17 Biofilms-Associated Infections

Continuous Challenges in Human and Animal Health

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17.1 DEFINITION, BIOFILMS CHARACTERISTICS, AND CHALLENGES IN ANTIMICROBIAL THERAPY

Biofilms can be defined as a structured consortium of microbial cells surrounded by the self-produced matrix (Figure 17.1) (Høiby 2017). Biofilms is known to be produced by many of bacteria including the important pathogen that cause life-threatening infections in humans and animals such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Salmonella* spp., *Escherichia coli*, etc. (Tasneem et al. 2018). These bacteria are known to cause a serious problem in human and animal health (Jamal et al. 2018; Abdullahi et al. 2016).

Structurally, the biofilms is built of individual (planktonic) bacterial cells attached with the self-released lipopolysaccharides, proteins, lipids, glycolipids, and nucleic acids. These components are recognized as extra-polymeric substances (EPSs). The EPS is responsible to promote adhesion and aggregation of bacteria to the surfaces and provides stability to the biofilms structure (Kamaruzzaman et al. 2018). The lipopolysaccharide produced by the bacteria is different from the bacteria species. For example, *P. aeruginosa* produces Pel (a cationic exopolysaccharide composed of 1–4 linked galactosamine and glucosamine sugars) and Psl (a pentasaccharide composed of D-glucose, D-mannose, and L-rhamnose) (Billings et al. 2013; Jennings et al. 2015) while *S. aureus* and *Staphylococcus epidermidis* produce poly-ß(1,6)-N-acetyl-D-glucosamine (PNAG) (Izano et al. 2008). The nucleic acid is known as extracellular DNA (eDNA) that interacts with extracellular calcium (Ca^{2+}) within the biofilms structure to induce bacterial aggregation via cationic bridging. The positive charge of Ca^{2+} repulses the negative charge of the biofilms's component, thus assisting the adherence of the biofilms to the material and tissue surface. The negatively charged eDNA chelates the action of cationic antimicrobial peptides of the immune system, thus acting as the defense mechanism to the structure (Okshevsky, Regina, and Meyer 2015). Due to the fragility of the structure, the characterization biofilms is often performed *in vitro.* The thickness of the biofilms grown in vitro can vary between the bacterial species, for example, *K. pneumoniae* 231 µm, *P. aeruginosa* 209 µm, and *S. aureus* 8 µm (Singla, Harjai, and Chhibber 2014; Werner et al. 2004; Kamaruzzaman et al. 2017). Figure 17.2 shows the structure of *S. aureus* biofilms grown *in vitro* and visualized by confocal microscope with a thickness of approximately 8.0 µm.

Formation of biofilms can be considered as the survival mechanism for the bacteria. However, in this form, they are inherently resistant to antibiotic action, thus provides additional challenges for the treatment of related infection. Bacteria in the biofilms form can be 10–1,000 times more resistant to antibiotics compared to their

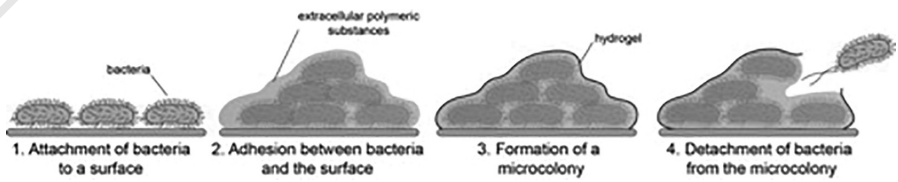

FIGURE 17.1 The process of biofilms formation. (Adapted from Kamaruzzaman, N.F., *Materials*, 11, 1–27, 2018. With permission.)

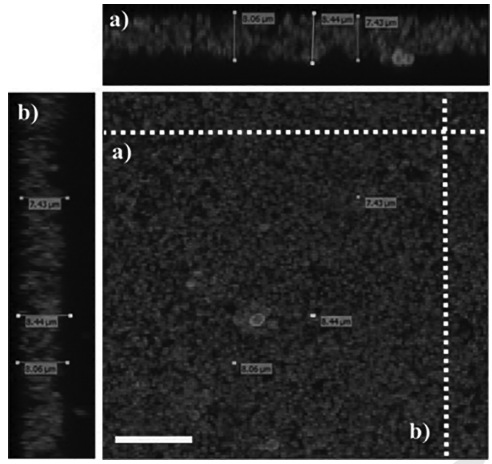

FIGURE 17.2 The three-dimensional structure of *S. aureus* biofilmss visualized with a confocal microscope. *S. aureus* biofilmss were cultured in tryptic soy broth for 48 h, fixed with 4% paraformaldehyde and treated with wheat germ agglutinin to stain n-acetylglucoseamine component of polysaccharide and DAPI to stain the bacteria nuclear material, followed by confocal microscopy z-stack projection that moved through 111 slices across the cell. (a) Horizontal cross-section of biofilms and (b) vertical cross-section of biofilms. White scale bar is 7.5 μm. The approximate thickness of the biofilms was 7.9 ± 0.5 μm. (Adapted from Kamaruzzaman, N.F., *Front. Microbiol*., 8, 1–10, 2017. With permission.)

