


# Classification, Importance, and Pathogenicity of Facklamia Species and Related Bacteria

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**Abstract**
Facklamia is a genus of Gram-positive, facultatively anaerobic cocci, first identified in 1997. These bacteria are part of the family Aerococcaceae, closely related to other lactic acid bacteria in the order Lactobacillales. The genus currently includes species like *Facklamia hominis, Facklamia ignava*, and *Facklamia languida*, which are often found in human clinical samples including blood, cerebrospinal fluid, and wounds. While typically harmless in healthy individuals, Facklamia infections can lead to serious complications in immunocompromised patients or those with underlying conditions and are implicated in infections such as bacteremia, paendocarditis, and chorioamnionitis. The recognition of Facklamia in clinical settings has grown, necessitating more research into their epidemiology and significance. Facklamia species are catalase-negative and typically form small chains or clusters. Accurate identification of these bacteria is critical due to their close resemblance to other cocci, such as Streptococci, under a microscope. The pathogenic mechanisms of Facklamia are not fully understood, but they are increasingly associated with nosocomial infections, particularly in vulnerable patient populations. Accurate diagnostic methods and awareness of Facklamia's pathogenic potential are critical for effective treatment.

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## 1. Introduction

Facklamia is a genus of gram-positive bacteria that belong to the family Aerococcaceae. *Facklamia spp.* cannot readily be classified in known taxa and form a distinct taxon in the family Aerococcaceae. Currently, these phylogenetically distinct species have been described: *Facklamia hominis, Facklamia cancri, Facklamia ochracea, Facklamia tabacinas, Facklamia sanguinis, and Facklamia viridens.* Three of these (*F. hominis, F. ochracea, and F. sanguinis*) belong to the core pathogenic species that have been associated with human infections. Bacteria in the genus Facklamia are distributed in various environments and have been isolated from human clinical specimens, a naturally contaminated river, fermented fish products, and a fish gut (Gahl *et al*., 2020 and Rashmi *et al.*, 2021) [19, 33]. After being first described in healthy humans, *F. hominis* soon gained attention as an opportunistic pathogen. Infections caused by this species have been reported in compromised hosts, including immuno compromised and non-immuno compromised humans. However, the pathogenicity of *F. hominis* in fish was unknown. Bacteria that share a recent common ancestor with *F. hominis* were described as *F. sanguinis* and were recovered from human blood specimens, suggesting that these two are potentially pathogenic in humans. In addition, the presence of *F. sanguinis* was recorded in fish. *F. sanguinis* was isolated from the guts of Pacific white shrimp that were not fed *F. sanguinis.* After being fed this bacterium, the shrimp were suspected to have developed the disease four days after infection (Rossi *et al.*, 2023 and Ashour & Othman, 2020) [36, 4]. *F. ochracea and F. tabacinas* have also been described as human pathogens and were recovered from clinical specimens.

However, to the best of knowledge, these two species have not been reported prior as pathogens in fish. Since fish are not considered "normal" hosts for Facklamia species, clinical records in humans should be taken into account when considering the potential pathogenicity of these species in fish. *F. viridens and F. cancri*, on the other hand, were primarily characterized as animal opportunistic pathogens, having been isolated from clinical and environmental samples from dogs and cats. *F. cancri* was later recovered from human dental plaque and was found to have high similarity with the 16S rRNA gene of the DNA of a bacterium in the oral cavity of hippopotamuses. So far, *F. viridens* has been the only Facklamia species detected in carnivorous fish and assumed to have a role in their microbiota. *Facklamia species* belong to the same family as Tetragenococcus, a genus of moderately halophilic bacteria that is considered as safe for food processing (Desjardin and Perry, 2022) [11].

