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Review Article

Chronic Infections, and Considerations for Medical Devices and Laboratory Testing Methods

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Abstract

Chronic diseases and associated chronic infections inflict an enormous clinical and economic burden on global public health. In recent years it has become increasingly evident that bacterial biofilm plays a pivotal role in chronic infections such as cystic fibrosis pneumonia, ventilator-associated pneumonia recurrent ear infections, periodontal disease, chronic wound infections, and catheter-associated urinary tract infections, and its economic impact is alarming. Additionally, dry surface biofilm is common on hospital surfaces, often harboring antibiotic-resistant bacteria. Consequently, there is an urgent need for medical devices (such as catheters and wound dressings) and associated surfaces that can either prevent biofilm formation, or combat biofilm in chronic infections. There is also a requirement for anti-biofilm devices to be tested using laboratory methods that are more representative of the way that bacteria predominantly exist in nature and disease (i.e., biofilm), which traditional and long-used microbiology techniques fail to account for.

The aims of this paper are to explore the relationships between chronic infections and biofilm and highlight the urgent need for anti-biofilm medical devices, and the associated laboratory testing capabilities that are required to demonstrate the effectiveness of such devices in helping to combat biofilm and chronic infections.

INTRODUCTION

Chronic diseases such as diabetes, heart disease, chronic lung diseases (e.g., cystic fibrosis), cancer, chronic wounds, obesity, and periodontal disease inflict a colossal clinical and economic burden on global health. Chronic disease is at epidemic level in the US, with ~50% of the US population having a chronic illness which accounts for ~86% of healthcare costs [1]. In 2011, the World Economic Forum estimated that the global cost of treating chronic diseases could reach $47trillion by 2030 [2]. In the US, an annual cost estimate of up to $96.8billion (bn) has been reported for the treatment of acute and chronic wounds [3]. Similarly, annual cost to the UK National Health Service (NHS) for treating chronic diseases amounts to billions of pounds (Figure 1) [4].

Chronic infections are a frequent consequence of underlying chronic diseases. These include chronic wound infections, ventilator-associated pneumonia, catheter-associated urinary tract infections, cystic fibrosis pneumonia, chronic ear infections, and periodontitis. The annual cost associated with the five most common hospital-acquired infections reported in the US has been estimated at $9.8bn [5]. This group includes two medical device-related infections, namely ventilator-associated pneumonia (US annual treatment costs ~$3bn in 2009 [5]) and catheter-associated urinary tract infections (US annual treatment costs ~$28million in 2009 [5]). The annual cost to the UK National Health Service (NHS) of managing hard-to-heal chronic wounds (which are considered to be infected wounds) has been reported at ~£5.6bn [4,6]. Tong et al. (2018), estimated that an annual cost of approximately $4.3bn was associated with recurrent ear infections in the US, largely due to frequent antibiotic use and likely associated bacterial resistance to antibiotics [7]. The overall indirect cost related to chronic sinusitis-related losses in work productivity in the US is estimated to be more than $20bn per year [8].

Given the magnitude of both clinical and economic consequences of chronic infections, the intention of this paper is to address causative agents in chronic infections, and to highlight how medical device development and related laboratory testing methods need to acknowledge and consider these clinical challenges to provide most effective medical devices that will improve the lives of people debilitated by chronic infections.

CHRONIC INFECTIONS AND BIOFILM

Underlying chronic diseases significantly increase the risk of chronic infections, and in the field of infectious diseases, biofilm is increasingly acknowledged as playing a pivotal role in chronic infections.

Biofilm is the predominant mode of bacterial life, involving attachment of bacterial cells to a viable or non-viable surface and