susceptibilities as individual (planktonic cells) (Mah and Toole 2001; La et al. 1987; Nickel et al. 1985). This could be due to the thick biofilms matrix that reduces permeation of antibiotics across the biofilms structure (Mah and Toole 2001; Nickel et al. 1985; Singh et al. 2016; Nguyen et al. 2011). Additionally, the eDNA and polysaccharide components of the biofilms can interact with the antimicrobials and prevent further penetration of the antibiotics across the structure (Billings et al. 2013; Johnson et al. 2013). Additionally, the physiological condition which is the lack of oxygen reduces the outer membrane potential of the bacteria within the biofilms and reduces uptake of antibiotics into the cells (Walters III et al. 2003; Borriello et al. 2004; P. S. Stewart et al. 2000). The physiology of the bacteria itself within the biofilms structure is another challenge as it is reported that the bacteria in the biofilms exist as small colony variants and thus present different phenotypes compared to the wild types (Waters et al. 2016). This variant was reported to have a better tolerance toward antimicrobials. Therefore, they have greater tolerance toward antimicrobials. Thus, all these characteristics of biofilms suggest the reason why persistent infections occur in the mentioned bacteria.

17.2 BIOFILMS-RELATED INFECTIONS IN HUMAN

Aggregation of one or more species of microbes particularly bacteria has recently gained more concern in medical history as it is rapidly becoming clear that the formation of a biofilms is the root cause of development of many persistent infections.

Biofilms can be found as the non-attached form as floating mats on the liquid surface or in a submerged state (Bjarnsholt et al. 2013). Biofilms can be formed on both biotic and abiotic surfaces. The growth and activity of bacteria in attached form are enhanced when they are attached to a surface (Heukelekian and Heller 1940) and thus responsible for causing persistent infections of the patients (Costerton, Stewart, and Greenberg 1999).

A few well-known examples of biofilms-associated infections can be collectively classified into device-related biofilms diseases such as catheter-associated urinary tract infection and prosthetic joint infection; non-device related chronic biofilms diseases viz. cystic fibrosis pneumonia, periodontitis, and chronic dermal wounds (P. S. Stewart 2014). Besides, biofilms-related device malfunction has arisen as a new problem in which chemical degradation and physical damage occur as the consequences of the growth of biofilms on the surface. This condition required device removal and introduce further complications to the patient (del Pozo and Patel 2007). All of the mentioned biofilms-related diseases contribute to patient morbidity and increased mortality and represents a considerable economic burden to both individual and country.

It is thus essential to extend our knowledge on the different biofilms-related diseases, the mechanisms involved in biofilms antimicrobial resistance in order to develop new and effective diagnostic, treatment and prevention strategies for this biofilms disease war. The novel strategies for the treatment of biofilms-related infections have been covered in our previous article (Kamaruzzaman et al. 2018). In this chapter, we will focus on the challenges, solutions, and future implications on the biofilms diseases mainly for device-related and non-device-related chronic biofilms diseases.

17.2.1 Device-Related Biofilms Disease

There are about 1 million cases with an estimated 60% of hospital-associated infections are due to biofilms that have formed on indwelling devices (Darouiche 2004). It was estimated that about 40% of the infections are associated with ventricular-assisted devices, 10% for ventricular shunts, 4% for pacemakers and defibrillator, 4% for mechanical heart valves, 2% for breast implants, and another 2% for joint prostheses (Figure 17.3) (Darouiche 2004). The composition of biofilms depends on the devices, and their duration of action may be composed of only a single or of different types of microbial species.

The process of biofilms formation is illustrated in Figure 17.1. The process is generally universal for many of the known bacteria forming bacteria, but the location and the extent of biofilms formation depend on the duration of implantation in the patient. It was reported that bacterial colonization of catheter can occur within the first 24 h of implantation, with the formation of the biofilms on the external surfaces continues within the next 10 days and in 30 days, biofilms could extend until inside the catheter lumen (Jamal et al. 2017). At the time of surgical implantation of medical devices, tissue damage may occur resulted in accumulation of platelets and fibrin at the location of suture and on the devices. Microbial cells have better ability to colonize these locations and eventually produce biofilms on these sites (Donlan and Costerton 2002).