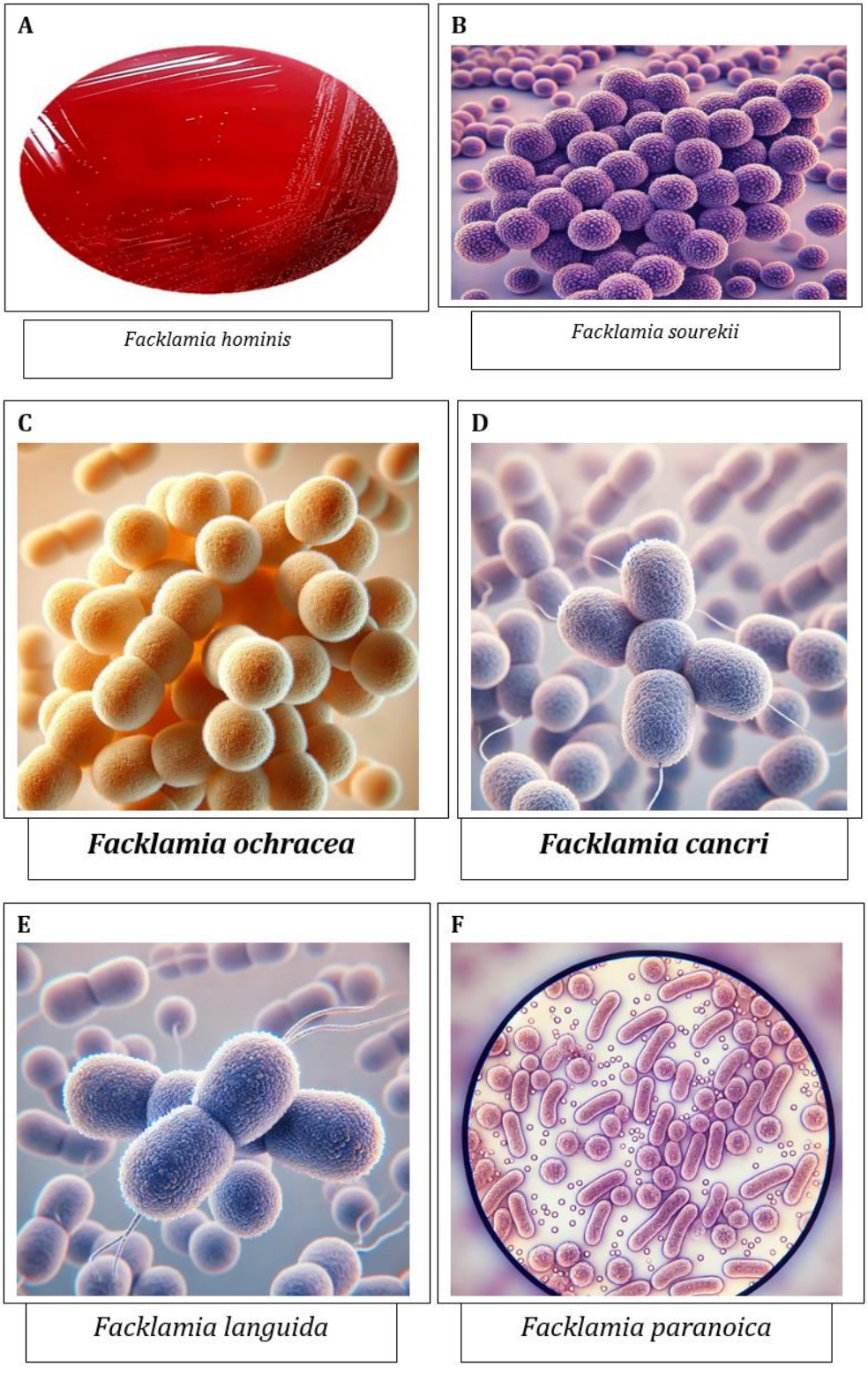



**Fig 1:** *Facklamia hominins* A on Blood Agar and from B-F Other Species of Facklamia under Microscope (Desjardin and Perry, 2022) [11]

## 2. Taxonomy of *Facklamia spp.*

The genus Facklamia has been explored with respect to the wide range of new taxa and at the same time the curious fact of this small and dispersed genus. *F. hominis* was the first species described in this genus, with later species.

Classification of *Facklamia spp*.
Domain: Bacteria
Phylum: Firmicutes
Class: Bacilli
Order: Lactobacillales
Family: Aerococcaceae
Genus: Facklamia
Species: Facklamia hominis, Facklamia paranoica, Facklamia languida, Facklamia ruminicola, Facklamia erythrocytoclastica,

Facklamia hominis is a Gram-positive, facultatively anaerobic cocci. It is part of the normal human microbiota, particularly in the female genital tract, but can act as an opportunistic pathogen in immuno compromised individuals or those with underlying health conditions. It is closely related to other species within the Facklamia genus, and accurate identification is important to distinguish it from other similar bacterial pathogens.

