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Review article
Pathogenesis and Toxins

Virulence arsenal of the most pathogenic species among the Gram-positive anaerobic cocci, *Finegoldia magna*

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ABSTRACT

This review focuses on the virulence arsenal of the most pathogenic species among Gram positive anaerobic cocci, *Finegoldia magna* according to recently published data from 2012 to 2016. Virulence factors like sortase dependent pili and *F. magna* adhesion factor (FAF) facilitate the start of the infection. Albumin binding protein (PAB) enhances *F. magna* survival. FAF, subtilisin-like extracellular serine protease (SufA) and superantigen protein L protect the bacteria from factors of innate defense system. SufA, capsule and tissue-destroying enzymes provide a deep penetration or spread of the infections and the protein L is associated with infection severity. Biofilm production results in infection chronification and complicated treatment as well as to persistence of multi-species biofilms. Resistance rates to quinolones (13.0->70%) and clindamycin (0–40.0%) are important, and resistance to penicillins (<4%), chloramphenicol (7.0%) and metronidazole (<7%) has been reported. *F. magna* should not be overlooked when present in monoinfections or mixed infections in humans.

Contents

1. Introduction

Gram-positive anaerobic cocci (GPAC) usually account for around 25–30% of the anaerobic bacteria isolated from clinical specimens [1].

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Among GPAC, *Finegoldia magna* (formerly *Peptostreptococcus magnus*) is the most pathogenic species [2], and although frequently found in polymicrobial infections, it is the GPAC most often isolated in pure culture from different clinical specimens [1,3]. The genus *Finegoldia* was named after Sidney M. Finegold, a leading specialist and researcher in the field of anaerobic microbiology [1].

F. magna is a Gram-positive anaerobic coccus, a human inhabitant of the mouth, gastrointestinal and genitourinary tract, skin (one of the most frequent anaerobes isolated from skin) as well as a highly successful opportunistic pathogen [4–6]. The first complete genome sequence of *F. magna* strain ATCC 29328 has been performed [7]. Interestingly, although in the well ventilated nasal cavity, *F. magna* was the most common obligate anaerobic species isolated, found in 38.2% of patients [8].

F. magna is usually detected from infections such as wound infections, soft tissue abscesses, diabetic ulcers and pressure ulcers, endocarditis, pneumonia, osteomyelitis and bone and prosthetic joint infections, septic arthritis and vaginosis [1,9–11]. In an analysis of 61 cases of anaerobic bone and joint infections, *F. magna* was the second most common isolate and was associated with ankle localization [12].

Fatal cases of *F. magna* monomicrobial bacteremia and of endocarditis of native valve resulting in left ventricular rupture have been observed [13,14]. In addition, the species has been associated with cases of infective endocarditis of prosthetic valves, necrotizing fasciitis, necrotizing pneumonia, mediastinitis, toxic shock syndrome and meningitis [1,10,13,15,16]. In our previous study, *F. magna* was the most common Gram-positive anaerobic species isolated from patients with chronic balanitis [17]. In a recent study, *F. magna* has been detected in 62.5% of diabetic foot ulcer specimens [18]. The species has been the most frequently reported GPAC causing prosthetic joint infections [19].

Being an opportunistic pathogen, *F. magna* involvement in infections is associated with host factors, e.g., immunodeficiency, wounds, aging or presence of foreign materials and devices as well as with the virulence factors of the strains [1,5].

2. Material and methods

In the present review, we performed a search of the literature published in 2012–2016 for the virulence factors, including the antibiotic resistance of *F. magna*.

Suitable publications were found in Medline, PubMed and Google Scholar using keywords alone or in word combinations such as “*Finegoldia*”, “*Finegoldia magna*” “anaerobic cocci”, or “anaerobes”, “anaerobic bacteria” and “opportunistic pathogen”, “pathogenic role”, “antibiotic resistance”, “susceptibility to antibiotics” or “virulence factors” as well as “virulence”, or “biofilm” (Table 1).

In order to clarify the role of the virulence factors, the following more general keywords were additionally searched for in combination with “*Finegoldia magna*” or “anaerobic bacteria”, e.g., “case report”, “host defence/defense”, “infection”, “inflammation”, “chemokines”, and “interactions”.

