Ocular Biofilms, Dry Eye and Peeq

Introduction

The Tear Film Ocular Society (TFOS) released the Dry Eye Workshop 2 (DEWS 2) report in 2017, which has become a cornerstone for eye doctors in guiding their clinical practices and managing patients with dry eye syndrome symptoms[1]. The significance of DEWS2 lies in its comprehensive and intricate information. However, its extensive nature poses a challenge for clinicians as it can sometimes obscure clarity regarding the primary underlying causes and the most effective treatments for dry eye amidst the wealth of details provided.

Rynerson et al. introduced a lesser-known theory about the development of dry eye syndrome approximately one year before DEWS2 was released. This theory suggests that dry eye syndrome originates from blepharitis, a common clinical condition, termed dry eye blepharitis syndrome (DEBS)[2]. Traditionally, blepharitis has been viewed as a minor inconvenience requiring treatment only when symptoms arise. However, the challenge lies in waiting for symptoms to manifest, as unregulated biofilm formation can cause substantial damage that becomes more difficult to reverse once symptoms occur.

The aim of this article is to consolidate and integrate DEBS with DEWS2 while emphasizing the importance of early intervention with Peeq to mitigate and eliminate biofilms, ultimately minimizing the effects of DEBS and Dry Eye.

Just as dentists and hygienists routinely remove plaque from teeth, eye care professionals employ in-office tools to eliminate biofilms from the eyelids. Peeq stands out as a unique at-home tool capable of reducing biofilms and preventing dry eye. According to DEWS 2, the prevalence of dry eye ranges from 5% to 50%. This wide range is attributed to variations in inclusion criteria across the reviewed studies for diagnosing dry eye. However, what appears evident is a fundamental association between bacterial colonization around the ocular surface and dry eye, which initiates decades before symptoms manifest. [3].

What Are Biofilms?

A biofilm is a sticky and slimy film of bacteria that coats a surface, in this case the ocular surface [4]. It is important to understand that bacteria typically does not exist individually but rather organized in biofilm colonies. These biofilms form a protective armor composed of a matrix of bacteria and their sugary coating (glycocalyx) that allow individual bacteria to stick to and communicate with one another. This protective armor

is significantly challenging to penetrate by human white blood cells, surgical iodine prep, and even antibiotics [5].

Any surface containing moisture and nutrients is an ideal location for biofilms to form and the eyelid margin provides a perfect environment for this growth. Additionally, it is likely that the growth of a biofilm throughout a lifetime leads us to see the clinical findings we see with the vast majority of patients with dry eye.

How Does a Biofilm Grow?

As discussed above, there is a low chance of survival for a single bacterium but a colony of billions of bacteria contained within a biofilm can easily survive. One measure of a biofilm is the amount of homoserine that the biofilm is producing. Homoserine is a chemical that bacterial cells secrete in order to communicate with other bacterial cells. Biofilms of toddlers contains very low amounts of homoserine showing that the biofilm in this state is not going to cause diseases. Biofilms of people in their 6th and 7th decade thicken and produce high levels of homoserine representing a high bacterial load [6].

Through this communication process a bacterial colony within the biofilm can sense (through elevated levels of homoserine) when the number of bacteria has become large enough (and protected by a thick enough biofilm) to activate genes that elicit an inflammatory response in their host [7]. These genes are responsible for increasing the virulence of the bacterial colony by producing factors (lipases, proteases, cytolytic toxins, etc) that liberate a larger food sources [8].

The biofilm waits to produce these virulence factors because the bacteria do not want to initiate an inflammatory response from the host until their numbers and protection from the biofilm is significant enough to withstand an immune response from the host.

How Can Biofilms Explain the Different Presentations of Dry Eye?

Not all strains of bacteria species are identical. For example, some strains of *Staphylococcus aureus (S. aureus) will create a biofilm that quickly matures and produces virulence factors that can lead to severe blepharitis and recurrent chalazions in a child. Other strains may produce a slow growing, thin biofilm that does not lead to problems until a patient is in their 70's or 80's [9,10].*

Since many factors exacerbate dry eye (e.g, reduced blinking, hormonal state, and medications) dry eye is thought to be multifactorial [11]. However the underlying etiology in the vast majority of cases is related to the process of biofilm production, communication and release of virulence factors. Once we understand this link, we can see how the different presentations of dry eye (blepharitis, meibomian gland dysfunction,

reduced aqueous production) are related, rather than being over-lapping distinct diseases.

How Can Biofilms Produce Clinical Findings of Dry Eye?

