

The Importance of Preventing and Managing Tear Dysfunction Syndrome in Allergic Conjunctivitis and How to Tackle This Problem

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■ Abstract

Tear dysfunction syndrome, also known as dry eye disease (DED), is a multifactorial disease of the ocular surface characterized by the loss of tear film homeostasis. DED shows a significant clinical overlap with ocular allergy (OA), which alters tear film homeostasis, thus predisposing the patient to DED. Both conditions constitute the most common ocular surface disorders and have a potentially severe impact on patients' quality of life. Clinical practice guidelines recommend topical therapies as first-line treatment for OA. However, eye drop formulations may contain additional substances that can contribute to ocular surface damage and the development of DED. Therefore, physicians treating ocular allergy should be aware of problems affecting the tear film, the role of tear film disruption in OA, and topical treatment to prevent or minimize DED. The aim of this review is to present an updated overview of the topic.

Key words: Allergic conjunctivitis. Tear dysfunction syndrome. Dry eye disease. Eye drops. Preservatives. Antihistamines. Benzalkonium chloride. Hyaluronic acid.

■ Resumen

El síndrome de disfunción lagrimal, también denominado enfermedad del ojo seco (EOS), es una enfermedad multifactorial de la superficie ocular caracterizada por la pérdida de la homeostasis de la película lagrimal. La EOS y la alergia ocular (AO) son patologías que comparten un abanico de signos y síntomas, y pueden aparecer simultáneamente; además, la AO altera la homeostasis de la película lagrimal, predisponiendo a la EOS. Estas dos afecciones constituyen los trastornos más frecuentes de la superficie ocular y pueden afectar notablemente la calidad de vida de los pacientes. Las guías de práctica clínica recomiendan terapias tópicas como tratamiento de primera línea para la alergia ocular. Sin embargo, las fórmulas de los colirios pueden contener aditivos y conservantes que pueden contribuir al daño de la superficie ocular y a la aparición de EOS. Por lo tanto, los facultativos que tratan la alergia ocular deben conocer las implicaciones que conlleva la alteración de la película lagrimal en la conjuntivitis alérgica, el potencial daño que pueden provocar los conservantes incluidos en los colirios empleados en el tratamiento tópico de esta patología, así como los tratamientos disponibles para manejar la EOS y la AO cuando la disfunción de la película lagrimal ya está establecida. El objetivo de esta revisión es presentar una visión general actualizada del tema.

Palabras clave: Conjuntivitis alérgica. Síndrome de disfunción lagrimal. Enfermedad del ojo seco. Colirio. Conservantes. Antihistamínicos. Cloruro de benzalconio. Ácido hialurónico.

Introduction

Ocular allergy (OA) and tear dysfunction syndrome (TDS), also known as dry eye disease (DED), are complex multifactorial diseases of the ocular surface characterized by ocular surface inflammation and loss of tear film homeostasis [1-3]. Even though OA and DED are different ocular disorders, they often coexist with overlapping symptoms and pathological mechanisms. Each, therefore, can be considered a condition that predisposes to, or at least facilitates, the other [4].

Differential diagnosis is often complicated, as the most common signs and symptoms in both entities include discomfort, ocular redness, and itchiness [3]. In fact, ocular itching, widely considered the diagnostic symptom of OA, is not specific to an allergic mechanism and may occur in DED. Alterations of the tear film and epithelial barrier and of the corneal innervation associated with OA can also pave the way to DED [7]. Furthermore, several topical and systemic medications commonly prescribed to treat OA may cause or exacerbate DED [3,5]. For instance, some compounds found in ophthalmic solutions for the regular treatment of OA promote development of DED, as their allergic, toxic, or inflammatory effects disrupt the tear film layer, inhibit aqueous secretion by the lacrimal glands, or directly damage the ocular surface epithelium [3].

OA and DED, the most common ocular surface disorders, have a potentially severe impact on patient quality of life (QOL) [3,6]. Adverse impact on the physical and mental well-being of affected patients generates a psychosocial burden, which in turn decreases overall QOL [7]. DED has been associated with both psychosocial and economic problems and has been found to negatively impact work productivity and activities of daily living [8,9].