For the antibiotic resistance rates in *F. magna,* data from Bulgaria, Korea, Russia, the Netherlands, USA and an international study (Tigecycline Evaluation and Surveillance Trial, TEST) were included [20], (Table 2). Unpublished data of our study are also included.

Table 1
Virulence factors of *Finegoldia magna* according to data of the last five years.

Virulence factor	Biological function	Role in infections	Reference
Adhesive protein FAF (*F. magna* adhesion factor)	Binds to keratinocyte and galectin-7 in the upper epidermal layers and to fibrillin-1 and -2. Binds to H2B and H4 histones of the skin epidermis.	Initial adherence of *F. magna* to the skin. Facilitates the bacterial penetration into the dermis. Protection from HIDS[a] (inactivates ABPs[b] like histones, LL-37 and midkine). Prevents wound healing.	[1,5,23,25,29,31,36]
Subtilisin-like extracellular serine protease (SufA)	Degrades collagen IV and collagen V, hydrolysis of the human fibrinogen and antibacterial peptides, inactivates chemokines, LL-37 and histones.	Adherence to and deep penetration into dermal tissues, inhibition of the fibrin network formation, suppression of HIDS, delayed wound healing.	[1,5,32,33]
Superantigen protein L	Superantigen activity, targeting B cells and immunoglobulins, inducing the release of pro-inflammatory mediators; interacting with a Toll-like receptor on alveolar macrophages. Inactivates the calprotectin.	Counteracts the nutritional immunity. Protection from HIDS (calprotectin). Weakened immune defense. Severe/ recurrent infections, Associated with bacterial vaginosis and lung inflammation. Possibly linked to bacteraemia and toxic shock syndrome.	[3,13,22,25,26]
Albumin binding protein PAB	Provides the cocci with fatty acids and maybe other nutrients.	Increase in *F. magna* growth rate and cell density or/and virulence.	[1,43,44]
Sortase dependent pili	Adhere to skin keratinocytes and extracellular matrix proteins	Initial colonization of the skin. Possible role in biofilm formation and modulation of the innate immunity.	[36]
Capsule	Capsule	Abscess formation	[1]
Tissue-destroying enzymes	Collagenase and gelatinase	Spread of infection, linked to abscesses and diabetic foot infections.	[1,5]
Biofilm production	Strong adherence to artificial medical devices, production of abundant matrix, co-aggregation with other intestinal anaerobes; differential special distribution	Chronification and persistence of the infections, resistance to antibiotics and hostile environment.	[4,45,46,48]
Antibiotic resistance	Possible strain resistance to erythromycin, tetracycline, clindamycin and quinolones. Rare resistance to metronidazole and penicillin. Unusual resistance to chloramphenicol.	Hampers the antibiotic therapy.	[1,51,54]

[a] HIDS- host innate defense system.
[b] ABP-antibacterial proteins/peptides.

Table 2
Antibiotic resistance in *Finegoldia magna* according to data of the last five years.