The following stages have been proposed [12]:

> ***Stage 1*. Folliculitis: inflammation and swelling of the lash follicles**. This is always the first stage of disease, as it permits easy migration of the encroaching biofilm down the lash. Folliculitis eventually progresses from a small "volcano sign" to profound tissue edema around the lash. In severe cases, a sheathing of the lash with biofilm—often mistaken as cylindrical dandruff—can be observed once the lash grows out from the follicle [13]. A thick biofilm attaches to and molds around the lash during dormancy, and then reveals itself once the lash leaves the follicle.
>
> ***Stage 2*. Meibomian gland dysfunction (MGD): impaction and inflammation of the MG.** Due to the MG's size relative to the lash follicle and the small ductule with constant efflux of lipids, it simply takes longer for biofilm to accumulate and thicken within the MG. First, a simple plugging of the MG with *meibofilm*—a mixture of biofilm and meibum—reduces the quantity and quality of the meibum, sometimes referred to as non-obvious MGD with minimal inflammation. As the biofilm thickens within the gland, it eventually undergoes quorum-sensing and begins releasing virulence factors. This produces the inflammation referred to as posterior blepharitis. At this point, domes of meibofilm appear over each meibomian ductule.
>
> It has long been thought that these little cream-colored domes over the MG were "caps" of keratin [14]. But since the posterior lid margin consists of a non-keratinized stratified squamous epithelium, this explanation is highly unlikely. Within the context of biofilms, it is easy to understand the true source of these domes.
>
> As the thickened meibofilm accumulates within the MG, the gland eventually reaches capacity. It may leak through the wall of the gland, causing a chalazion. The column of meibofilm gets forced up the ductule in an effort to escape the gland, but instead encounters a 40- to 50-year-old biofilm that has literally sealed off the orifice. The meibofilm bulges up against this original biofilm but cannot escape. Imagine covering the top of a toothpaste tube with a clear plastic wrap, then squeezing the tube. This is what happens to the MG when little domes of meibofilm become trapped atop each orifice. During MG probing, it is the penetration of this original biofilm that the practitioner may feel as the probe "pops" through [15].
>
> ***Stage 3*. Lacrimilitis: impaction and inflammation of the accessory lacrimal glands of Krause and Wolfring**. This always occurs *after* MGD. This is easy to

understand if one reviews the lid anatomy and location of these tear glands. The glands of Wolfring are located along the top of the tarsal plate, and the glands of Krause are deep within the fornices [16]. These 2 areas are quite distant from the margin, delaying access to a growing biofilm. However, biofilms can “seed” new areas by constantly dispersing tiny bits of biofilm into their environment (in this case, the tear film). If this happens hundreds of times a day, for 60 to 70 years, it is not inconceivable that a microscopic bit of biofilm eventually accesses these glands. It is also possible for biofilms to slowly creep up the inside of the palpebral conjunctiva in an attenuated state (due to the constant blinking of the lids) and, after many years, reach the lacrimals by direct extension.

What are other impacts of biofilms not contained in the original description of DEBS?