The nature of an indwelling foreign body is a double-edged sword, since, apart from their outstanding benefits, infectious complications are regularly observed

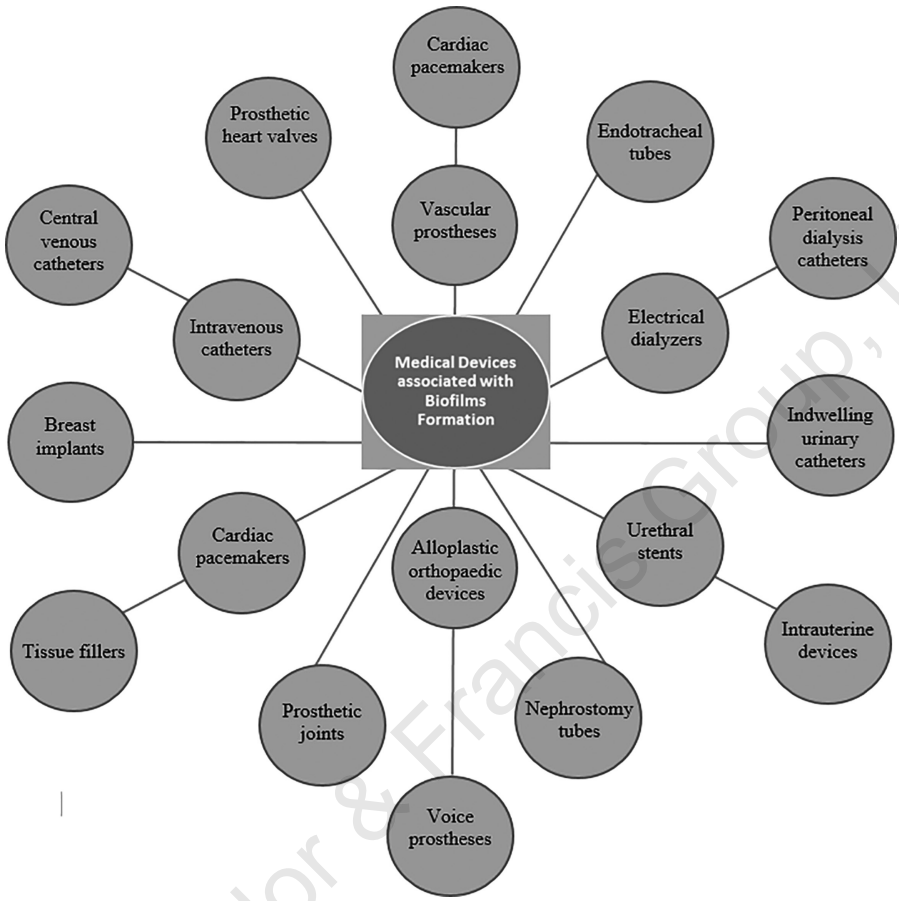

FIGURE 17.3 Medical devices that are associated with the device-related biofilms diseases.

(Fux et al. 2003). Soon after a foreign body enters into a host, the host–pathogen dynamic started to be profoundly influenced (Gristina et al. 1988). The mechanisms of this host–pathogen dynamic begin when the mere presence of the foreign body (i) enables an invasion of bacterial inoculum that can lead to infection, (ii) permits the non-pathogenic organism to opportunistically colonize the foreign body and infect, (iii) allows a pathogen to persist undetected at the site of the infection, (iv) induces a chronic local inflammatory response, and (v) limits the induction and effectiveness of a humoral response in the presence of chronic, persistent infection (Nickel et al. 1985).

Stable communities of bacteria in biofilms often walled off the human immune system, resulting in chronic low-grade inflammation. Due to the physiological heterogeneity of the bacteria within the biofilms, they are also extremely difficult to eradicate using existing antimicrobials (Kamaruzzaman et al. 2018). One of the major challenges in reducing the device-related biofilms diseases is the design and construction of implanted medical devices that able to control the deposition of these

host molecules that form host-conditioned surfaces to limit opportunities for adherence to free-floating (planktonic) bacteria via their matrix attachment adhesions.

17.2.1.1 Strategies to Reduce Bacterial Colonization on Indwelling Devices

To overcome bacteria colonization and biofilms formation on the indwelling devices, researchers tried to understand the underneath factors that promote attachment of bacteria on the surface of the device. It was reported that physicochemical properties of the devices' surface play a role to reduce attachment of microbes, for example, hydrophobicity can increases attachment of the bacteria to surface and low hydrophobicity increases repulsion force between the bacteria and the surface (Tribedi and Sil 2014). Many bacteria are more likely to attach to the hydrophobic and non-polar surfaces like Teflon silicon, stainless steel, and other plastics; however, some of the bacteria including the human-associated bacterium *S. epidermidis* prefer polar and hydrophilic substrates (Ista, Baca, and Lbpez 1996).

