Virulence factors of human pathogens: an always-needed approach

Fatores de virulência de patógenos humanos: uma abordagem sempre necessária

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ABSTRACT

Hospital infections caused by resistant bacteria are a worldwide public health problem that mainly affects immunocompromised patients. These infections are mainly caused by inadequate antibiotic prescriptions, self-medication and long hospital stays. The World Health Organization mentions a list of resistant bacteria, especially Gram-negative ones considered as priorities for research, discovery and development of new drugs. These pathogens to survive and propagate use a varied set of strategies known as virulence factors. The present study corresponds to a review of the state-of-the-art related to main factors associated with pathogenicity in clinical important Gram-positive and Gram-negative bacteria. The virulence factors, alone or together, guarantee important defenses to the host organism's immune system, as well as adverse external conditions. Consequently, there is an increase in morbidity and mortality rates in hospital
environments. Thus, effective microbial control measures are needed, especially in health institutions; also, the encouragement of new therapeutic approaches that target the main virulence factors.

Keywords: bacterial infections, pathogenicity, prevention, public health.

INTRODUCTION

The increase in the number of hospital infections caused by multi-resistant microorganisms is a worldwide health problem. These infections, known as Healthcare-associated Infections (HAI), are mainly caused by the persistent use of antibiotics, the self-medication of patients, and exposure to the hospital environment for long periods, especially in Intensive Care Units (ICUs) (Oliveira et al. 2017; Oliveira et al. 2020).

Some competent agencies survey the HAI in hospital sectors, such as the Agência Nacional de Vigilância Sanitária (ANVISA) in Brazil. Through these surveys, in 2017, the World Health Organization (WHO) summarized and published a list of resistant bacteria to be considered as a priority in the research, discovery, and development of new antibiotics, classifying them as critical, high, and medium priority (WHO 2017). Among the pathogens mentioned are species of the Enterobacteriaceae family and other microorganisms from other families such as Staphylococcus aureus, Acinetobacter baumannii, and Pseudomonas aeruginosa.
The success of the infection caused by these bacteria is determined by the sum of resistance and pathogenic mechanisms actions, the latter known as virulence factors. These factors can act individually or together to disrupt the host's defense mechanisms. The knowledge about these factors, mode of action, and regulation are relevant to the development of new therapies, also aiding in health control measures (Wilson et al. 2002; WU et al. 2008; Mulani et al. 2019; Leitão 2020).

Since epidemiological studies are essential tools to keep bacterial virulence profiles up to date and contribute to appropriate clinical treatments, the present study searched the literature for the main virulence factors of pathogenic species of the *Enterobacteriaceae* family, as well as other human pathogens.

**Cell wall**

One of the main components of the bacterial cell wall is the peptidoglycan, a highly conserved complex macromolecule formed by N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) monomers and linked by a β-1,4-O-glycosidic bond (Pyclik et al. 2020). Other components may be present in its structure, such as lipoproteins, polysaccharides, and glycolipids, which can attribute different physicochemical properties to these living beings (Radkov et al. 2018). The presence of a complex cell wall in bacteria was a significant factor in the evolution of these microorganisms; besides being essential for cell growth and viability, this structure also provides mechanical resistance and protection against environmental stress (Claessen and Errington 2019).

The cell wall constitution differentiates Gram-positive from Gram-negative microorganisms. In Gram-negative bacteria, the peptidoglycan layer is thinner (5 nm) and is located between the cytoplasmic and outer membranes. In Gram-positive group, this peptidoglycan layer is intercalary with teichoic acid and lipoteichoic acid (Fig 1.). It forms a thicker structure (20-50 nm) located on the periplasmic side of the cytoplasmic membrane (Radkov et al. 2018).
Teichoic acid is a polymer that plays a significant role in the cell wall of Gram-positive bacteria. They are involved in various cellular processes such as morphology, cell division, and nutrient absorption. Furthermore, they are significant virulence factors and play a relevant role in biofilm formation and antimicrobial resistance (van der Es et al. 2018). Depending on their binding to the cell wall, they can be of two groups: lipoteichoic acid (LTA), anchored to the lipids of the cytoplasmic membrane, and wall teichoic acid (WTA), which is firmly bound to the peptidoglycan layers (van der Es et al. 2016; Rohde 2019).