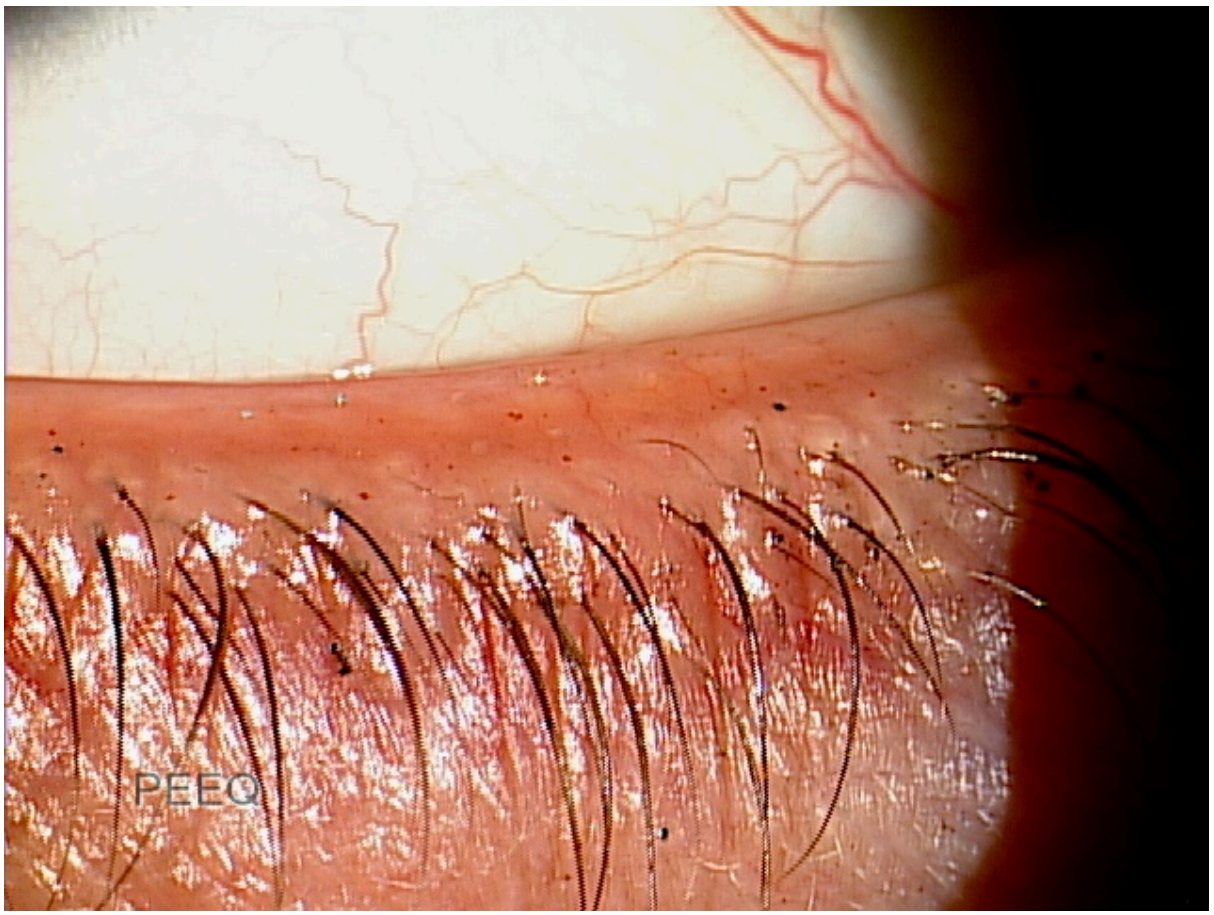
Throughout any of the stages outlined in DEBS, tear film instability may arise. Depending on the severity and persistence of this instability, varying degrees of ocular surface inflammation can occur. Often, this inflammation is perceived as an acute and independent condition, rather than being recognized as a potential acute exacerbation of a chronic condition like DEBS. Common acute inflammatory conditions, including conjunctivitis, episcleritis, pingueculitis, and internal hordeola (styes), are frequently overlooked in this context. It's crucial to identify these acute conditions as potential indicators of underlying biofilm-related chronic issues to facilitate early treatment and minimize the long-term consequences of DEBS.

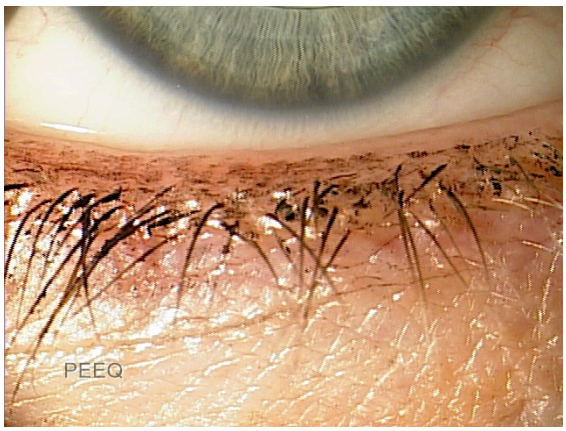
How Can Peeq Prevent This Process?

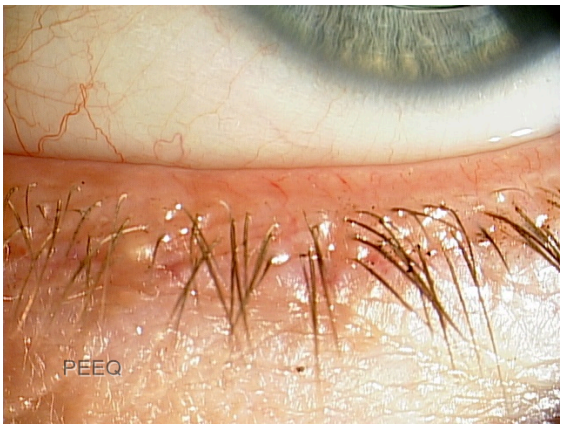
The challenge with the current technologies is that they are expensive and they require precision to be done safely, which limits the ability to be widely adopted by both practitioners and the public. Peeq allows for safe, cost-effective at home cleaning that can reduce biofilms to prevent signs and symptoms of dry eye disease.