By understanding the tendencies of the microbes in forming the biofilms on different hydrophobicity and topographical surface, various studies have been conducted to modify the medical device surface as a method to reduce and to avoid bacteria adhesion and biofilms formation. The research trends are now directed toward addressing the development of preventive strategies, rather than treatment approaches, as it is well known that bacteria in the biofilms form are inherently difficult to be killed (Catt and Cappitelli 2019). Currently, there are three major methods for improving the anti-biofilms properties of the medical devices (Table 17.1).

17.2.2 Non-device-Related Chronic Biofilms Disease

Other than causing indirect complications to the device implanted in humans, biofilms-forming bacteria have been revealed to be associated with a wide array of chronic infections and complicate the majority of bacterial infections in humans.

TABLE 17.1
Methods of for Improving the Antibiofilms Properties of Medical Devices

Methods	Description	References
1) Incorporation of novel materials	Novel materials such as ceramics and composites with antimicrobial infused can be incorporated to reduce attachment of biofilms to the surface of devices	Brentel et al. (2011); Du et al. (2012); Zhang et al. (2013); Wang, Shen, and Haapasalo (2013)
2) Physical surface modification	Smoother surface on the device can be introduced, for example, by mechanical modification of the surface as non or nano-porous to reduce attachment of the bacteria	Feng et al. (2015); Desrousseaux et al. (2013); Lagree et al. (2018)
3) Chemical surface modification	The device surfaces can be coated with additional material, for example, surfactants and antimicrobials to reduce attachment and survivability of the bacteria on the surface	Prijck, Smet, and Coenye (2010); Merchan et al. (2010); Lopez et al. (2011); Armentano et al. (2014)

These include chronic rhinosinusitis (CRS) (Fastenberg et al. 2016), airway infections in cystic fibrosis (Høiby et al. 2017), chronic obstructive pulmonary disease (COPD) (Hassett, Borchers, and Panos 2014), endocarditis (Jung et al. 2012), periodontitis (Lasserre, Brecx, and Toma 2018), conjunctivitis (Bispo, Haas, and Gilmore 2015), otitis media (Kaya et al. 2013), decubitus and diabetic ulcers (Kunimitsu et al. 2019), urinary tract infections and prostatitis (Soto 2014; Delcaru et al. 2016). The bacteria not only able to form biofilms on the foreign devices, they are also capable of forming bacteria on tissue inside the bodies. Within the period of development, the bacterial physiology, including the generation of genetic and phenotypic variability will be influenced, as well as the ability of resisting antibiotics after being regularly exposed to sub-minimum inhibitory concentrations molecules. Collectively, these effects would accelerate the emergence and spread of antibiotic-resistant bacteria and thus the biofilms (Andersson and Hughes 2014). The following section describes in detail regarding two important biofilms-related infections, periodontal disease, chronic wound infections, and sinusitis.

17.2.2.1 Periodontal Disease

One example of biofilms-associated infection is periodontal diseases, the most common infectious diseases in oral cavity associated with the establishment of pathogenic biofilms that trigger an immune and inflammatory host response, leading to the destruction of supporting periodontal tissues and eventual tooth loss (Eke et al. 2012). These diseases have also been indicated as potential risk factors for several systemic diseases (Cullinan and Seymour 2013; Li et al. 2000). Oral cavity is an optimum environment for the commensal bacteria, and in conditions where the oral health is not well maintained or in immunosuppressed patient, the pathogenic species may colonize and initiate infection (Zuanazzi et al. 2010). High levels of medically important pathogens in these periodontitis-associated microbiotas may pose a risk for systemic dissemination and development of infections at distant body sites due to the anatomical proximity of the periodontal biofilms to the gingival blood stream.

Periodontitis is characterized by irreversible and progressive degradation of periodontal tissues. The warm moist dental pocket between teeth and gingival tissues provides with an ideal hatchery for microbial growth and proliferation. Therapeutic regimens such as restorations, non-surgical or surgical periodontal therapies, root canal therapy, and dental implants are well accepted; however, secondary biofilms infections still cannot be completely eliminated. Dental materials used and the location of biofilms play the major role on the consequences of these secondary infections (Allaker 2010). There are few major strategies summarized by Cloutier, Mantovani, and Rosei (2015) on the development of devices with antibiofilms activities, for example, antimicrobial agent release, contact killing, and multifunction (Cloutier, Mantovani, and Rosei 2015). The advantages and disadvantages on each of the methods are also summarized by Jiao et al. (2019) as described in Table 17.2.