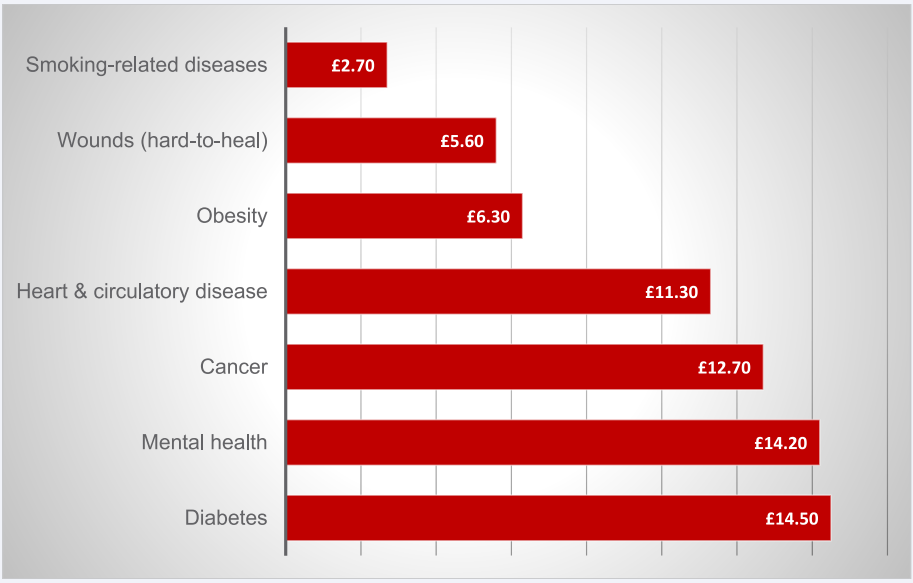

Figure 1 Annual cost of chronic diseases to the UK NHS 2017/2018 (£billions). Adapted from Guest 2021 [4].

subsequent aggregation of cells encased within a self-produced polymeric matrix (the biofilm component). Biofilm consequently becomes a bacterial fortress, protecting them from external environmental threats such as antimicrobial agents and host inflammatory cells, providing nutrients, and acting as a base to release free-living planktonic cells that may cause a secondary acute infection. All told, biofilm causes significant challenges in infection management. Recently, an in-depth market analysis commissioned by the UK National Biofilms Innovation Centre (NBIC) estimated that the global economic impact of biofilm amounts to more than $5000bn a year [9]. Based on this analysis, the biofilm-attributed costs in specific chronic infections range from a $281bn global impact in chronic wounds, to an approximately $1bn impact in catheter-associated infections (Figure 2) [9].

Although bacterial biofilm is one of the oldest lifeforms on Earth dating back billions of years, the implications of bacterial attachment in nature and disease have emerged essentially within the last century or so. The role of biofilm in biofouling of the surface of engineering structures such as pipework, and the hulls of ships and submarines has been evident since the early 1900's, but it was not until the 1970's that the implications of biofilm in human infections became evident. In 1978, JW Costerton and colleagues from the University of Calgary, Canada published a seminal paper in the *Scientific American* journal titled 'How bacteria stick'[10]. At the time, Costerton et al., described bacteria attaching tenaciously and exquisitely to surfaces ranging from rocks in an alpine stream, to human teeth and lung mucosa, via a mass of tangled polysaccharides surrounding colonies of bacterial cells which he referred to as 'glycocalyx' [10]. It was not until 1985

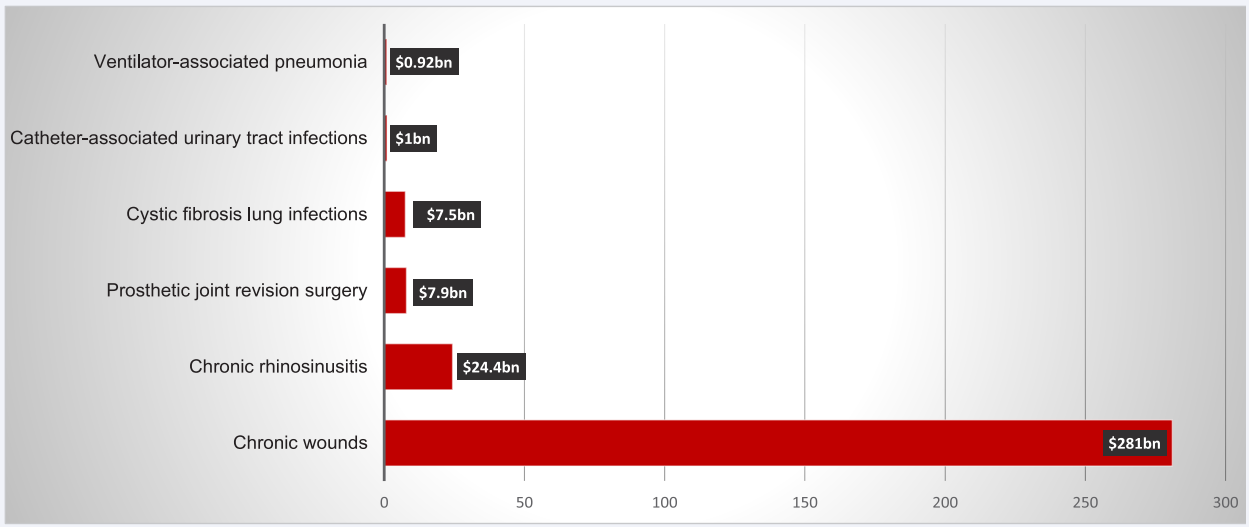

Figure 2 Estimated economic impact of biofilm in chronic infections ($billions). NBIC 2022 [9].

