples of women with symptoms of bacterial vaginosis than in those from women who are asymptomatic [34, 35, 39, 41]. Indeed, the presence of *Sneathia* is positively associated with the diagnostic criteria of bacterial vaginosis [36]. A recent study further indicated that *Sneathia* had among the greatest relative abundance and effect size of the vaginal bacteria associated with preterm birth (delivery at <37 weeks of gestation) [9]. *Sneathia* is also one of the most frequently detected bacteria in amniotic fluid of patients with PPROM [3, 7] or spontaneous preterm labor [1, 2, 5, 8, 9]. The results of these and other investigations, which are discussed in greater detail below, suggest that *Sneathia* has the capacity for ascending invasion of the upper reproductive tract during pregnancy. Thus, it is becoming increasingly apparent that *Sneathia* infections are associated with critically important obstetric and gynecologic pathologies.

This review represents the first comprehensive summary of how *Sneathia* species affect women's reproductive health and neonatal outcomes. Specifically, we discuss the culture and molecular methods for the isolation and/or identification of *Sneathia* species, the mechanisms of their virulence, their role in the etiology and pathogenesis of different types of obstetric and gynecologic pathologies, and the antibiotic therapies used to resolve *Sneathia* infections.

Identification of *Sneathia* as a novel pathogen

The existence and pathogenic potential of *Sneathia* species were unrecognized until the development and application of DNA sequencing technologies that allowed for their reliable identification in clinical samples. The first report describing a new infectious agent, *Leptotrichia sanguinegens*, in the pathogenesis of postpartum and neonatal bacteremia, and its isolation in culture, was provided by Hanff et al in 1995 [12]. The symptoms of the bacterial infection included post-partum fever and elevated white blood cell count, both of which were successfully treated with the antibiotics ampicillin and gentamicin [12]. In 2001, several bacterial isolates from blood and amniotic fluid were found to resemble *Leptotrichia sanguinegens*. However, the comparison of the DNA nucleotide sequences encoding for the 16S rRNA gene, and detailed analyses of the morphological and metabolic characteristics, showed that these isolates should not be classified within the *Leptotrichia* genus [30]. They were instead classified as a new genus, *Sneathia*, named after the British microbiologist Peter Sneath, a pioneer of bacterial systematics [30]. A year later, a novel bacterium with similar characteristics was isolated from amniotic fluid of a woman following intrauterine fetal demise. This bacterium was named *Leptotrichia amnionii* based on the site of its localization and isolation [48]. In 2004, DNA sequencing indicated that *Leptotrichia amnionii* should also be re-classified to the *Sneathia* genus; it was renamed as *Sneathia amnii* [53].

It should be noted that, until recently, some studies still applied the outdated taxonomic terminology classifying *Sneathia* as *Leptotrichia* (examples are shown in Tables 1–4). In this review, we will use the newly accepted taxonomic nomenclature, referring to *Leptotrichia sanguinegens* and *Leptotrichia amnionii* as *Sneathia sanguinegens* and *Sneathia amnii*, respectively.

Methods for the detection of *Sneathia* in clinical samples

Both species of *Sneathia* are fastidious bacteria with complex and demanding nutritional requirements. Growth media are typically supplemented with blood or serum [12, 28, 30]. Nevertheless, it is incredibly difficult to isolate *Sneathia* in culture from clinical specimens even when using nutrient-rich, blood-supplemented media. A summary of the data regarding the isolation and culture of *Sneathia* from clinical specimens is presented in Table 1.

In the first days following inoculation, cultures of *Sneathia* species progress in their growth through a prolonged lag-phase [12, 28, 30, 48, 54]. Although *Sneathia* cultures can tolerate transient exposures to aerobic atmospheres [28], and have even shown a limited capacity to grow in such environments [12], *Sneathia* cultures are typically maintained under anaerobic conditions [12, 28, 30, 48, 52, 54]. Morphological characteristics of *S. amnii* cultures, as revealed through scanning electron microscopy, include a discernible cell polymorphism with elongated bacilli, short bacilli, and cocci [28]. Cell heterogeneity, including an increased proportion of cocci and the development of bacterial L-forms (i.e. cell-wall deficient morphotypes), is significantly increased in older cultures [28].

As shown in Tables 1 and 2, despite some early reports of the isolation of cultures of both *Sneathia* species from amniotic fluid [30, 48], more recent attempts to recover *Sneathia* isolates from the amniotic cavity [2, 5, 7, 55], the chorioamnion [11], and pelvic [19] or vaginal [56] samples were not successful. Thus, it is very difficult to isolate, propagate, and quantify *Sneathia* in culture in the laboratory. Another explanation for diminished efforts aimed at *Sneathia* isolation in culture appears to be a wider application of molecular methods that allow for the rapid and specific identification and quantification of *Sneathia* in clinical specimens, even when it is present at low concentrations.

Molecular techniques such as polymerase chain reaction (PCR) amplification and 16S rRNA gene sequencing provide alternative means for detecting *Sneathia* species in clinical samples, even when *Sneathia* is just one component of mixed microbial communities in these samples. Herein, we will focus on the studies that used PCR and/or 16S rRNA gene sequencing for the identification of *Sneathia* in perinatal contexts, as summarized in Table 2. PCR has been used for the molecular detection of *Leptotrichia/Sneathia* spp. in vaginal [11, 34, 57, 58], chorioamnion [11] and amniotic fluid [3, 5–7, 59–61] samples. Targeted sequencing of the whole 16S rRNA gene, or one or more of its variable regions, is another approach recently used for the identification of *S. amnii*, *S. sanguinegens*, or *Sneathia* spp. in general in specimens obtained from the vagina [8–10], upper genital tract [19, 43, 46], and neonatal stool and skin [13, 62, 63]. Currently, publicly available 16S rRNA gene sequence data exist only for two *Sneathia* type strains that have been identified to the species level, *Sneathia amnii* SN35 and *Sneathia sanguinegens* CCUG 41628. The near complete 16S rRNA gene sequences of these isolates are 96.2% similar based on nucleotide matching, with the greatest variability occurring in the V1-V2 regions of the gene. Molecular assays targeting these regions may allow for reliably distinguishing the presence of the two species in clinical samples, but the description of additional isolates from both species is required to determine if there exists consistent differences in the 16S rRNA genes of the two species. Regardless, sequence-based diagnostic tests, whether of the 16S rRNA gene or other gene targets, typically have longer turnaround times than end-point or quantitative real-time PCR,

which could potentially delay decision-making in a clinical context [64]. Taken together, these findings indicate a need for the further development of rapid and specific diagnostic laboratory tests for the rapid identification and quantification of individual *Sneathia* species in clinical specimens.

Genomic characteristics of *Sneathia* and the molecular mechanisms of *Sneathia* virulence

Genomic characteristics of Sneathia—The application of modern genomic and molecular biological analyses recently provided significant insights into the pathways underlying the virulence and pathogenesis of *Sneathia* infections [28, 65]. The chromosomal DNA of members of the bacterial family Leptotrichiaceae is heavily of the A-T type [21, 28]; Leptotrichiaceae genomic DNA has G-C content values of 24–34%, which are low for bacteria [21, 66, 67]. Leptotrichiaceae also has a small genome size that typically varies between 1.2–2.5 mega base pairs (Mbp) [21]; this is only a quarter to half the size of the *Escherichia coli* genome. Notably, two genera within the family Leptotrichiaceae have uniquely small genomes with high coding density, suggesting that they are only distantly related to other family members. Specifically, it was reported that *Sneathia amnii* and its close phylogenetic relative *Streptobacillus moniliformis* [28, 53], a zoonotic pathogen, have the smallest genome sizes in the family Leptotrichiaceae, at 1.34 and 1.67 Mbp, respectively [28, 68]. Ninety-two percent of the *S. amnii* genome is comprised of protein-coding genes, which is comparable to the coding gene density of the *S. moniliformis* genome but is higher than that of other members of the family Leptotrichiaceae [28]. This suggests that for *S. amnii* and *S. moniliformis* there is a selective cost associated with genome size [28].

