Microbial Infections and Virulence Factors

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Contents

Abstract

Infection is defined as invasion and colonization processes of pathogenic or harmful microorganisms on host cells. A diverse array of microorganisms such as bacteria, virus, fungi, and protozoa attack or infect host cell. They deploy enormous strategies to target or manipulate the host cell or to escape from host immunity. Virulence factors have been secreted as a either cell associated or secreted out of cells upon infection. Infection also depends on health of host cells. Pathogens secrete different types of toxins or enzymes or some molecules to destroy the immunity of the host cells. These are encoded by either chromo-

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some or plasmid of host cells. Even drug resistant property is one of the tactics to destroy the antibiotics. Sometimes they modify themselves or mimic like host molecules upon infection and hence immune cells do not identify them. Nowadays these peculiar behaviors of microbial pathogen draw attention to many scientists worldwide. They not only affect humans, but they also infect other organisms that are economically important for human welfare. Some deadly diseases such as swine flu or dengue or other fatal diseases are really concern for human society. Every year these deadly diseases affect more than half of the people have been infected by these deadly diseases. In this section, we will discuss and shed the light on human pathogens and their disease characteristic. We will even discuss the virulence factors that aid the pathogen to progress the disease.

Keywords
Infection · Pathogen · Immune compromised · Virulence factor

1.1 Introduction

Infection is defined as multiplication or colonization of microorganisms on the host system or invading into the host cells. Despite the presence of substantial number of bacteria in the human body, their occurrence in healthy persons is usually limited to some body parts like the skin, vagina, the mucosae of nasal and buccal cavities and, most significantly, the gastrointestinal part (Schommer and Gallo 2013; Costello et al. 2009; Lemon et al. 2010). However, opportunistic pathogens colonize on the host cells for prolonged period and they cause diseases occasionally. Among the microorganisms, most deadly microorganism is virus which has the ability to hijack the host system to replicate themselves. It is very difficult to diagnose as well as to eradicate the viral diseases completely. Fungi deploy different cell associated virulence factors or secrete virulence factors to modify the host cell completely. Vector borne microbial infection is another global problem. Here we will summarize some human microbial diseases and their virulence factors.

1.1.1 Colonization of Host Surfaces by Pathogenic Microorganisms

Roughly 300–400 m^2 of surface area are represented by respiratory, digestive, and urogenital mucosae (200 times more than that of the skin) and hence these sites make maximum contact with bacteria. These sites consist of three layers: an epithelium, a loose connective tissue layered lamina propria, and the thin layered smooth muscles. These mucosal surfaces constitute frontline barriers and hence limit the

invasion by both pathogenic and commensal bacteria. These sites are not suitable for colonization of the pathogens. Ciliary movement has been observed of the epithelial cells that aid to clear the pathogens from the host system. Various molecular strategies have been deployed by pathogenic bacteria for adherence to these epithelia and to proliferate at their surface by circumventing the high defense barriers.

1.1.2 Initiation and Maintenance of Pathogens in Intracellular Lifestyle

Bacterial pathogens have diverse advantages by maintaining intracellular lifestyle, i.e., they are not attacked by humoral and complement-mediated immune system; a broad range of nutrients are accessible to them and they avoid shear stress-induced clearance. However, these intracellular bacteria are targeted by different mechanisms employed by the host cells. Thus, intracellular pathogens have evolved different strategies to successfully establish and maintain an intracellular infection for a prolonged period.

1.1.3 Crossing of Host Barriers by Pathogens

Diverse types of sentinel cells like dendritic cells (DCs) and M cells continuously sense the existence of pathogenic bacteria rich mucosal environment. Though there is coordination between innate and adaptive immune response to utmost the colonization of pathogens in the host, sometimes pathogens use as entry portals. Specialized cells such as M cells are found in the intestinal epithelium and other epithelia in humans. M cells transport antigens from the lumen to cells of the immune system. Thus, they initiate an immune response or tolerance. Their function is different from that of their adjacent epithelial cells. Antigens of the mucosal environment are recognized by DCs and play a middle role in the adaptive immunity. Mucosal tissues are enriched with these cells but sometimes these cells may migrate to mesenteric lymph nodes, where they interconnect with lymphocytes.

1.2 Microbial Infections

1.2.1 Bacterial Infections

Staphylococcus aureus is a classic opportunistic pathogen which causes skin and soft tissue infection (SSTI) worldwide. Various infections are caused by them, ranging from self-limiting skin infections to extreme life-threatening pneumonia, bacteremia, and endocarditis (Moran et al. 2006; David and Daum 2010; Talan et al. 2011). There are several microorganisms which cause skin infection. Life-threatening condition with high mortality happens when bacteria infect the central nervous system (CNS). Additionally, it may cause permanent neurological deficits

in survivors (Geyer et al. 2019). Sometimes, some diseases are caused by two different genera of microorganisms like cystic fibrosis (CF). CF lung is first colonized by *S. aureus*, but in the adulthood stage, *Pseudomonas aeruginosa* acts as the second colonizer, the most common isolated bacterium causing chronic lung infections (LiPuma 2010). More specifically, methicillin-resistant *S. aureus* (MRSA) is an infamous cause of healthcare-associated and community-associated disease along with *Acinetobacter baumannii*, with an estimated prevalence of about 30%. They colonize in chronic obstructive lung disease (COPD) affected hospitalized patients (Furuno et al. 2008; David and Daum 2010).

Bacterial meningitis, another deadly disease in sub-Saharan Africa, is caused by both *Neisseria meningitides* and *Streptococcus pneumoniae*. *S. pneumoniae,* the second most common pathogen, causes higher morbidity and mortality than *N. meningitides* in the same region (Ramakrishnan et al. 2009; Gessner et al. 2010; Mihret et al. 2016). *Haemophilus influenzae* also contributes to 2% of meningitides (Mihret et al. 2016). Brucellosis, a zoonotic disease, in humans the disease is identified by recurrent undulant fever, endocarditis, debilitating arthritis, and meningitis (Corbel 1997; Godfroid et al. 2011). It causes considerable economic loss and becomes a major public health burden (Pappas et al. 2005; Pappas 2010). Keratitis, a common form of corneal blindness across the globe, is caused by both bacteria and fungi. *P. aeruginosa,* an opportunistic human pathogen, causes chronic pulmonary infections in cystic fibrosis (CF) patients (Winstanley and Fothergill 2009). *P. aeruginosa* also affects immune-compromised individuals having human immunodeficiency virus (HIV) or undergoing cancer chemotherapy and those with burn wounds (Lau et al. 2004).

