Expert Consensus Recommendations for the Management of Ocular Surface Inflammation in Patients With Glaucoma

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Précis: We have developed through a consensus process 24 clinical recommendations for the comprehensive management of ocular surface inflammation in glaucoma patients, including diagnostic criteria, prevention measures, and treatment strategies according to ocular surface disease severity.

Purpose: To obtain expert consensus on the diagnosis, prevention, and management of ocular surface inflammation (OSI) in patients with glaucoma.

Methods: An international steering committee of glaucoma and/or ocular surface disease (OSD) experts and a wider faculty of members from the Educational Club of Ocular Surface and Glaucoma (ECOS-G) collaborated to develop clinical recommendations on best practice in the management of OSI in glaucoma patients using a nonanonymous interactive quasi-Delphi process. Clinical recommendations were formulated by the steering committee based on an analysis of the recent literature to determine unmet needs, together with a web-based interactive survey of faculty members' opinion in seven identified areas of OSI management in glaucoma. Topics included (1) diagnosis of OSD, (2) diagnosis of OSI, (3) causes of OSI, (4) impact of OSD/OSI, (5) prevention of OSI, (6) treatment of OSI, and (7) inflammation and the deep structures of the eye. Faculty members were invited to vote on the clinical recommendations, and the steering committee then determined whether consensus had been achieved.

Results: Consensus was obtained on 24 clinical recommendations by 80%–100% of faculty members. There was consensus that OSI should be investigated in all glaucoma patients. The main prevention measure in glaucoma patients with pre-existing OSD was the elimination/minimisation of preserved medications, especially BAK-preserved eye drops. A subtractive treatment strategy rather than an additive strategy is recommended according to OSI/OSD severity to improve the ocular health and/or before glaucoma surgery.

Conclusion: These recommendations for the management of OSI in glaucoma should be useful to guide decision-making in clinical practice.

Key Words: expert consensus, glaucoma, inflammation, management, ocular surface

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Glaucoma is a group of progressive optic neuropathies characterized by a degeneration of retinal ganglion cells and retinal nerve fiber layers that result in changes in the optical nerve head.[1] This is the second leading cause of blindness in the world and the most common cause of irreversible blindness,[2] affecting between 2% and 3% of the worldwide population over 40 years, and up to 9% of the population over 80 years.[3,4] The pathogenesis of glaucoma is incompletely understood, but involves neurodegeneration mediated by oxidative stress, apoptosis and neuroinflammation.[5] Higher intraocular pressure (IOP) is associated with optic nerve damage development and progression and thus IOP-lowering eye drops are indicated to prevent or slow-down the rate of progression of the disease. As a chronic condition, this requires lifelong management, often with multiple topical treatments administered daily.[6]

A prevalent comorbidity in patients with glaucoma is ocular surface disease (OSD), accounting for 51% of patients including 21% of severe cases,[7] which involves several disorders of cornea, conjunctiva, eyelids, and lacrimal glands. The main components of OSD are dry eye disease, blepharitis, and meibomian gland dysfunction (MGD).

According to the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[8] The main risk factors of OSD in glaucoma patients are age, number of daily glaucoma eye drops, preserved medication

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use, glaucoma treatment duration and severity.[9–13] OSD in glaucoma is likely to be the result of interactions between the ocular surface and the active compounds of eye drops, acting either alone or in combination with the preservatives and excipients.

Preserved topical glaucoma medications may cause and/or exacerbate pre-existing OSD more than preservative-free treatment,[6] this adverse effect has been mainly associated with the preservative. Benzalkonium chloride (BAK) is still the most commonly used preservative in eye drop formulation, which may disrupt all layers of the tear film and damage conjunctival and corneal epithelial cells, including corneal nerve endings, leading to aggravation of OSD.[14–16]

OSD is frequently associated with ocular surface inflammation (OSI) even in asymptomatic patients. Increased levels of cytokines are common in the tears of primary open angle glaucoma patients.[17] Patients on long-term glaucoma treatment show significant subclinical ocular inflammation, characterized by overexpression of human leukocyte antigen class II antigens (HLA-DR), intercellular adhesion molecule (ICAM-1), cytokines, chemokines, matrix metalloproteinases (MMP-9), infiltration of immune-inflammatory cells in the conjunctiva and cornea, and fibroblast activation in the conjunctiva and subconjunctival space.[18–24]

OSD/OSI may have a significant adverse impact on patients' visual function and quality of life,[13,25] which, in turn, may produce poor adherence to treatment, and compromise the efficacy of IOP-lowering therapy and adversely impact ocular surgery outcome.[26]

Although OSD is relatively common in glaucoma patients, currently it remains overlooked and undertreated. Diagnosis may be difficult because there is a poor correlation between the signs and symptoms of OSD, and suboptimal consistency and reliability of clinical tests, such as corneal staining, conjunctival staining, and tear break-up time (TBUT).

Although clinicians involved in glaucoma care are encouraged to assess ocular surface health routinely, this is often not a priority.[27–30] Many ophthalmologists feel that the ocular surface health is not adequately managed in glaucoma patients,[28,30] and instead OSD is addressed only in glaucoma patients with pre-existing signs and symptoms. In a previous survey on OSD in glaucoma patients conducted by the Educational Club of Ocular Surface and Glaucoma (ECOS-G) among ophthalmologists from different countries, most reported that preservative-free eye drops should be used, but prescription practice does not reflect this finding.[31] In one survey between 2013 and 2020 in an ophthalmic Hospital in Madrid, Spain, it was shown that BAK-preserved eye drops accounted for 91.1% of the total prescriptions in 2013 and for 34.2% of total prescriptions in 2020, indicating the trend to avoid BAK in glaucoma eye drops.[32] In addition, it should be mentioned that preservative-free glaucoma eye drops are not available in all countries.[33] In some countries, there are few preservative-free options on the market and the preserved medication is often expensive and not reimbursed.

There are currently no consensus recommendations or guidelines for the comprehensive management of OSD/OSI in glaucoma patients, other than to avoid preservative eye drops in patients with pre-existing OSD,[6,34] and advise that BAK-preserved eye drops should be used with caution in dry eye patients and in patients in whom the cornea may be compromised, and that prolonged use should be monitored.[35]

As an initiative of ECOS-G, we have developed consensus recommendations aiming to help ophthalmologists in the diagnosis, prevention, and treatment of OSD/OSI in glaucoma patients.