Within the genome of *S. amnii*, genes for DNA replication and cell cycle regulation are abundant, while those for cell signaling, cell motility, and the production of secondary metabolites are rare [28]. *S. amnii* lacks enzymes required for the synthesis of many amino acids and therefore this bacterium must rely on hosts and other members of the microbiome for these acids and/or their precursors [28]. *S. amnii* is also limited in its potential carbon and energy sources; it can ferment glucose, maltose, and glycogen [28]. Glycogen, in particular, is prevalent and abundant in the vaginal ecosystem [69]. Therefore, although carbon sources are very limited for *S. amnii*, the sources that this bacterium can use are reflective of the principal niche it inhabits – the human vagina. This suggests that the reduction in genome size and restricted metabolic capabilities for *S. amnii* are products of its intimate association with its human host.

To date, *S. amnii* is the lone *Sneathia* species to have its genome sequenced, annotated, and published [28].

Molecular mechanisms of Sneathia virulence—*Sneathia amnii* has strong hemolytic properties, as demonstrated by *in vitro* tests on both brain-heart infusion (BHI) agar containing 10% human blood and incubation with freshly isolated human erythrocytes [65]. Similarly, *S. moniliformis*, which is responsible for rat-bite fever, has hemolytic strains [29]. Rat-bite fever normally presents as severe inflammatory responses such as high fever, swollen lymph nodes, and acute systemic inflammation [29]. Unlike *Sneathia* species,

S. moniliformis is not primarily known for obstetric and gynecologic infections, despite occasionally causing them [47, 70, 71].

The vaginal cytokine profiles of non-pregnant women with vaginal *S. amnii or S. sanguinegens* infections exhibit elevated levels of pro-inflammatory cytokines [72–74], such as IL-8 and IL-1β [72]. Moreover, co-cultures of human vaginal epithelial cells with *S. amnii* or *S. sanguinegens* show upregulated secretion of pro-inflammatory cytokines including IL-1α, IL-1β, and IL-8 [72]. Ascending infections by *Sneathia* spp. during pregnancy are consistently associated with intra-amniotic inflammation [1, 2, 5, 7, 43, 44, 46, 55, 59] and acute histological chorioamnionitis [7, 13, 45, 55, 75]. These data suggest possible involvement in the control of immune responses to *Sneathia* antigens by vaginal or cervical immune cells, such as antigen-presenting cells [72, 73] (see Figure 2).

A few studies have attempted to elucidate the mechanisms driving *Sneathia* virulence. For example, it was reported that *S. amnii* is capable of damaging the fetal membranes, as shown in co-culture experiments with sections of human chorionic tissue from healthy term births [65]. After 18 hours of incubation, histological examination demonstrated that bacterial cells destabilized the surface layers of the tissue and invaded into the fetal membranes, damaging the trophoblast and causing a loss of tissue viability [65]. *Sneathia amnii* is also capable of adhering to the surface of cervical epithelial cancer cells in culture resulting in the dissociation of intercellular epithelial contacts, cell rounding, and progressive loss of adherence [28]. These effects were evident after just two hours of exposure, indicating a capacity for rapid infectivity by *S. amnii*.

It was also found that the co-culture of *S. amnii* with either human amniotic epithelial cells isolated from normal term placentas or chorionic trophoblast cells from a choriocarcinoma cell line led to decreased cell viability and increased degenerative changes [65]. This bacterial cytotoxicity results in the detachment of host cells from each other and from the underlying substrates. The molecular basis of the adhesive capacity of *S. amnii* cells might be the presence of a gene encoding a putative fibronectin-binding protein, and at least one adhesion homolog [28]. It appears that, because of these binding sites, *S. amnii* may attach to host cells through fibronectin molecules bound to cell integrins and other extracellular matrix proteins.

An important mechanism underlying *S. amnii* virulence is the production and release of a pore-forming cytotoxin CptA that destabilizes host cell membranes [65]. As shown in Figure 2 for erythrocytes, it causes the permeabilization of membrane lipid bilayers, leakage of cytoplasmic content, and irreversible injury to host cells [65]. Additionally, *S. amnii* appears to release hydrolytic enzymes that can cross tissue barriers and membranes. To penetrate the vaginal and cervical epithelial and mucous layers and enter into underlying host tissues, *S. amnii* may activate a protease capable of cleaving and degrading sialylated proteins [28] (see Figure 2). These data support reports of elevated sialidase activity in vaginal specimens containing *Leptotrichia/Sneathia* spp. [76]. The *S. amnii* genome also appears to encode proteins similar to invasins, such as a YadA-like surface protein, and putative internalins that facilitate the crossing of epithelial and connective tissue barriers and gestational membranes [28].

Taken together, these results show that *Sneathia* (at least *S. amnii*) virulence and pathogenicity are products of several molecular mechanisms that allow *Sneathia* to pass tissue and cell barriers and to spread within infected tissues. It is becoming increasingly likely that these characteristics are essential to the invasive ascent of *Sneathia* from the lower reproductive tract into the fetal membranes, amniotic fluid, and placenta. The putative mechanism of *Sneathia*'s ascending infection is illustrated in Figure 3. However, our current understanding of detailed cellular and molecular mechanisms underlying *Sneathia* virulence, particularly in the context of obstetric and gynecologic disease, remain limited.

Sneathia in female reproductive disease

Bacterial vaginosis—*Sneathia* spp. have been identified as members of Community State Type IV (CST-IV) of the vaginal microbiome, which is characterized by a diminished presence of *Lactobacillus* species in the vagina [27]. Although CST-IV is an asymptomatic phenotype in many women, patients diagnosed with bacterial vaginosis have a vaginal microbiome with a CST-IV composition [27, 77]. They also have vaginal secretions with an elevated pH compared to women with *Lactobacillus*-dominant CSTs [27]. Most importantly, in the context of this review, there is an increased presence of *Sneathia* spp. in the vaginal microbiome of women with bacterial vaginosis diagnosed by increased Nugent scores [38–40, 78–80], Nugent-Boon scores [81], or Amsel test criteria [34, 78–80].

Bacterial vaginosis is a common clinical condition [82, 83] characterized by a general absence of *Lactobacillus* species, accompanied by evident vaginal discharge and an unpleasant odor [34, 84, 85]. The specific etiology of bacterial vaginosis remains incompletely understood [86]. Currently, the formation of a bacterial biofilm is considered a primary mechanism underlying the development and progression of bacterial vaginosis [87–89]. A bacterial biofilm is a structured community of bacterial cells secured within a self-produced extracellular matrix that is adherent to an inert surface or biological tissue [90, 91]. Several genera, especially *Gardnerella*, but also *Atopobium*, *Mobiluncus*, *Peptostreptococcus*, *Prevotella*, and *Sneathia*, are associated with both the condition of bacterial vaginosis and biofilm formation [41, 87, 89, 91, 92].

In one association study, an increased relative abundance of *S. sanguinegens* in the vaginal microbiome was associated with the presence of clue cells (i.e. vaginal epithelial cells with bacteria attached to their surface) and bacterial biofilms in vaginal fluids [41], suggesting that *Sneathia* spp. may be important contributors to the process of vaginal biofilm formation [41]. Also, the detection of *Sneathia* spp. in the anal canal of asymptomatic women was reported to correlate with a higher predisposition for and recurrence of bacterial vaginosis [25]. Similarly, *Sneathia* spp. can inhabit the male urogenital tract [50, 93], and carriage of *Sneathia* by male partners has been associated with incidences of bacterial vaginosis [94]. Thus, the potential transmission of *Sneathia* spp. from extra-vaginal reservoirs on the body or the body of sexual partners might contribute to the increased risk of *Sneathia* colonization of the female genital tract [25]. It is not uncommon for bacterial vaginosis to precede severe obstetric [95–98] and gynecologic [99–101] complications, such as pelvic inflammatory disease [99, 102]. In agreement with these observations, *Sneathia* spp. have been found in the cervix [18], endometrium [18], and in the surgically removed fallopian tubes and pelvic

pus [19, 103] of women diagnosed with pelvic inflammatory diseases. Taken together, these findings provide insights into the pathways underlying the persistence and progression of *Sneathia* in the female reproductive tract and its potential contribution to the occurrence and recurrence of bacterial vaginosis.