Clostridia, strict anaerobic bacteria, have been isolated from necrotizing infections in humans (Zhao-Fleming et al. 2017). In recent times, several bacterial species especially Clostridia like *Clostridium butyricum, C. perfringens*, and *C. neonatale* have been associated with necrotizing enterocolitis (NEC) outbreaks (Hosny et al. 2017; Roze et al. 2017). Life-threatening diseases in humans and animals are caused by pathogens, carried by well-known house fly. More than 100 pathogens including bacteria, viruses, fungi, and parasites (protozoans and metazoans) have been connected with the insect (Tsagaan et al. 2015; Nassiri et al. 2015). *S. pneumoniae* (Pneumococcus) is a gram-positive, α-hemolytic, and facultative anaerobic organism which inhabits the nasopharynx. Upper or lower meningitis, respiratory infections, and septicemia are caused by *S. pneumoniae*. *S. pneumoniae* operates major diseases with a considerably high mortality (Manco et al. 2006). *Yersinia pestis* causes another deadly disease, plague. It was the causative agent of epidemics in Europe during the first and second pandemics, including the Black Death, infamous for their widespread mortality and lasting social and economic impact (Bramanti et al. 2019). A life-threatening disease called Rocky Mountain spotted fever is caused by *Rickettsia rickettsii,* an obligately intracellular bacterium. Ticks spread this disease to human beings (Dantas-Torres 2007). Gas gangrene or clostridial myonecrosis is caused by *C. perfringens* type A. This disease causes rapid spread of tissue necrosis combined with a lack of leukocyte infiltration at the site of infection (Rood 1998). A chronic infectious disease called leprosy or

Hansen's disease is caused by *Mycobacterium leprae*. However, it was discovered that *M. lepromatosis* caused diffuse lepromatous leprosy (DLL) in human (Han et al. 2008; Scollard 2016). A potentially deadly disease tularemia in mammals including humans is caused by the intracellular pathogen *Francisella tularensis* (Tärnvik 1989). Psittacosis, an animal vector-borne disease, is caused by *Chlamydia psittaci.* Transmission of this fatal disease can happen to humans coming in close association with a variety of birds, most frequently Psittacidae (parrots, lories, parakeets, and cockatoos) or Columbiformes (pigeons). Exposure to equine placental material as a risk factor for transmission of Psittacosis has also been discovered recently (Polkinghorne and Greub 2017). Lyme borreliosis (LB), a tick-borne disease, is also endemic and causes serious public health problems in USA and Europe (Rosenberg 2018; Sprong et al. 2018). LB is caused by the genus Borrelia, a spirochete. Persistent infections both in the vertebrate host and tick vector are established by these pathogens (Rego et al. 2019).

1.2.2 Fungal Infections

Not only bacteria but also fungi are similarly efficient to produce several diseases in human system. Filamentous fungi such as *Aspergillus fumigatus* and the *Scedosporium apiospermum* species complex (16–58% and 9–10% respectively), the most common pathogens, are isolated from cystic fibrosis (CF) patients (Noni et al. 2017; Reece et al. 2017). *Scedosporium boydii*, *S. apiospermum*, and *S. aurantiacum* are frequently involved with CF patients whereas *S. ellipsoidium* and *S. minutisporum* are periodically involved with CF patients, suffering from CF lung infections with a geographically variable prevalence (Blyth et al. 2010; Zouhair et al. 2013; Sedlacek et al. 2015). Human lung mycetoma, caused by uncommon CF pathogen *S. Angustum,* is a previously reported disease (Kravitz et al. 2011). *Fusarium* spp. causes from mild superficial infections to invasive systemic infections. Localized diseases such as onychomycosis and keratitis are also caused by *Fusarium* spp. in normal hosts. Invasive fusariosis affected the lungs, sinuses, and visceral organs and necrotic skin lesions and positive blood cultures are developed in 60% of individuals with immune-compromised conditions (Nelson et al. 1994; Nucci et al. 2003; Lionakis and Kontoyiannis 2004). Not only healthy individual, sometimes immuno-compromised individual may also be affected. *Aspergillus*, most ubiquitous in nature, infects immune-compromised host and causes invasive aspergillosis which is limited to lungs (Steinbach et al. 2012; Camargo and Husain 2014; Husain et al. 2017).

1.2.3 Viral Infections

Viruses are the most crucial human pathogens among all others microorganisms. Recently, Zika virus infection has been highlighted. Upon Zika virus infection, flu-like symptoms appear; mild infection with joint pain, low to moderate fever, headache, fatigue, and rash (Posen et al. 2016; Kindhauser et al. 2016; Shuaib et al.

2016). Another deadly virus is human cytomegalovirus (HCMV) which causes a chronic infection with lifelong latency in humans. HCMV, an opportunistic pathogen, causes infection in immunosuppressed individuals causing birth defects (Mocarski et al. 2007). Japanese encephalitis (JE) causes uncontrolled inflammatory disease to the central nervous system. Neurotropic flavivirus, JE virus (JEV) cause Japanese encephalitis (JE) (Misra and Kalita 2010). Transmission of JEV occurs by mosquito vector. JEV transmits in a zoonotic cycle where pig acts as an amplifier and water bird acts as reservoir hosts (Solomon 2004). Dengue is another example of mosquito-borne disease and a global public health problem. Approximately 390 millions are affected annually due to dengue infections (Bhatt et al. 2013) (Fig. 1.1). Dengue virus DENV infections occur from asymptomatic cases to life-threatening hypovolemic shock (WHO 2009). Some viral diseases resolve within 2–6 weeks like hepatitis in humans. However, the hepatitis can become chronic in pregnant women and in immune-compromised individuals (Purcell and Emerson 2008; Aggarwal and Jameel 2011; Pérez-Gracia et al. 2017). Hepatitis E virus is transmitted with the consumption of meat, liver, sausages, and offal products derived from domestic pig, deer, and wild boar (Tei et al. 2004; Colson et al. 2010, 2012). The bite of infected mosquitoes can sometimes be dangerous as it transmits yellow fever virus (YFV), a member of the Flavivirus genus, to susceptible hosts like humans or non-human primates. Main availability of YFB is in endemic parts of Africa and South America, including Brazil (Barrett and Monath 2003). Rift valley fever is caused by Rift Valley fever virus (RVFV) in ruminants as well in humans (Bird et al. 2009). The large enveloped DNA virus poxvirus family infects a wide variety of hosts. Poxvirus outbreaks are caused by zoonotic infections of cowpox virus, monkeypox 70 virus, and recently discovered poxvirus species (Di Giulio and Eckburg 2004; Vora et al. 2015). Tick-borne encephalitis is the most occured viral disease in the Central Europe. It is one of the most famous arthropod borne diseases. The TBE virus (TBEV) belongs to the genus Flavivirus (family Flaviviridae). It consists of three different subtypes: (a) the European subtype, transmitted mainly by *Ixodes ricinus*, (b) the Siberian subtype, and (c) the Far Eastern subtype, which are mainly transmitted by *I. persulcatus* (Süss 2011). Tick and their vertebrate hosts spread the TBE virus, within particular geographical area (Dobler et al. 2011).