Antibiotic	Country	Specimens	No. of strains	Method	Resistance breakpoint used (mg/L)	% of resistance (MIC, mg/L)	Reference
Penicillins							
Penicillin G	Russia	Clinical	38	MICE	>0.5[a]	2.6	[51]
	Globally	Clinical	208	BMM	≥2[b]	3.4	[20]
Amoxicillin	The Netherlands	Clinical	61	E test	>8[a]	0	[52]
Cephalosporins							
Cefoxitin	Korea	Clinical	15	ADM	≥64[b]	0	[54]
Beta-lactams/beta-lactamase inhibitors							
Amoxicillin/clavulanate	Bulgaria	Clinical	16	E test, BST	>8/2[a]	0	Boyanova*
	Russia	Clinical	38	MICE	>8/2[a]	0	[51]
Piperacillin-tazobactam	Korea	Clinical	15	ADM	≥128/4[b]	0	[54]
	USA	DFI	20	BMM	≥128/4[b]	0	[53]
	Globally	Clinical	208	BMM	≥128/4[b]	0	[20]
Carbapenems							
Ertapenem	USA	DFI	20	BMM	≥16[b]	0	[53]
Imipenem	Korea	Clinical	15	ADM	≥16[b]	0	[54]
	Russia	Clinical	38	MICE	>8[a]	0	[51]
Meropenem	Globally	Clinical	208	BMM	≥16[b]	0	[20]
Lincosamides							
Clindamycin	Bulgaria	Clinical	16	E test, BST	>4[a]	31.2	Boyanova*
	Korea	Clinical	15	ADM	≥8[b]	40.0	[54]
	The Netherlands	Clinical	61	E test	>4[a]	8.0	[52]
	USA	DFI	20	BMM	≥8[b]	0	[53]
	Globally	Clinical	208	BMM	≥8[b]	16.3	[20]
Nitroimidazoles							
Metronidazole	Bulgaria	Clinical	16	E test, BST	>4[a]	6.2	Boyanova*
	Korea	Clinical	15	ADM	≥32[b]	0	[54]
	Russia	Clinical	38	MICE	>4[a]	2.6	[51]
	The Netherlands	Clinical	61	E test	>4[a]	0	[52]
	USA	DFI	20	BMM	≥32[b]	0	[53]
	Globally	Clinical	208	BMM	≥32[b]	0	[20]
Quinolones							
Ciprofloxacin	Russia	Clinical	38	MICE	NA	68.4 at MIC, >32	[51]
Levofloxacin	Bulgaria	Clinical	16	E test, BST	≥8[b]	31.2	Boyanova*
	Russia	Clinical	38	MICE	NA	71 at MIC, >32	[51]
Moxifloxacin	Korea	Clinical	15	ADM	≥8[b]	13.0	[54]
Glycylcyclines							
Tigecycline	Korea	Clinical	15	ADM	≥16	0	[54]
	Globally	Clinical	208	BMM	NA	0 at MIC, >2	[20]
Amphenicols							
Chloramphenicol	Korea	Clinical	15	ADM	≥32	7.0	[54]

DFI-diabetic foot infections.
ADM-agar dilution method; BMM-broth microdilution method; BST-breakpoint susceptibility method; MICE- M.I.C. Evaluator, (Oxoid, England).
MIC-minimal inhibitory concentration.
Boyanova*-Boyanova, unpublished data.
NA-not available.
[a] EUCAST breakpoints.
[b] CLSI breakpoints.

3. Results

Some of the virulence factors of *F. magna* are present in most isolates; others are produced by a minority of the isolates, some factors act at the beginning of the infection and others provide its persistence, severity or chronification, moreover, some virulence factors of the species exhibit structural or functional similarities to those of *Streptococcus pyogenes* or *Staphylococcus aureus* [1,3].

3.1. Superantigen protein L

Bacterial superantigens are proteins that can produce a massive activation of human immune cells and a following powerful immune response with the release of inflammatory mediators that may lead to a fatal outcome [21]. B cell superantigens can react with large sets of B-cells bearing immunoglobulin receptors of a given variable-gene family and immunoglobulins in the serum, although the host has not encountered the B cell superantigens beforehand [22].

A well studied superantigen targeting B cells is *Staphylococcus aureus* Protein A [23]. Some *F. magna* strains also possess such a virulence factor. *F. magna* immunoglobulin-binding B cell superantigen (protein L) is detected in about 10% of the isolates [1]. The virulence factor is a surface protein of 76–106 kDa exhibiting 4 to 5 homologous Fab binding domains [24].

Protein L superantigen activity is associated with recognizing and binding conserved motifs in the variable domain of human light Ig chain with a high affinity for immunoglobulin κ-chains of V_kI, V_kIII and V_kIV-gene families [1,22]. This way, its superantigen activity leads to the release of histamine and pro-inflammatory mediators following the activation of basophils and mast cells [1,3,13].

It has been observed in mice that even limited exposure to protein L reduces the B cell:T cell ratio as well as, in general, the k-bearing B cells [3]. These effects can lead to weakened immune defenses and severe or persistent and recurrent infections from the bacterial pathogens [3]. Importantly, the effects induced by the superantigen may alter immune responsiveness to new bacterial infections and memory (recall) responses [3].