A role for Sneathia in human papilloma virus infection and cervical cancer—Recent data suggest that *Sneathia* infections in the urogenital tract are associated with increased risk of several other common types of gynecologic disease. Infections with *Sneathia* spp. have also been found to accompany sexually transmitted diseases [51], including HIV [73, 104], suggesting *Sneathia* spp. may be opportunistic pathogens. Conversely, *Sneathia*, with its capacity to disintegrate the stability of the fetal membranes and epithelial cell layers *in vitro* [28, 65] may potentiate local inflammation and tissue damage [72, 73], thereby increasing the risk of acquisition of HIV [73, 104] and other sexually transmitted infections [51]. That is, *Sneathia* may actually be a primary agent of disease.

Of special interest are recent reports implicating *Sneathia* spp. in the pathogenesis of human papilloma viral infections. Cervical cancer is one of the most common types of female malignancies [105, 106], and human papillomavirus (HPV) is considered the principal cause of cervical intraepithelial neoplasia [107] and cervical cancer [105, 108]. HPV infection leads to the development of pre-malignant epithelial lesions in the cervix, which can progress into malignant neoplastic growth and cervical carcinogenesis [109–111]. Several studies of cervical and vaginal microbiomes have revealed a greater relative abundance of *Sneathia* spp. in specimens obtained from women diagnosed with HPV infection [33, 112–115]. For example, a study of identical female twins showed that the vaginal microbiomes of HPV-infected individuals contained much lower levels of the normally dominant *Lactobacillus* spp. and significantly elevated levels of *Fusobacteria* and *Sneathia* spp. than those of their non-infected genetically identical siblings [112]. Moreover, *Sneathia* spp. were detected in HPV-infected patients with different types of cervical intraepithelial lesions [15–17], including high squamous intraepithelial lesions that are indicative of chronic HPV infection [15]. *Sneathia amnii*, at least, can adhere to the surface of malignant cervical epithelial cells [28]. This suggests a potential for toxic products released by adherent *Sneathia* to alter the characteristics of host tissue and directly mediate effects on the cervical microenvironment.

An analysis of correlations between the severity of cervical neoplasms and variation among vaginal microbiomes found that *Sneathia* spp. were enriched in all precancerous women with cervical epithelial neoplasia, accompanied by decreased *Lactobacillus* dominance and abnormally increased vaginal pH [17]. However, the abundance of *Sneathia* does not appear to be elevated in vaginal specimens received from patients with invasive cervical carcinoma [17]. One potential explanation is that *Sneathia* is outcompeted by other bacterial species under conditions of changing tissue environment, including possible pH shifts at the advanced stages of tumor growth [17]. This suggests that the activation of *Sneathia* growth is positively associated with HPV infection, onset of cervical intraepithelial neoplasia, and precancerous neoplastic progression. These findings also suggest that the shift in the composition of cervicovaginal microbiomes of HPV-infected patients may have a

potential predictive value for clinical prognosis of cervical intraepithelial neoplastic tumor progression [17].

Sneathia infections and adverse perinatal outcomes

Infections with *Sneathia* spp. are associated with several adverse perinatal conditions and outcomes such as 1) spontaneous preterm birth, particularly PPROM, 2) clinical chorioamnionitis, 3) septic abortions, 4) neonatal sepsis, 5) intrauterine fetal demise, and 6) maternal intrapartum and postpartum septic complications.

Spontaneous preterm birth—Data summarizing the detection of *Sneathia* spp. in amniotic fluid in cases of spontaneous preterm birth are presented in Table 2. In these studies, spontaneous preterm labor was defined as regular contractions accompanied by cervical change at less than 37 weeks of gestation. PPROM was defined as spontaneous rupture of the membranes at less than 37 weeks of gestation and at least one hour before the onset of contractions. Births that followed spontaneous preterm labor and PPROM are collectively referred to as spontaneous preterm births [116, 117]. A transabdominal amniocentesis may be performed at the onset of preterm labor and PPROM to diagnose the presence of intra-amniotic inflammation and/or microbial invasion of the amniotic cavity [2, 3, 5, 7, 55, 118].

Among patients with preterm labor and intact membranes, *Sneathia* was one of the most frequently detected bacterial genera in amniotic fluid (Table 2). Patients diagnosed with *Sneathia* intra-amniotic infection showed signs of intra-amniotic inflammation [1, 2, 5, 55, 119] and delivered preterm with further histological manifestations of acute chorioamnionitis [2, 5, 55]. Intra-amniotic infection by *Sneathia* spp. in these cases was detected by using PCR [1, 59], PCR/ESI-MS [5], and 16S rRNA gene sequencing approaches [2, 43, 44, 46, 55, 119, 120].

A recent study showed that *Sneathia* spp. were found in both the vaginal secretions and amniotic fluid of the same women with preterm labor and intact membranes [55]. The patients examined in this study were diagnosed with intra-amniotic inflammation and subsequently delivered preterm with signs of funisitis and acute chorioamnionitis [55]. This suggests ascension of *Sneathia* from the vagina into the amniotic cavity and supports the findings presented above regarding the virulence properties of *Sneathia* [28, 65].

Along with these observations in women with spontaneous preterm labor with intact membranes, *Sneathia* spp. were among the most common bacteria detected in amniotic fluid of women with PPROM [3, 7]. Moreover, the detection of *Sneathia* spp. was associated with intra-amniotic infection and adverse pregnancy outcomes [7, 43–46]. *Sneathia* spp. were also detected in amniotic fluid of an otherwise asymptomatic woman with a sonographic short cervix, although surprisingly in this case the woman delivered at term with no signs of intra-amniotic inflammation [61].

Several studies of the vaginal microbiome have showed a positive correlation between the relative abundance of *Sneathia* spp. and the occurrence of preterm birth in African American [4, 8, 9] and Caucasian [10] women. In a cohort of primarily African American women with

a prior history of preterm birth, women with increased absolute abundance of *Sneathia* spp. in the vagina in first and early second trimesters were significantly more likely to experience a spontaneous preterm delivery [4]. Moreover, longitudinal studies showed that levels of *S. amnii* [9] and *S. sanguinegens* [8] in the vagina were significantly associated with increased risk of preterm birth in cohorts of predominantly African-American women. Similarly, increased levels of *S. sanguinegens* were evident in the vaginal samples of Caucasian women with preterm labor and birth [10]. Furthermore, in a recent study of a cohort of predominantly African-American women, women who ultimately experienced spontaneous preterm birth exhibited stronger negative associations between *S. sanguinegens* and the immune mediators CCL26, CCL22, CCL2, CXCL10, and IL-16 in vaginal fluid than did women who ultimately delivered at term [121].

Overall, *Sneathia* spp. are one of the most frequently detected bacterial taxa in the amniotic cavity in women with spontaneous preterm birth [2, 3, 7]. However, further studies of the purported etiologic and causative links between vaginal and intra-amniotic infections with *Sneathia* and spontaneous preterm birth are needed to better understand the pathogenic mechanisms involved.