1.3 Virulence Factors Associated with Microbial Infections

Virulence factors are produced by pathogenic microorganisms to promote diseases (Table 1.1). These factors are either protein or carbohydrate or lipid in nature. Virulence factors are either secreted or cell mediated or cytosolic in nature and they can interfere the immune system of host cells. The cytosolic factors aid the bacterium to undertake quick adaptive—physiological, metabolic, and morphological

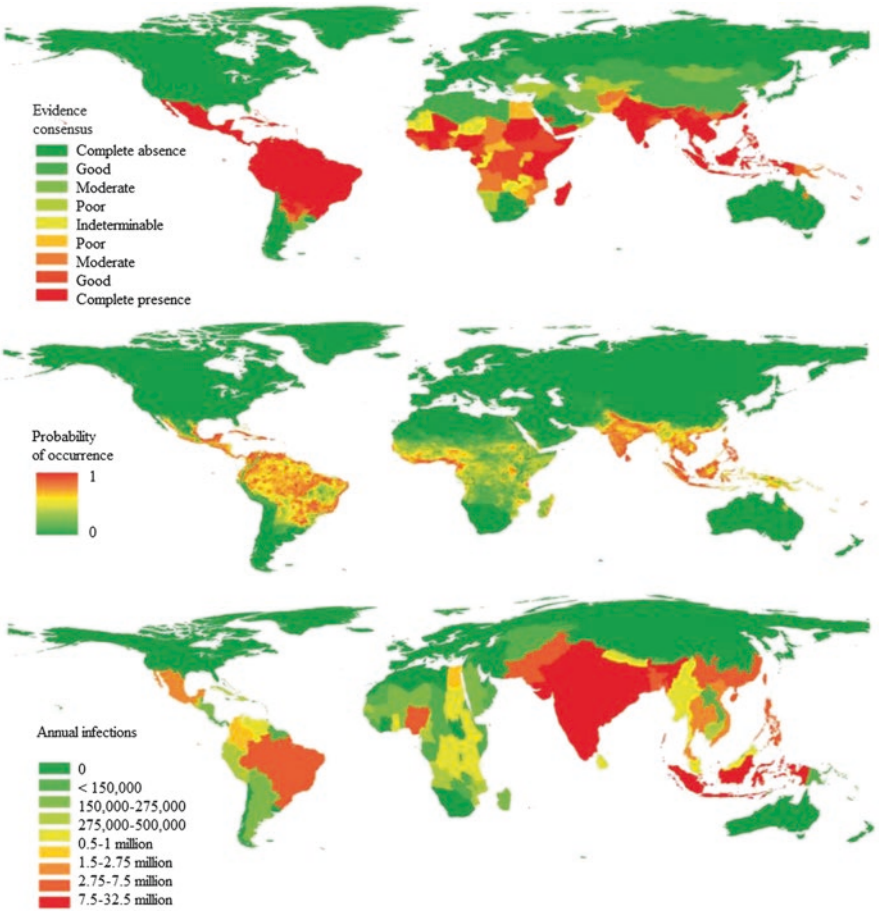

Fig. 1.1 Global evidence consensus, risk, and burden of dengue in 2010 (Bhatt et al. 2013). (Reprinted with permission [License number: 4595801418447])

shifts for the survival within host cells. The bacterium adheres and evades the host cell by the membrane-associated virulence factors. The secretory factors help the bacterium to avoid the innate and adaptive immune response mounted within the host. The host cells are killed by the synergistic effect of secretory virulence factors of extracellular pathogens. Sometimes, they intoxicate food items by secreting toxins into them and upon injecting this contaminated food item, human will be diseased. Virulence property of an organism enables to infect the host cell and causes a disease.

Table 1.1 Microbial virulence factors involved in bacterial pathogen dissemination through mammalian host

Virulence factors	Microorganism involved	Mechanism of action
Coagulase	*S. aureus*	Coagulates the fibrinogen in plasma (Shaw et al. 1951)
Collagenase	*Clostridium* spp.	Breaks down the collagen to allow the pathogen to spread (Wiinsch and Heidrich 1963)
Deoxyribonuclease (along with calcium and magnesium)	*Staphylococci*, *C. perfringens*	Lowers viscosity of exudates and allowing the pathogen more mobility (Erickson and Deibel 1973; Stern and Warrack 1964)
Hyaluronidase	Groups A, B, C, and G *Streptococci*, *Staphylococci*, *Clostridia*	Hydrolyzes hyaluronic acid and renders the intercellular spaces amenable to passage by the pathogen (Wessels and Bronze 1994; Canard et al. 1994; Hart et al. 2009)
Leukocidins	*Staphylococci*, *Streptococci*	Forms pore on leukocytes and causes degranulation of lysosomes within leukocytes (Gillet et al. 2002)
Porins	*Salmonella typhimurium*	Inhibits leukocytes phagocytosis by activating the adenylate cyclase system (Tufano et al. 1984)
Pyrogenic exotoxin B (cysteine protease)	Group A *Streptococci*, *Streptococcus pyogenes*	Degrades proteins (Kuo et al. 1998)
Streptokinase (fibrinolysin)	Groups A, C, and G *Streptococci*, *Staphylococci*	Plasmin is activated by binding to plasminogen and thus allows the pathogen to move from the clotted area (Cederholm-Williams et al. 1979)
Lecithinase or phospholipase	*Clostridium* spp.	Destroys lecithin and allows pathogen to spread (Hayward 1943)
Protein A	*S. aureus*	Binds with IgG and thus prevents complement from interacting with bound IgG (Forsgren and Sjöquist 1966)
Hemolysin	*Escherichia coli*, *C. perfringens*	Lyses erythrocytes and makes iron available for microbial growth (Mitsui et al. 1973; Mackman and Holland 1984)
Elastase and alkaline protease	*P. aeruginosa*	Cleaves laminin associated with basement membranes (Morihara and Homma 1985)

1.3.1 Extracellular Virulence Factors

Many pathogenic microorganisms secrete extracellular proteases and cell wall degrading enzymes, toxins that perform as important virulence factors. They are either encoded by plasmid or chromosome. Moreover, conditions like pH, bile, bicarbonate, mucus, alkalinity, and high osmolarity alter the expression of virulence factors in the gastrointestinal tract due to modulation of virulence factors of some enteropathogenic pathogenic strains by different host factors (Hofmann 1999; Begley et al. 2005; Chiang 2013). Two main virulence factors like the cytotoxin-associated gene A and the vacuolating cytotoxin A are present in gram-negative *Helicobacter pylori* (Fig. 1.2).

An increased risk of developing gastric cancer is caused by these virulence factors. Thus, they regulate their virulence property to the most conducive niche of infection. *E. coli* (STEC) causes food-borne disease worldwide by producing Shiga toxin. Pathogenic STEC or enterohemorrhagic *E. coli* (EHEC) causes intestinal disorders including watery or bloody diarrhea. These disorders may ultimately develop to life-threatening diseases such as thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (HUS). Keystone pathogen *Porphyromonas*