Calprotectin makes up about 40% of the cytosolic protein pool of

the neutrophils, suppresses the growth of many bacteria and fungi, shows immunomodulatory activities and is important for *S. aureus* survival within abscesses [25]. The antimicrobial activity of calprotectin has been associated with its ability to chelate zinc and manganese [25]. Much like *S. aureus, F. magna* counteracts the activity of the calprotectin. *F. magna* protein L can bind and inactivate the calprotectin, and protects the bacteria from calprotectin-mediated killing [25,26]. This is an example of bacterial activity disrupting the immune responses directed at limitation of nutrients (the nutritional immunity).

F. magna superantigen protein L is involved as well in the development of lung inflammation by a different mechanism (an innate MyD88 dependent pathway), i.e., an interaction of the protein L with a Toll-like receptor on alveolar macrophages [22]. Therefore, the protein L also interacts with factors of the innate immune system such as the antibacterial proteins S100A8/A9 (without Ig binding) and Toll-like receptors [22,26].

The protein L has been linked to bacterial vaginosis [27]. Importantly, this virulence factor is the probable cause of a fatal monomicrobial *F. magna* bacteraemia and toxic shock syndrome described by Rosenthal et al. [13].

A recent study of Lorenzo et al. [28] suggests a possibility of using B-cell superantigens such as *F. magna* protein L in the treatment of B cell malignancies. The protein L induced *in vitro* as well as *in vivo* apoptosis of both human and murine k+B-cell lymphomas [28]. The mechanism involved the intrinsic apoptotic pathway initiated by the mitochondria [28].

3.2. Surface-associated protein F. magna adhesion factor (FAF)

Helical coiled coil protein (Protein FAF, *F. magna* adhesion factor) is expressed by most (>90%) of the *F. magna* isolates, although showing strain-dependent sequence variations [1,29]. This protein exhibits structural and locational similarities to M proteins of *Streptococcus pyogenes* [1]. FAF can be found in surface associated or extracellular forms [1,29]. Since most *F. magna* clinical isolates express FAF, this protein participates in both the bacterial colonization and infection process [1].

To establish the initial adherence to the skin, *F. magna* cell wall adhesion protein FAF binds to the keratinocyte cell marker galectin-7 (an epidermal skin protein concentrated in the upper epithelial levels and a lectin showing affinity for β-galactose containing oligosaccharides) in the upper levels of the skin epithelium [5]. The possible effect of the extracellular FAF activity could be the prevention of re-epithelialization (healing) of the wounds [5].

Surface protein FAF can also bind to fibrillin-1 and -2 (responsible for the integrity of the dermal layer and connective tissue) to set up the infection in the deeper dermal layer of the skin [5].

Antibacterial proteins, e.g., the protein midkine are bactericidal or bacteriostatic molecules and a key arm of innate immunity [30]. Through FAF, *F. magna* binds to the noncollagenous glycoprotein BM-40 in the lower epidermal parts and in wound fluids, and can also bind and inactivate antibacterial properties of the midkine [1,31]. Addition of some innate antibiotics, e.g., the midkine to the therapeutic regimens alone or in combination with antibiotics is an interesting topic of research [30].

Histones also are antimicrobial peptides of the host innate defense system and represent highly alkaline proteins in cell nuclei, cytoplasm and extracellular fluids, which regulate DNA expression and are mediators of inflammation and bacterial killing [32]. Binding to histones of the skin epidermis, the surface and extracellular adhesion protein FAF counteracts the strong histone H2B and H4 bactericidal activity [32,33]. In addition, FAF-positive *F. manga* strains have been observed to be more resistant to killing from the antimicrobial peptide LL-37 (see below) than the bacteria, which do not produce FAF [1].

3.3. Subtilisin-like extracellular serine protease (SufA)

F. magna cell wall-attached subtilisin protease SufA is a protein of the subtilisin-like serine protease family, which has been found to completely degrade collagen IV (the backbone of the skin basement membrane) to allow *F. magna* to penetrate into the deep dermal tissue sites as well as to degrade collagen V into small fragments in order to facilitate the bacterial adherence to the dermal layer [5]. This virulence factor can hydrolyze the human fibrinogen and to suppress the fibrin network formation, most possibly leading to delayed wound healing [1,34,35].

Chemokines are small globular proteins that control the biological activities of the many types of leukocytes [37]. For instance, the antibacterial chemokine MIG/CXCL 9 is a γ-interferon- induced monokine, produced by the keratinocytes during inflammation [37]. The peptide LL-37, the only member of the human cathelicidin family, is a significant effector molecule of the innate immunity and possesses both antibacterial and immune system–modulating activities [38].