Sneathia infections in the pathogenesis of clinical chorioamnionitis—Clinical chorioamnionitis is one of the most common obstetric pathologies associated with intra-amniotic bacterial infection [122–125]. The diagnostic criteria of clinical chorioamnionitis are based on the studies of Gibbs *et al.* [126, 127], and refer to the presence of maternal fever associated with clinical signs (i.e., foul-smelling discharge, uterine tenderness, maternal and fetal tachycardia) as well as laboratory abnormalities (i.e., leukocytosis) [6]. However, such clinical criteria do not accurately identify patients with proven intra-amniotic infection (i.e., those with microorganisms detected by culture or molecular microbiologic techniques and an associated intra-amniotic inflammatory response) [128]. In women with clinical chorioamnionitis and proven intra-amniotic infection [6], local and systemic maternal-fetal inflammatory processes are considered to be immune responses to ascending microbial invasion of the amniotic cavity [55, 118, 129–149]. Polymicrobial infections of the amniotic cavity are often observed in patients diagnosed with clinical chorioamnionitis [6, 150–152] and are generally associated with a greater level of inflammatory response than infections with a single microorganism [6]. A key challenge in understanding the role of *Sneathia* spp. in the pathogenesis of clinical chorioamnionitis and other obstetric pathologies is elucidating their specific contributions under conditions in which they are but one member of a mixed microbial community responsible for polymicrobial infections.

In two studies of women diagnosed with clinical chorioamnionitis at term and polymicrobial invasion of the amniotic cavity, *Sneathia* spp. were detected in amniotic fluid using PCR/ESI-MS [6] and 16S rRNA gene sequencing [47]. Bacterial cultures from these patients proved to be negative for *Sneathia* [6, 47], but this may be due to the fastidious culture requirements of this genus [28]. Another study reported polymicrobial invasion that included infection with *Sneathia* spp. in the chorioamnion and vaginal swabs of the same patient with mild symptoms of clinical chorioamnionitis at term [11]. In this study, *Sneathia* spp. were identified by 16S rRNA gene PCR. However, attempts to isolate the bacteria in culture were again unsuccessful.

Thus, these findings indicate that *Sneathia* infections play an important role in the pathogenesis of clinical chorioamnionitis. Further studies examining the mechanisms of virulence of *Sneathia* spp. and their capacity to initiate maternal-fetal inflammatory responses are warranted.

Sneathia and neonatal sepsis—Neonatal sepsis has been defined as an invasive bacterial infection of the blood and/or the cerebrospinal fluid that occurs in the first three months after birth [125, 153]. The first study suggesting the contribution of *S. sanguinegens* to the pathogenesis of neonatal bacterial sepsis was published in 1995 [12]. *Sneathia* infection was identified in blood cultures of two vaginally delivered infants: one of them was born at 35 weeks and the other was born at 41.5 weeks, both were afebrile. The second infant had tachycardia and signs of respiratory distress associated with increased respiratory rate that required positive pressure for respiratory support. The indication for septic workup was a foul smell from the neonates. In another study, stool samples obtained from 106 extremely preterm neonates (i.e. those born earlier than 28 weeks of gestation) revealed that a higher relative abundance of *Sneathia* spp. during the first week of life was associated with histological chorioamnionitis with funisitis and a higher risk of late onset neonatal sepsis or death [13]. Recently, it was reported that a high relative abundance of *Sneathia* spp. in the vaginal microbiome during pregnancy was associated with histological chorioamnionitis with funisitis and early onset neonatal sepsis [14]. Taken together, these data indicate that intra-amniotic *Sneathia* infections during pregnancy have deleterious effects on neonatal life.

Septic abortion, intrauterine fetal demise, and stillbirth—To date, there have been three studies implicating *S. amnii* in septic complications of pregnancy leading to fetal death. The first report included the isolation of *S. amnii* in anaerobic culture from maternal blood after a septic abortion at 15 weeks [52]. Another clinical case reported the identification of *S. amnii* through anaerobic culture of the amniotic fluid of a patient with intrauterine fetal demise [48]. In a third case, *S. amnii* was identified in the lung tissue of a stillborn infant using 16S rRNA gene sequencing [49]. In this case, histopathological analysis of the placenta and umbilical cord revealed the manifestations of acute chorioamnionitis and funisitis, and rare Gram-negative coccobacilli were detected in the umbilical artery. However, 16S rRNA gene sequencing did not detect *S. amnii* in the placental tissue [49]. These findings suggest the involvement of *Sneathia* in the pathogenesis of septic abortion, intrauterine fetal demise, and stillbirth. However, the question as to whether *Sneathia* is a causative primary agent of infection leading to fetal death needs to be further examined.

Peripartum septic maternal complications—Postpartum infections, including blood stream infections (bacteremia), are a subset of maternal pathological conditions occurring between delivery and the 42nd day postpartum [154]. *S. sanguinegens* has been isolated in blood culture from a patient diagnosed with postpartum bacteremia [12]. *S. sanguinegens* and *S. amnii* were further isolated from the blood cultures of three patients diagnosed with intrapartum and postpartum maternal fever [54]. Two out of three of these patients showed symptoms of fetal distress during delivery; both were infected with *S. amnii*. However, in all three cases, the newborns did not develop any detectable clinical or laboratory evidence of

infection. Most recently, using 16S rRNA gene sequencing, Kotaskova *et al.* [155] reported that *S. sanguinegens* was detected in prosthetic valve tissue in a patient with postpartum endocarditis developed following postpartum fever and spontaneous preterm birth. Repeated blood cultures for this patient were negative. The results of these studies suggest that *Sneathia* infection can spread from the reproductive tract to other organs and systems of the body. Collectively, these findings show that *Sneathia* species appear to be important infectious agents contributing to the pathogenesis of postpartum bacteremia.

Antibiotic treatment of *Sneathia* infections

In the previous sections of this review, we discussed several pathological conditions associated with *Sneathia* infections. Administration of antibiotics is the standard treatment for these infections [156, 157]. To date, literature reporting successful antibiotic therapies for *Sneathia* infections remain very limited. The current literature is summarized in Table 3.

Briefly, metronidazole is a first-line therapy for the treatment of bacterial vaginosis; this bactericidal antibiotic targets mainly anaerobic bacteria, including *Sneathia* [157]. Metronidazole treatment leads to a significant decrease in the absolute [37, 57, 80] and relative abundance [158, 159] of *Sneathia* spp. in vaginal secretions and/or urine of non-pregnant women, as determined using culture-independent molecular techniques [37, 57, 80, 158, 159]. Among pregnant women with bacterial vaginosis, metronidazole treatment did not significantly affect *Sneathia* infection when applied vaginally [58]; however, it did resolve *Sneathia* infection when the antibiotic was taken orally [58]. Furthermore, oral administration of tinidazole (an antibiotic that targets bacterial DNA integrity, repair, and transcription [160]) either alone [80] or in combination with probiotics [161], as well as oral administration of rifaximin [162] (an antibiotic that inhibits bacterial RNA synthesis [163, 164]), appear to effectively decrease the relative and absolute abundance of *Sneathia* spp. in the vaginal fluid of women with bacterial vaginosis.

A principal challenge of bacterial vaginosis treatment is a high recurrence rate of the infection within one year [165]. Notably, among women successfully treated for bacterial vaginosis with rifaximin, there was a reduction in the prevalence and absolute abundance of *Sneathia* spp. after seven days, yet there was an increase in *Sneathia* spp. after 28 days [162]. Similarly, in a separate study of bacterial vaginosis [80], *Sneathia* spp. were seldom detected at high absolute abundances in the vaginal fluids of women who remained responsive to antibiotic treatment after 7–10 days, yet in women who remained responsive to antibiotic treatment after 40–45 days *Sneathia* spp. were abundant.