LTAs are present in all species of the Gram-positive group, except for some strains of Micrococcus ssp. WTAs are mainly found in Bacillus subtilis, S. aureus, S. epidermidis, Streptococcus pneumoniae, and Enterococcus spp. (Rajagopal and Walker 2017). Depending on the condition of the medium, the synthesis of LTA or WTA can be interrupted without higher complications for the bacterial cell; However, if the interruption occurs simultaneously, it can be lethal (Rohde 2019). For S. aureus, there shown that WTA is essential for virulence and bacterial resistance (β-lactams), while LTA is relevant in cell viability and division processes (Rismondo et al. 2018). One study, which analyzed modified teichoic acids (without d-alanine), demonstrated reduced colonization and adhesion of Methicillin-Resistant S. aureus (MRSA) and Vancomycin-Resistant E. faecalis (VRE) to nasal epithelial cells (Naclerio et al. 2020). These data
suggest that LTA and WTA are essential for biofilm formation and may play vital roles in these pathogens.

Gram-negative bacteria, in turn, have a cellular envelope consisting of two membranes, an internal one formed by a phospholipid bilayer and an external one composed of Lipopolysaccharides (LPS), also known as endotoxin (Szentirmai et al. 2021). The LPS molecule has a tripartite structure formed by a conserved hydrophobic part (lipid A), a central oligosaccharide (nucleus), and an O antigen (repeated oligosaccharide units), the latter being a variable and essential structure for microbial virulence (Maldonado et al. 2016; Sweeney and Lowary 2019). The physiological changes that occur in the LPS O antigen in \textit{P. aeruginosa} isolates, for example, are crucial to avoid detection and promote the establishment of chronic infection (McCarthy et al. 2017).

Among the benefits of LPS, the participation of the structural integrity of the outer membrane and the formation of a barrier against the entry of toxic substances stand out (Auer and Weibel 2017; Scala et al. 2020). In addition, LPS act to modulate virulence, innate and adaptive host immune responses, as well as bacterial sepsis, which represents one of the most important virulence factors in Gram-negative bacteria (Barakat et al. 2019).

In bacterial sepsis, LPS is notably recognized as the fundamental mediator of septic shock. Upon entering the host cell, it is recognized by the Toll-like receptor4 (TLR4) and triggers an inflammatory cascade, responsible for the aggressive pathogenesis of sepsis and septic shock (Martin and Bachman 2018). In Gram-positives, teichoic acids are mainly responsible for septic shock (Wilson et al. 2002). Almost three decades ago, there shown that some antibiotics can contribute to an extra release of LPS during septic shock caused by \textit{Enterobacter cloacae} (Crosby et al. 1994). These data continue to be valuable, as the proper prescription of medications is essential for the success of clinical treatments.

**General characteristics of toxins**

Among the virulence factors described for bacteria, there are some proteins secreted in the extracellular environment. Some of them are known as toxins which are protein and non-protein molecules produced to destroy or damage the host's cells. These substances modify the host cell environment and are responsible for cell-bacteria interactions (Fig 1.). Toxins are divided into endotoxins, such as LPS produced by Gram-
negative bacteria, and exotoxins, which are polypeptides produced by Gram-negative and Gram-positive bacteria (WU et al 2008; Levinson 2010; Szentirmai et al 2021).

There are other protein toxins with proteolytic function, such as toxins that are heat stable or modify the host cell's exoskeleton. Proteolytic toxins, which break down specific proteins in host cells, can cause paralysis (botulism and tetanus) and breakdown of the cell-matrix, spreading infection. Depending on where they are released, these substances characterize clinical manifestations of the disease, altering the release of neurotransmitters. Several bacteria have this type of toxin, with a variety of enzymatic actions (Wilson 2002; Otto 2015; Lahiani et al. 2017). Tetanus toxin (TeNT), produced by the bacterium Clostridium tetani, for example, is highly potent and its GABA or glycine inhibitory action on spinal cord interneurons results in host paralysis or death (Pirazzini et al. 2016).