In order to prevent or minimize the discomfort of DED associated with OA, physicians treating OA should be aware of issues related to the tear film and tear film disruption and how eye drop formulae and additives impact the physiology of the allergic eye, leading to DED. This review aims to address knowledge gaps and to update information on the relationship between OA and DED, the influence of ophthalmic products for treating OA in patients with DED, the consequences of this approach, and the importance of preventing them.

2. The Physiology of the Tear Film and Events Leading to Tear Film Dysfunction

2.1. Structure of the Tear Film: Normal Physiological Condition

The tear film is the interface between the ocular surface epithelium and the environment. It consists of an aqueous-mucin layer containing fluid and soluble factors produced by the lacrimal glands and mucin secreted by goblet cells, all of which are covered by a lipid layer [10]. The volume, composition, and health of the tear film are regulated by the lacrimal functional unit, which consists of the ocular surface (cornea, limbus, conjunctiva, conjunctival blood vessels), tears, and their associated machinery (lacrimal glands,

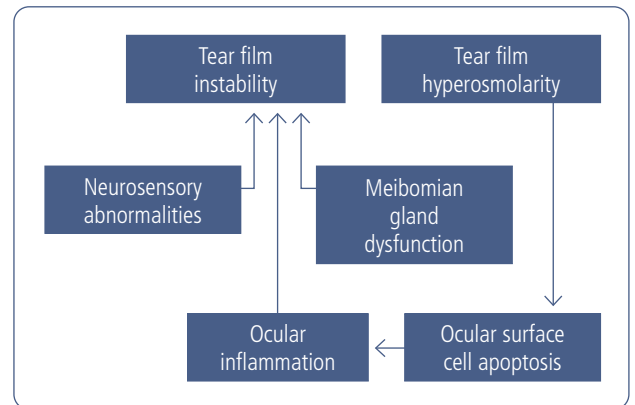


Figure 1. The vicious cycle of tear dysfunction syndrome.

meibomian glands, goblet cells, epithelial cells, nasolacrimal duct), and relevant components of the nervous, endocrine, immune, and vascular systems [4,10]. The eye also presents physiological barriers, including complex junctions in the conjunctival and the corneal epithelium, the blood-aqueous barrier, and the blood-retinal barrier. The critical function of the corneal epithelium is to act as a physical and immune barrier, preventing the entry of pathogens and allergens. It also has other, specialized functions, such as tissue homeostasis. Epithelial barrier disruption leads to DED and tear film instability in allergic patients [3,11].

2.2 Pathological Mechanisms Leading to Tear Film Dysfunction: The Vicious Cycle

Onset of DED involves several pathophysiological pathways, all of which finally lead to a dysfunctional lacrimal unit [10]. This vicious cycle is based on the underlying causes of DED and a series of complex mechanisms underlying biological dysfunction (Figure 1) [12]. Tear film instability induces tear film hyperosmolarity, leading to ocular surface cell apoptosis and ocular inflammation. In turn, ocular inflammation induces, through different mechanisms, instability of the tear film. Additional mechanisms leading to tear film instability include meibomian gland dysfunction, mucin dysfunction, and neurosensory abnormalities [12]. Meibomian gland dysfunction results in lipid layer deficiency and decreased mucin concentration, which in turn induces an accumulation of inflammatory factors that penetrate tight junctions and cause epithelial cell death and tear film disruption [13].

2.2.1 Impact of allergy on the ocular surface

Although OA and DED are different eye disorders, ample evidence suggests that their pathophysiological mechanisms are similar [3] and that tear film instability plays a leading role in their pathogenesis. In fact, tear film alterations are often observed in patients with OA, and epithelial barrier dysfunction is a hallmark of several allergic disorders [11].

The analysis of biomarkers present in tears and on the ocular surface has recently revealed that proinflammatory cytokines usually considered specific to OA are also