The "Education Club of Ocular Surface and Glaucoma (ECOS-G) is a group of more than 100 glaucoma and ocular surface experts which was created in October 2015 in partnership with Théa, at the initiative of 3 founders and chairmen (Profs Christophe Baudouin, John Thygesen, and Jose Benitez del Castillo). The first meeting took place in 2016, and since then an annual meeting has taken place. This is a group that is by invitation. Each year, the chairs propose projects to the ECOS members, who vote to determine which projects will be carried out. This led to publications, reviews for ophthalmologists, and tools to help them manage surface problems in patients. There is no membership. Experts are invited to participate in the annual meeting, free of charge, and without honorarium (financial compensation). Théa provides logistical support for the meeting, which is hosted by an external communication agency which works with the chairmen. It is an educational club. There is no product promotion. Activities of the ECOS-G are exclusively supported by Théa and not by any other pharmaceutical laboratory.

METHODS

This study was based on a quasi-Delphi process facilitated by 2 independent communication agencies (Phase 3 Medical Communications Ltd, Yeovil, Somerset, United Kingdom and Chill Pill Media Ltd, London, United Kingdom). Our objective was to develop comprehensive recommendations to diagnose, prevent, and treat ocular inflammation in glaucoma patients, according to OSD/OSI severity. For this purpose, an international steering committee of 7 senior glaucoma and cornea/OSD experts who treat glaucoma patients with inflammation and OSD collaborated to develop clinical recommendations on best practice in the management and treatment of OSI/OSD in glaucoma patients. The group was co-chaired by 2 senior experts (C.B. and E.M.), and each member of the steering committee was equally responsible for input into the final recommendations. To ensure that the group's recommendations are widely applicable to expert colleagues managing patients with OSI/OSD associated with glaucoma, all ECOS-G members (about 100 ophthalmologists) were invited to participate using a quasi-Delphi methodology described previously.[36,37] The quasi-Delphi process consisted of 3 main steps: (1) a gap analysis based on a search of the recent scientific literature and validated by the steering committee; (2) an online survey in order to seek the opinion and judgment of the faculty of experts in the field of OSD/OSI in glaucoma patients (stage 1 of the quasi-Delphi) and; (3) an online vote step (stage 2 of the quasi-Delphi) to determine whether there was consensus on the clinical recommendations developed from the answers given in stage 1. The quasi-Delphi process was facilitated by the use of a proprietary digital interactive Stakeholder Engagement Platform (iSTEP, Phase 3 Medical Communications Ltd, South Warnborough, UK), together with online meetings and one face-to-face meeting as described in Figure 1. I-STEP is an interactive, user-friendly and convenient data capture system. The responses provided by each participant

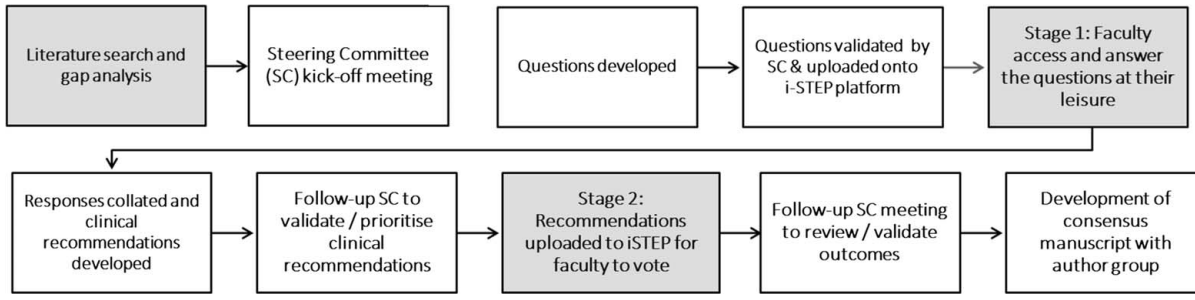


FIGURE 1. Quasi-Delphi process for the development of clinical recommendations.

can be viewed by others to facilitate exchange, discussions of practices, and points of view. This helped to maximize engagement and optimize data capture. Overall, 58 ECOS-G members from 24 countries (Algeria, N = 1 faculty member; Austria, N = 5; Belgium, N = 4; Bulgaria, N = 1; Croatia, N = 1; Denmark, N = 1; Finland, N = 1; France, N = 1; Germany, N = 4; Greece, N = 3; Italy, N = 2; Mexico, N = 3; Norway, N = 1; Poland, N = 2; Portugal, N = 3; Russia, N = 3; Romania, N = 2; Slovenia, N = 2; Spain, N = 3; Sweden, N = 2; Switzerland, N = 4; The Netherlands, N = 1; Ukraine, N = 4; and United Kingdom, N = 4) voted for consensus recommendations, while 54 completed the survey. Note that a preservative-free option was available in all these countries.

Step 1: Gap Analysis

The steering committee first met in an online meeting to review the scientific literature and identify unmet needs (gap analysis) in the management of ocular surface in glaucoma, including current diagnosis and treatment. A literature search of the PubMed database was performed in January/February 2021 to identify current clinical practice, clinical controversies, and unmet needs regarding the diagnosis, treatment, and management of ocular inflammation in glaucoma patients. The following key words or combinations were agreed by the steering committee: "Glaucoma," "Ocular surface disease," "Ocular surface inflammation," "Guidelines," "Consensus," "Best practice," "Diagnosis," "Treatment," "Management," "Prevention," "Challenge," "Quality of life," "Outcomes," "Inflammation," "Preservative," "Preservative-free," "Surgery," "Addition strategy," "Intraocular pressure," "Trabecular meshwork," and "Dry eyes." The search was from the last 5 years (January 1, 2015–December 31, 2020). A total of 74 scientific publications of interest were retrieved from the literature search. After reading the full papers, 30 relevant publications were identified, including 16 key articles.[5,6,27–29,34,38–47] Potential gaps were identified and discussed to raise a series of questions for the ECOS-G members.

Step 2: Survey of the ECOS-G Members (Stage 1 of the Quasi-Delphi Process)

In a second step, a faculty of 54 experts in glaucoma and ocular surface, completed a questionnaire based on the gap analysis from the literature search and validated by the steering committee. The questionnaire aimed to collect their current opinion in 7 domains: (1) Diagnosis of OSD in glaucoma (4 questions), (2) Diagnosis of OSI in glaucoma (7 questions), (3) Causes of OSI (3 questions), (4) Impact of OSD and OSI on glaucoma management (4 questions), (5) Preventing OSI in glaucoma patients (2 questions), (6) Treating OSI in glaucoma patients (5 questions), and (7) Inflammation and deep structures of the eye (5 questions). The iSTEP platform allowed the participants asynchronous access to answer the questionnaire and to upload any supporting documents to the answers provided.