The α (Hla) toxin produced by S. aureus was the first bacterial pore-forming toxin to be described. This toxin binds to the membrane of target cells and interrupts essential metabolic processes, and consequently causes the lysis of human erythrocytes (Lahiani et al. 2017). This bacterium produces three groups of toxins that directly harm the host: toxins that modify the membrane (working mediated or independent of the receptor), toxins that interfere with the receptor's function (do not damage the membrane), and secreted enzymes that degrade the molecules of the host or affect important host defense mechanisms (Kong et al. 2016; Acosta et al. 2017).

In Enterococcus spp., cytolysin was one of the main virulence factors discovered. Its secretion damages the host cell membrane and facilitates infection (Gao et al. 2018). It is a modified protein toxin that is secreted into the extracellular environment in the form of two structural subunits (CylL-L and CylL-S). The genes related to the production of cytolysins are cylLL, cylLS, cylM, cylB, cylA, cylL, and cylR2, which can form an operon that may be located in regions of pathogenicity (Terra et al. 2018).

Gram-negative bacteria, in turn, have the secretion systems (T1SS to T6SS) as one of their main virulence factors (Economou et al. 2006; Dalbey and Kuhn 2012). Enterobacteria are capable of producing these systems as Escherichia coli, which presents T6SS subdivided into three groups: T6SS-1 to T6SS-3 (Russell et al. 2014). While Proteus mirabilis is capable of producing the types I, III, IV, V, and VI, which provide cofactors and regulate intracellular metabolism. The hemolysin synthesized by this species for example, appears to be a significant virulence factor in the pathogenesis of
this species since strains that produce this toxin are more lethal and toxic to human renal epithelial cells (Armbruster and Mobley 2012; Armbruster et al. 2017).

*Providencia* spp. represent other human pathogens that largely produce secretion systems, such as type III (T3SS), in which proteins (effector proteins) can manipulate host cell activity and toxins can cause cell lysis (Galac and Lazzaro 2012). More recently, Yuan et al. (2020) demonstrated that *Providencia* spp. can acquire genes by Horizontal Gene Transfer (THG) and transcribe the components of almost all secretion systems (T1SS, T3SS, T4SS and T6SS). However, they highlight the T4SS type, which can transport substrates in host cells and favor bacterial adaptation, and the T6SS type divided into: T6SS-1, involved in biofilm formation, T6SS-2 with colonization, survival or invasion and T6SS-3 as antibacterials.

In *Pseudomonas* species, a series of virulence factors allow their adherence to tissue surfaces, causing damage, facilitating their dissemination and nutrient supply, and increasing their survival rate (Santajit et al. 2019). One of these factors is Exotoxin A, which is the most toxic virulence factor of the pathogenic bacteria. The toxin regulation mechanism is complex and not fully understood so far. Different studies have established a relationship between the toxin and iron metabolism. Efficient iron absorption is a significant factor for host colonization (Michalska and Wolf 2015).

Although endotoxins are essential for many Gram-negative species, some manage to survive in their absence, as is the case of *A. baumannii* (Sperandeo et al. 2017). Another example is *Klebsiella pneumoniae*; although the presence of LPS contributes to its virulence profile, other factors such as capsular polysaccharide synthesis also play significant roles in its pathogenicity (Aytenfisu et al. 2019).

**General characteristics of bacterial capsule**

The capsules are usually made up of polysaccharides and coat some species of bacteria. These structures are not essential for cell viability; however, encapsulated microorganisms can cause more severe infections as they reduce the host's immune response (Fig 1.). The protection propelled by the capsules can facilitate both the spread of bacteria from one host to another and increase the complications of infectious conditions (Singh et al. 2011; Champion et al. 2018).

Encapsulated bacteria are more virulent than non-encapsulated ones. They have a higher capacity to invade tissues (Rendueles et al. 2018) since capsules are responsible for blocking component 3 (C3) of the complement system, thus interfering in the immune
response. The capsules protect bacterial cells from reactive oxygen species generated by the host and prevent phagocytosis by macrophages. Besides, they inhibit the bactericidal action of antimicrobial peptides from the host. Among the various advantages that they provide, there is also observed the downregulation of pro-inflammatory cytokines, which usually act by promoting the inflammatory process and ensuring that reactions occur, and the invading agent is eliminated (Hiemstra et al. 2016; Rendueles et al. 2017).