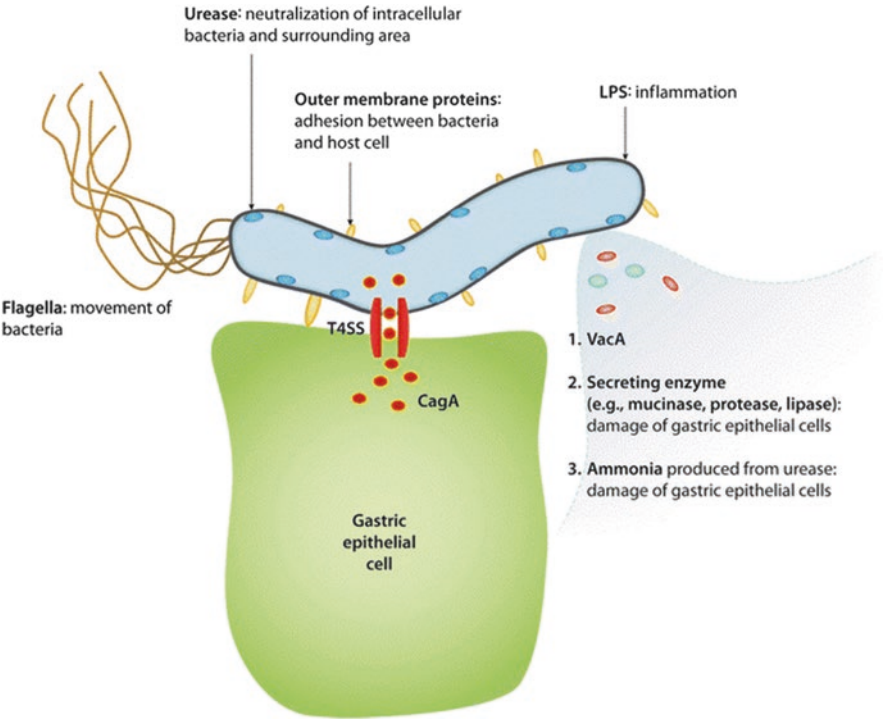

Fig. 1.2 Pathogenic virulence factors of *H. pylori* and their functions. *CagA* cytotoxin-associated gene A, *T4SS* type IV secretion system, *VacA* vacuolating cytotoxin, *LPS* lipopolysaccharide (Kim 2016). (Reprinted with permission [License number: 4593700407377])

gingivalis causes periodontal dysbiosis (Hajishengallis 2014). It processes several virulence factors that act as immunogenic molecules. *P. gingivalis* produces most important protease, termed as Gingipains (cysteine proteases) (Guo et al. 2010). Heme acquisition is one of the main functions of the gingipains protease (Smalley and Olczak 2017). Elastase, rhamnolipids, alginate, and lipopolysaccharide (LPS) of *Pseudomonas* facilitate *acute Pseudomonas* infection into a chronic infection (Bjarnsholt et al. 2010; Girard and Bloemberg 2008).

Clathrin-coated vesicle trafficking is modulated by *Chlamydial trachomatis* CT229. It controls the trafficking of both transferrin and the mannose-6-phosphate receptor for proper development. CT229 regulates several host vesicular trafficking pathways, essential for chlamydial infection (Faris et al. 2019). Adherence is another crucial virulence factor for most of the pathogens. Adhesin-deficient *S. aureus* was eliminated rapidly and it suggested adherence played crucial function for maintaining colonization process (Mulcahy et al. 2012; Weidenmaier et al. 2004). *C. trachomatis* and *L. monocytogenes* secrete the second messenger cyclic dimeric (c-di)-AMP that binds straight to stimulator of interferon (IFN) genes (STING) (Woodward et al. 2010; Barker et al. 2013), whereas STING is activated by several other pathogens in a cyclic GMP–AMP synthase (cGAS)-dependent manner (Zhang et al. 2014; Watson et al. 2015). However, *Brucella abortus* functions differently. STING directly detects bacterial cyclic dinucleotides (CDNs) and hence response of type I IFN is triggered. This leads to the upregulation of several IFN-related genes, including guanylate-binding proteins (GBPs) (Costa Franco et al. 2018).

Majority of *S. aureus* isolates secrete alpha-hemolysin (Hla), a toxin which forms pore (Li et al. 2009). Hla hijacks the host molecule ADAM10, a disintegrin and metalloprotease 10, and disrupts cell junctions. Thus it infects invariably (Kennedy et al. 2010; Inoshima et al. 2012; Malachowa et al. 2013). Neuraminidase, produced by *S. Pneumoniae,* cleaves sialic acid from cell surface glycans and mucin. It exposes host cell surface receptors and thus it promotes *S. Pneumoniae* to colonize on the upper respiratory tract (Kelly et al. 1967; O'Toole et al. 1971; Paton et al. 1993). Toxin is another secreted virulence factor that facilitates pathogenic microorganisms to invade the immune system. *Bacillus anthracis,* a gram-positive endospore forming android shaped bacteria, causes Anthrax. *B. anthracis* carries two extrachromosomal plasmids, namely pXO1 and pXO2. Plasmid pXO1 encodes protective antigen, edema factor, lethal factor, and anthrax toxin activator A (AtxA). All these toxins act as a central regulator for toxin synthesis (Hammerstrom et al. 2011). These secreted toxins require a short duration of time to establish a systemic infection. Moreover, the capsule synthesizing proteins are encoded by plasmid pXO2. Disruption occurs on the membrane integrity of host cells due to pore forming anthrolysin O, another crucial virulence factor (Shannon et al. 2003). *S. dysgalactiae* secretes hyaluronidase whose molecular weight is approximately 55 kDa. However, the value of this protein has not been determined (Sting et al. 1990). *S. zooepidemicus* produces a lytic enzyme called zoocin A (zooA). The cell walls of some closely related streptococcal species are specifically targeted by zooA. The sequence of zooA was determined by cloning it (Simmonds et al. 1997). Group B *Streptococcus* strains produce 12 kDa molecular

Table 1.2 Major differences between exotoxin and endotoxin

Exotoxin	Endotoxin
Gram-positive and gram-negative microorganisms	Integral part of cell wall of gram-negative microorganisms
Protein (polypeptide)	Lipopolysaccharide (LPS)
Diffusible, secreted by living cells	Nondiffusible and released on cell lysis
Highly antigenic	Poorly antigenic
Very high toxicity	Low toxicity
Unstable at temperature ˃60 °C and toxicity destroyed rapidly	Stable at ˃60 °C or more than that for several hours without losing toxicity
It can be converted into toxoid	No effect, cannot be converted

weight novel pyrogenic toxin which causes streptococcal toxic shock-like syndrome (TSLS) (Schlievert et al. 1993). *C. perfringens* type A produces the most toxic extracellular enzyme alpha-toxin which is strictly required for its pathogenicity (Awad et al. 1995; Ellemor et al. 1999). Alpha-toxin hydrolyzes both major constituents of eukaryotic cell membranes phosphatidylcholine and sphingomyelin due to its phospholipase activity (Rood 1998; Titball and Rood 2000). Enterotoxin, produced by *S. aureus*, causes several diseases and food-borne diseases are one of them. Staphylococcal food-borne diseases are the most occurred (Archer and Young 1988; Bean et al. 1990; Bunning et al. 1997). Botulism toxin is a neurotoxin and causes severe food-borne illness. Another neurotoxin is tetanus toxin which consists of a heavy chain and light chain. Light chain translocates to the cytosol by binding neuroselectively followed by internalization and intraneuronal sorting. Light chain cleaved at a single site of Synaptobrevin and SNAP-25 with unique selectivity and thus synaptic transmission is catalytically inhibited (Poulain et al. 1988; Bittner et al. 1989; Mochida et al. 1990; Kurazono et al. 1992; Niemann et al. 1994). Neurotoxin complex of *C. botulinum* type A consists of a core neurotoxin protein, several toxin-associated hemagglutinin (HA) proteins, and a non-toxin non-hemagglutinin (NTNH) protein. The continuous advancement in the knowledge of the botulinum toxin's molecular mechanism has aided to proceed parallel in their clinical use (Cordivari et al. 2004; Grumelli et al. 2005).