Step 3: Development and Subsequent Vote on the Clinical Recommendations (Stage 2 of the Quasi-Delphi Process)

The results of the survey were collated and analyzed between May and July 2021 and reviewed by the steering committee. Following clinical recommendations were drafted in November 2021. These draft recommendations were then reuploaded to the iSTEP platform, and the expert faculty was invited to vote on each of the clinical recommendations. Each recommendation was proposed with a supporting rationale and literature references, together with the results from the survey in Step 2. Participants (58 ECOS-G members) had to vote whether they agreed or disagreed with the proposed recommendations. If they did not agree or could not answer, the participants had to provide the reason using a free text box, and they were not able to progress to the next recommendation unless they had given a reason. The threshold for consensus was set by the Steering Committee at $\geq 75\%$ of respondents' agreement. Finally, the steering Committee met to review the results of the stage 2 vote, to determine whether consensus had been achieved, and to refine the wording of the clinical recommendations if required at a meeting in March 2022.

RESULTS

The stage 1 survey was completed by 54 expert members of the faculty (54% were specialists in glaucoma, 31% specialists in cornea/ocular surface disease, and 15% in both glaucoma and OSD). Results of the stage 1 survey are provided in the supplementary file (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924).

Following analysis of the survey results from stage 1, 24 clinical recommendations were drafted and voted on by the faculty members, who either agreed or disagreed with the proposed recommendation (stage 2). Consensus was obtained by all or nearly all faculty members (80%–100% agreement) for all recommendations. Recommendations R2, R5, R12, R14, R20, R23, and R24 needed rewording to reach consensus and at the end consensus was reached for all.

Final recommendations are listed in Table 1.

TABLE 1. Final Recommendations for Diagnosis, Prevention, and Treatment of OSI in Glaucoma Patients

Diagnosing ocular surface disease in glaucoma	
R1	It is our opinion that all glaucoma patients should be examined for any signs or symptoms of OSD
R2	There are many signs and symptoms indicative of OSD. The following signs and symptoms are the most frequent ones and can be used to diagnose OSD in glaucoma patients: Symptoms: red eyes, gritty or sandy eyes, and burning sensation; Signs: conjunctival hyperemia, low TBUT, eyelid redness and/or swelling, and corneal staining. Also consider patient-reported outcome measures and dry eye questionnaires as part of diagnosis
Diagnosing ocular surface inflammation in glaucoma	
R3	It is our opinion that OSI plays a role in OSD in glaucoma patients and should be investigated
R4	It is important to look for signs of OSI in glaucoma patients, even if they do not present with symptoms
R5	We advise close monitoring of the following signs and symptoms for early detection of OSI in glaucoma patients with OSD. Symptoms: red eyes, burning sensation, gritty/sandy eyes and dryness; signs: conjunctival hyperemia, corneal staining, blepharitis, and low TBUT
R6	It is our opinion that hyperemia alone is insufficient to diagnose OSI and other signs should be investigated in glaucoma patients
R7	As well as routine clinical tests, we advise that additional tests may be used to identify OSI if available
Causes of ocular surface inflammation	
R8	We recommend avoiding the use of multiple glaucoma medications and the long-term use of treatments that increase the risk of OSI in glaucoma patients
R9	We advise that glaucoma treatment selection should avoid the use of medications that increase the risk of OSI and OSD, such as those containing BAK or other preservatives, and any other drugs suspected of causing allergy and/or inflammatory reactions
Impact of ocular surface inflammation on glaucoma management	
R10	We recommend that clinical guidelines should include advice on ocular surface health evaluation, and that comprehensive management of OSI is implemented to improve glaucoma outcomes for patients
Preventing ocular surface inflammation in the glaucoma patient	
R11	In our opinion, it is important to prevent development of OSI in patients with glaucoma
R12	We advise avoiding the use of BAK-containing treatments to prevent OSI developing in glaucoma patients, and if BAK-containing treatments are used they should be withdrawn before surgery where possible
R13	We recommend that meibomian gland dysfunction/blepharitis should be managed actively to prevent OSI in patients with glaucoma, as well as in other patients
Treating ocular surface inflammation in the glaucoma patient	
R14	We recommend that a subtraction strategy is adopted to prevent or treat inflammation in glaucoma patients, which involves: Removing active compounds responsible for allergic/toxic reactions; Stopping BAK-containing and other preservative-containing formulations; Switching medications to minimize preservative exposure; Discontinuing unnecessary topical medications; and consider laser/surgery (eg, SLT) for reduction of IOP-lowering drops
R15	We also suggest that a combined subtraction/addition approach may be beneficial for some glaucoma patients
R16	We recommend stopping topical medications suspected of causing allergy and/or inflammatory reactions or switching to BAK-free options or adding in artificial tears (without preservatives) if OSD/OSI occurs during glaucoma treatment
R17	We recommend considering BAK-free medications as initial glaucoma treatment in patients with pre-existing OSD, depending on local availability and reimbursement
R18	We recommend optimizing topical glaucoma medications, and consider topical immunomodulators and tetracyclines, preservative-free artificial tears, lid hygiene, and topical corticosteroids as important treatment strategies for managing OSI
R19	We consider that treating OSI may help to improve compliance and to control IOP in patients with glaucoma
R20	It is our opinion that OSD and OSI should be fully investigated and managed in those glaucoma patients who are likely to need ocular surgery
R21	We advise considering the reduction of preserved eye drops and eye drops containing any drugs suspected of causing allergy and/or inflammatory reactions as part of preoperative preparation to reduce surgery failure
R22	We recommend treating the ocular surface with topical anti-inflammatory drugs before trabeculectomy (including all filtering surgeries and bleb-forming surgeries); this may improve the ocular surface and may help to improve surgical outcomes if preventive and/or subtraction strategies are not possible
Inflammation and the deep structures of the eye	
R23	Further research is required into the association of OSI and OSD with inflammation of the deeper eye structure. Pending the outcome of such research, it is our opinion that OSD and OSI need to be actively diagnosed and managed in glaucoma patients to reduce inflammation of the deeper eye structures
R24	Further research is required into the use of BAK-containing and other preservative-containing treatments and inflammation of the deeper eye structure. Pending the outcome of such research, it is our opinion that the use of BAK-containing and other preservative-containing treatments should be avoided or minimized in glaucoma to prevent damage to the deep eye structures

BAK indicates benzalkonium chloride; IOP, intraocular pressure; OSD, ocular surface disease; OSI, ocular surface inflammation; PF, preservative-free; SLT, selective laser trabeculoplasty; TM, trabecular meshwork.