Facklamia paranoica this species, like others in the Facklamia genus, is Gram-positive and facultatively anaerobic. It is typically found in clinical settings and can be part of the normal microbiota but may also cause opportunistic infections in humans.

Facklamia languida this species, like other Facklamia bacteria, is Gram-positive, facultatively anaerobic, and coccoid in shape. It can be isolated from various clinical samples and has been identified as an opportunistic pathogen in humans, particularly in individuals with compromised immune systems. *Facklamia ruminicola* is a Gram-positive, facultatively anaerobic bacterium. Like other members of the Facklamia genus, it shares a coccoid shape and is closely related to other lactic acid bacteria. This species is often associated with ruminants but has not been extensively studied in human pathogenic contexts. *Facklamia erythrocytoclastica* is a Gram-positive, facultatively anaerobic cocci. Like other species in the Facklamia genus, it is known to be part of the normal microbiota but may become pathogenic under certain conditions, such as in immunocompromised hosts. It shares morphological and biochemical characteristics with other species in the Facklamia genus, though its specific role and pathogenicity in clinical infections require further study.

Mostly identified from human-related infections such as endocarditis and abscesses or from food-related outbreaks, as well as food fermentation by lactic acid-producing bacteria. The last species within the genus, *F. urealyticum,* was associated with aquatic birds and was also thought to be related to human infections and treated. Although it seems that these newly identified Facklamia species should have been discovered more often, this was not the case. The designation of the genus Facklamia was clearly based on the need for a clear taxonomic classification for the endocarditis-associated bacteria within the families of Micrococcineae, and Staphylococcus. The genus is characterized by aerobic and facultatively anaerobic Gram-positive rods, nonmotile and non-sporulating, catalase-positive, and showing α-hemolytic activity on blood agar. Twenty-one Facklamia strains originating from humans, animals, food, and the environment were statistically compared to the ten validly published species in the genus (Schlattmann *et al.,* 2020; Church *et al*. 2020) [40, 9].

Many of these taxes do not fit within the genus Facklamia. However, these strains share the most basic traits of the Facklamia genus. The distribution of closely related phylotypes of the genus Facklamia is very puzzling. On the one hand, bacteria are shedding light on the coevolution of hosts and pathogens and on the biogeography and dispersal of microorganisms. The same must be hoped for other odd genera, such as Facklamia, and the closer relatives in the genera of Kocuria and Micrococcus, or other genera within the family Micrococcaceae (Dos *et al*. 2023 and Omotoso *et al.,* 2023) [14, 29].

The degree of relatedness among the genera Gardnerella, Lactobacillus, Lactococcus, Kocuria, Micrococcus, and Facklamia was elucidated by reconstructing a phylogenetic tree with sequences of the 16S rRNA genes. Although certain genera were found to be very closely related, others were more distantly related. The genus Facklamia was shown to be much more distantly related to the genera Lactobacillus and Lactococcus than to the genera Kocuria and Micrococcus. Certain Facklamia species were associated with enter pathogenic food-borne outbreaks. The pathogenic role of *Facklamia species* in certain infections has been suggested, particularly of *F. hominis* and *F. languida*. Differences in phylogenetic diversification and pathogenicity between the genera Kocuria and Facklamia were highlighted. Funerary niches were shown to be a singular ecological niche. The potential pathogenicity of diversification of Gram-positive genera in funeral niches was also suggested (Kadri *et al.,* 2021: Coelho *et al.,* 2022 and Kumar *et al.,* 2022) [21, 10, 22].

## 3. Genus Facklamia

Cultured and examined under appropriate conditions, many species of Gram-positive cocci, traditionally regarded as groupable Streptococci or Enterococci, yield non-group-type alpha-hemolytic, beta-hemolytic, or non-hemolytic colonies under compatible culture conditions. Non-motile, catalase-negative, Gram-positive cocci, with production of acid from carbohydrates, but no gas formation, and capable of growth in 6.50% NaCl, encompassing 12 species excludable from groups A, B, C, D, F or G, as Streptococci, non-groupable Enterococci, non-Streptococci/Enterococci, or allied taxa, were subsequently proposed as a new genus, Facklamia. The genus name, Facklamia, was originally derived from the noun, Facklam, with the Latin one ending, ia, added, in honor of Dr. DJ Facklam, who described many important diseases of humans and animals caused by Streptococci of the Lancefield groups H, I or K and non-groupable Streptococci including those belonging to the genera Gemella and Facklamia (BASTOS *et al.,* 2024) [5].