Clinical Examples:

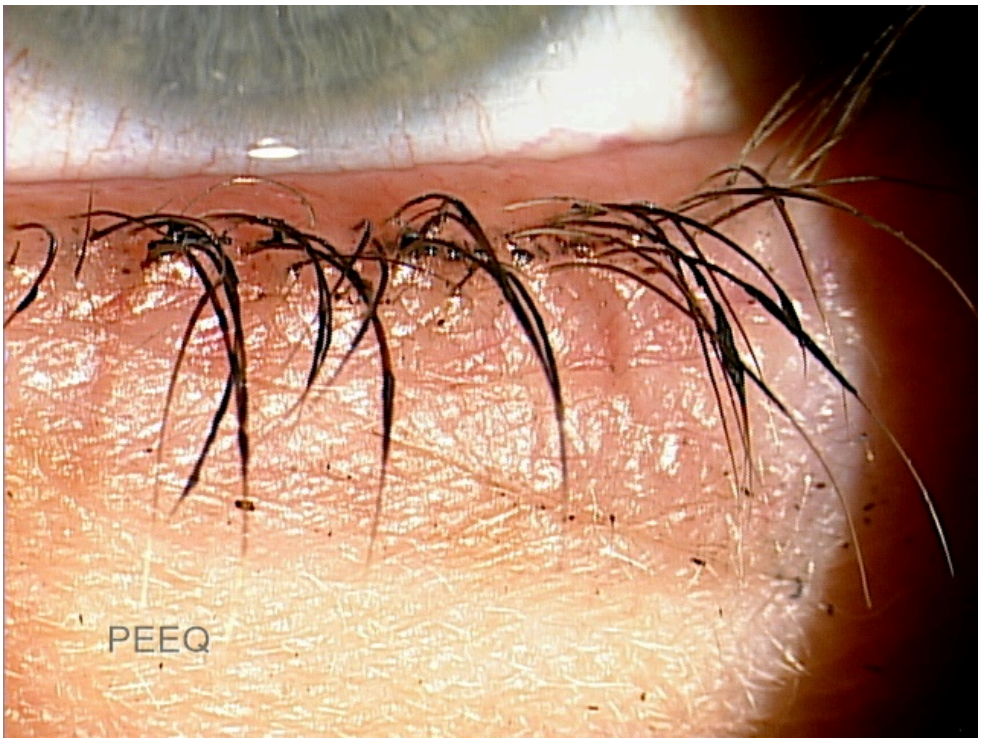
Example #1: Before and after Peeq

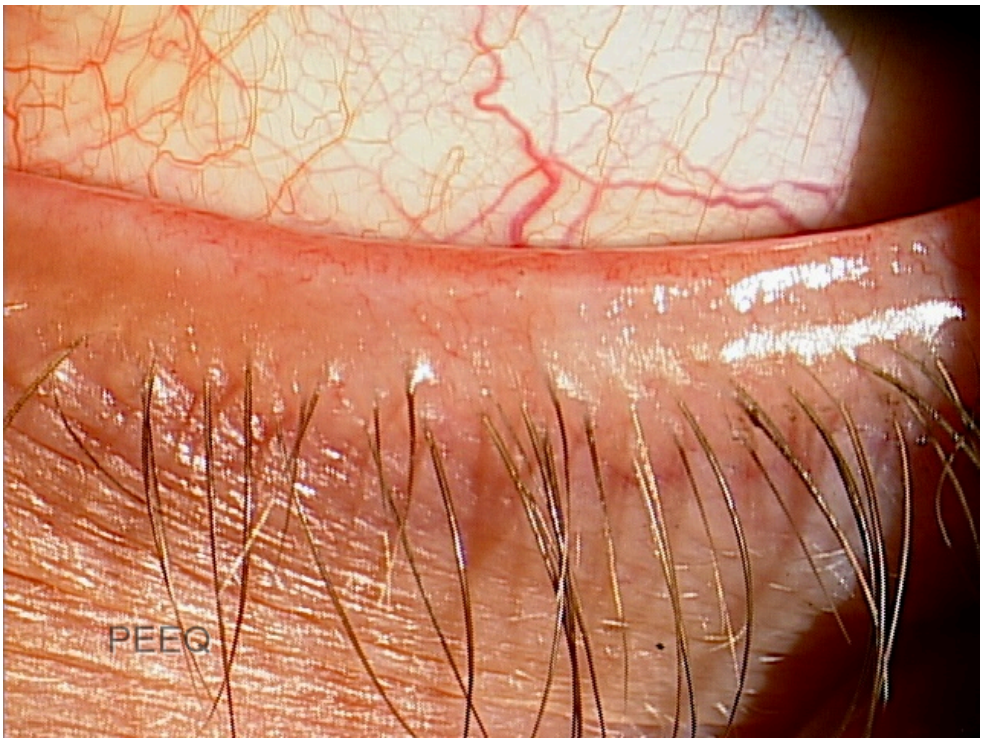






Example #2: Before and after Peeq





Example #3: Before and after Peeq