Recommendations for Diagnosing OSD in Glaucoma Patients (R1, R2)

According to the stage 1 survey, most faculty members reported that between 20% and 40% of their glaucoma patients have OSD (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924). A combination of signs and symptoms are used by the experts to diagnose OSD. According to a majority of faculty members, the three most common symptoms reported are red eyes, gritty/sandy eyes and burning sensation. Typical signs for OSD reported by the members were mainly conjunctival hyperemia, and also low TBUT, eyelid redness/swelling or corneal staining. Following, the vote in stage 2, consensus was reached (95% and 91%, respectively) in the following 2 recommendations (R1 and R2):

R1: "It is our opinion that all glaucoma patients should be examined for any signs or symptoms of ocular surface disease (OSD)" (95.1% agreement).

R2: There are many signs and symptoms indicative of OSD, but only a specific combination of signs and symptoms should be used to diagnose OSD in glaucoma patients (91.0% agreement).

Differences in opinion highlighted by members were that a combination of signs and symptoms may be absent in patients with glaucoma, and some patients may experience symptoms but have very limited signs. It was also suggested that patient-reported outcome measures and dry eye questionnaires to diagnose OSD in glaucoma patients should be used. The proposed recommendation was reworded by the steering committee (Table 1) to specify clearly the main symptoms (red eyes, gritty/sandy eyes, and burning sensation) and signs [conjunctival hyperemia, low tear break-up time (TBUT), eyelid redness and/or swelling, corneal staining] as part of the diagnosis.

Recommendations for Diagnosing OSI in Glaucoma Patients (R3–R7)

Results from the stage 1 survey showed that all faculty members strongly agreed that OSI plays a role in glaucoma patients with OSD (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924). They reported that about 50% of their glaucoma patients with OSD have both signs and symptoms of OSI and that it is important to look for signs of OSI in glaucoma patients. The most frequently reported symptoms are dryness, gritty/sandy eyes, burning sensation, and red eyes. Because OSI and OSD symptoms are obviously the same, they also agreed that additional tests may be useful to identify OSI. The most frequently used additional tests in the survey were tear osmolarity (64% of respondents), analysis of inflammatory markers (49%), and ocular redness index (46%). There was a majority consensus (89%–100%) in the following recommendations (R3–R7):

R3: "It is our opinion that ocular surface inflammation (OSI) plays a role in OSD in glaucoma patients and should be investigated" (100% agreement).

R4: "It is important to look for signs of OSI in glaucoma patients, even if they do not present with symptoms" (94.4% agreement).

R5: We advise close monitoring of the following signs and symptoms for early detection of OSI in glaucoma patients with OSD: "Symptoms: Red eyes, burning sensation, gritty/sandy eyes and dryness; Signs: Conjunctival hyperemia, corneal staining, and low TBUT" (98.1% agreement).

R6: "It is our opinion that hyperemia alone is insufficient to diagnose OSI and other signs should be investigated in glaucoma patients" (100% agreement).

R7: "As well as routine clinical tests, we advise that additional tests may be used to identify OSI if available" (88.5% agreement).

At the final meeting, the steering committee agreed that blepharitis should be added as an additional sign of OSI in R5 (Table 1).

Recommendations on the Causes of Ocular Surface Inflammation (R8, R9)

From the stage 1 survey, the most frequent factors associated with OSD are BAK-preserved treatments, pre-existing OSD, and multiple glaucoma treatments (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924). A majority of faculty members also considered that multiple glaucoma treatments (with or without preservatives), preserved treatments (especially BAK-preserved treatments) and long treatment duration are also risk factors for OSI. There was convincing evidence that some medications (especially if they contain a preservative) can either cause OSD or worsen pre-existing OSD. In the second voting stage, consensus was achieved among 93% and 95% of the faculty members regarding the causes of OSI in all glaucoma patients (R8, R9):

R8: We recommend avoiding the use of multiple glaucoma medications and the long-term use of treatments that increase the risk of OSI in glaucoma patients (93.0% agreement).

R9: We advise that glaucoma treatment selection should avoid the use of medications that increase the risk of OSI and OSD, such as those containing benzalkonium chloride (BAK) or other preservatives, and any other drugs suspected of causing allergy and/or inflammatory reactions (94.5% agreement).

Recommendations on the Impact of OSD and OSI on Glaucoma Management (R10)

From the survey results, 80% of the faculty members considered that the ocular surface health of their glaucoma patients was adequately managed, but sometimes referral to a corneal specialist or to another ophthalmology department was required. Poor treatment adherence, poor quality of life, and failure of filtering surgery are identified as negative consequences of OSD/OSI, as recently reviewed by a TFOS expert meeting in 2022.[48] The faculty members almost all recognized that a comprehensive management of OSI in glaucoma patients could lead to a better glaucoma outcome (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924). Thus, there was a consensus (100% agreement) with the following recommendation (R10):

R10: We recommend that clinical guidelines should include advice on ocular surface health evaluation, and that comprehensive management of OSI is implemented to improve glaucoma outcomes for patients (100% agreement).

Recommendations for Preventing OSI in Glaucoma Patients (R11–R13)

According to the results from the survey, the faculty members generally agreed that it is important to prevent OSI, especially in patients with symptomatic OSD, in patients scheduled for ocular surgery, or in those taking multiple topical medications, and, to a lesser extent, in patients with advanced glaucoma. They agreed that OSI in glaucoma patients could be aggravated by BAK-containing treatment and by the presence of MGD/blepharitis (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924). This led to a consensus (84%–100% agreement) on the following 3 recommendations (R11, R12, R13):

R11: In our opinion, it is important to prevent development of OSI in patients with glaucoma (100% agreement).

R12: We advise avoiding the use of BAK-containing treatments to prevent OSI developing in glaucoma patients, and if BAK-containing treatments are used they should be withdrawn before surgery (83.6% agreement).