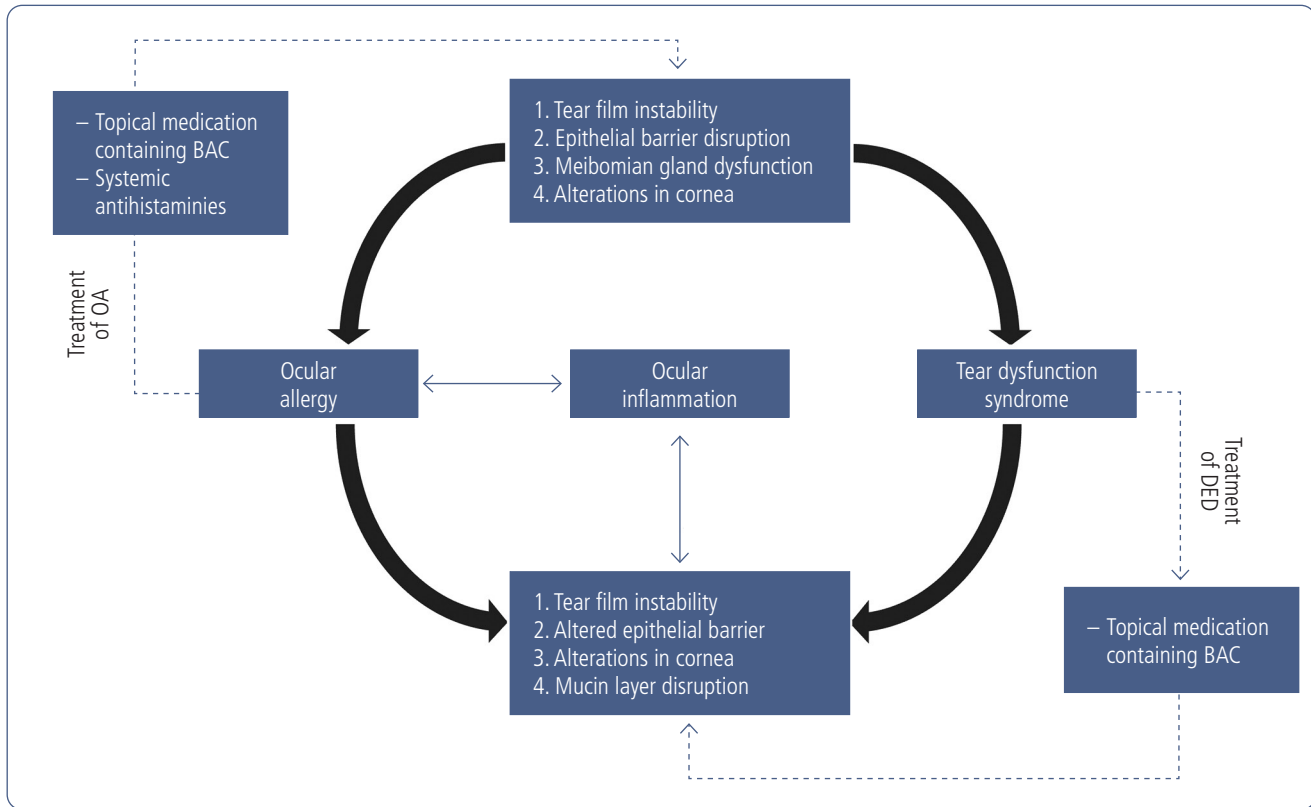


Figure 2. The vicious cycle of ocular allergy and tear dysfunction syndrome. BAC indicates benzalkonium chloride; DED, dry eye disease; OA, ocular allergy.

overexpressed in patients with DED, a disorder that seems to share inflammatory mechanisms with OA. These cytokines comprise IL-4, IL-5, and IL-13 from the T_H2 inflammatory pathway and IL-1 α , IL-1 β , IL-17, tumour necrosis factor, and interferon γ from the T_H1 – T_H7 pathway. Moreover, altered levels of mucins (MUC1, MUC2, MUC4, MUC5, and MUC16) are common abnormalities in the tear film mucous layer in both conditions [4,11].

Changes caused by allergic conjunctivitis induce tear film instability and lead to the development of DED. Allergens with intrinsic proteolytic activity can degrade conjunctival epithelial tight junctions, destabilize E-cadherin, and cross the epithelium [11]. Furthermore, once in the submucosal space, allergens interact with specific IgE bound to the high-affinity IgE receptor located on the surface of dendritic and conjunctival mast cells. In a T_H1 IgE-mediated allergic reaction, mast cells degranulate, immediately releasing histamine and other mediators stored in the granules. The further release of cytokines leads to a T_H2 inflammatory response, predominantly in allergic conjunctivitis [14,15], and mixed T_H2 and T_H3 inflammatory responses in more severe forms of OA (vernal and atopic keratoconjunctivitis) [16]. T_H2 -associated cytokines (IL4, IL-5, IL-13) and histamine, when overexpressed, contribute to long-term conjunctival epithelial metaplasia, disruption of the corneal epithelium, and stimulation of goblet cell secretion, which could modify tear film [3]. Epithelial barrier dysfunction in OA also maintains and contributes to the vicious cycle of allergic inflammation by facilitating the

paracellular transport of allergens, pathogens, pollutants, and other harmful triggers [11].