All of these above discussed toxins are exotoxins. Gram negative bacteria contain another type of toxin and this has been called endotoxin as it is cell associated and not secreted out of the cells (Table 1.2). Lipopolysaccharide (LPS) acts as an endotoxin secreted from gram-negative microorganisms. LPS is made of three parts: core polysaccharide, lipid A, and O antigen. Among these, O antigen is the most variable part and as a result, antibody could not recognize O antigen. Nowadays, LPS is well-known as a crucial factor responsible for toxic indication of severe gram-negative infections and generalized inflammation (Alving 1993). Both types of toxins have many differences (Table 1.2).

1.3.2 Cell Associated Virulence Factors

Capsule is a classic example among cell associated virulence factors. The capsule of *B. anthracis* consists of poly-γ-d-glutamic acid. It blocks the phagocytosis *of B. anthracis* during infection and hence it is weakly immunogenic in nature (Makino et al. 2002). Host cell phagocytic receptors and/or specific pattern recognition receptors (PRRs) recognize various cell surface ligands of mycobacteria like HSP70, phosphatidylinositol mannoside (PIM), 19 kDa lipoarabinomannan (LAM), and lipoprotein (Dorhoi et al. 2011). However, uptake by some of the receptors is advantageous for the pathogen's survival. Another encapsulated bacteria is *Streptococcus* which causes some serious invasive infections, including septicemia, pneumonia, and meningitis. They contain capsular material which contains sialic acid and it acts as a virulence factor (Jacques et al. 1990).

1.4 Conclusion

Microbial infection is one of the serious problems worldwide and it needs to be focused. More than half of the human death occurs annually due to microbial infections. Poor hygiene, overuse of antibiotics, and lack of education are the main reasons for microbial infection. However, very few pathogens have been discovered till date. Microbes deploy several novel strategies to attack host cells and sometimes it is very hard or almost impossible task to treat these microbial diseases. Microbes cause infections by secreting various virulence factors that manipulate the host cell system. It can be either secreted or cell associated. Sometimes, they cause disease indirectly like in case of food-borne illness where microbes secrete toxins into the food and the humans are infected with those toxin-contaminated foods. Further studies on the pathogenic microorganisms aid to discover more novel pathways and virulence factors that harm human host cells.

References

Aggarwal R, Jameel S (2011) Hepatitis E. Hepatology 54:2218–2226

Alving CR (1993) Lipopolysaccharide, lipid A, and liposomes containing lipid A as immunologic adjuvants. Immunobiology 187:430–446

Archer DL, Young FE (1988) Contemporary issues: diseases with a food vector. Clin Microbiol Rev 1:377–398

Awad MM, Bryant AE, Stevens DL, Rood JI (1995) Virulence studies on chromosomal α-toxin and θ-toxin mutants constructed by allelic exchange provide genetic evidence for the essential role of α-toxin in *Clostridium perfringens*-mediated gas gangrene. Mol Microbiol 15:191–202

Barker JR, Koestler BJ, Carpenter VK, Burdette DL, Waters CM, Vance RE, Valdivia RH (2013) STING-dependent recognition of cyclic di-AMP mediates type I interferon responses during *Chlamydia trachomatis* infection. MBio 4:e00018–e00013

Barrett AD, Monath TP (2003) Epidemiology and ecology of yellow fever virus. Adv Virus Res 61:291–315

Bean NH, Griffin PM, Goulding JS, Ivey CB (1990) Foodborne disease outbreaks, 5-year summary, 1983–1987. MMWR CDC Surveill Summ 39:15–57

Begley M, Gahan CG, Hill C (2005) The interaction between bacteria and bile. FEMS Microbiol Rev 29:625–651

Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Catherine L, Moyes CL, Drake JM, Brownstein JS, Hoen AG, Sankoh O, Myers MF, George DB, Jaenisch T, Wint GRW, Simmons CP, Scott TW, Farrar JJ, Hay SI (2013) The global distribution and burden of dengue. Nature 496:504–507

Bird BH, Ksiazek TG, Nichol ST, MacLachlan NJ (2009) Rift Valley fever virus. J Am Vet Med Assoc 234:883–893

Bittner MA, DasGupta BR, Holz RW (1989) Isolated light chains of botulinum neurotoxins inhibit exocytosis. J Biol Chem 264:10354–10360

Bjarnsholt T, Jensen PØ, Jakobsen TH, Phipps R, Nielsen AK, Rybtke MT, Nielsen TT, Givskov M, Høiby N, Ciofu O, Scandinavian Cystic Fibrosis Study Consortium (2010) Quorum sensing and virulence of *Pseudomonas aeruginosa* during lung infection of cystic fibrosis patients. PLoS One 5:e10115

Blyth CC, Middleton PG, Harun A, Sorrell TC, Meyer W, Chen SC (2010) Clinical associations and prevalence of *Scedosporium* spp. in Australian cystic fibrosis patients: identification of novel risk factors? Med Mycol 48:S37–S44

Bramanti B, Dean KR, Walløe L, Chr Stenseth N (2019) The third plague pandemic in Europe. Proc Biol Sci 286(1901):20182429

Bunning VK, Lindsay JA, Archer DL (1997) Chronic health effects of microbial foodborne disease. World Health Stat Q 50:51–56

Camargo JF, Husain S (2014) Immune correlates of protection in human invasive aspergillosis. Clin Infect Dis 59:569–577

Canard B, Garnier T, Saint-Joanis B, Cole ST (1994) Molecular genetic analysis of the nagH gene encoding a hyaluronidase of *Clostridium perfringens*. Mol Gen Genet 243:215–224

Cederholm-Williams SA, Decock F, Lijnen HR, Collen O (1979) Kinetics of the reactions between streptokinase, plasmin, and lX2-antiplasmin. Eur J Biochem 100:125–132

Chiang JYL (2013) Bile acid metabolism and signaling. Compr Physiol 3:1191–1212

Colson P, Borentain P, Queyriaux B, Kaba M, Moal V, Gallian P, Heyries L, Raoult D, Gerolami R (2010) Pig liver sausage as a source of hepatitis E virus transmission to humans. J Infect Dis 202:825–834

Colson P, Romanet P, Moal V, Borentain P, Purgus R, Benezech A, Motte A, Gérolami R (2012) Autochthonous infections with hepatitis E virus genotype 4, France. Emerg Infect Dis 18:1361–1364

Corbel MJ (1997) Brucellosis: an overview. Emerg Infect Dis 3:213–221

Cordivari C, Misra VP, Catania S, Lees AJ (2004) New therapeutic indications for botulinum toxins. Mov Disord 8:S157–S161

Costa Franco MM, Marim F, Guimaraes ES, Assis NRG, Cerqueira DM, Alves-Silva J, Harms J, Splitter G, Smith J, Kanneganti TD, de Queiroz NMGP, Gutman D, Barber GN, Oliveira SC (2018) *Brucella abortus* triggers a cGAS-independent STING pathway to induce host protection that involves guanylate-binding proteins and inflammasome activation. J Immunol 200:607–622

Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R (2009) Bacterial community variation in human body habitats across space and time. Science 326:1694–1697

Dantas-Torres F (2007) Rocky Mountain spotted fever. Lancet Infect Dis 7:724–732

David MZ, Daum RS (2010) Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev 23(3):616–687