R13: We recommend that meibomian gland dysfunction/blepharitis should be managed actively to prevent OSI in patients with glaucoma, as well as in other patients (98.1% agreement).

Minor word changes to R12 were decided by the steering committee, because it is sometimes not always possible to withdraw BAK-preserved eye drops before glaucoma surgery (Table 1).

Recommendations for the Treatment of OSI in Glaucoma Patients (R14–R22)

According to the survey results, the faculty members strongly preferred a subtractive rather than an additive treatment strategy; when OSD/OSI occurs during glaucoma treatment, a majority of faculty members either switch to BAK-free glaucoma medication, stop the suspected medication, and/or add artificial tears. In patients with preexisting OSD, they generally initiate a glaucoma medication without BAK. In patients with OSI, the faculty members reported it is very important to optimize the topical glaucoma medication and to use preservative-free artificial tears. They reported that it was somewhat important to consider lid hygiene, topical corticosteroids or immunomodulators, or oral tetracycline/tetracycline derivatives. They also either agreed or strongly agreed that OSI treatment could be helpful for controlling IOP, because this should improve compliance. They strongly agreed that a reduction of preserved and proinflammatory eye drops before surgery can reduce the risk of failure. Nine recommendations (R14–R22) were drafted, and after voting, consensus agreement was achieved by 96%–100% of the faculty members:

R14: We recommend that a subtraction strategy is adopted to prevent or treat inflammation in glaucoma patients, which involves: "Removing active compounds responsible for allergic/toxic reactions; Stopping BAK-containing and other preservative-containing formulations; Switching medications to minimize preservative exposure; and Discontinuing unnecessary topical medications" (96.6% agreement).

R15: We also suggest that a combined subtraction/addition approach may be beneficial for some glaucoma patients (100% agreement).

R16: We recommend stopping topical medications suspected of causing allergy and/or inflammatory reactions or switching to BAK-free options or adding in artificial tears (without preservatives) if OSD/OSI occurs during glaucoma treatment (96.4% agreement).

R17: We recommend considering BAK-free medications as initial glaucoma treatment in patients with preexisting OSD, depending on local availability and reimbursement (96.4% agreement).

R18: We recommend optimizing topical glaucoma medications, and consider topical immunomodulators and systemic tetracyclines, preservative-free artificial tears, lid hygiene, and topical corticosteroids as important treatment strategies for managing OSI (96.3% agreement).

R19: We consider that treating OSI may help to improve compliance and to control IOP in patients with glaucoma (100% agreement).

R20: It is our opinion that OSD and OSI should be fully investigated and managed in those glaucoma patients who are likely to need surgery (96.3% agreement).

R21: We advise considering the reduction of preserved eye drops and eye drops containing any drugs suspected of causing allergy and/or inflammatory reactions as part of preoperative preparation to reduce surgery failure (94.3% agreement).

R22: We recommend treating the ocular surface with topical anti-inflammatory drugs before trabeculectomy; this may improve the ocular surface and may help to improve surgical outcomes if preventive and/or subtraction strategies are not possible (98.1% agreement).

One recommendation (R14) was slightly reworded to consider laser/surgery (SLT) as an option to reduce IOP-lowering drops. A minor wording change was also made for R20 before final approval by the steering committee (Table 1).

Inflammation and Deep Structures of the Eye (R23, R24)

There is some concerns about the possible diffusion of inflammatory mediators and also diffusion of BAK itself from the ocular surface to deeper ocular tissues in glaucoma patients with OSI/OSD. The faculty members strongly agreed or agreed that OSD is associated with trabecular meshwork inflammation and damage that can lead to increased aqueous humor outflow resistance and progressive loss of efficacy of IOP-lowering drugs (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/IJG/A924). There was generally less agreement for an association between OSD and inflammation of other deep ocular structures, including the lens epithelium or the retina. Two recommendations (R23, R24) on inflammation and deep eye structures were voted on and obtained 94.8% and 93.0% agreement. The drafted recommendations were slightly reworded by the steering committee before final approval.

R23: OSD and OSI need to be actively diagnosed and managed in glaucoma patients to reduce inflammation of the deeper eye structure: "conjunctiva, subconjunctiva, and trabecular meshwork" (94.8% agreement).

R24: "The use of BAK-containing and other preservative-containing treatments should be avoided or minimized in glaucoma to prevent damage to the deep eye structures" (93.0% agreement).

DISCUSSION

The main objective of this quasi-Delphi consensus was to formulate a series of expert-validated recommendations on OSD/OSI diagnosis, prevention, and treatment. Consensus on 24 clinical recommendations was obtained from an international faculty of experts in glaucoma and/or ocular surface disease. Here, we discussed all consensus recommendations with current supporting evidence from the literature, in line with the survey in this study, and we expanded the discussion beyond the scope of the study to propose treatment algorithms which could help ophthalmologists in their practice.

Diagnosis

We advise to examine all glaucoma patients for signs and symptoms of OSD (Consensus agreement, R1). The diagnosis of OSD in glaucoma patients may be difficult, as complex interactions exist between different components of the ocular surface and there is an absence of widely accepted diagnostic criteria.[29,42] There is agreement that OSI plays a role in OSD in glaucoma patients (Consensus agreement, R3), thus this was not unexpected to find similar symptoms for OSD and OSI as mentioned by the faculty members.