In addition to the studies concerning the clinical effectiveness of the antibiotic therapies presented above, there have been four reports characterizing the sensitivity of *Sneathia* isolates in culture to different antibiotics [28, 52, 54, 166]. These findings are summarized in Table 4, and suggest that different *Sneathia* species may differ in their sensitivity to different antibiotics depending on the source of their isolation. For example, multiple isolates of *S. amnii* and *S. sanguinegens* cultured from the blood were reported to be resistant to vancomycin [54]; yet, *S. amnii* isolated from vaginal fluid was sensitive to this antibiotic [28]. This finding may be due to intraspecific variation in the structure of the cell envelope

[28], or intraspecific genetic heterogeneity resulting from horizontal gene transfer, including the acquisition of plasmids conferring antibiotic resistance [167, 168].

Further investigation of the molecular mechanisms underlying the sensitivity and resistance of *Sneathia* to different antibiotics is essential for a better understanding of the pathogenesis and treatment of *Sneathia* infections. Genomic analysis of different *Sneathia* isolates may reveal the existence of distinct strains of *Sneathia* and allow for the development of targeted antibiotic therapies that will help in the management of recurrent bacterial vaginosis and other *Sneathia* associated pathologies in obstetric and gynecologic clinical practice.

Conclusions and future directions

The data presented in this review suggest a significant role for *Sneathia* infections in the pathogenesis of PPROM [3, 7, 43–46], spontaneous preterm labor [1, 2, 4, 5, 8–10], chorioamnionitis [6, 11], stillbirth [48, 49], bacterial vaginosis [34, 38–41, 57, 79–81], HIV infection [73, 104], and cervical cancer [15–17]. Several of these pathologies, such as spontaneous preterm birth and intrapartum-related complications associated with bacterial infections, are among the leading causes of death [169–172] and long-term disabilities [173, 174] in children under five years of age.

A growing body of evidence suggests that *Sneathia* spp. can become opportunistic pathogens following shifts in the vaginal microbiome away from *Lactobacillus*-dominated communities [14]. Furthermore, although *Sneathia* spp. are not the only bacteria associated with bacterial vaginosis [34, 38–40, 42, 78–81, 175], they do appear to play a key role in biofilm formation observed in this clinical condition [41]. This capacity may be instrumental in the development and progression of bacterial vaginosis.

Recent results of *in vitro* and *in silico* experiments open the door for further elucidation of the mechanisms underlying *Sneathia* spp. virulence and their capacity for ascending invasion into fetal membranes [28, 65]. The potential capacity of *Sneathia* spp. for attaching to and damaging host cells using cytolytic [65] and cytotoxic [28] compounds enables their progressive invasion through the vaginal and cervical epithelium into deeper layers of tissue, where they cause tissue injury. Tissue damage might be further enhanced by a pore-forming cytotoxin that destabilizes lipid cell surface membranes leading to leakage of hemoglobin from erythrocytes and the permeabilization of cervical, amniotic and chorionic surface layers [65]. Given the fact that *Sneathia* spp. are non-motile, these abilities may be instrumental to their ascending invasion through the female urogenital tract (Figure 3).

New evidence demonstrates that the virulence of vaginal bacteria and the progression of the bacterial infection might significantly vary among different strains of the same species [92, 176–178] and be affected by the location of the bacteria within the tissue, as well as the stage and depth of their invasion during the process of infection [179]. For this reason, it is important to examine virulence among conspecific *Sneathia* strains. Moreover, recent studies of the vaginal microbiome showed that the presence and growth characteristics of different vaginal bacterial species might be affected by the genetic polymorphisms within human populations [18, 180] and the intensity of local host immune responses [72,

181, 182]. Additional genomic [18, 28], metagenomic [183–185], metabolomic [186] and proteomic [187–189] approaches are needed to further elucidate the mechanisms underlying the virulence of *Sneathia* spp. and strains. Further studies in this field will advance our understanding of the etiological and pathogenic factors involved in *Sneathia* infections in reproductive and perinatal medicine and serve to evaluate the potential value of *Sneathia* spp. as prognostic biomarkers of adverse outcomes for both mothers and newborns.

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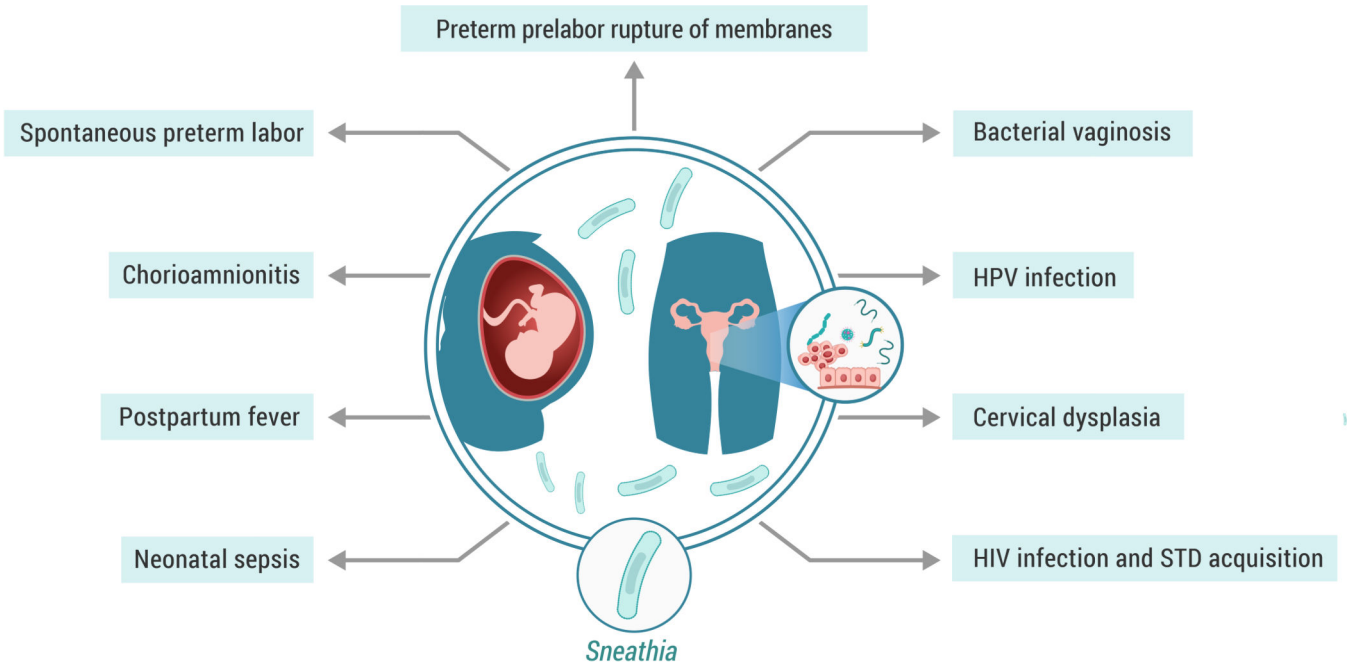

Figure 1. *Sneathia* in female reproductive disease

During pregnancy, *Sneathia* spp. are involved in the pathogenesis of preterm prelabor rupture of membranes, spontaneous preterm labor, clinical and histological chorioamnionitis, postpartum fever, as well as neonatal sepsis and bacteremia. In non-pregnant women, the presence of *Sneathia* spp. in the vaginal fluid is associated with bacterial vaginosis, HPV infection, cervical dysplasia, and increased risk of HIV infection and sexually transmitted diseases (STD).