SufA can hydrolyze antibacterial peptides that are involved in human innate immunity such as LL-37 and MIG/CXCL 9, counteracting successfully the host defense mechanisms [37,39]. Intriguingly, SufA of *F. magna,* cleaves the chemokine and AMP MIG (CXCL9), which become inactive against *F. magna*, although remaining antibacterial against other potentially pathogenic skin species, e.g., *S. pyogenes* [6,37,40]. Another activity of SufA is to cleave breast and kidney-expressed chemokine CXCL14/BRAK, leading to a decrease in its activity against both *F. magna* and *S. pyogenes* [31,37]. Moreover, the histones, after being bound by FAF, can be destroyed by SufA of *F. magna* by a proteolytic degradation [33].

A synthesized phosphonic analogue of arginine and lysine, Cbz-6-AmNpthP (OPh)2 has been found to prevent the human fibrinogen degradation and to inhibit *F. magna* with antibacterial activity *in vitro* similar to that of gentamicin (minimal inhibitory concentration, MIC value, 1.4 mg/L), without important cytotoxic effects on eukaryotic cells in cell lines [35].

3.4. Sortase dependent pili

The properties of sortase-dependent pili are to adhere and attach to the host cells during infection and to contribute to bacterial aggregation in order to enhance the tissue colonization and the bacterial resistance to the immune defense, to participate in biofilm formation and to interact with the host innate immune system [36].

According to the first description of *F. magna* pilus structures, two supposed sortase-dependent pilus proteins were found in *F. magna* pilus locus and one of them has been recognized as Fmp1 major pilus subunit because of its high resemblance to other major pilus proteins in important Gram-positive pathogens [36]. Using transmission electron microscopy, it has been found that by adhering to human skin keratinocytes, the pili can play an important role in the initial colonization of the skin by *F. magna* [36].

3.5. Peptostreptococcal albumin-binding protein (PAB)

Albumin is the most abundant plasma protein and acts as a transport protein many substances like nutrients, hormones, and toxins, and as a binding protein to some drugs [41].

Albumin-binding domain is a small, three-helix bundle domain detected in different surface proteins of the Gram-positive bacteria [42]. This protein probably gives selective advantages to the

bacteria such as an enhancement in the growth rate and cell density and an increase in virulence, most likely by providing the cocci with fatty acids and maybe other nutrients carried by the human serum albumin [1,43,44].

Protein PAB of *F. magna* and streptococcal protein G have been found to share a common origin [42]. Interestingly, the albumin-binding domain ALB8-GA has only been observed in human *F. magna* isolates and thus, it maybe has changed to bind human serum albumin with better affinity than its antecedent [42].

3.6. Other virulence factors

To enhance its virulence, *F. magna* can also produce a capsule, hippurate hydrolase and tissue-destroying enzymes such as collagenase and gelatinase [1]. Most of these factors have been associated with abscesses and diabetic foot infections [1].

3.7. Biofilm production

A microbial biofilm is a structured conglomerate attached on living or inert surfaces of microbial cells surrounded by a self-produced extracellular polymer matrix [45,46]. Biofilm formation often involves quorum sensing and is a successful microbial adaptation of microbes to hostile environments [46]. Quorum sensing involves the property of the bacteria to communicate using small organic signaling molecules according to the population density [47]. Importantly, the biofilms usually cause chronic infections, which persist despite appropriate antibiotic therapy and the immune defense mechanisms of the host [45]. The bacteria in biofilms are much more resistant to chemical, immune and antibiotic agents/factors than the planktonic (free) organisms [47].

Mixed biofilm formation resulting in obstruction of biliary stents is quite common. A study on the polymicrobial biofilm production of anaerobes cultured from biliary stents, has been performed using field emission scanning electron microscopy and confocal laser scanning microscopy [4]. The results have revealed the properties of *F. magna* to be strongly adherent and to grow as mono as well as dual-species biofilms [4]. Interestingly, *B. fragilis* and *F. magna* exhibited mutualistic and synergistic co-aggregation with either *Bacteroides fragilis* strain BfBs12 or *Clostridium difficile* strain CdiBs21 possibly due to the rich and increased extracellular polymeric substances' matrix in the mixed biofilms in the presence of *F. magna* hair-like projections on the surface [4]. *F. magna* formed an abundant matrix, unlike *B. fragilis* and when both species were grown together, *B. fragilis* grew immersed in matrix of the *F. magna* [4].