that Costerton introduced the term 'biofilm' into medicine [11]. In 1999, Costerton et al., reported that biofilms are a common cause of persistent chronic infections such as periodontitis, otitis media, osteomyelitis, cystic fibrosis pneumonia, and device-related chronic infections such as catheter-associated urinary tract infection, ventilator-associated pneumonia, and orthopaedic implants [12]. This begins to indicate the magnitude of the clinical consequences of biofilm, and since the turn of the century, many studies and publications have demonstrated the vital association between biofilm and chronic infections, none more so than the work of Randall Wolcott. Wolcott and colleagues have published widely on chronic infections, with the viewpoint that chronic infections should be considered as biofilm infections [6,13,14]. Infections that are recurrent and respond poorly to antimicrobial therapy are typical characteristics of biofilm infections. Whereas metabolically sessile biofilm bacteria persist due to their tolerance to antimicrobial therapies and can ultimately induce a hyper-inflammatory host response that is destructive to host tissue and beneficial to biofilm (i.e., parasitic existence), mature biofilm may also shed metabolically active planktonic cells that can invade viable host tissue and cause an active acute infection causing obvious signs of inflammation (e.g., heat, swelling, redness, pain) [15]. Although antimicrobial therapy may be effective in eliminating planktonic bacteria in an acute infection, since biofilm persists it may give rise to subsequent and recurrent infections.

Given the pivotal role of biofilm in chronic infections, it is vital that the medical device industry considers this clinical scenario when designing and developing products such as indwelling devices (e.g., urinary catheters, endotracheal tubes, sutures), implanted devices (e.g., hip and knee prostheses), and tissue irrigants and wound dressings. Additionally, development of such devices requires the consideration of appropriate microbiology laboratory test methods that simulate how bacteria exist predominantly both in nature and disease (i.e., in biofilm form). These aspects will be addressed in the following sections.

MEDICAL DEVICES AND BIOFILM CONTROL

With the knowledge that biofilm is the predominant mode of bacterial life and that it is a principal cause of chronic infections, embarking on measures to combat biofilm, whether it be associated directly with host tissue or via contamination of medical devices, is vital.

The most obvious approaches to combatting biofilm are to either *prevent bacterial attachment and biofilm formation*, or to *disrupt established biofilm* to enable antimicrobial agents to work more effectively (i.e., combination anti-biofilm/antimicrobial technologies). For medical devices, the primary objective is to prevent bacterial attachment to relevant surfaces at the outset. Ongoing and increasing materials science research is primarily focused on optimizing the physicochemical properties of polymer surfaces. *Passive* approaches (i.e., without using antimicrobial agents) include altering the hydrophobicity, roughness, porosity, and composition of surfaces [16]. Altering surface topography to minimize surface area for bacterial attachment using biomimetics is also an active area of research. Examples include mimicking shark skin, and gecko-like skin that exhibit hydrophobic, low adhesion, anti-wetting, self-cleaning and antimicrobial properties [16]. Phosphorylcholine, a biomimetic compound coated onto silicone and fluoroplastic tympanostomy tubes is one of the few commercially available technologies that has been FDA-cleared for resisting biofilm formation [17]. Active antimicrobial approaches include the use of biosurfactants, phytochemicals, antimicrobial peptides [18], but as with the passive approaches, translation of these diverse laboratory research efforts to commercially available products is lacking [16,18,19]. For greater success, greater collaboration between academia, industry, and specialist testing laboratories is essential to ensure that products are designed with user needs in mind, together with a good understanding of the likely regulatory hurdles and testing requirements during a new product development process. In this respect, consideration of chemical agents and physical processes that have previously been reviewed and approved for safety and efficacy by regulatory authorities are likely to offer a least troublesome and quickest route to approval for new devices. An example of this involves the development of an anti-biofilm wound dressing to eliminate biofilm in chronic wound infections. The objective of this development project was to identify safe, effective, and regulatory-acceptable anti-biofilm agents that could break down chronic wound biofilm which would subsequently enable a combined antimicrobial agent (ionic silver) to work more effectively against exposed bacterial cells released from the disrupted biofilm [20]. Following a period of extensive research, two anti-biofilm agents (EDTA - a metal chelator, and benzethonium chloride – a surfactant) were shown to work synergistically with ionic silver using customized and validated biofilm models [21]. By identifying and utilizing anti-biofilm agents previously accepted by regulatory authorities, the regulatory pathway for this new medical device was relatively smooth and quick. The clinical outcomes associated with this combination anti-biofilm/antimicrobial wound dressing have been shown to be extremely effective in the management of chronic wound infection [22].