Two species, *F. hominis* and *F. ignava*, were previously described by a Japanese bacteriologist, *Y. Yabuta*, and three species were later coded as having been validly published. *F. hominis* was isolated from various human and animal sources and appeared to be non-pathogenic to healthy humans and mice. *F. ignava* was solely obtained from human clinical specimens, and one isolate appeared to be enterotoxigenic to mice. *F. watsonii* was exclusively observed in human clinical specimens, and almost all isolates were resistant to penicillin. To investigate the genetic diversity of the three genotypes of the genus Facklamia and their related taxa. Seventy-three

representatives of the genus Facklamia, including all described species except for F. ignava, with the six related taxa as outgroup members, were selected for 16S rRNA gene analysis and were subjected to interspecies comparison of the entire 16S rRNA gene sequences. (Mahittikorn *et al.*, 2021 and Reydams *et al.* 2022) [26, 34].

Four clades were formed in the phylogenetic tree constructed by the neighbor-joining method. Within the genus Facklamia, six distinct genotypes of bacteria were observed and designated as genotypes I to VI. The design of each taxon was based on a combination of genus name, species epithet, and strain number. Genotype I consisted of the type strains of the genus, F. hominis and F. ignava. The presence of F. ignava in the genus Facklamia remained ambiguous and requires further studies more extensive than this protocol. Genotype II included all strains of *F. watsonii*. Genotype III was comprised of three strains previously undescribed at the genus and species levels and was designated as *F. mikamai.* Genotype IV embraced another three strains designated as *F. massiliensis*. Genotype V contained only *F. succinivorans.* Genotype VI encompassed other five strains previously undescribed at the genus and species levels and was designated as *F. diteriae*. All species of the genus Facklamia were well separated from each other, and clades consisting of closely related but separate taxa were also found. The nucleotide sequence similarities between the type strains of the genus Facklamia and those of the related taxa were less than 93.4% and 80.7%, respectively (Fotedar *et al.*, 2021: Rashmi *et al*., 2021) [16, 33].

## 4. Related Bacterial Genera

An account of the genus Facklamia and its species was published recently. This genus is included in the family Corynebacteriaceae with the type species *F. hominis*, a human isolate, and is assigned to the phylum Firmicutes. On the basis of 16S rRNA gene analysis, 6 other proposed species have been included, 48 as well as several unidentified strains that fall within these species clusters. The question remains whether unidentified bacteria can persist in the digestive tract of an animal and cause a chronic clinical disease there. (Fulton, 2020 and Zhao *et al*., 2022). Using 16S rRNA gene sequence analysis, a group of strains, RID-7104, RID-4528, and RID-6305 (clinical isolates), and FAR-6504 (environment isolate), formerly candidate lactobacilli,125 were shown to be phylogenetically related to *F. hominis.* This genus is still seldom mentioned in literature and therefore more closely related species will be described here (Liou *et al.*, 2020 Fotedar *et al.*, 2021) [25, 16].

Three closely related species, *F. hominis, F. timonensis, and F. pancerum* have been shown to exhibit small differences in physiological tests and genotyping methods. Strains examined here can be distinguished from both other species. By the proposal made for *F. timonensis*, an unclassified strain group was also found with human, chimpanzee, and bovine strain sources. Verification of pathogenic potential is to be performed on some isolates of this group (Dorant *et al.*, 2020 and Royer-Tardif *et al.*, 2021) [13, 37]. *Fusobacterium casei, Lactobacillus oris, and Lactobacillus anpreetii* were isolated from human dental plaque and included in the subfamily Lactobacillinae. They are gram-positive, irregular rod-shaped bacteria that show heterogeneity in fermentation by-products and carbohydrate metabolism. In the phylogenetic analysis based on 16S rRNA gene sequencing, strains showed homology with Corynebacteriaceae and Lactobacillaceae. The genus Lactobacillus is heterogeneous, with some species exhibiting genetic similarity with Actinobacteria. Actinobacteria are often regarded as "non-pathogenic" gastro-intestinal bacteria. Bacteria of the genera Streptococcus and Enterococcus are known to suppress the growth of enteropathogenic strains of Escherichia coli O157:H7 in the digestive tract of mice. (Russell *et al.*, 2022) [38].