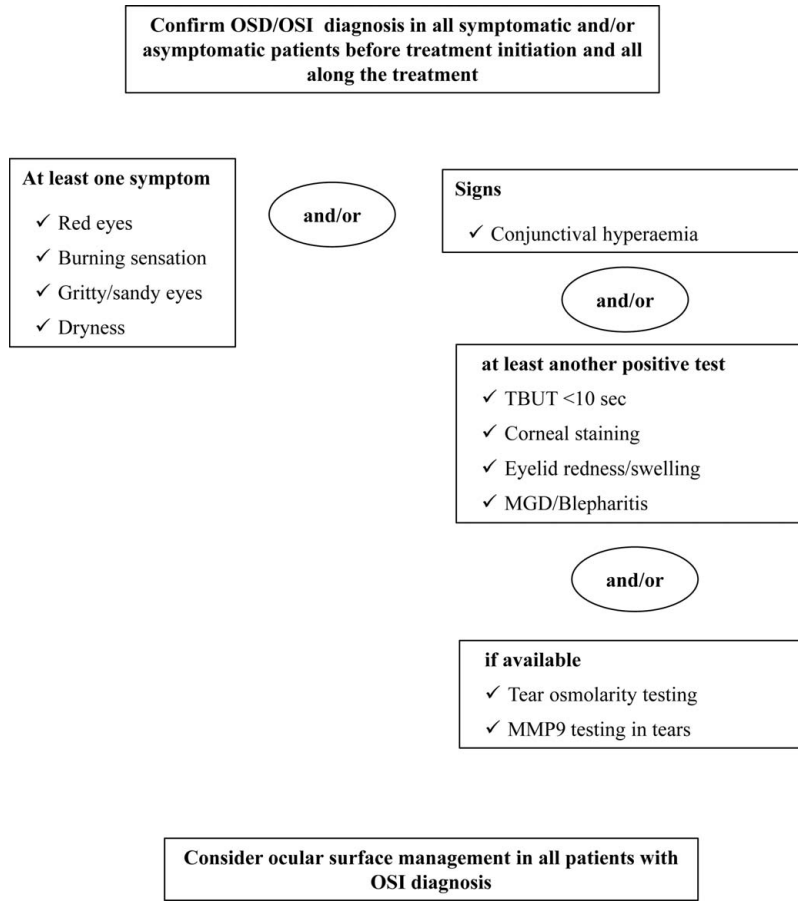


FIGURE 2. How to diagnose ocular surface inflammation in glaucoma patients?

As summarized in Figure 2, we propose to look for the main symptoms for early detection of OSI, that is, red eyes, burning sensation, gritty/sandy eyes, and dryness sensation (Consensus agreement, R5). Since many patients may be asymptomatic or think that their ocular surface symptoms do not matter as long as the IOP is controlled, it is important to look for ocular signs (Consensus recommendation, R4). There is also agreement that hyperemia alone is not sufficient to diagnose OSI (Consensus agreement, R6). Indeed, it is known that prostaglandins and Rho-kinase inhibitors (not yet available in Europe) topical medications produced conjunctival hyperemia, which is usually not associated to any other ocular surface signs. The pathophysiological mechanisms are not well known but may be related to NO synthase stimulation leading to vasodilation (PGAs), or to increased calcium concentration in the intracellular space (Rho-kinase inhibitors) leading to vascular smooth muscle relaxation leading to vasodilation.[49] The transient hyperemia is noninflammatory and is a consequence of vasodilating effect of these drug.

In addition to conjunctival hyperemia, we advise to look for objective signs of corneal damage (punctate superficial keratitis) and tear film dysfunction (Consensus agreement, R5), which may be easily and rapidly achieved by corneal staining and TBUT measurements. It is also advised to look for the presence of MGD/blepharitis, that is, crusting/discharge on eyelashes, epiphora, obstructed meibomian glands, and altered meibum. Additional tests may be used to identify OSI (Consensus agreement, R7). Although this was not a consensus recommendation, this includes tear hyperosmolarity and MMP-9 measurements although they are not always available in all practices. Tear film hyperosmolarity is considered as an objective marker of dry eye disease and can be an indirect sign of inflammation.[50,51] Although routine tear osmolarity is not widespread in real life practice, the test is nowadays accessible, and feasible with a minimum volume of tears in all patients, using handheld osmometers A tear osmolarity >308 mOsm/L is a sensitive indicator for dry eye disease.[29] Intereye osmolarity >8 mOsm/L may be also considered as a sign of DED according to the TearLab user manual, although this was questioned recently by Nilsen et al[52] as not consistent with other signs and symptoms of DED.

MMP-9 levels in tears is also a valuable test available on the market to confirm the diagnosis of OSI since they well correlated with other markers of inflammation and OSD, including TBUT, Schirmer's test, and corneal staining.[24,46,53,54]

Prevention

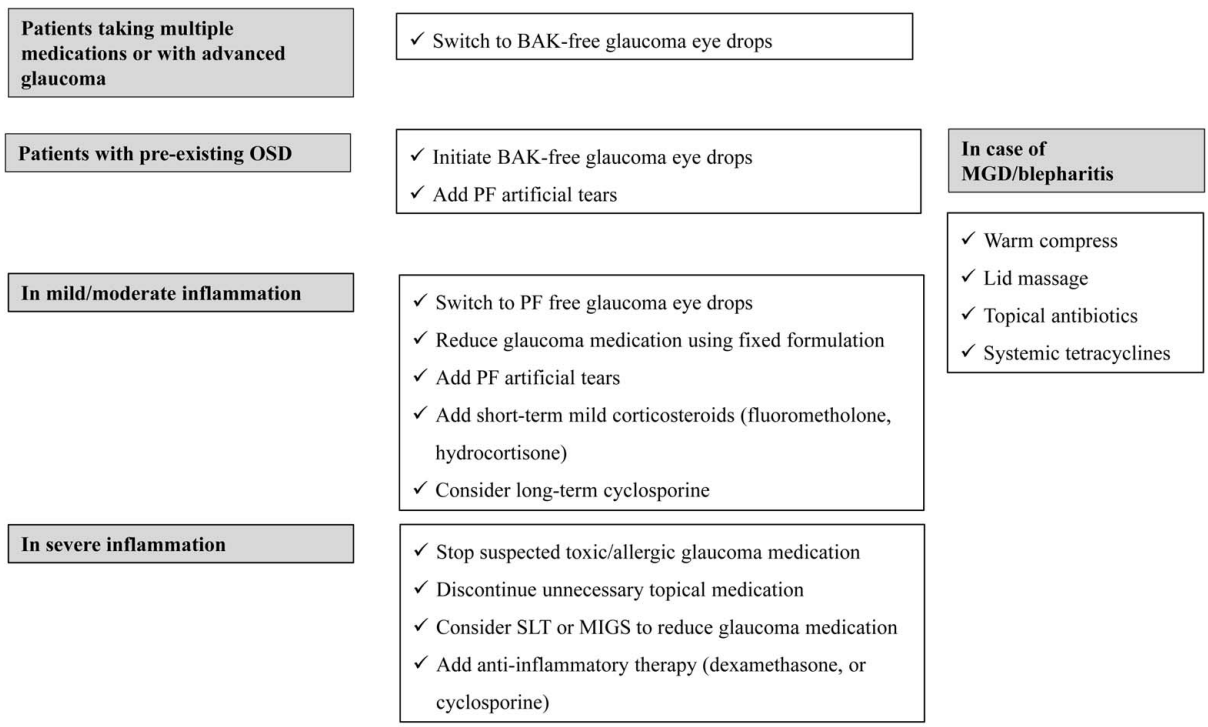
One challenge is to manage OSI before the development of more severe OSD, which can lead to worse topical treatment compliance and hence IOP control and worse surgical outcomes.[29] It is thus important to prevent the development of OSI in patients with glaucoma (Consensus