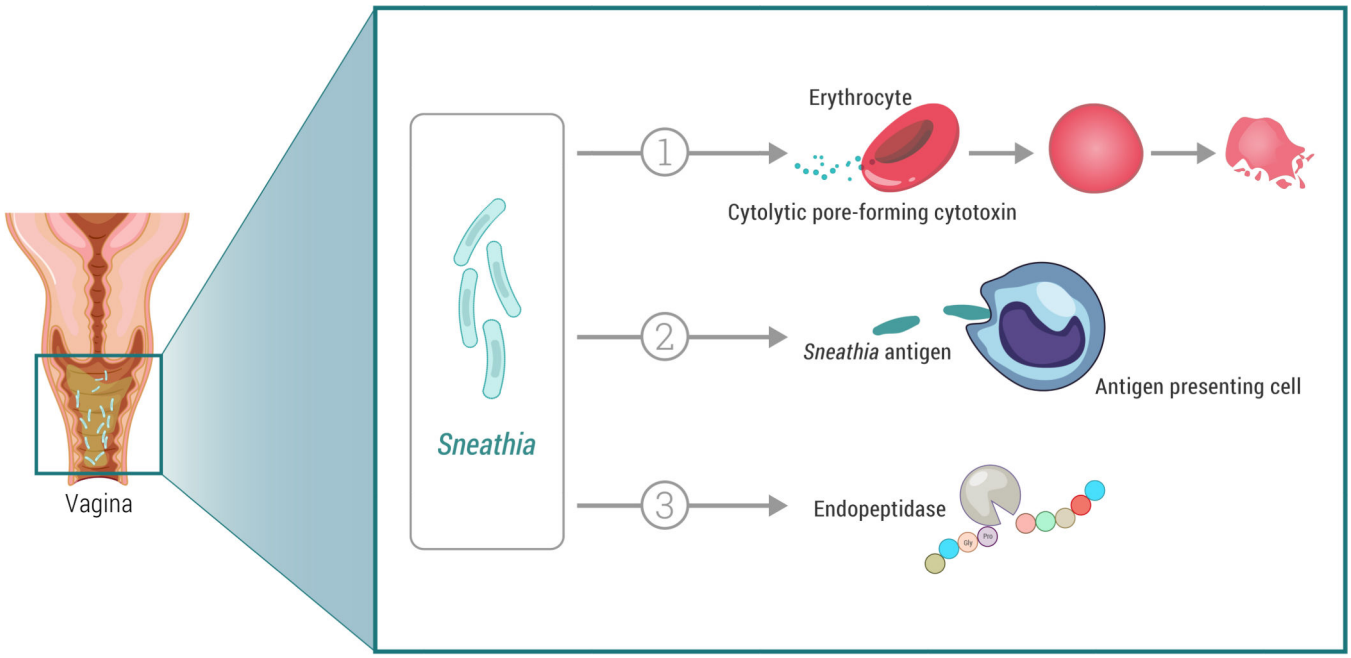

Figure 2. Potential *Sneathia* virulence factors

1. Pore-forming cytotoxin CptA (cytopathogenic toxin component A) could damage and/or lyse erythrocytes, vaginal and cervical epithelial cells, and cells of fetal membranes. Preliminary evidence is from *in vitro* studies of *S. amnii* [28, 65].

2. *Sneathia* antigens may be sensed by vaginal and cervical antigen presenting cells and/or other immune cells causing inflammatory responses. Preliminary evidence is from microbial and immune mediator profiling of the human genital tract, transcriptional profiling of cervical antigen presenting cells, and *in vitro* co-culture studies of human vaginal epithelial cells and S. amnii or S. sanguinegens [72, 73].

3. O-sialoglycoprotein endopeptidase may help *Sneathia* to transverse the cervix via cervical mucus. Preliminary evidence is from a genomic analysis of *S. amnii* [28].

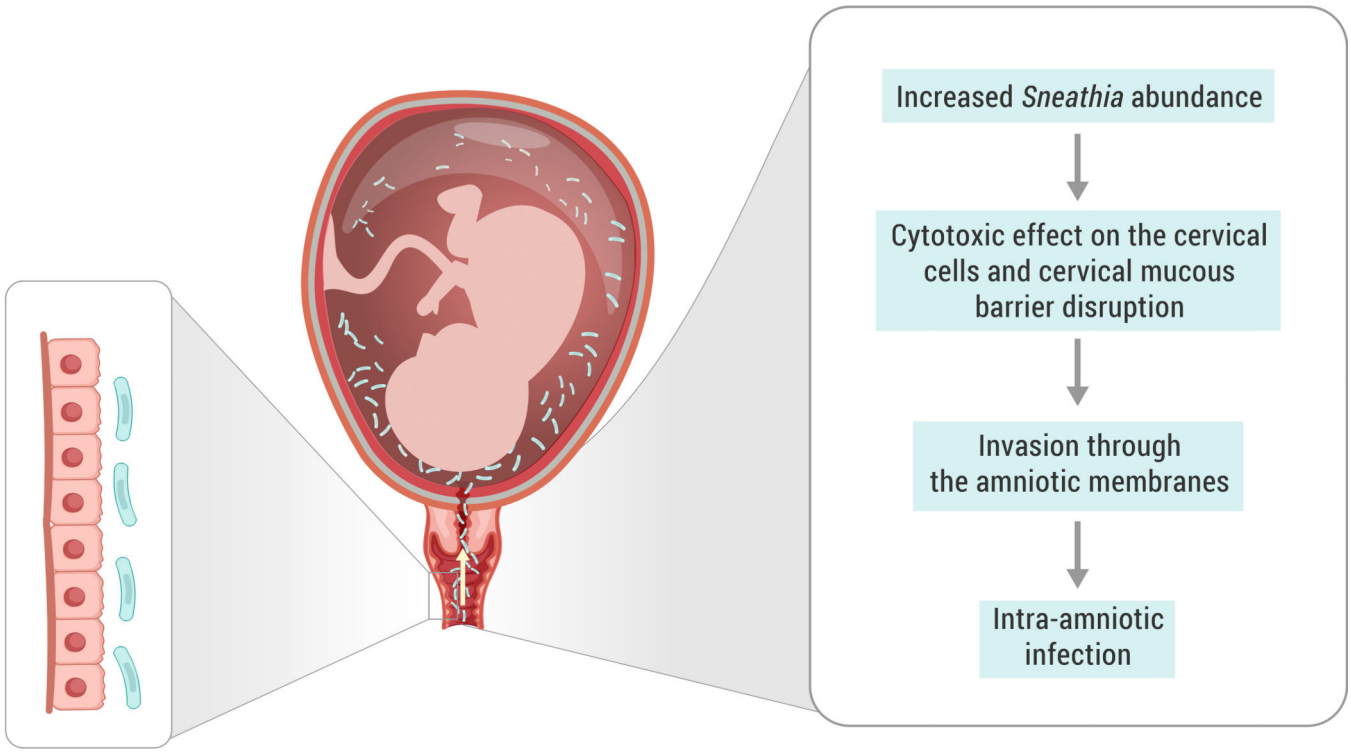

Figure 3. Putative mechanism of *Sneathia* ascending infection during pregnancy

Increased abundance of *Sneathia* in the vaginal microbiome facilitates biofilm formation and/or further spread of *Sneathia* to the cervical canal. *Sneathia*'s virulence factors affect the cervical epithelium and help the bacteria spread via cervical mucus. The putative invasins and pore-forming cytotoxin promote penetration of the chorioamniotic membranes and lead to intra-amniotic invasion. Further spread of *Sneathia* in the amniotic cavity and injury of amniotic cells promotes inflammation, leading to intra-amniotic infection.

Table 1.