17.2.2.2 Chronic Wound Infections

Another most reported non-device-related chronic biofilms disease is the chronic wounds in which biofilms appeared on almost 60% of the specimens in comparison with only 6% of biopsies from acute wounds (James et al. 2007). Biofilms were

TABLE 17.2
Advantages and Disadvantages of the Antimicrobials Approaches on Dental Materials

Approaches	Advantages	Disadvantages
Antimicrobial agent release	• High local doses of antimicrobial agents at a specific site	• Limited antimicrobial agents reservoirs (lack of long-term effect)
Contact killing	• Broad-spectrum and strong contact-killing activity • Low risks of antimicrobial resistance development	• Exhibit only bacteriostatic effects • No effects on planktonic bacteria • Problem on "surface biofouling" • Potential cytotoxic
Multifunctional	• Able to activate microbicidal activity in response to the microenvironment • Other non-antimicrobial benefits (remineralization)	• Selection on the combination for synergistic antimicrobial and beneficial properties

Source: Adapted from Jiao, Y., *Int. J. Oral Sci.*, 11, 1–11. With permission.

suspected as one contributing factor that delayed healing or contribute to the recurring infections. The mechanism could be due to the constant stimulation of the inflammatory response that is released by the host cells as the signal for removal of the biofilms. This resulted in damage of normal and healing tissues, proteins and immune cells on the surrounding areas, and contributing to the impairment of healing process (Lawrence et al. 2007). Besides, the chronic inflammatory response does not guarantee for biofilms removal, and it has been hypothesized that, contradictory, this response favors the formation of biofilms. Lawrence et al. (2007) suggested the inflammatory response may induce exudate release from the biofilms that consequently serve as the source of nutrition and helps perpetuate the biofilms (Lawrence et al. 2007).

Similar to biofilms in periodontitis, for chronic wound biofilms, the microenvironment of the wound provides an ideal milieu for the microbes to sustain (Wolcott, Rhoads, and Dowd 2008). This has been partly the challenge of chronic wound management, with increased resilience and complexity to standard approaches of care. With only relatively recent recognition of the existence of biofilms in wounds and their role in delayed healing and chronicity, the development of effective therapeutic strategies to date has been very limited (Metcalf, Parsons, and Bowler 2016). However, wound care researchers can still benefit from the knowledge gained in other industries and in related healthcare areas such as dentistry and indwelling medical devices, because the treatment strategy options are well developed and broadly similar. Although the intention to prevent, remove, and kill bacterial biofilms is the same, challenge in selecting appropriate wound treatments that can be acutely sensitive and fragile must be balanced of safety versus efficacy.

17.2.2.3 Chronic Rhinosinusitis

There is also increasing evidence that chronic inflammations caused by the biofilms are critical to the pathophysiology of CRS (Fastenberg et al. 2016). The common

bacteria associated with CRS are *P. aeruginosa* and *S. aureus* (Cryer et al. 2004; Boase et al. 2013; Cryer et. al., 2004; Foreman and Wormald, 2010). The bacteria were reported to form biofilms on silicon elastic devices removed from patients (Ferguson and Stolz 2005). Additionally, biofilms were also found in all sinonasal mucosal samples collected from 16 patients undergoing sinus surgery (Cryer et al. 2004). Thus, biofilms does play a role in causing persistency of the disease in humans despite surgery intervention and targeted long-term antibiotic therapy (Palmer 2006).

17.3 BIOFILMS-ASSOCIATED INFECTIONS IN ANIMAL HEALTH AND THEIR POTENTIAL FOR ZOONOSIS TRANSMISSION

The general impact of biofilms on animal health has been covered extensively by Abdullahi et al. (2016). The following part of this chapter will focus on the burden of biofilms-related infections in the livestock animal that causes economic losses to the farmers, as well as the potential transmission of biofilms-forming bacteria to human as zoonosis diseases. Zoonosis is infectious diseases that can be transmitted from animals to humans. Sixty-one percent of the pathogens known to infect humans are zoonotic (Percival and Garcı 2011). Most emerging infectious diseases considered to be serious public health problems have zoonotic origins, and approximately three-quarters have originated from wild animals (Shin and Park 2018). Close contact with the animal via inhalation, ingestion, contaminated mucous membranes, and damage of intact skin are possible transmission routes of zoonotic pathogens (Shin and Park 2018). The risk is particularly high for personnel that work closely with the animal, for example, veterinarian and farmers. Transmission of zoonotic pathogens in foodborne diseases includes undercooked meat or other animal tissues, seafood, and invertebrates, as well as unpasteurized milk and dairy products and contaminated vegetables (Shin and Park 2018). Additionally, insects serve as important biological or mechanical vectors in transmitting some organisms (Iannino et al. 2018). Pathogens that associated with zoonotic infections are known to form biofilmss (Percival and Garcı 2011). Biofilms are one of the bacterial mechanisms to survive and thrive in the environment. Table 17.3 summarizes pathogens that can form biofilms with the potential of zoonosis transmission to humans.