agreement, R11). As previously reported, the severity of OSD increases with the number of topical antiglaucoma medications used in treatment due to multiple, daily exposures of the ocular surface to toxic compounds, including the drug itself or preservatives.[29] One major cause of OSI is the use of multiple glaucoma medication and the long-term use of treatments (Consensus recommendation, R8). Another cause is the use of BAK-preserved glaucoma medication, and more generally all preserved glaucoma medications (Consensus recommendation, R9). Thus, in line with others, multiple glaucoma medications, especially those containing a preservative, administered over the long-term should not be used and the least toxic preserved eye drops (ie, eye drops formulated with Polyquad and Purite) or preservative-free eye drops should be used.[16,27,34] However, less toxic preserved glaucoma eye drops are not available in all countries, and they are more expensive and may be not reimbursed. The option of preservative-free formulations is gaining increasing interest,[32] and have been developed and approved in many countries.

As proposed previously, prevention of OSD in patients receiving topical glaucoma therapy can be achieved by reducing exposure to BAK, using preservative-free medications, alternative preservatives, or concurrent treatments of OSD.[47] Nevertheless, despite accumulating evidence for the inflammatory and toxic effect of BAK on the ocular surface, its elimination from all glaucoma eye drops is still debated.[40,44,55] Thygesen considered that in absence of any cost consideration or positive indication for preserved medication, preservative-free glaucoma medication for all patients appears an appropriate strategy.[55] This may be impractical in some countries, like in the United States where this option is considered only in case of severe OSD. Some authors reported that there is no justification for routine use of PF medication in glaucoma patients without significant OSD and especially those requiring only 1 or 2 medications per day.[44] A recent systematic review and meta-analysis in glaucoma patients did not show a clinically significant difference in safety between BAK-preserved eye drops, alternatively preserved eye drops or PF eye drops.[40] However, it is agreed that there is a need for longer clinical trials since clinically relevant side effects may occur after long-term use of BAK.[40] In contrast, there is convincing evidence from a number of prospective clinical studies that PF-antiglaucoma eye drops were as efficacious as the preserved formulation to lower IOP, but with a better tolerance as assessed by ocular hyperemia and other ocular signs including eyelid redness, eyelid swelling, corneal staining, conjunctival staining, and TBUT.[24,39,45,56–63] In this context, our consensus recommendation is to avoid the use of BAK-containing treatments to prevent OSI in glaucoma patients and if BAK-containing treatments are used they should be withdrawn where possible (Consensus recommendation, R12). As indicated by one previous study,[64] BAK-containing eye drops should be withdrawn 3–4 weeks before surgery to help recovery of the conjunctiva.

For patients with pre-existing OSD, it is preferable to consider BAK-free medication as initial glaucoma treatment, although this depends on local availability and reimbursement considerations (Consensus agreement, R17).

Beside BAK-containing eye drops considerations, it is known that patients with a higher burden of antiglaucoma treatments had more unstable tear films and more severe



PF: preservative-free; MGD: meibomian gland dysfunction; MIGS: minimally invasive glaucoma surgeries ; IOP: intraocular pressure; SLT: Selective laser trabeculoplasty;

FIGURE 3. A stepwise treatment plan to manage chronic OSD/OSI disease/inflammation in glaucoma patients.

MG dropout. Therefore, MGD should be particularly looked for in glaucoma patients following a higher burden antiglaucoma regimen.[65,66] This led to another important recommendation to actively manage MGD/blepharitis to prevent OSI in patients with glaucoma (Consensus recommendation, R13).

Treatment Strategy

There is a consensus agreement that treatment of OSI may help to improve compliance and thereby to control IOP in glaucoma patients (Consensus agreement, R19). Based on an individual (patient-by-patient) approach, various strategies of OSI treatment may be considered, including stopping medications suspected of causing allergy and/or inflammatory reactions (subtractive strategy), switching to BAK-free options, or adding artificial tears (without preservatives) if OSD/OSI occurs during glaucoma treatment (Consensus recommendation, R16). In Figure 3, we propose a stepwise treatment plan for various situations of patients with OSD/OSI. For all glaucoma patients, the first measure in the management of OSD/OSI is to optimize the topical glaucoma medication (Consensus agreement, R18). This can be primarily achieved by the elimination or minimization of preserved formulations, that is, the exacerbating factors.[6,28,47,67] Although this was not specifically discussed by the ECOS-G members during the mini-Delphi process, the newer generation of BAK-free, but preserved, antiglaucoma medications (eg, Purite) may be an option when available, as they have shown less toxicity in vitro and in animal studies. However, further studies are required to confirm the toxicity profile of these "less-harmful" preservatives, especially over the long-term, and to fully establish any potential differences between preservation methods.[38,40,45] This subtractive strategy was shown to improve ocular surface in glaucoma patients with chronic OSD/OSI while IOP was stabilized or improved. Reducing the amount and number of topical treatments (using fixed combinations) can also decrease ocular inflammation in glaucoma patients.[16,29,68,69] Thus, to treat inflammation in glaucoma patients, the consensus recommendation is removing all compounds responsible for allergic/toxic reactions (consider active substances which may produce conjunctival hyperemia, and some adjuvants and pH of the eye drop formulation), stopping BAK-containing and other preservative-containing formulations; in the absence of established differences between preservative methods, switching medication to minimize preservative exposure, discontinuing unnecessary topical medications; and considering selective laser trabeculoplasty (SLT) to reduce the number of IOP-lowering drops (Consensus agreement, R14).