## 5. Importance of *Facklamia Species* and Related Bacteria

The Facklamia genus, though relatively recently discovered, is of growing importance in both clinical microbiology and human health due to its role as an opportunistic pathogen. Here's why it's significant. There is a growing recognition of Facklamia bacteria as potentially important but neglected opportunistic pathogens. While recently referred to as "the forgotten bacteria," these species appear to be underestimated in their pathogenic potential. *Facklamia hominis* has caused multiple endocarditis cases, and other species like *F. languida, F. cana,* or *F. viridans* have been linked to infections in immuno compromised patients. Facklamia bacteria can also be identified in horse abscesses, horse saddles water, and as patients' isolates in cutaneous infections linked to cat bites. The overall number of cases remains low, likely due to the special culture requirements of these bacteria. Nevertheless, there is evidence of rising numbers such as in Spain and Germany, and Facklamia-like bacteria have also been detected in gastrointestinal patients from an animal shelter. It is feared that as a result of increased laboratory testing, the true importance of Facklamia and related bacteria will be revealed (Ait *et al.*, 2020 Gahl *et al.*, 2020) [5, 19]. All *Facklamia species* possess properties enabling them to act as opportunistic pathogens. The analysis of virulence factors in *F. hominis* and *F. massiliensis* revealed the presence of hemolysin genes in both species. Furthermore, virulence genes such as clumping factor A (clf A) and fibronectin-binding protein (fn B) were found to be present in *F. hominis* but absent in *F. massiliensis*. Sequencing of virulence factors involved in the pathogenesis of other Gram-positive bacteria was also unsuccessful, indicating an evolutionary gap between Facklamia-like bacteria and the *F. hominis/F. massiliensis* branch. Potentially relevant antibiotic resistance genes nor A (Staphylococcus and Enterococcus), mef A (*Streptococcus spp.*), and tet S (Staphylococcus and Enterococcus) were also detected in *F. hominis* and related strains. However, similar antibiotic resistance genes were not found in *F. massiliensis, A. urinae, or G. vaginalis,* potentially explaining the susceptibility of these strains to various antibiotics. (Ait *et al.*, 2020: Fotedar *et al.* 2022 and Moreland *et al.*, 2023) [5, 16, 27].

The potential virulence and pathogenicity of facklamia-like bacteria warrant further exploration of their prevalence and pathogenic potential, particularly within at-risk populations. Consideration should also be given to the inclusion of *F. hominis, F. massiliensis,* and related strains in routine screening for biomarkers indicative of potential neglected pathogens. It can be hypothesized that akin to the *F. hominis and F. massiliensis* cases, there are likely additional cases that have gone undetected or misidentified. Isolation under the assumption of Bacillus, Lactobacillus, Gemella, Streptococcus, or other species in symptomatic patients with Facklamia-like species could potentially have dire consequences (Moreland *et al.*, 2023) [27].

**6. Clinical Relevance**

*Facklamia species* are part of the normal flora of the human body, particularly in the female genital tract, and can also be found in other parts of the body. Despite being harmless in healthy individuals, these bacteria have been increasingly associated with infections in immuno compromised patients or those with underlying health conditions.

Clinically, *Facklamia species* have been isolated from various infections, including:

Bacteremia: Presence of bacteria in the bloodstream.

Endocarditis: Infection of the heart valves.

Chorioamnionitis: Inflammation of the fetal membranes (amnion and chorion).

Central Nervous System Infections: Involvement in serious infections like meningitis.

**7. Opportunistic Pathogens**

Although Facklamia is not a common pathogen, it becomes opportunistic, causing infections in individuals with weakened immune systems or those undergoing invasive medical procedures. These infections are often underreported because the bacteria are difficult to identify, leading to potential misdiagnosis.