Other OA changes related to tear film instability and development of DED have been documented. Meibomian gland dysfunction is commonly associated with OA [17]. An imbalance between metalloproteinases and their tissue inhibitors, which are involved in tissue remodelling, has also been documented in severe forms of OA [3].

Consequently, the alterations described in OA could lead to tear film instability, thereby maintaining and worsening symptoms and signs of OA and leading to DED.

2.2.2 Impact of ophthalmic solutions on the ocular surface

In addition to the damage caused by allergic conjunctivitis on the ocular surface, topical and systemic medications used to control and relieve signs and symptoms of OA can contribute to the development of DED and exacerbate ocular impairment. In fact, some systemic antihistamines used to treat severe forms of OA and other allergic diseases can increase ocular dryness owing to anticholinergic adverse effects. Furthermore, many ophthalmic medications contain compounds (excipients) and preservatives that induce tear film barrier dysfunction and instability [11,16,18]. Long-term use may, therefore, cause additional ocular surface damage [16,18]. Preservatives are required in multidose ophthalmic formulations to provide antimicrobial activity and ensure product sterility [19]. The preservatives used in ophthalmic solutions include detergents

(benzalkonium chloride [BAC]), ionic buffers (propylene glycol), alcohols, and parabens. However, BAC, found in around 70% of ophthalmic formulations, is by far the most frequently used, and its impact on the ocular surface has been extensively studied [3]. BAC may alter tear film stability, cause corneal and conjunctival epithelial cell apoptosis, damage corneal nerves [20], reduce the number of goblet cells, and disrupt the mucin layer [2]. In vitro studies and murine models [21,22] suggest that prolonged exposure of the conjunctival epithelium to BAC reduces immune tolerance and that BAC activates the nuclear factor κ B pathway [3], exerting proinflammatory action that leads to ocular damage. The cytotoxic effects of BAC on ocular tissue cells have been extensively documented, and this ocular surface toxicity appears with an estimated BAC threshold concentration of 0.005% [19].

In conclusion, OA, allergic conjunctivitis itself, and the preservatives present in many ophthalmic solutions used for treatment constitute a vicious cycle. Allergic conjunctivitis also contributes to the development of DED through epithelial barrier dysfunction, alterations in the tear film and cornea, and meibomian gland dysfunction, thus exacerbating symptoms. In this situation, patients and doctors may increase the use of topical and systemic medicines to achieve control of symptoms. However, symptoms are eventually aggravated because of ocular toxicity induced by BAC, tear film dysfunction, and eye dryness induced by some antihistamines (Figure 2).

3. How to Avoid Dry Eye Disease While Treating Ocular Allergy

3.1 Managing Ocular Allergy When Dry Eye Disease Is Already Established

Since inflammation is the common pathogenic mechanism in OA and DED, the therapeutic approach overlaps, and clinicians should plan a strategy that simultaneously addresses both conditions [3,6]. Treatment of the signs and symptoms of OA should not contribute to the development of DED, and, equally, treatment of DED should avoid extending or maintaining ocular surface inflammation, which would exacerbate OA symptoms. Management strategies include environmental measures, in addition to nonpharmacological, pharmacological, and, eventually, surgical measures applied in a stepwise approach [3]. Avoiding causative allergens and nonspecific triggers (eg, sun, warm climates, wind, flowers and plants, salty water) and increased hygiene procedures should always be the first approach in management of OA and DED. Pharmacological measures include topical therapy with antihistamines [23-26] and drugs known as dual-action agents [27-35], all of which are effective in reducing the signs and symptoms of allergic conjunctivitis. These options are considered first-choice, although outcomes may be influenced by formulations, presentations, and dosing. When available, preservative-free topical ophthalmic formulations for treating allergic conjunctivitis and other forms of OA are highly recommended, as they avoid exacerbation of established DED [23,27,31].