Fascinatingly, in a study on murine wound model on a biofilm involving *Pseudomonas aeruginosa, S. aureus, Enterococcus faecalis*, and *F. magna,* the biofilm has shown a differential special distribution [48]. Conversely, *P. aeruginosa* outcompeted the other bacteria in a mixed planktonic culture [48].

Evaluating microbiota in chronic wounds of 2963 patients by 16S rDNA pyrosequencing, Wolcott et al. [49] detected *F. magna* in 34% of cases with decubitus ulcers, 25% of diabetic foot ulcers, 20% of non-healing surgical wounds and 21% of venous leg ulcers.

Treatment of bacterial biofilm infections encompasses several recommendations and for this purpose, many strategies are being evaluated such as quorum sensing inhibitors and anti-quorum sensing peptides, bacteriophage therapies, disruption of bacterial amyloids, however, there is an vital need for the development of new anti-biofilm effective antibiotics, new anti-virulence drugs, biofilm matrix degrading/dissolving drugs such as enzymes or chelators, topical antimicrobial treatment etc. [45,46]. For example, a novel bacterial deoxyribonuclease, NucB, isolated from a marine strain of *Bacillus licheniformis* has been evaluated for biofilm forming bacteria isolated from chronic rhinosinusitis, some of which involved *F. magna* [50].

3.8. Antibiotic resistance

F. magna usually exhibits resistance rates of ≤10–20% to penicillin, clindamycin and metronidazole and >20% to erythromycin or tetracycline [1].

According to the data of the last five years, the resistance rate to penicillins has been <5% [20,51,52]. No resistance to beta-lactam/beta-lactamase inhibitors and carbapenems has been reported in this period [20,51–53, Boyanova, unpublished data]. However, although *F. magna* is not a beta-lactamase producer, adding avibactam to ceftaroline reduced the ceftaroline MIC_{90} from 0.5 mg/L of ceftaroline alone to 0.125 mg/L for ceftaroline-avibactam [53].

However, clindamycin resistance of *F. magna* has been found to vary widely (from 0 to 40.0%) and to increase continuously in both *F. magna* and *Peptoniphilus* species [54,55]. In a multicenter study of antibiotic susceptibility of anaerobes in Korea, clindamycin resistance rate in *F. magna* has been 40% versus only 5% for other gram-positive cocci and 13% of the 15 isolates have been moxifloxacin resistant [54].

Metronidazole resistance in *F. magna* has been seldom reported [51]. In a Cancer Research Center in Russia, among 38 *F. magna* isolates, one (2.6%) isolate was penicillin resistant (MIC, ≥32 mg/L), one (2.6%) strain was metronidazole resistant (MIC, ≥32 mg/L) and most (71%) isolates had high-level (MIC, ≥32 mg/L) resistance to levofloxacin [51].

Among 16 *F. magna* clinical isolates in our study in 2011–2013, about 1/3 (31.2%) were clindamycin or levofloxacin resistant, one strain (6.2%) was metronidazole resistant and no amoxicillin/clavulanate resistance was found [Boyanova, unpublished data].

Although ≥90% of GPAC are susceptible to metronidazole, uncommon *nimB*-positive and metronidazole-resistant strains of *F. magna* have been found [1]. Quinolone resistance varied between 13.0 and 71.0% according to the recent data [51,54]. Conversely, many *F. magna* strains were resistant to quinolones such as ciprofloxacin, levofloxacin and moxifloxacin [51,54].

In addition, the MIC_{50} (minimum inhibitory concentration that inhibit the growth of 50% of the bacteria) to penicillin G, amoxicillin–clavulanic acid, tigecycline and clindamycin as well as MIC_{90} to moxifloxacin and levofloxacin of *F. magna* have been higher than those of other GPAC [1].