While biofilm associated with indwelling and implanted devices can cause devastating and persistent chronic infections, it is important to acknowledge that dry surface biofilm (DSB) is ubiquitous in healthcare facilities and is a further concern regarding spread of infection. DSBs have been recovered from computer keyboards and hand sanitizing units despite prior cleaning [23], and DSB containing antibiotic resistant bacteria has been shown to persist for up to 12 months on equipment and furniture in an intensive care unit, despite prior terminal cleansing with detergent and disinfectant [24].

LABORATORY TEST MODELS

Costerton (1978), stated that since the pioneering work of Pasteur in the 1800's, microbiologists have largely studied 'naked mutants' in the laboratory [10]. By this he meant that for bacteria growing on culture media biofilm offers no selective advantage because they exist in a non-threatening, nutritious environment where they can expend their energy on proliferation [10]. Costerton subsequently devoted his research to studying how bacteria function in real life (i.e., predominantly as biofilm) and digressed from their unreal (planktonic) life in laboratory culture media.

Costerton (2003), observed that when bacteria were grown in

conventional laboratory cultures, they were generally susceptible to antibiotics, but the same antibiotics failed to resolve the clinical bacterial infections. Also, recovery of organisms from clinical infections was not always evident by traditional culture techniques. When the bacteria were investigated directly from infected tissue using microscopy, matrix-enclosed biofilm communities were observed which were often not culturable [25]. Wolcott (2008), subsequently reported that planktonic laboratory techniques such as culturing may lead to an inaccurate or incomplete diagnosis because cultures do not detect biofilm cells that are viable but not culturable [13].

The evolution of microbiological techniques in recent decades has shown a necessary transition from traditional planktonic culture techniques to biofilm models that mimic how bacteria exist and cause chronic infections *in vivo*. However, the development and validation of representative biofilm models has been challenging involving the introduction of more sophisticated molecular and microscopy techniques. Routine medical microbiology laboratories still largely rely on traditional culture methods, which ultimately means that laboratory results do not necessarily reflect the clinical situation, particularly with respect to antibiotic susceptibilities. Presently, medical device companies developing anti-biofilm surfaces and devices rely on specialist laboratories that have the expertise and capabilities to provide essential data for regulatory submissions, using standardized or customized biofilm models. In her review of the progress in biofilm research from bench to bedside, Rumbaugh (2020), reported that the number of laboratories providing biofilm testing services is small (i.e., Perfectus Biomed [UK], BioFilm Control [France], and 5D Health Protection Group Ltd [UK] [19]. However, the number of specialist biofilm testing facilities is increasing, indicating the growing demand for such services in this field.

Aside from the importance of anti-biofilm devices in preventing and treating chronic infections, there is also a critical need to utilize and test devices and materials for control of dry surface biofilm in healthcare environments that can prevent the spread of healthcare-associated infections, including the transmission of antibiotic resistant bacteria.

SUMMARY

From this review, it is evident that chronic diseases and associated chronic infections inflict a huge clinical and economic burden on global public health. Bacterial biofilm is increasingly acknowledged as being the root of chronic infections due to its prevalence in both nature and disease, its ability to protect encased bacteria from antimicrobial agents and immune cells, and its ability to cause recurrent and persistent infections. The economic significance of biofilm in chronic infections is alarming. Since biofilm is ubiquitous in nature, it also forms on inanimate surfaces (e.g., wet surfaces such as drainpipes, or dry surfaces such as hospital beds, stethoscopes, computer equipment). Consequently, there is a vital need for medical devices and associated surfaces that can either prevent bacterial attachment and biofilm formation or treat biofilm-induced chronic infections. This is particularly important for indwelling devices such as catheters, and implanted devices such as knee and hip prostheses. While materials science research into anti-biofilm materials and surfaces is progressing, little progress has been made in terms of regulatory-approved and commercially available devices. Consideration is being given to combination anti-biofilm/antimicrobial devices that can disperse biofilm and enable antimicrobial agents such as antibiotics and antiseptics to work more effectively.

There is also a requirement for anti-biofilm devices to be tested using laboratory methods that are more representative of the way that bacteria predominantly exist in nature and disease (i.e., biofilm), which traditional and long-used microbiology techniques fail to account for. There are a growing number of specialist biofilm testing laboratories using standardized and customized biofilm models to test anti-biofilm medical devices and surfaces, which highlights increasing recognition in this field.

This review has highlighted the relationships between chronic infections and biofilm, the urgent need for anti-biofilm medical devices, and the associated laboratory testing capabilities that are required to demonstrate the effectiveness of such devices in helping to combat biofilm and chronic infections.

CONFLICT OF INTEREST

The author provides consultancy services to Perfectus Biomed Group.

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