Di Giulio DB, Eckburg PB (2004) Human monkeypox: an emerging zoonosis. Lancet Infect Dis 4:15–25

Dobler G, Hufert F, Pfeffer M, Essbauer S (2011) Tick-borne encephalitis: from microfocus to human disease. Progress in parasitology. Parasitol Res Monogr 2:323–331

Dorhoi A, Reece ST, Kaufmann SH (2011) For better or for worse: the immune response against *Mycobacterium tuberculosis* balances pathology and protection. Immunol Rev 240:235–251

Ellemor D, Baird R, Awad M, Boyd R, Rood J, Emmins J (1999) Use of genetically manipulated strains of *Clostridium perfringens* reveals that both alpha-toxin and theta-toxin are required for vascular leukostasis to occur in experimental gas gangrene. Infect Immun 67:4902–4907

Erickson A, Deibel RH (1973) Turbidimetric assay of staphylococcal nuclease. Appl Microbiol 25:337–341

Faris R, Merling M, Andersen SE, Dooley CA, Hackstadt T, Weber MM (2019) *Chlamydia trachomatis* CT229 subverts Rab GTPase-dependent CCV trafficking pathways to promote chlamydial infection. Cell Rep 26:3380–3390

Forsgren A, Sjöquist J (1966) "Protein A" from *S. aureus*: I. Pseudo-immune reaction with human γ-globulin. J Immunol 97:822–827

Furuno JP, Hebden JN, Standiford HC, Perencevich EN, Miller RR, Moore AC, Strauss SM, Harris AD (2008) Prevalence of methicillin-resistant *Staphylococcus aureus* and *Acinetobacter baumannii* in a long-term acute care facility. Am J Infect Control 36:468–471

Gessner BD, Mueller JE, Yaro S (2010) African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. BMC Infect Dis 10:22–31

Geyer S, Jacobs M, Hsu NJ (2019) Immunity against bacterial infection of the central nervous system: an astrocyte perspective. Front Mol Neurosci 12:57–65

Gillet Y, Issartel B, Vanhems P, Fournet J-C, Lina G, Bes M, Vandenesch F, Piémont Y, Brousse N, Floret D, Etienne J (2002) Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359:753–759

Girard G, Bloemberg G (2008) Central role of quorum sensing in regulating the production of pathogenicity factors in *Pseudomonas aeruginosa*. Future Microbiol 3:97–106

Godfroid J, Scholz HC, Barbier T, Nicolas C, Wattiau P, Fretin D, Whatmore AM, Cloeckaert A, Blasco JM, Moriyon I, Saegerman C, Muma JB, Al Dahouk S, Neubauer H, Letesson JJ (2011) Brucellosis at the animal/ecosystem/human interface at the beginning of the 21st century. Prev Vet Med 102:118–131

Grumelli C, Verderio C, Pozzi D, Rossetto O, Montecucco C, Matteoli M (2005) Internalization and mechanism of action of clostridial toxins in neurons. Neurotoxicology 26:761–767

Guo Y, Nguyen KA, Potempa J (2010) Dichotomy of gingipains action as virulence factors: from cleaving substrates with the precision of a surgeons knife to a meat chopper-like brutal degradation of proteins. Periodontol 2000 54:15–44

Hajishengallis G (2014) Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. Trends Immunol 35:3–11

Hammerstrom TG, Roh JH, Nikonowicz EP, Koehler TM (2011) *Bacillus anthracis* virulence regulator AtxA: oligomeric state, function and CO(2) signalling. Mol Microbiol 82:634–647

Han XY, Seo YH, Sizer KC, Schoberle T, May GS, Spencer JS, Li W, Nair RG (2008) A new *Mycobacterium* species causing diffuse lepromatous leprosy. Am J Clin Pathol 130:856–864

Hart ME, Hart MJ, Roop AJ (2009) Genotypic and phenotypic assessment of hyaluronidase among type strains of a select group of Staphylococcal species. Int J Microbiol 2009:61437

Hayward NJ (1943) The rapid identification of *Cl. welchii* by Nagler tests in plate cultures. J Pathol Bacteriol 55:285–293

Hofmann AF (1999) Bile acids: the good, the bad, and the ugly. News Physiol Sci 14:24–29

Hosny M, Cassir N, La Scola B (2017) Updating on gut microbiota and its relationship with the occurrence of necrotizing enterocolitis. Hum Microb J J4:14–19

Husain S, Silveira FP, Azie N, Franks B, Horn D (2017) Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance® registry analysis. Med Mycol 55:269–277

Inoshima N, Wang Y, Bubeck Wardenburg J (2012) Genetic requirement for ADAM10 in severe *Staphylococcus aureus* skin infection. J Invest Dermatol 132:1513–1516

Jacques M, Gottschalk M, Foiry B, Higgins R (1990) Ultrastructural study of surface components of *Streptococcus suis*. J Bacteriol 172:2833–2838

Kelly RT, Farmer S, Greiff D (1967) Neuraminidase activities of clinical isolates of *Diplococcus pneumoniae*. J Bacteriol 94:272–273

Kennedy AD, Bubeck Wardenburg J, Gardner DJ, Long D, Whitney AR, Braughton KR, Schneewind O, DeLeo FR (2010) Targeting of alpha-hemolysin by active or passive immunization decreases severity of USA300 skin infection in a mouse model. J Infect Dis 202:1050–1058

Kim JM (2016) H. pylori virulence factors: toxins (CagA, VacA, DupA, OipA, IceA). In: Helicobacter pylori. Springer, Singapore, pp 77–88

Kindhauser MK, Allen T, Frank V, Santhana RS, Dye C (2016) Zika: the origin and spread of a mosquito-borne virus. Bull World Health Organ 94:675–686C

Kravitz JN, Steed LL, Judson MA (2011) Intracavitary voriconazole for the treatment of hemoptysis complicating *Pseudallescheria angusta* pulmonary mycetomas in fibrocystic sarcoidosis. Med Mycol 249:198–201

Kurazono H, Mochida S, Binz T, Eisel U, Quanz M, Grebenstein O, Poulain B, Tauc L, Niemann H (1992) Minimal essential domains specifying toxicity of the light chains of tetanus toxin and botulinum neurotoxin type A. J Biol Chem 267:14721–14729

Kuo CF, Wu JJ, Lin KY, Tsai PJ, Lee SC, Jin YT, Lei HY, Lin YS (1998) Role of Streptococcal pyrogenic exotoxin B in the mouse model of group A streptococcal infection. Infect Immun 66:3931–3935

Lau G, Hassett D, Ran H, Kong F (2004) The role of pyocyanin in *Pseudomonas aeruginosa* infection. Trends Mol Med 10:599–606

Lemon KP, Klepac-eraj V, Schiffer HK, Brodie EL, Lynch SV, Kolter R (2010) Comparative analyses of the bacterial microbiota of the human nostril and oropharynx. MBio 1:e00129–e00110

Li M, Diep BA, Villaruz AE, Braughton KR, Jiang X, DeLeo FR, Chambers HF, Lu Y, Otto M (2009) Evolution of virulence in epidemic community-associated methicillin-resistant *Staphylococcus aureus*. Proc Natl Acad Sci U S A 106:5883–5888