17.3.1 Mastitis

Mastitis is a disease affecting ruminant specifically large and small ruminant (cows, sheep, and goats). Mastitis is caused by several pathogens including *S. aureus*, *E. coli*, and *Streptococcus agalactiae* (Dogan et al. 2006). Globally, the disease causes economic losses between 16 and 26 billion Euros annually (Gonçalves et al. 2018). Infections by these bacteria cause inflammation in the udder, and the toxin released by the bacteria can cause necrosis of the mammary udder cell, reducing milk production, and thus affecting economic outcome by the farmer (Henriques et al. 2016). The treatment that involves administration of antibiotics has only been partially successful. The disease often recurs and persistent in the animal, causing irreversible

TABLE 17.3
Diseases Associated with the Biofilms-Forming Pathogen with the Potential for Zoonoses Transmission

Disease	Causative Agent	Host	References
Mastitis	*Staphylococcus aureus*, *E. coli*, *S. agalactiea*	Human, small and large ruminant	El-Mahallawy et al. (2017); Vishnupriya et al. (2014)
Wound infection	*Acinetobacter baumanii*	Human, dogs, cats, horse	Tomaras et al. (2003); Maisch et al. (2012); Yang et al. (2019)
Pneumonia	*Mannheimia hemolytica*	Human, cattle	Morck et al. (1990); Takeda et al. (2003); Boukahil and Czuprynski (2015)
Bite wound infection	• *Actinobacillus lignieresii*, *A. equuli*, and *A. suis* • *Staphylococcus aureus* (MRSA), *S. intermedius*	• Human, cattle, horses, pigs • Human, dog, pigeon	Weyant et al. (1996); Raad et al. (2007); Neill et al. (2007)
Cat scratch disease	• *Bartonella henselae* and *B. Quintana*	Human, dogs, cats	Shin and Park (2018)
Fish tank granuloma	*Mycobacterium marinum*	Human, fish	Hashish et al. (2018)
Gastric ulcers, gastritis	*Helicobacter pylori*	Human Oral cavity of dogs	Kandulski, Selgrad, and Malfertheiner (2008); Hathroubi et al. (2018)
Meningitis	*Streptococcus suis* type 2	Human, pig	T. Bjarnsholt (2013); Lun et al. (2007)
Gasteroenteritis	*Aeromonas hydrophila*	Human, reptiles, amphibians, fish	Lynch et al. (2002)
Salmonellosis	*Salmonella gastroenteritis*, *Salmonella enterica* subspecies I, *Salmonella enteritidis*	Human, reptiles, birds, dogs, cats	Shin and Park (2018)
Diarrhea	• *Vibrio cholera and V. parahaemolyticus* • *Escherichia coli 0157*	Human, aquatic organism, birds, reptiles, mammals	Alam et al. (2007); Cantas and Suer (2014)

damage to the udder cells (Zhao and Lacasse 2008). To avoid further losses in the farm productions, animal will be culled.

Persistency of the disease in an animal is believed to be due to several factors. This includes continues development of antimicrobial resistance causing the pathogen to be non-responsive to the antibiotic therapy (Beuron et al. 2014). Additionally, the ability of *S. aureus* to invade and survive within the bovine mammary epithelial cells can cause it to escape the antibiotic therapy, as due to their physicochemical properties, not all antibiotics are able to cross the mammalian cells to exert its activities (Kamaruzzaman et al. 2017). Additionally, the ability of the infecting pathogens

to form biofilms on the surface of the mammary udders are other factors that cause ineffectivity of the antibiotics to completely kill the bacteria during the treatment (Henriques, Gomes, and Jos 2016; Fox, Zadoks, and Gaskins 2005; Bardiau et al. 2013). It is well known that bacteria susceptibility toward antimicrobials is reduced when in the form of biofilms. Surprisingly, it was reported that the antibiotic which is commonly used for the mastitis treatment, enrofloxacin has been shown to promote biofilms formation of *E. coli* (Costa et al. 2012). Biofilms formation has also been influenced by milk components and the acidic pH of the environment. This is particularly important as the antibiotics commonly used for mastitis treatment are acidic antibiotics (Costa et al. 2012). Thus, all these evidence directed the role of biofilms to cause persistent mastitis infections in animals.