Characteristics of *Sneathia* cultures isolated from patients during pregnancy or postpartum

Authors	Year	Sample type	Clinical diagnosis	*Sneathia* species isolated	Number of cases	Culture conditions	Days in culture	Colony morphology
Hanff et al. [12]	1995	Maternal blood	Postpartum fever, neonatal bacteremia	*S. sanguinegens* (*L. sanguinegens*)	4	Aerobic and anaerobic blood culture bottles; Successful subculture into anaerobic blood agar, chopped-meat glucose medium and chocolate agar supplemented with 20% fresh rabbit, horse, sheep, or human blood	3	Pinpoint convex colonies
Collins et al. [30]	2001	Blood and amniotic fluid	No details of clinical pathology were provided	*S. sanguinegens*	1	Anaerobic blood and chocolate agar plates with additional supplementation of blood or serum	3	Pinpoint convex colonies
Shukla et al. [48]	2002	Amniotic fluid	Intrauterine fetal demise (amniotic fluid was sampled before labor induction)	*S. amnii* (*L. amnionii*)	1	Anaerobic culture on blood and chocolate agar	3	Very small gray colonies, <1 mm in diameter
De Martino et al. [54]	2004	Maternal blood	Peripartum maternal fever	*S. amnii* (*L. amnionii*) (2) and *S. sanguinegens* (1)	3	Anaerobic blood culture vials; Anaerobic subculture on chocolate-polyvitex agar	2–4	Not provided
Boennelycke et al. [52]	2007	Maternal blood	Second trimester spontaneous septic abortion	*S. amnii* (*L. amnionii*)	1	Anaerobic blood culture bottles	1	Not provided
Harwich et al. [28]	2012	Vaginal fluid	Preterm labor at 26 weeks of gestation	*S. amnii*	1	Anaerobic culture on chocolate agar enhanced with human serum or BHI (brain-heart infusion) agar containing 10% fresh human blood; was able to tolerate transient exposure to air	2–3	Flat colonies, ~1 mm in diameter, crystalline on chocolate agar, or mucoid, raised, amorphous, ~2 mm in diameter, on BHI agar supplemented with human blood

Table 2.

Identification of *Sneathia* in upper reproductive tract and neonatal samples using culture-independent methods

Authors	Year	Gestational age at collection	Clinical pathology	Sample type	*Sneathia* species identified	Number of cases	Number of cases with *Sneathia* infections	Was cultivation of *Sneathia* attempted?	Culture-independent methods used to detect *Sneathia*	How was *Sneathia* associated with the clinical pathology?
Gardella et al. [1]	2004	22 – 34 weeks	Preterm labor with intact membranes	Amniotic fluid	*S. sanguinegens* (*L. sanguinegens*)	5	2	Yes, not successful	16S rRNA gene PCR and sequencing	*S. sanguinegens* was detected in the culture-negative amniotic fluid samples from women with preterm labor with intact membranes and intra-amniotic inflammation.
DiGiulio et al. [2]	2008	18 – 35 weeks	Spontaneous preterm labor with intact membranes and preterm birth	Amniotic fluid	*S. sanguinegens*; *Sneathia amnii* (*L. amnionii*)	113	6	Yes, not successful	16S rRNA gene end-point PCR and sequencing	*S. sanguinegens* and *S. amnii* were detected in the amniotic fluid from women with preterm labor and birth. *S. sanguinegens* was one of the most common taxa identified. All these cases were diagnosed with intra-amniotic inflammation.
DiGiulio et al. [3]	2010	15 – 37 weeks	Preterm prelabor rupture of membranes	Amniotic fluid	*S. sanguinegens*; *S. amnii* (*L. amnionii*)	204	6	Yes, not successful	16S rRNA gene and group-specific end-point PCR and sequencing	*S. sanguinegens* and *S. amnii* were detected in amniotic fluid from women with PPROM. *S. sanguinegens* was one of the most common taxa identified.
DiGiulio et al. [59]	2010	20 – 40 weeks	Preeclampsia	Amniotic fluid	*Sneathia/ Leptotrichia spp.*	62	3	No	16S rRNA gene and group-specific end-point PCR and sequencing	Three out of six patients diagnosed with microbial invasion of the amniotic cavity had a positive PCR for *Sneathia/Leptotrichia* spp..
Marconi et al. [119]	2011	<37 weeks	Preterm labor with intact membranes	Amniotic fluid	*S. amnii* (*L. amnionii*)	40	1	No	16S rRNA gene PCR and sequencing	*S. amnii* (*L. amnionii*) was detected in an amniotic fluid sample from a woman with preterm labor and intact membranes and intra-amniotic inflammation.
Kacerovsky et al. [120]	2013	24 – 37 weeks of gestation	Preterm prelabor rupture of membranes	Amniotic fluid	*S. sanguinegens*; *S. amnii* (*L. amnionii*)	145	2	No	16S rRNA gene PCR and sequencing	*S. sanguinegens* and *S. amnii* (*L. amnionii*) were detected in the amniotic fluid from women with PPROM.
Aujoulat et al. [63]	2014	26 – 29 weeks	Early preterm Infants	Neonatal stool	*S. sanguinegens*	30	1	No	16S rRNA gene PCR and sequencing; PCR-TTGE *	*S. sanguinegens* (co-colonization with staphylococci and unidentified bacteria) was detected in one neonate's

Authors	Year	Gestational age at collection	Clinical pathology	Sample type	*Sneathia* species identified	Number of cases	Number of cases with *Sneathia* infections	Was cultivation of *Sneathia* attempted?	Culture-independent methods used to detect *Sneathia*	How was *Sneathia* associated with the clinical pathology?
										stool who died at day nine of life due to a non-digestive, unspecified cause.
Romero et al. [5]	2014	20 – 35 weeks	Preterm labor with intact membranes	Amniotic fluid	*Sneathia* spp.	142	2	Yes, not successful	PCR/ESI-MS **	*Sneathia* was detected in two amniotic fluid samples from women with preterm labor and intact membranes and with intra-amniotic inflammation and histological chorioamnionitis.
Romero et al. [6]	2015	38 – 40 weeks	Clinical chorioamnionitis at term	Amniotic fluid	*Sneathia* spp. alone and with *Gardnerella vaginalis* or *Ureaplasma* spp.	46	3	Yes, not successful	PCR/ESI-MS **	*Sneathia* was detected in the amniotic fluid of women with clinical chorioamnionitis at term; polymicrobial invasion was detected in all these samples.
Romero et al. [7]	2015	20 – 35 weeks	Preterm prelabor rupture of membranes	Amniotic fluid	*Sneathia* spp.	59	6	Yes, not successful	PCR/ESI-MS **	*Sneathia* was among the most frequent microorganisms detected in amniotic fluid of women with preterm prelabor rupture of membranes. *Sneathia* positive cases were associated with acute inflammation in the placenta and amniotic cavity.
Romero et al. [61]	2015	16 – 32 weeks	Asymptomatic sonographic short cervix ≤25 mm	Amniotic fluid	*Sneathia* spp.	231	1	Yes, not successful	PCR/ESI-MS **	*Sneathia* was detected in one term case (no intra-amniotic inflammation).
Carlstein et al. [47]	2016	42 weeks	Postterm pregnancy, prolonged prelabor rupture of membranes, clinical chorioamnionitis	Amniotic fluid	*S. sanguinegens*	1	1	Yes, not successful	16S rRNA gene sequencing	*S. sanguinegens* was found in amniotic fluid of a woman with clinical chorioamnionitis at term after labor induction with an intracervical balloon.
Puri et al. [13]	2016	≤28 weeks	Early preterm infants	Neonatal stool	*Sneathia* spp.	106	3	No	16S rRNA gene sequencing	The preterm infants with chorioamnionitis and funisitis had higher relative abundances of *Sneathia* in their stool; the presence of *Sneathia* in stool was associated with a higher risk of sepsis or death.
Urushiyama et al. [75]	2017	26 – 37 weeks	Histological chorioamnionitis	Amniotic fluid	*S. sanguinegens*	79	Not reported	No	16S rRNA gene sequencing	*S. sanguinegens* was found to be among the top