In cases where symptoms are severe, an OA flare-up occurs, or the patient develops concomitant allergic rhinitis symptoms,

topical ophthalmic treatment needs to be combined with a systemic antihistamine. New, nonsedating antihistamines with zero or very low affinity for muscarinic receptors should be preferred over the old first-generation sedating types to prevent ocular dryness as a cholinergic adverse effect and to preserve psychomotor performance. Topical ophthalmic corticosteroids should be limited to more severe forms of OA or uncontrolled exacerbations [3,36,37], since their use is associated with potentially significant adverse reactions (increased intraocular pressure, development of cataracts, delayed wound healing, and increased susceptibility to infection or superinfections) [6]. However, if needed, low-penetrance topical corticosteroids (loteprednol, fluorometholone, hydrocortisone acetate, clobetasone, desonide, and rimexolone) are preferred. High-penetrance corticosteroids (prednisolone, dexamethasone, and betamethasone) should only be reserved by ophthalmologists if uncontrolled inflammation persists and patients are closely monitored, especially in long-term treatments [3].

Once patients already have symptoms of DED, treatment should follow a stepwise process [3]. Distinguishing between aqueous-deficient and evaporative DED is critical to selecting the most appropriate management strategy [2,38]. All therapeutic steps should include tear substitutes as the mainstay of management. Tear substitutes are not considered a pharmacological treatment but aim to replace 1 or more layers of the tear film. Countless preparations are available. If possible, artificial tears and lubricant solutions should be preservative-free to avoid inducing toxicity on the ocular surface [2,39]. Next, depending on the clinical entity of DED, treatment should focus on products aimed at supplementing the lipid, aqueous, or mixed lipid-aqueous deficiency [2,3].

The last interventions in this stepwise management of OA and DED include more intensive measures such as topical cyclosporine A or calcineurin inhibitors in severe forms of OA (vernal or atopic keratoconjunctivitis), oral secretagogues, therapeutic contact lenses, long-term treatment with topical corticosteroids, and even amniotic membrane grafting in severe forms of DED [2,3]. Finally, surgical interventions are uncommon but sometimes required to address complications such as corneal plaques, giant papillae, and corneal ulcers [3].

3.2 Other Nonpharmacological Approaches to Managing Tear Film Dysfunction in Patients With OA

In addition to the abovementioned treatments, modern DED treatments incorporate nonpharmacological, natural products and substances such as ectoine [39-41] and blood-derived products [42-47] to manage superficial ocular inflammation.

Ectoine is a bacteria-derived extremolyte that can protect proteins and biological membranes, such as the ocular surface, from damage caused by extreme environmental conditions [39]. Several studies support the effectiveness of ectoine in the treatment of ocular surface irritations and inflammations. The agent is an alternative nonpharmacological treatment option for DED [39,40] and an add-on therapy to antihistamines that accelerates symptom relief in patients with allergic conjunctivitis [41].

Other approaches with blood derivatives have been developed for the treatment of ocular surface disorders,

including platelet-rich plasma, plasma rich in growth factors, and autologous serum [42-47]. However, the available evidence on the efficacy of these compounds is not consistent, as a meta-analysis pooling 19 clinical trials demonstrated similar efficacy of blood therapy to artificial tears [44]. According to recent data, plasma rich in growth factors is more efficacious than autologous serum in reducing the signs and symptoms of DED [42]. For this reason, more robust studies are required to assess the sustainability and applicability of blood derivatives in managing DED and complementary therapy in other ocular diseases such as allergic conjunctivitis.

3.3 Avoiding the Use of Preservatives

There is sufficient evidence proving the link between the presence of BAC and the development of DED. Physicians should always consider this fact when prescribing first-line treatment for OA [23-26,31-35]. Topical treatments for OA are available in multidose systems or single-dose preservative-free presentations [27,31]. Most multidose topical ophthalmic medications contain a preservative [48], very often BAC [24-26,28-30,32-35], and they usually exceed the ocular surface toxicity threshold of BAC (0.005%). Nowadays, thanks to the development of new formulations and eye drop administration devices, preservative-free preparations are available for patients who prefer multidose presentations [23].