The problem with mastitis does not stop only in animals. The bacteria associated with mastitis can also be transmitted to humans via milk-borne zoonoses. For example, a study has reported transmission of methicillin-resistant *S. aureus* and *E. coli* isolated from milk in bovine mastitis cases to the animal handlers (Costa et al. 2012; El-Mahallawy et al. 2017). Thus, this implication showed the importance of proper control of mastitis cases, not only to reduce the disease burden in animals but to control the possible transmission of the bacteria to humans.

17.3.2 Pneumonia

Mannheimia hemolytica is the pathogen that is associated with pneumonia and hemorrhagic septicemia in sheep, buffalo, and cattle, and various diseases in poultry and other domesticated animals (Confer 2017). It is part of the bovine nasal flora and colonizes the nasal cavity and tonsillar crypts in cattle and sheep, yet this bacterium causes a devastating disease in cattle which is pneumonic mannheimiosis (shipping fever) (Boukahil and Czuprynski 2015; Lopez and Martinson 2017). The bacteria have been reported to form biofilms on the surfaces of bovine respiratory epithelial cells (Boukahil and Czuprynski 2016). Mannheimia hemolytica has occasionally been isolated from human cases of septicemia, upper respiratory tract infections, and animal bite wounds. Unpasteurized milk can be a risk of infection to dairy consumers (Confer 2017).

17.3.3 Fish Tank Granuloma

Both pathogenic and non-pathogenic species of mycobacteria are capable of forming biofilms, and this capability is not essentially a virulence mechanism (Hashish et al. 2018). *Mycobacterium marinum* is a non-tuberculous mycobacterium (NTM) (Chakraborty and Kumar 2019). It grows in macrophage and aquatic environments. It grows at 28°C–35°C and causes infection in fish (Sunil et al. 2018). It also can infect humans resulting in granulomatous skin lesions. The transmission of disease occurs particularly with personnel handling fish, thus named as "fish tank granuloma." The signs of infection such as reddish bumps (papules) that enlarge over time, along with swollen on the site of the infection (Mason et al. 2016). The international incidence and prevalence of *M. marinum* infection are unknown due to the lack of international surveillance. However, a study conducted in France demonstrated the incidence of

M. marinum infection to be 0.04 per 100,000 inhabitants per year (Mazumder and Gelfand 2019). The treatment requires the usage of multiple anti-mycobacterial for a long period of time. Such drug-tolerant chronic infection is often associated with *in vivo* biofilms (Chakraborty and Kumar 2019). The study of environmental and pathogenic NTM biofilms is especially important because of the industrial and medical implications for infection by pathogenic NTM species (Primm, Lucero, and Falkinham 2004). Specifically, *M. marinum* is a concern in re-circulating water systems in intensive aquaculture farming because once *M. marinum* bacteria are established, they are difficult to eradicate (Sunil et al. 2018).

17.3.4 Salmonellosis

Centers for Disease Control and Prevention (CDC) reported that Salmonella infection in humans caused 450 deaths in the United States annually (CDC 2018). The importance of food-producing animals as the reservoirs for non-typhoidal serovars affecting humans is well-established (Percival and Garcı 2011). *Salmonella enterica* subspecies I is the causative agent for Salmonellosis in humans and other warm-blooded animals (Stevens, Humphrey, and Maskell 2009). Biofilms-forming abilities of Salmonella are correlated with its persistence in fishmeal and feed factories. Studies on Salmonella in fish factories suggest that biofilms-forming ability may be an important factor for the persistence of Salmonella in the environment (Vestby et al. 2009). *Salmonella enteritidis* is the most common serotype isolated in poultry farm and is responsible for many cases of food poisoning in human beings worldwide. Almost 50% of them are able to produce biofilms (Marin, Hernandiz, and Lainez 2007).

17.3.5 Gasteroenteritis

Most gastroenteritis cases (>85%) are attributed to *Aeromonas hydrophila* (Daskalov 2017). *Aeromonas* sp. are Gram-negative and rod shaped. They are motile aquatic bacteria considered important pathogens in reptiles, amphibians, and fish. They are known to be a major problem in fish farming. Fish are thought to act as a reservoir of *Aeromonas hydrophila* possibly leading to infection in mammals (Percival and Garcı 2011). In humans, *Aeromonas* sp. are known to cause gastroenteritis (from mild to cholera-like symptoms) and other infections such as endocarditis, septicemia, hemolytic uremic syndrome, peritonitis, respiratory infections, myonecrosis, osteomyelitis, ocular infections, and meningitis. *Aeromonas hydrophila* has been reported to grow well in biofilms detected in drinking water systems (State et al. 2015).