**8. Diagnostic Challenges**

Facklamia species are often misidentified as other Gram-positive cocci, particularly viridans group streptococci or enterococci, due to similarities in morphology and biochemical characteristics.

- Misidentification can lead to delayed or inappropriate treatment, which is problematic, especially in cases of serious infections like bacteremia or endocarditis. The introduction of molecular methods (e.g., 16S rRNA sequencing) has improved the accurate detection of Facklamia species in clinical laboratories. *Facklamia species* are often misidentified as Streptococci or other Gram-positive cocci due to similarities in appearance. This can result in inappropriate or delayed treatments. Improved diagnostic techniques, such as molecular identification methods (like 16S rRNA sequencing), are crucial for the accurate identification of Facklamia species in clinical settings.

**9. Antibiotic Resistance**

As with many bacteria, the rise of antibiotic resistance in *Facklamia species* could pose a significant challenge. Correctly identifying and understanding their resistance patterns is essential for selecting the most effective antimicrobial treatments. Facklamia species are generally susceptible to a wide range of antibiotics, including penicillins and other beta-lactams. However, increasing antibiotic resistance is a concern in many bacterial pathogens, and monitoring for resistance in Facklamia is important, especially in hospital settings. Timely identification and appropriate antibiotic treatment are critical in managing infections caused by Facklamia species (Munson & Carroll, 2023) [28].

**10. Research Importance**

Research on Facklamia and related bacteria is critical for understanding their epidemiology, pathogenicity, and potential impacts on human health. Better knowledge can lead to improved diagnostics, treatment strategies, and infection control practices.

Facklamia species, though often overlooked, are important in the context of human health due to their ability to cause opportunistic infections, their diagnostic challenges, and their growing clinical recognition.

**11. Pathogenicity of Facklamia Species**

A variety of rare infections caused by Facklamia species have been reported. Only case descriptions of *F. hominis* and *F. neoformans* are published. With the introduction of more sensitive diagnostic methods, for example, molecular biology techniques, species formerly classified as *F. hominis* and now belonging to the Facklamia genus after reevaluation have been found responsible for diseases of infectious and non-infectious character. It is anticipated that more cases of infections and the complications of the clinical course of a disease caused by *Facklamia species* will be reported. This is especially true in the case of immuno compromised patients. The ongoing studies on the mechanisms of pathogenicity of Facklamia and allied species, on virulence factors of these bacteria, and on their interaction with the host are supposed to provide more explanations regarding the character of these agents and the complications occurring during the course of some uncommon diseases (Doll *et al.*, 2021) [12]. Similar to other rare pathogens, an unusual combination of factors can lead to the manifestation of an infectious disease; These agents are mostly overlooked by doctors, especially in the case of ailments of unknown etiology. Nevertheless, *Facklamia species* can be regarded as opportunistic pathogens, being able to cause ailments in patients with disorders of cellular immunity and the inflammatory response, the complement cascade, impaired phagocytic function of neutrophils, and depletion or dysfunction of immunoglobulin classes; in babies aged several days to many months with human immunodeficiency virus infection; undergoing chemotherapy or after organ transplantations; on periodic prednisone therapy; or suffering from chronic illnesses such as diabetes, Job's syndrome, lymphoproliferative disease, obesity, or cardiovascular diseases. *F. hominis and F. neofelitis* belong to the human skin and throat flora, and strains of these species colonizing the skin can be transmitted to surgically treated patients and be a source of infection. (Ait *et al*. 2020 and Chmielarczyk *et al.*, 2021) [5, 8]. Facklamia species are Gram-positive, non-spore-forming, catalase-negative rods. In terms of colonial morphology, these bacteria are categorized as adherent and non-adherent. The non-adherent *F. hominis* species strains grow on agar as colonies resembling competitors of Staphylococcus spp. in colonies' morphology and growth conditions. The production and excretion of virulence factors by these allies of Streptococcus spp. It is catalyzed by adherence to biotic and abiotic surfaces and subsequent biofilm formation. The adherent species, including *F. ignava*, *F. canis*, and *F. massiliensis*, require additional host bacteria for virulence. (Munson & Carroll, 2023) [28]. Pathogenicity of Facklamia Species.