Authors	Year	Gestational age at collection	Clinical pathology	Sample type	*Sneathia* species identified	Number of cases	Number of cases with *Sneathia* infections	Was cultivation of *Sneathia* attempted?	Culture-independent methods used to detect *Sneathia*	How was *Sneathia* associated with the clinical pathology?
										10 dominant taxa in the group with histological chorioamnionitis stage III.
Musilova et al. [44]	2017	24 – 37 weeks	Preterm prelabor rupture of membranes	Amniotic fluid	*S. sanguinegens* alone and with *Ureaplasma* spp.; *S. amnii* (*L. amnionii*) alone and with *Ureaplasma* spp. or *Chlamydia trachomatis*	479	5	No	16S rRNA gene sequencing	*S. sanguinegens and S. amnii* (*L. amnionii*) were detected in amniotic fluid samples with or without intra-amniotic inflammation from women with PPROM.
Musilova et al. [43]	2017	24 – 37 weeks	Preterm prelabor rupture of membranes	Amniotic fluid	*S. sanguinegens* alone and with *Ureaplasma* spp.	287	2	No	16S rRNA gene sequencing	*S. sanguinegens* was detected in amniotic fluid samples with intra-amniotic inflammation from women with PPROM.
Musilova et al. [46]	2018	34 – 37 weeks	Preterm prelabor rupture of membranes	Amniotic fluid	*S. sanguinegens*	159	1	Yes, the results were not specified	16S rRNA gene sequencing; MALDI-TOF*** was used for isolates	*S. sanguinegens* was detected in amniotic fluid samples with intra-amniotic inflammation from women with PPROM.
Hornychova et al. [45]	2018	24 – 37 weeks	Preterm prelabor rupture of membranes; HPV infection	Amniotic fluid	*S. sanguinegens*	100	1	Yes, the results were not specified	16S rRNA gene sequencing of isolates	*S. sanguinegens* was detected in amniotic fluid from a woman with PPROM, diagnosed with cervical HPV infection, intra-amniotic inflammation and histological chorioamnionitis and funisitis.
Lannon et al. [11]	2019	≥37 weeks	Clinical chorioamnionitis	Vaginal fluid, chorio-decidual space, chorioamnion	*Leptotrichia/ Sneathia* spp.	23	1	Yes, not successful	qPCR assay	*Leptotrichia/Sneathia* spp. were detected simultaneously in the chorioamnion space and vaginal fluid in a woman with mild chorioamnionitis.
Vitorino et al. [49]	2019	39 weeks	Neonatal congenital pneumonia (diagnosed postmortem, stillbirth case) from mother with histological acute chorioamnionitis	Neonatal lung, Cerebro-spinal fluid, blood	*S. amnii*	1	1	Yes, not successful	16S rRNA gene PCR and sequencing	*S. amnii* was attributed as the cause of congenital pneumonia.

Authors	Year	Gestational age at collection	Clinical pathology	Sample type	*Sneathia* species identified	Number of cases	Number of cases with *Sneathia* infections	Was cultivation of *Sneathia* attempted?	Culture-independent methods used to detect *Sneathia*	How was *Sneathia* associated with the clinical pathology?
Romero et al. [55]	2019	20 – 40 weeks	Intra-amniotic inflammation or infection with intact membranes	Amniotic fluid, vaginal fluid	*Sneathia* spp.	8	4	Yes, not successful	16S rRNA gene sequencing	*Sneathia* was one of the species most commonly shared between paired amniotic fluid and vaginal samples in women with intra-amniotic infection and intact membranes.

* PCR-TTGE - polymerase chain reaction coupled with temporal temperature gradient gel electrophoresis

** PCR/ESI-MS - broad-range polymerase chain reaction coupled with electrospray ionization mass spectrometry

*** MALDI-TOF - matrix-assisted laser desorption ionization time-of-flight—mass spectrometry

Table 3.

Use of antibiotics for the treatment of *Sneathia* infections

Authors	Year	Sample type	*Sneathia* species	Clinical diagnosis	Method of *Sneathia* detection	Antibiotic administration	Effect of antibiotic treatment
Mitchell et al. [58]	2009	Vaginal secretion	*Leptotrichia/ Sneathia* spp.	Bacterial vaginosis in pregnancy	qPCR assay	Oral or vaginal administration of metronidazole	There were decreases in the concentrations of *Leptotrichia/Sneathia* in women receiving oral metronidazole, but not in the vaginal treatment subgroup; however, the cure rate and persistence after treatment were not different between these two groups.
Ling et al. [158]	2013	Vaginal secretion	*Sneathia* spp.	Bacterial vaginosis	16S rRNA gene sequencing	Intravaginal administration of metronidazole or intravaginal probiotic (*L. crispatus*)	There was an equivalent decrease in *Sneathia* spp. among women treated with intravaginal metronidazole or intravaginal probiotic (*Lactobacillus crispatus*).
Macklaim et al. [161]	2015	Vaginal secretion	*Sneathia* spp.	Bacterial vaginosis	16S rRNA gene sequencing	Oral administration of tinidazole with or without oral probiotic (*Lactobacillus rhamnosus* and *L. reuteri* strains)	The combination of tinidazole with oral probiotic (*Lactobacillus rhamnosus* and *L. reuteri* strains), but not tinidazole alone, significantly decreased the relative abundance of *Sneathia.*
Cruciani et al. [162]	2015	Vaginal secretion	*Sneathia* spp.	Bacterial vaginosis	VaginArray (PCR-based microarray tool)	Intravaginal administration of rifaximin	Rifaximin resulted in a significant drop in the absolute abundance of *Sneathia* in most women.
Hilbert et al. [80]	2016	Vaginal secretion	*Leptotrichia/ Sneathia* spp.	Bacterial vaginosis	qPCR assay	Oral metronidazole or tinidazole, intravaginal metronidazole suppository, intravaginal metronidazole plus miconazole, clindamycin cream	*Leptrotrichia/Sneathia* were largely undetectable after 7–10 days in the resolved and recurrent bacterial vaginosis groups, however, it was detected 40–45 days later in both groups.
Balkus et al. [37]	2017	Vaginal secretion	*Leptotrichia/ Sneathia* spp.	Women with a high-risk of vaginal infections	qPCR assay	Intravaginal administration of metronidazole plus miconazole or placebo	The combination of metronidazole and miconazole significantly reduced the abundance of *Leptotrichia/ Sneathia* compared to the placebo group.
Gottschick et al. [41]	2017	Vaginal secretion	*S. amnii*	Bacterial vaginosis	16S rRNA gene sequencing	Oral administration of metronidazole	The relative abundance of *S. amnii* was significantly reduced after treatment.
Brown et al. [14]	2018	Vaginal secretion	*S. sanguinegens; Sneathia* spp.	Preterm prelabor rupture of membranes (PPROM)	16S rRNA gene sequencing	Oral administration of erythromycin	The prophylactic oral administration of erythromycin to patients who experienced PPROM with *Lactobacillus*-dominant vaginal microbiomes led to a shift in the vaginal microbiota and the detection of *S. sanguinegens* and unclassified *Sneathia* in the vaginal fluid after treatment.

Table 4.

Antibiotic sensitivity and resistance in clinical *Sneathia* isolates

Authors	Year	Source of isolation	Bacterial species	Clinical diagnosis	Antibiotic sensitivity	Antibiotic resistance
De Martino et al. [54]	2004	Maternal blood	*S. amnii* (*L. amnionii*), *S. sanguinegens*	Intrapartum and postpartum fever	Amoxicillin, amoxicillin-clavulanic acid, piperacillin, piperacillin-tazobactam, cefotaxime, imipenem, chloramphenicol and metronidazole	Vancomycin, intermittent susceptibility to erythromycin
Boennelycke et al. [52]	2007	Maternal blood	*S. amnii* (*L. amnionii*)	Septic abortion at 15 weeks of gestation	Penicillin, metronidazole	Not reported
Bachy et al. [166]	2011	Joint fluid and synovial biopsy	*Sneathia* spp.	Elbow septic arthritis	Imipenem, clindamycin, rifampicin, tetracycline and chloramphenicol	Erythromycin, aminoglycosides, fluoroquinolones
Harwich et al. [28]	2012	Vaginal microbiome	*S. amnii*	Preterm labor at 26 weeks of gestation	Metronidazole, vancomycin	Nafcillin, tetracycline, ciprofloxacin