Lionakis MS, Kontoyiannis DP (2004) Fusarium infections in critically ill patients. Semin Respir Crit Care Med 25(2):159–169

LiPuma JJ (2010) The changing microbial epidemiology in cystic fibrosis. Clin Microbiol Rev 23:299–323

Mackman N, Holland IB (1984) Functional characterization of a cloned haemolysin determinant from *E. coli* of human origin encoding information for the secretion of a 107 K polypeptide. Mol Gen Genet 196:129–134

Makino S, Wataraj M, Cheun HI, Shirahata T, Uchida I (2002) Effect of the lower molecular capsule released from the cell surface of *Bacillus anthracis* on the pathogenesis of anthrax. J Infect Dis 186:227–233

Malachowa N, Kobayashi SD, Braughton KR, DeLeo FR (2013) Mouse model of *Staphylococcus aureus* skin infection. Methods Mol Biol 1031:109–116

Manco S, Hernon F, Yesilkaya H, Paton JC, Andrew PW, Kadioglu A (2006) Pneumococcal neuraminidases A and B both have essential roles during infection of the respiratory tract and sepsis. Infect Immunol 74:4014–4020

Mihret W, Lema T, Merid Y, Kassu A, Abebe W, Moges B, Tenna A, Woldegebriel F, Yidnekachew M, Mekonnen W, Ahmed A, Yamuah L, Silamsaw M, Petros B, Oksnes J, Rosenqvist E, Ayele S, Aseffa A, Caugant DA, Norheim G (2016) Surveillance of bacterial meningitis, Ethiopia, 2012–2013. Emerg Infect Dis 22:75–78

Misra UK, Kalita J (2010) Overview: Japanese encephalitis. Prog Neurobiol 91:108–120

Mitsui K, Mitsui N, Hase J (1973) *Clostridium perfringens* exotoxins II. Purification and some properties of θ-toxin. Jpn J Exp Med 43:377–391

Mocarski ES, Shenk T, Pass RF (2007) Cytomegaloviruses. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA et al (eds) Fields virology, 5th edn. Lippincott, Williams & Wilkins, Philadelphia, pp 2701–2772

Mochida S, Poulain B, Eisel U, Binz T, Kurazono H, Niemann H, Tauc L (1990) Exogenous mRNA encoding tetanus or botulinum neurotoxins expressed in Aplysia neurons. Proc Natl Acad Sci U S A 87:7844–7848

Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan DA (2006) Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med 355(7):666–674

Morihara K, Homma JY (1985) Pseudomonas proteases. In: Holder IA (ed) Bacterial enzymes and virulence. CRC Press, Boca Raton, FL, pp 41–79

Mulcahy ME, Geoghegan JA, Monk IR, O'Keeffe KM, Walsh EJ, Foster TJ, McLoughlin RM (2012) Nasal colonisation by *Staphylococcus aureus* depends upon clumping factor B binding to the squamous epithelial cell envelope protein loricrin. PLoS Pathog 8:e1003092

Nassiri H, Zarrin M, Veys-Behbahani R, Faramarzi S, Nasiri A (2015) Isolation and identification of pathogenic filamentous fungi and yeasts from adult house fly (Diptera: Muscidae) captured from the hospital environments in Ahvaz city, Southwestern Iran. J Med Entomol 52:1351–1356

Nelson PE, Dignani MC, Anaissie EJ (1994) Taxonomy, biology, and clinical aspects of *Fusarium* species. Clin Microbiol Rev 7:479–504

Niemann H, Blasi J, Jahn R (1994) Clostridial neurotoxins: new tools for dissecting exocytosis. Trends Cell Biol 4:179–185

Noni M, Katelari A, Kapi A, Stathi A, Dimopoulos G, Doudounakis SE (2017) *Scedosporium apiospermum* complex in cystic fibrosis; should we treat? Mycoses 60:594–599

Nucci M, Anaissie EJ, Queiroz-Telles F, Martins CA, Trabasso P, Solza C, Mangini C, Simões BP, Colombo AL, Vaz J, Levy CE, Costa S, Moreira VA, Oliveira JS, Paraguay N, Duboc G, Voltarelli JC, Maiolino A, Pasquini R, Souza CA (2003) Outcome predictors of 84 patients with hematologic malignancies and Fusarium infection. Cancer 98:315–319

O'Toole RD, Goode L, Howe C (1971) Neuraminidase activity in bacterial meningitis. J Clin Investig 50:979–985

Pappas G (2010) The changing Brucella ecology: novel reservoirs, new threats. Int J Antimicrob Agents 36(Suppl. 1):S8–S11

Pappas G, Akritidis N, Bosilkovski M, Tsianos E (2005) Brucellosis. N Engl J Med 352:2325–2336

Paton JC, Andrew PW, Boulnois GJ, Mitchell TJ (1993) Molecular analysis of the pathogenicity of *Streptococcus pneumoniae*: the role of pneumococcal proteins. Annu Rev Microbiol 47:89–115

Pérez-Gracia MT, Suay-García B, Mateos-Lindemann ML (2017) Hepatitis E and pregnancy: current state. Rev Med Virol 27:e1929

Polkinghorne A, Greub G (2017) A new equine and zoonotic threat emerges from an old avian pathogen, *Chlamydia psittaci*. Clin Microbiol Infect 23:693–694

Posen HJ, Keystone JS, Gubbay JB, Morris SK (2016) Epidemiology of Zika virus. 1947–2007. BMJ Glob Health 1:e000087

Poulain B, Tauc L, Maisey EA, Wadsworth JDF, Mohan PM, Dolly JO (1988) Neurotransmitter release is blocked intracellularly by botulinum neurotoxin, and this requires uptake of both toxin polypeptides by a process mediated by the larger chain. Proc Natl Acad Sci U S A 85:4090–4094

Purcell RH, Emerson SU (2008) Hepatitis E: an emerging awareness of an old disease. J Hepatol 48:494–503

Ramakrishnan M, Ulland AJ, Steinhardt LC, Moïsi JC, Were F, Levine OS (2009) Sequelae due to bacterial meningitis among African children: a systematic literature review. BMC Med 7:47

Reece E, Segurado R, Jackson A, McClean S, Renwick J, Greally P (2017) Co-colonisation with *Aspergillus fumigatus* and *Pseudomonas aeruginosa* is associated with poorer health in cystic fibrosis patients: an Irish registry analysis. BMC Pulm Med 17:70

Rego ROM, Trentelman JJA, Anguita J, Nijhof AM, Sprong H, Klempa B, Hajdusek O, Tomás-Cortázar J, Azagi T, Strnad M, Knorr S, Sima R, Jalovecka M, Havlíková SF, Ličková M, Sláviková M, Kopacek P, Grubhofer L, Hovius JW (2019) Counter attacking the tick bite: towards a rational design of anti-tick vaccines targeting pathogen transmission. Parasit Vectors 12(1):229