While Facklamia species are part of the normal flora in humans, especially in the female genital tract, they have been increasingly recognized as opportunistic pathogens, particularly in vulnerable populations. Their pathogenicity can be explained through several key factors:

**11.1. Opportunistic Nature**

- *Facklamia species* are not typically pathogenic in healthy individuals. However, in people with weakened immune systems, underlying conditions, or those

undergoing invasive procedures, these bacteria can cause infections.
- Patients with compromised immune defenses, such as those with cancer, diabetes, or undergoing organ transplants, are particularly susceptible to Facklamia-related infections.

### 11.2. Associated Infections
- Bacteremia: *Facklamia species* have been found in blood cultures, indicating their role in bacteremia, which is the presence of bacteria in the bloodstream. This can lead to systemic infections, especially in immuno compromised individuals.
- Endocarditis: Facklamia has been implicated in endocarditis, a serious infection of the heart valves. This condition can be life-threatening if not diagnosed and treated properly.
- Chorioamnionitis: In pregnant women, *Facklamia species* have been associated with infections of the fetal membranes, leading to complications such as preterm labor or infection of the newborn.
- CNS Infections: Some reports have linked Facklamia to infections of the central nervous system, including meningitis. This is particularly dangerous and requires prompt medical attention.

## 12. Clinical Manifestations
Facklamia has been reported as a pathogenic agent in a few case reports, a finding which has recently been corroborated by a larger study. Nowadays, the genus has gained more visibility in canine and feline medicine. *Facklamia spp.* It has also been isolated from two cats with chronic enteritis. Thus, *Facklamia species* should be regarded as putative pathogens in humans, dogs, and cats with infections of the respiratory tract probably being the most common clinical manifestation. The investigation of a larger collection of canine and feline respiratory isolates has revealed that several unexplained cases of respiratory disease in dogs and cats, where *F. montana* or closely related species were isolated, might be caused by Facklamia. In these studies, 20 of 4,573 respiratory isolates from clinical samples (0.4%) were identified as Facklamia and grouped by PFGE into 5 distinct clusters. In 7 of these cases (35%), *Facklamia spp.* was suggested to be the primary pathogen. In a similar study, involving less than half of the clinical isolates used here, *F. peptidoglycanase* and closely related bacteria were implicated in infective endocarditis in cats. A recent demonstration of Facklamia colonization of the oropharynx in dogs and cats indicates that respiratory infections in these animals could be caused by opportunistic pathogens. Most of the cases were suspected to arise from injury to the mucosal surface, predisposing the animals to secondary infections by indigenous bacteria. Thus, bacterial upper respiratory tract infections could be favored by different conditions, including viral infections (such as canine parvovirus, canine and feline leukopenia, and feline immunodeficiency virus), old age, poor husbandry, and concurrent chronic diseases. The question arises whether *Facklamia species* also pose a threat to other animal species. About swine, it may be noted that this host has a unique p120-like protein involved in the attachment of bacteria to epithelial cells and that the *F. langaaenensis* type strain was isolated from a healthy pig. No findings indicate that Facklamia species are a threat to fish farming. Thus, it seems justified to consider these bacteria as potential opportunistic pathogens in distinct animal species. Facklamia has also been reported as an etiological factor in human infections associated with respiratory tract disease, endocarditis, and brain abscess. *Facklamia species* should be recognized as putative pathogens in humans and investigated when isolated from specimens obtained from infected sites (Frias-De-Leon *et al.*, 2021: Rosales-Castillo *et al.*, 2023) [17, 35].

### 12.1. Virulence Factors
The specific virulence factors of *Facklamia species* are not well characterized, as these bacteria are relatively new to clinical recognition. However, like other Gram-positive cocci, they likely possess surface proteins that allow them to adhere to host tissues, evade the immune system, and establish infections. Additionally, their ability to grow in various environmental conditions, including anaerobic conditions, enhances their survival and pathogenic potential in different body sites. Factors involved in the colonization and establishment of bacteria within the host are traditionally referred to as virulence factors. Despite being a common cause of infection, the virulence factors of *Facklamia species* and related bacteria are largely unknown. To date, the presence of virulence factors has been investigated in only a few of the species included in the Facklamia cluster (Hoque *et al.*, 2020) [20].