In Korea, no resistance has been detected to metronidazole, tigecycline, imipenem, cefoxitin and cefotetan [54]. In the USA, 30% of 10 *F. magna* isolates evaluated have been non-susceptible to clindamycin, while all isolates have been metronidazole susceptible [56]. In a US study, MIC_{90} of levofloxacin (>32 mg/L) against *F. magna* isolates from diabetic foot infection was very high [53].

Tigecycline was active against *F. magna* in two recent studies [20,54].

Strikingly, in Korea, two *F. magna* isolates (7% of all isolates) have been non-susceptible (MICs of 16–32 mg/L) to chloramphenicol as well [54].

4. Discussion

The virulence factors of *F. magna* can act consecutively throughout the course of the infection, which, in single clinical cases, can lead to a fatal outcome [13].

The adhesion factor FAF allow the bacteria to attach to the human epidermis and to counteract the activity of innate immunity, e.g. the midkine, peptide LL-37, chemokine MIG/CXCL 9 and histones [5,30–37]. The recently described sortase-dependent pili most probably also contribute to *F. magna* adhesion to the host

tissues at the start of the infection [36].

Several virulence factors such as FAF, SufA and superantigen protein L inactivate factors of innate defense system. For instance, *F. magna* protein L inactivates a component of the innate immunity, the calprotectin and, in addition, interacts with Toll-like receptor on alveolar macrophages, affecting the innate MyD88 dependent pathway [22,25]. SufA also counteracts antimicrobial peptides providing the host innate immune system such as chemokines, LL-37 and histones (Table 2). Albumin binding protein (PAB) is associated with *F. magna* survival in the host tissues.

The spreading of the infection can be due to FAF, binding to fibrillin-1 and -2 to disrupt the integrity of both dermal layer and connective tissue [5]. SufA furthermore enhances the bacterial penetration into the deep dermal tissue sites by degradation of collagen IV and hydrolysis of the human fibrinogen [5,35].

The persistence of the infections can be associated with collagenase and gelatinase, owing tissue-destroying activities, FAF, binding to galectin-7 and maybe hindering the wound healing (re-epithelialization), SufA, inhibiting the fibrin network formation and biofilms [1,5,44]. *F. magna* is a strongly adherent species to artificial medical devices and is able to produce a rich matrix of extracellular polymeric substances in mixed biofilms with *C. difficile* and *B. fragilis* as well as to maintain the special distribution of the biofilms with other bacteria [4,48].

The severity and, in single clinical cases, the fatality of the infection can be influenced by the protein L, which acts as a B cell superantigen and can induce a massive secretion of pro-inflammatory mediators [3,13].

The major factors of *F. magna* hampering the successful antibiotic therapy are the presence of biofilms in the chronic infections [45] as well as the antibiotic resistance. Although the species is not among the most resistant anaerobic species like *Bacteroides* and *Parabacteroides* species [57], *F. magna* displays a relatively high (>30.0% in some studies) resistance to clindamycin, high quinolone resistance rates (often >30%) and, in some studies, rare resistance to penicillin G, metronidazole and chloramphenicol [20,51,54,57]. Moreover, *F. magna* usually exhibits higher resistance rates and higher MICs to antibiotics than those in other GPAC [1,54].

The importance of *F. magna* and its virulence factors in human infections implies a need for correct species identification by classical (Gram-staining morphology, and growth and biochemical reactivity characteristics) methods and wider implementation of molecular and new methods. For instance, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) use provided a high (>95%) species level identification of *F. magna* in a multi-center evaluation study [58]. The susceptibility testing of the strain, especially when isolated in monoinfections, can be important to detect the infrequent resistance of *F. magna,* e.g., that to penicillins.

5. Conclusions

In conclusion, we should take into account the participation of *F. magna* in various human infections, representing often mixed infections, but sometimes monoinfections as well, the presence of many virulence factors, some of which like FAF have been found in most of the isolates and some others like protein L and penicillin resistance in a small proportion of the strains. Different virulence factors of *F. magna* facilitate different stages of the infections, from the attachment of the bacteria to the chronification of the infections and to the unsuccessful therapy in cases of biofilm production or antibiotic resistance to the agent used. The significance of *F. magna* in human infections should not be underestimated and the correct diagnosis and appropriate treatment of the associated infections according to *in vitro* susceptibility testing results, especially when the species is isolated in monoinfections are justified.

Conflict of interest

The authors have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work.

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