Rood JI (1998) Virulence genes of *Clostridium perfringens*. Annu Rev Microbiol 52:333–360
Rosenberg R (2018) Vital signs: trends in reported vectorborne disease cases—United States and territories, 2004–2016. MMWR Morb Mortal Wkly Rep 67:496–501
Rozé JC, Ancel PY, Lepage P, Martin-Marchand L, Al Nabhani Z, Delannoy J, Picaud JC, Lapillonne A, Aires J, Durox M, Darmaun D, Neu J, Butel MJ, Chollat C, Nutrition EPIPAGE 2 study group; EPIFLORE Study Group (2017) Nutritional strategies and gut microbiota composition as risk factors for necrotizing enterocolitis in very-preterm infants. Am J Clin Nutr 36:821–830
Schlievert PM, Gocke JE, Deringer JR (1993) Group B streptococcal toxic shock-like syndrome: report of a case and purification of an associated pyrogenic toxin. Clin Infect Dis 17:26–31
Schommer NN, Gallo RL (2013) Structure and function of the human skin microbiome. Trends Microbiol 21:660–668
Scollard DM (2016) Infection with *Mycobacterium lepromatosis*. Am J Trop Med Hyg 95:500–501
Sedlacek L, Graf B, Schwarz C, Albert F, Peter S, Würstl B, Wagner S, Klotz M, Becker A, Haase G, Laniado G, Kahl B, Suerbaum S, Seibold M, Tintelnot K (2015) Prevalence of *Scedosporium* species and *Lomentospora prolificans* in patients with cystic fibrosis in a multicenter trial by use of a selective medium. J Cyst Fibros 14:237–241
Shannon JG, Ross CL, Koehler TM, Rest RF (2003) Characterization of anthrolysin O, the *Bacillus anthracis* cholesterol-dependent cytolysin. Infect Immun 71:3183–3189
Shaw C, Stitt JM, Cowan ST (1951) Staphylococci and their classification. J Gen Microbiol 5:1010
Shuaib W, Stanazai H, Abazid AG, Mattar AA (2016) Re-emergence of Zika virus: a review on pathogenesis, clinical manifestations, diagnosis, treatment, and prevention. Am J Med 129:879.e7–879.e12
Simmonds RS, Simpson WJ, Tagg JR (1997) Cloning and sequence analysis of zooA, a *Streptococcus zooepidemicus* gene encoding a bacteriocin-like inhibitory substance having a domain structure similar to that of lysostaphin. Gene 189:255–261
Smalley JW, Olczak T (2017) Heme acquisition mechanisms of *Porphyromonas gingivalis*—strategies used in a polymicrobial community in a heme-limited host environment. Mol Oral Microbiol 32:1–23
Solomon T (2004) Flavivirus encephalitis. N Engl J Med 351:370–378
Sprong H, Azagi T, Hoornstra D, Nijhof AM, Knorr S, Baarsma ME, Hovius JW (2018) Control of Lyme borreliosis and other Ixodes ricinus-borne diseases. Parasit Vectors 11:145
Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche HU, Apewokin S, Horn DL (2012) Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect 65:453–464
Stern M, Warrack GH (1964) The types of *Clostridium perfringens*. J Pathol Bacteriol 88:279–282
Sting R, Schaufuss P, Blobel H (1990) Isolation and characterization of hyaluronidases from *Streptococcus dysgalactiae*, *S. zooepidemicus* and *S. equi*. Zentralbl Bakteriol 272:276–282
Süss J (2011) Tick-borne encephalitis 2010 epidemiology, risk areas, and virus strains in Europe and Asia—an overview. Ticks Tick Borne Dis 2:2–15
Talan DA, Krishnadasan A, Gorwitz RJ, Fosheim GE, Limbago B, Albrecht V, Moran GJ, EMERGEncy ID Net Study Group (2011) Comparison of *Staphylococcus aureus* from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. Clin Infect Dis 53:144–149
Tärnvik A (1989) Nature of protective immunity to *Francisella tularensis*. Rev Infect Dis 11:440–451
Tei S, Kitajima N, Ohara S, Inoue Y, Miki M, Yamatani T, Yamabe H, Mishiro S, Kinoshita Y (2004) Consumption of uncooked deer meat as a risk factor for hepatitis E virus infection: an age- and sex-matched case-control study. J Med Virol 74:67–70
Titball R, Rood J (2000) Bacterial phospholipases. In: Aktories K, Just I (eds) Bacterial protein toxins. Springer, Berlin, pp 529–556
Tsagaan A, Kanuka I, Okado K (2015) Study of pathogenic bacteria detected in fly samples using universal primer-multiplex PCR. Mong J Agric Sci 15:27–32

Tufano MA, Berlingieri MT, Sommese L, Galdiero F (1984) Immune response in mice and effect on cells by outer membrane porins from *Salmonella typhimurium*. Microbiologica 7:353–366

Vora NM, Li Y, Geleishvili M, Emerson GL, Khmaladze E, Maghlakelidze G, Navdarashvili A, Zakhashvili K, Kokhreidze M, Endeladze M, Mokverashvili G, Satheshkumar PS, Gallardo-Romero N, Goldsmith CS, Metcalfe MG, Damon I, Maes EF, Reynolds MG, Morgan J, Carroll DS (2015) Human infection with a zoonotic orthopoxvirus in the country of Georgia. N Engl J Med 372:1223–1230

Watson RO, Bell SL, MacDuff DA, Kimmey JM, Diner EJ, Olivas J, Vance RE, Stallings CL, Virgin HW, Cox JS (2015) The cytosolic sensor cGAS detects *Mycobacterium tuberculosis* DNA to induce type I interferons and activate autophagy. Cell Host Microbe 17:811–819

Wessels MR, Bronze MS (1994) Critical role of group A streptococcal capsule in pharyngeal colonization and infection in mice. Proc Natl Acad Sci U S A 91:12238–12242

Weidenmaier C, Kokai-Kun JF, Kristian SA, Chanturiya T, Kalbacher H, Gross M, Nicholson G, Neumeister B, Mond JJ, Peschel A (2004) Role of teichoic acids in *Staphylococcus aureus* nasal colonization, a major risk factor in nosocomial infections. Nat Med 10:243–245

Winstanley C, Fothergill J (2009) The role of quorum sensing in chronic cystic fibrosis *Pseudomonas aeruginosa* infections. FEMS Microbiol Lett 290:1–9

Woodward JJ, Iavarone AT, Portnoy DA (2010) c-di-AMP secreted by intracellular *Listeria monocytogenes* activates a host type I interferon response. Science 328:1703–1705

World Health Organization (2009) Dengue guidelines for diagnosis, treatment, prevention and control. WHO, Geneva, pp 1–160

Wiinsch E, Heidrich HG (1963) Zur quantitaiven Bestimung der Kollagenase. Hoppe Seylers Z Physiol Chem 333:149–151

Zhang Y, Yeruva L, Marinov A, Prantner D, Wyrick PB, Lupashin V, Nagarajan UM (2014) The DNA sensor, cyclic GMP-AMP synthase, is essential for induction of IFN-b during *Chlamydia trachomatis* infection. J Immunol 193:2394–2404

Zhao-Fleming H, Dissanaike S, Rumbaugh K (2017) Are anaerobes a major, underappreciated cause of necrotizing infections? Anaerobe 45:65–70

Zouhair R, Rougeron A, Razafimandimby B, Kobi A, Bouchara JP, Giraud S (2013) Distribution of the different species of the *Pseudallescheria boydii*/*Scedosporium apiospermum* complex in French patients with cystic fibrosis. Med Mycol 51:603–613