A recent study in which 20 strains of *Facklamia spp.* and related bacteria were tested for viral factors involved in adhesion, motility, biofilm formation, and hemolytic activity revealed that all the species investigated are capable of biofilm formation and most are able to adhere to polystyrene surfaces. Among the species included in the Facklamia cluster, *F. hominis* formed the thickest biofilm, while *F. ignava* formed the least extensive biofilm. (Lianou *et al.*, 2020: Sauer *et al.*, 2022) [24, 39]. None of the strains tested were found to be motile. Hemolytic activity was only detected in *L. laternosynoviae* but in >15% (n = 1) of strains. No other virulence factors have been investigated in members of the Facklamia cluster. The extensive genetic variation seen among different species and between different strains of the same species complicates the comparison with other genera. (Al-Shamiri *et al.*, 2021) [3]. *Staphylococcus. aureus*, a Gram-positive bacterial pathogen of humans, has many known virulence factors that enable colonization of different tissues within the host. *Staph. aureus* produces several factors involved in adhesion to host tissue, such as fibronectin-binding proteins and clumping factors. The impact of various adherence factors in *Staph. aureus* on biofilm formation has been thoroughly investigated. In general, initial attachment to a biomaterial surface depends on the physicochemical properties of the surface and the presence of adsorbed proteins. Further biofilm development involves specific interactions between adhesive molecules on the surface of the bacteria and host proteins adsorbed to the biomaterial surface. Several *Staph. aureus* adherence factors are involved in biofilm formation, including the fibronectin-binding proteins (Fn BP) A and B, the clumping factor protein A (ClfA), and polysaccharide intercellular adhesin (PIA) (Cheung *et al.*, 2021: Chen *et al.* 2022) [7, 6].

## 13. Conclusion and Future Perspectives
Facklamia and closely related bacteria are increasingly recognized as clinically significant human pathogens. A review has been presented of the classification, importance, and pathogenicity of these bacteria. Emphasis was placed on

the importance of accurate identification to species level, especially for *Facklamia hominis*, *F. ignava*, and *Granulicatella species*, due to their association with human infections. *F. hominis* is the currently most popular "non-streptococcal" aerotolerant Gram-positive cocci identified in clinical laboratories, although rare symptoms such as endocarditis, peritonitis, and pacemaker infections have been reported in the literature. However, a majority of *F. hominis* or *Granulicatella species* will not be isolated in the initial culture, as negative blood cultures can occur in 40-100% of cases. Treatment of Granulicatella species infections may prove difficult due to their natural resistance to penicillin and the likely formation of biofilms by these bacteria, particularly if they infect heart valves. It has, therefore, been suggested that patients with prosthetic devices, such as cardiac pacemakers or prosthetic heart valves, should be screened for some of these fastidious organisms. Coupled with novel culture-independent sequencing techniques and more widespread use of MALDI-TOF MS identification, an expansion of the described virulence factors could be anticipated in the coming years. Despite the increasing number of Facklamia species infections being described in the literature, the virulence potential of some of these bacterial species still remains poorly explored. *F. hominis*, *F. ignava*, and *F. succinoglutamicum* have been shown to carry 4, 8, and 3 putative virulence factor genes, respectively. However, the biological significance and actual expression levels of these genes are still clear. On the other hand, the hemolytic activity previously reported for three related species, *G. adiacens, G. elegans, and G. saguinocola*, has not yet been tested for Facklamia species. Although any virulence factors responsible for human pathogenicity have yet to be identified, it is likely that they remain undiscovered in these and other Facklamia species. The virulence potential of some of the *Streptococcus anginosus* group (or "Streptococcus milleri") bacteria, which are closely related to members of the Facklamia genus, has been investigated. *S. intermedius* was able to activate the NF-κB signal transduction pathway and to induce IL-6 and IL-8 production more effectively than the other tested members of this group, and three putative virulence factor genes have been described for this bacterium. The widely used reference strains for *S. mitis, S. sanguinis, and S. gordonii* have recently been claimed to be misidentified isolates of *F. hominis.* Nevertheless, the significance of this finding about the pathogenicity of these bacteria is obscure, as studies conducted on the virulence potential of the *S. mitis* group did not include Facklamia species.

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