In this regard, recent guidelines for managing OA recommend preservative-free eye drops whenever possible to minimize possible toxic effects on the ocular surface [6,16,36].

3.4 Breaking the Vicious Cycle: Ophthalmic Solutions That Prevent the Breakdown of Tear Film Homeostasis

In addition to preservative-free topical solutions to treat the signs and symptoms of allergic conjunctivitis or other types of OA, an attempt should be made to restore tear film homeostasis in the case of tear film dysfunction. This can be done by adding topical moisturizing and lubricating solutions with an aqueous and/or lipid base [2,38] to eye drop formulations. When choosing an artificial tear product, health care providers should consider its hydrating capacity and viscosity, indicating higher viscosity products for more severe cases of DED [2].

Many ingredients are used in artificial tear substitutes to treat the signs of DED [12,49]. Wetting and lubricant agents prevent and treat tear film instability and include oily agents (liposomal sprays, oils, and cationic emulsions), viscosity-enhancing agents (carbomer, carboxymethylcellulose, hydroxypropyl guar, and hyaluronic acid), and electrolytes (NaCl, CaCl₂, MgCl₂, KCl) [12]. Osmo-protectants (L-carnitine, erythritol, and trehalose) correct tear film hyperosmolarity. Artificial tears, defined as ocular surface modulators, target ocular inflammation and ocular surface apoptosis [12,49] by including antioxidants (vitamins A and E, coenzyme q10), cytoprotective agents (trehalose), and carbomer and hyaluronic acid, both of which promote wound healing [12].

Hyaluronic acid, when added or coformulated with ophthalmic formulations, is a powerful ally, as it reduces allergic inflammation, hydrates and lubricates the ocular

surface, and has been shown to improve wound healing and prevent eye dryness [12]. Preclinical and clinical studies have demonstrated that artificial tears containing hyaluronic acid provide acute and long-term therapeutic benefits in DED, including enhancement of corneal epithelium healing, improvement of ocular surface function [50], normalization of clinical parameters (conjunctival goblet cell density, tear break-up time, the ocular surface disease index, and the Schirmer test result), and relief and reduced frequency of DED symptoms (hyperemia, chemosis, and conjunctival redness) [51,52]. Moreover, it has been shown that combining hyaluronic acid with active pharmaceutical compounds increases drug bioavailability on the ocular surface owing to the high viscosity of hyaluronic acid [53].

Additionally, evidence from in vivo trials has shown that hyaluronic acid, and especially high-molecular-weight hyaluronic acid, accelerates epithelial wound healing after corneal debridement and abrasion and alkali burn injuries, thus reducing inflammation [2,12,54,55]. In this regard, coformulating topical treatments for managing OA with hyaluronic acid can prevent DED, thus breaking the vicious cycle of ocular allergy-inflammation and tear film dysfunction that dries the ocular surface and may eventually induce DED.

4. Conclusions and Take-home Messages

We conclude that the first therapeutic option for any kind of OA, mainly allergic conjunctivitis, should be a preservative-free ophthalmic solution with an active drug targeting the disorder. This should contain a lubricating/moisturizing agent such as hyaluronic acid to prevent DED. Our take-home messages are as follows:

- OA and DED are different and very prevalent diseases with overlapping signs and symptoms and shared physiological mechanisms that lead to the loss of tear film homeostasis. In the case of OA, alterations of the tear film, epithelial barrier, and corneal innervation can pave the way to DED.
- Most topical formulations for OA contain BAC as a preservative; this causes alterations of the tear film and epithelial barrier dysfunction, which also lead to DED.
- Symptomatic treatment of OA should not contribute to iatrogenic ocular surface damage; therefore, an appropriate treatment choice requires physicians to be aware of DED.
- Single-dose and multidose preservative-free eye drops can prevent or reduce DED in OA, and topical moisturizing and lubricating solutions may prove helpful.
- Hyaluronic acid, as a choice of lubricant, targets several pathological mechanisms of DED, reduces ocular inflammation, and acts as an ocular surface modulator, promoting wound healing and preventing tear film instability. It may also increase the bioavailability of drugs and other compounds in eye drop formulations.
- A preservative-free ophthalmic solution containing hyaluronic acid could effectively prevent ocular inflammation and TDS when used to treat the signs and symptoms of ocular allergy.

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Conflicts of Interest

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