Strains of *K. pneumoniae*, for example, that cannot synthesize the capsule is far less virulent than isogenic encapsulated ones in mouse models. Besides, hypervirulent strains this species produce a hypercapsule, also known as hypermucoviscosity, which consists of a more robust mucoviscous exopolysaccharide bacterial coating than the typical capsule. This hypercapsule can significantly contribute to hypervirulence in *K. pneumoniae* (Shon et al. 2013; Paczosa and Mecsas 2016).

Gram-positive bacteria can also synthesize capsules, as in *E. faecalis*. The capsular polysaccharide biosynthesis of this species is encoded by the cps operon, which includes 11 genes. However, only seven of these are essential for capsule production (cpsC, cpsD, cpsE, cpsG, cpsI, cpsJ and cpsK). Previous genetic evidence has shown that *E. faecalis* isolates can be classified into one of the three polymorphisms of the cps operon. CPS 1 has only cpsA and cpsB, whereas CPS 2 has all 11 genes of the cps operon, and CPS 5 has all genes except cpsF. CPS 2 and 5 express the capsular polysaccharide, whereas CPS 1 does not express it. The presence of a capsule has been associated with pathogenic strains of *E. faecalis* isolated from hospitalized patients (Saffari et al. 2017).

Capsular polysaccharides are also produced by *Streptococcus pneumoniae* strains, in which the capsule represents its main virulence factor (Kallin 1998). Another example of encapsulated Gram-positive bacteria is *S. aureus* serotypes CP5 and CP8, which are the most frequent and encoded by chromosomal genes (Singh et al. 2011; Acosta et al. 2017). Capsules have shown to be a significant virulence factor and can be investigated as a target for therapeutic interventions development, as well as metal ions can act as substances necessary for bacterial metabolism.

**Metal ion absorption capacity**

Some metals such as Copper (Cu), Iron (Fe), and Zinc (Zn) act as fundamental micronutrients for numerous biological systems, having unquestionable importance for the survival of various organisms, including bacterial pathogens. The absorption of metallic ions such as Fe$^+$ and Zn$^+$ is vital for some bacteria, while others are cytotoxic
(Hg\(^+\) and Cu\(^+\)) being accidentally absorbed by these microorganisms (Begg 2019; Prince and Boyd 2020) (Fig 1.). In bacteria, low amounts of metals activate pathways involved in import and mobilization, while excess metals induce efflux and storage (Chandrangsu et al. 2017).

The literature reveals that depending on the metal ion or its concentration, several metabolic processes in bacteria can be inhibited or stimulated. It indicates the existence of homeostatic regulation mechanisms for these ions. Metal-dependent regulatory proteins (metalloregulators) act by maintaining metal homeostasis, detecting the bioavailability of metal ions, controlling the transcription of genes involved in import, storage, distribution, and ionic flow (Chandrangsu et al. 2017). These sensors interact reversibly with one or more metal ions, changing the affinity of the regulatory protein for specific DNA sequences (Stubbe and Cotruvo 2011; Cotruvo and Stubbe 2012).

It is important to emphasize that, unlike other essential nutrients types, metal ions are not biochemically synthesized and cannot be degraded; therefore, homeostasis mainly depends on the modulation of transport to both intracellular and extracellular environments. Some of these ions, such as Fe\(^+\), are essential in considerable amounts to keep the countless biochemical processes of bacteria in perfect working order. Others such as Zn\(^+\) are only needed in small quantities (Gonzalez et al. 2019). When present in excess in a cell, zinc tends to occupy nonspecific binding sites, compete with other essential metals or disrupt electron transport systems, and, consequently, disrupt significant metabolic and cellular pathways (Capdevila et al. 2016; Kandari et al. 2021).

Some studies report that hosts of pathogenic bacteria use a control mechanism known as nutritional immunity. This strategy uses nutrient deprivation or metal poisoning to combat this pathogen (Begg 2019; Vaidya et al. 2018). Kaur et al. (2020) observed that A. baumannii has a specialized system for maintaining metal concentrations under pathophysiological conditions. It can circumvent a potential nutritional immunity of the host. This system is composed of the protein Multicopper Oxidase (MCOs), which, according to the authors, is a significant component of the metal ion homeostasis machine in this bacterium.