17.3.6 Diarrhea

Diarrheal diseases are a major cause of morbidity and mortality worldwide with a particular impact on children (Guzman-Otazo et al. 2019). Cholera is an acute, diarrheal illness caused by infection of the intestine with the toxigenic bacterium *Vibrio cholerae serogroup* O1 or O139. An estimated 2.9 million cases and 95,000 deaths occur each year around the world (CDC 2018). Enterohemorrhagic *E. coli* (EHEC)

occurs largely as a single serotype (O157:H7) causing sporadic cases and outbreaks of hemorrhagic colitis characterized by bloody diarrhea (Guentzel 1996).

17.3.7 Meningitis

Meningitis is a disease in piglet and human caused by the bacteria *Streptococcus suis* type 2. The bacteria can be isolated from carrier adult pigs' upper respiratory tract, tonsils, and feces of infected herds, known to form biofilms and inherently more resistant to penicillin G and ampicillin (Percival and Garcı 2011; Huong et al. 2014). It has been isolated from human patients worked in pig industry in several Asian and European countries, Canada, New Zealand, Australia, and Argentina (Lynskey, Lawrenson, and Sriskandan 2011; Lun et al. 2007). The prevalence of *S. suis* infection is the highest in Asia with the primary risk factors are thought due to occupational exposure and eating of contaminated food (Huong et al. 2014). The pooled proportions of case-patients with pig-related occupations and history of eating high-risk food were 38.1% and 37.3%, respectively (Huong et al. 2014).

17.3.8 Bite Wound Infection

Actinobacillus genus is a Gram-negative bacterium commensal of equine oral cavity and upper respiratory tract found to be responsible for sleepy foal disease (Stewart et al. 2002). *Actinobacillus lignieresii*, *Actinobacillus equuli*, and *Actinobacillus suis* can be present in the oropharyngeal flora of cattle, horses, and pigs, respectively. Human bitten by these animals may be exposed to these pathogens and potentially developed bite wound infections (Percival and Garcı 2011). It has been roughly estimated that the horse bites account for as high as 20% of overall animal bites in Turkey, which comes after dog bites which are 70%. More extensive muscle damage may develop in most of the horse attacks, which is different from small animal bites (Cantas and Suer 2014). A report stated that a 53-year-old butcher affected with septicemia and acute septic shock caused by *A. equuli* (Ashhurst-smith, Norton, and Thoreau 1998).

17.3.9 Cat Scratch Disease

Cat scratch disease (CSD) is a zoonosis caused by *Bartonella henselae*, a fastidious, hemotropic, Gram-negative bacterium. Cats and dogs are the principal mammal reservoir of the pathogen, and transmission to human can occur through animal scratches and bites. Worldwide, 55% of cases were reported in children younger than 18 years of age and 60% of these are males (Damborg et al. 2015; Nelson, Saha, and Mead 2016). In the United States, CSD is not a notifiable condition. Thus, information on the epidemiology of this disease has been limited to clinical case series and analyses of hospital discharge databases (Nelson, Saha, and Mead 2016). This disease affected immunocompromised patients either through acute or chronic infection with vascular proliferative or suppurative manifestations (Iannino et al. 2018). Previous reports stated that Bartonella infection can be treated using azithromycin, penicillin, tetracyclines, cephalosporins, and aminoglycosides (Breitschwerdt 2014).

To reduce the level of bacteremia in an infected cat or dog effectively, doxycycline, amoxicillin, enrofloxacin, and rifampin are given for a long duration (more than 4 weeks) (Iannino et al. 2018).

17.4 WAY FORWARD AND CONCLUSION

Biofilms are a mechanism posed by the bacteria for their survival in the environment. Biofilms-related infections are known to cause persistent infections in human and animal. The emergence of zoonotic pathogens that can cause infection also has only recently being understood. Understanding the physiology of the pathogen is important, as it will determine the suitable therapy for the infection to avoid recurrence and failure in the treatment. Though there were many studies being conducted to assess antibiotics efficacy in the common pathogen such as *S. aureus*, *P. aeruginosa*, *E. coli*, the same knowledge is still inadequate infancy in regard to antibiotics antibiofilms efficacy against the zoonotic pathogens (Bal et al. 2017). Thus, studies need to be done to ascertain this condition to ensure the right treatment is given whenever the infections are reported in humans. This knowledge will help not only to ensure suitable antibiotics given for the recovery of the patient, the correct usage of the antibiotics will reduce exposure of pathogens to the unnecessary antibiotics, and eventually reduce the emergence of antibiotic resistant.

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