Rizvi et al. (2020) show that bacteria such as P. aeruginosa and Bacillus subtilis are efficient in removing some metallic ions. While, Fathollahi et al. (2021) demonstrate that high concentrations of metals interfere with bacterial metabolism, reducing the potential for biosorption. Thus, these studies demonstrate that homeostatic balance is
crucial, as frequent exposure to undesirable metals results in the development of survival alternatives such as biofilm production (Araújo et al. 2019).

**Fimbrial adhesins**

Among the virulence factors present on the surfaces of pathogenic bacteria, there are different types of filamentous proteins, such as fimbrial adhesins, which can promote cell adhesion and biofilm development. Generally, fimbriae differ from flagella in size and diameter (Fig 1.). In addition, they are not responsible for bacterial cell mobility. There are a variety of fimbriae, especially in Gram-negative bacteria, which interact with specific receptors present on inert surfaces and host cells (Zamani and Salehzadeh 2018).

Among the variety of fimbriae responsible for bacterial adhesion, type 1 is highlighted, which can recognize glycoprotein receptors that contain mannose residues. These are heteropolymers formed by the main FimA subunit and three auxiliary subunits: FimF, FimG, and FimH. Other common fimbrial adhesins are the P-type, which bind to glycolipid receptors and present as their main component the PapA, adapter subunits, and terminal PapG. In addition to these, type 3 are also highlighted, which bind to the target substrate using the MrkD subunit associated with the fimbrial stem that constitutes the MrkA protein (Zamani and Salehzadeh 2018; Alkhudhairy et al. 2019). In several species of the *Enterobacteriaceae* family, genes encoding fimbriae are identified, as well as in bacteria from other families such as *A. baumannii* (Mohajeri et al. 2016; Tavakol et al. 2018) and *P. aeruginosa*, which synthesizes type IV pili to aid in surface adhesion (Laverty et al. 2014).

Type 1 fimbriae are widely identified in Uropathogenic *Escherichia coli* (UPEC) strains. It is one of the relevant virulence factors in the adhesion of these pathogens in the urinary tract (Zamani and Salehzadeh 2018; Behzadi 2020). These fimbriae are also identified in other enterobacteria such as *Samonella* spp., *Klebsiella* spp., *Enterobacter* ssp. among others (Zeiner et al. 2012; Melo et al. 2014; Azevedo et al. 2018). Likewise, type 3 fimbriae are found in bacteria of this family like in *Citrobacter* spp and *Proteus* spp (Ong et al. 2010, Armbruster et al. 2017).

Investigating the biofilm formation of *E. coli* and *K. pneumoniae* Hancock et al. (2011) observed that the biofilm of a given species is dependent on the experimental condition. In addition, they emphasized that for the formation of biofilm, the balance of genetic factors such as the expression of fimbriae and biochemical factors such as the availability of nutrients, the characteristics of the adherent surface, and the growth
medium is essential. Subsequently, it was shown that the interaction of these pathogens with host cells is mediated by the expression of multiple fimbriae (Alcántar-Curiel et al. 2013; Izquierdo et al. 2014).

Bacteria that usually cause urinary tract infections, such as *P. mirabilis* and *E. coli*, can adhere to urinary mucosal cells by expressing different types of fimbriae during the infectious process. These bacteria resist hydrodynamic forces derived from the effect of urination by firmly adhere to the epithelial tissue of the bladder (Armbruster and Mobley 2012; Cordeiro et al. 2016). The adherence of *P. mirabilis* to biotic and abiotic surfaces can be mediated by the expression of 17 distinct fimbriae, especially the MR/P type fimbriae (Armbruster et al. 2018). Studies on the factors, contribute to biofilm formation are relevant, as new targets can be discovered and new therapeutic strategies developed, such as anti-adhesive drugs (Krammer et al. 2018).

**Bacterial biofilm**

Biofilm begins with microbial adhesion to a surface, where there is proliferation and formation of a community (Tretin et al. 2013). These, in early stages and maturation, are regulated by chemical signals called Quorum-Sensing (QS). This regulation leads to a general change in gene expression, increasing virulence, accelerating the gain of antimicrobial resistance, allowing microorganisms to have a unified response, facilitating the dissemination of beneficial mutations, and improving access to nutrients (Fig 2.). Thus, the biofilm favors adaptation to adverse environmental changes (Verderosa et al. 2019; Gebreyohannes et al. 2019).

Most biofilm is composed of exopolysaccharides (EPS), but they also contain water, lipids, nucleic acid, and extracellular proteins, forming a porous architecture with channels that allow the passage of nutrients. Biofilm formation depends on various conditions such as the types of microorganisms involved, the adhesion surfaces, pH, and temperature (Fig 2.). Furthermore, it can be influenced by different processes, such as stress caused by unfavorable environments (Flemming et al. 2016; Gebreyohannes et al. 2019; Vestby et al. 2020).

Among the biofilm-forming pathogens most commonly associated with human infections is *K. pneumoniae*, which can produce a thick layer of biofilm and usually expresses type 1 and type 3 fimbriae, besides capsules that facilitate adherence to epithelial cells and immune, as well as to inanimate surfaces (Bandeira et al. 2017; Araújo et al. 2019). Another example is *P. aeruginosa*, which is capable of adhering to medical
equipment and host tissues using flagella, pili, and fimbriae, which contribute to its initial adhesion and perpetuation (Laila and Santos 2016; Kim and Lee 2016). *A. baumannii* also stands out in biofilm formation, using a series of physicochemical and genetic factors and persisting in unfavorable environments (McConnell et al. 2012; Lemos et al. 2014).

Fig 2. Schematic and scanning microscopy images of the biofilm formation phases. 1: Bacterial cells in free or dispersed form of the biofilm; 2 and 3: bacteria in the initial stage of adhesion, in the reversible stage; 4: cell communication phase, with the beginning of the irreversible stage; 5: biofilm in the maturation phase, in the irreversible stage; 6: robust biofilm, 7: Biofilm disruption and cell dispersion.

Beyond these pathogens, *Providencia stuartii* can effectively adhere to and invade epithelial cells according to their growth stage (Kurmasheva et al. 2018). However, few studies associate some mechanism involved with biofilm development in this species (El Khatib et al. 2017; El Khatib et al. 2018). In *E. cloacae* and *E. hormoaechei*, the biofilm is a virulence factor that deserves to be highlighted, especially in hospitalized patients who use clinical devices. Its formation can be triggered by flagella, genes encoding type 1 and type 3 adhesins, which play a key role in bacterial adhesion and biofilm formation (Davin-Regli et al. 2019).

To Gram-positive pathogens, *S. aureus* is one of the most common biofilm-forming bacteria. The development of its biofilm occurs in several phases, and its initial adhesion depends on its surface molecules, such as murein hydrolase AtlA, fibronectin-binding proteins, and teichoic acids (Gebreyohannes et al. 2019). *E. faecium* is the second most frequent species of the genus and is considered one of the priority pathogens.
Besides external factors, biofilm formation has several genes and proteins involved in its growth. They participate from the initial adhesion such as EbpABC, Esp, BepA, and PTS group proteins. Also, the AtlA gene, which plays a fundamental role in its formation and maturation (Gao et al. 2018; Ch'ng et al. 2019).

Most microorganisms in nature live in biofilm form, thus representing a considerable challenge for medical teams. The main challenge is the high tolerance to the host's immune responses and the consequent increase in morbidity and mortality in hospital environments (Tretin et al. 2013; Rumbaugh and Sauer 2020; Vestby et al. 2020). Biofilms are variable between different species, involving a series of internal and external factors. Therefore, knowledge of their training dynamics is essential for the control strategies development and new therapeutic targets (Jamal et al. 2018; Verderosa et al. 2019; Lima et al. 2020).

**CONCLUSION**

Pathogenic bacteria represent a severe public health problem due to different pathogenicity and virulence factors. The information set presented in this study reveals the growing adaptability of these species and their treatment and control problems. Understanding the virulence dynamics of these pathogens is important to help in monitoring, combating, and preventing strategies in the hospital environment and the community.

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