In an additive strategy, preservative-free lubricants (eg, hyaluronate, carmellose, hypromellose, polyvinyl alcohol) or osmoprotectants have been shown to maintain the tear film homeostasis physiology.[70,71] According to previous guidelines, when subtractive strategies are not feasible, that is, in more severe cases, some anti-inflammatory options (short-term topical corticosteroids, cyclosporine) may be prescribed to improve OSD in glaucoma patients.[28,46,47] Although not discussed by the ECOS-G member during the mini Delphy process, the choice of steroids depends on the severity of inflammation and on the patient's presumed steroid response on IOP: weak (or soft) topical steroids (eg, PF fluorometholone 0.1%, desonide 0.025% or prednisolone phosphate 0.5%, prednisolone acetate 1.0%, hydrocortisone 0.5%) for mild ocular surface inflammation and more potent topical steroids (eg, dexamethasone 0.1% or prednisolone acetate 1%) for severe inflammation. It was also proposed that the frequency of drop administration should be titrated according to disease severity.[42] In this context, our consensus recommendation is considering topical immunomodulators, preservative-free artificial tears, lid hygiene, and topical corticoids as important treatment options for managing OSI in glaucoma patients (Consensus recommendation, R18). Alternatively, a combined subtraction/addition approach may be beneficial for some glaucoma patients (Consensus agreement, R15).

In case of blepharitis and MGD, aggressive treatment should be used to minimize the symptoms and signs of OSD. Lid hygiene (lid cleaning to remove crusts and debris; warm compresses, and lid massage) should reduce the blepharitis effect on the ocular surface and improve the tear film quality and ocular surface.[72] In line with our Consensus recommendation (R18), topical (erythromycin, azithromycin), and systemic antibiotics (tetracycline, doxycycline, minocycline, azithromycin) with anti-inflammatory properties should be considered as a treatment strategy for managing OSI in glaucoma patients.

Although this was not discussed by the ECOS-G members, in case of severe OSD/OSI, the patients may be unable to tolerate any topical medication and thus the cessation of all topical medications, including topical glaucoma treatment may be necessary. In this case, and in order to further control IOP, oral carbonic anhydrase (acetazolamide) may be started to reduce IOP.[29,73] In addition, management of glaucoma with laser trabeculoplasty, conventional surgery or minimally invasive glaucoma surgeries, depending on patient needs, may avoid or decrease reliance on topical glaucoma medications, potentially avoiding the initiation or progression of OSD.[46,47]

OSI Treatment Before Ocular Surgery

The long-term use of topical antiglaucoma medications causes OSD with overexpression of inflammatory markers, and subconjunctival fibrosis secondary to either clinical or subclinical chronic inflammation.[5] Such proinflammatory reactions may promote scarring of the filtering blebs following glaucoma-filtering surgery. Thus, in agreement with previous guidelines,[74] preoperative optimization of the ocular surface and a reduction of the ocular inflammation is recommended (Consensus recommendation R20). As proposed in Figure 4, we propose to restore ocular surface homeostasis as much as possible before surgery. Although there is no consensus, this may be achieved 3–4 weeks before surgery.[64] On an individual basis, ocular surface can be optimized by discontinuation of proinflammatory agents, reduction of the preserved eye drops (Consensus recommendation, R21), and reduction in the number of topical drugs being administered. Topical anti-inflammatory drugs, for example, a short course of "soft" corticosteroid, should be administered in cases where preventive and/or subtractive strategies are not possible (Consensus recommendation, R22). These recommendations apply to all surgeries or bleb-forming surgeries where the ocular surface is involved and excessive fibrose may impair surgical outcome. Although there is no previous recommendation on preoperative management of minimally invasive glaucoma surgery (MIGS), including Xen implants and tube-shun, one study proposed to use preoperative preservative-free medication to improve the wound healing process after Xen implants.[75]

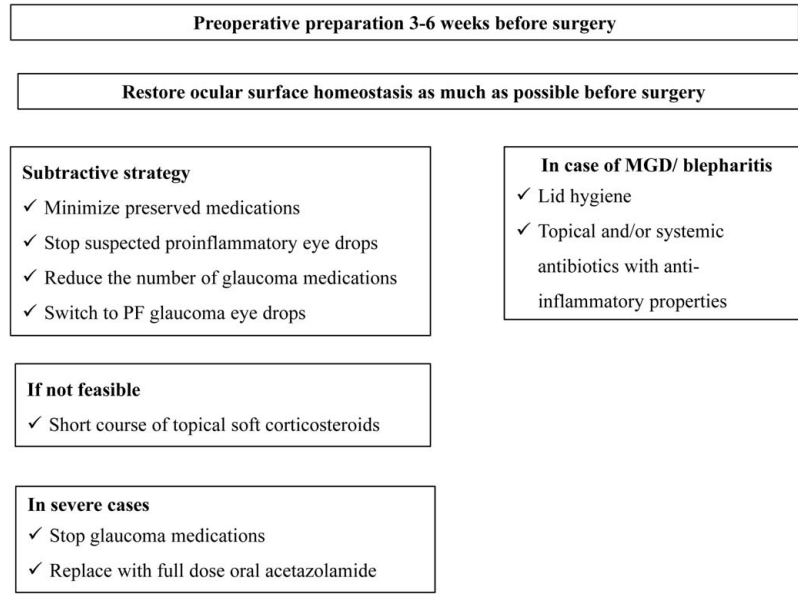


FIGURE 4. Treatment plan for patients with chronic ocular surface disease/inflammation and surgical intervention (preoperative management).

Although this was not discussed for a consensus, in cases of more severe OSD/OSI, we propose stopping all eye drops and to start oral acetazolamide. As required, lid hygiene and topical and/or systemic antibiotics with anti-inflammatory properties can be proposed (in line with the Consensus recommendation R18).

Impact on Deep Structure

The diffusion in deep tissues of inflammatory mediators present at the ocular surface, and/or the direct toxicity of the preservative on the trabecular meshwork are among the hypotheses to explain the association between OSD/OSI and uncontrolled IOP in glaucoma patients.[76,77] An accumulation of BAK has been found in the trabecular meshwork of patients treated with BAK-preserved medications for several years.[77] Overall, trabecular meshwork involvement as a result of iatrogenic inflammation may create a vicious cycle: an increase in medication, increases inflammation, increasing resistance to aqueous humor outflow, and requiring an increase in medication.[5] Although more research is still required to establish the association between OSD/OSI and inflammation in deeper eye structures in glaucoma patients, there is a consensus agreement for accurate diagnosis and treatment of OSD/OSI to reduce inflammation of the deeper eye structures (Consensus recommendation, R23). Removing BAK-preserved eye drops may also limit the inflammation of deeper eye structures (Consensus recommendation). The downstream parts of the outflow pathways, such as veins, collector channels, and episcleral veins were not discussed during the Delphi process. However, subconjunctival scarring and fibrosis may also involve downstream channels before surgery.

In conclusion, there is a consensus agreement that OSI may compromise corneal and conjunctival function and may adversely impact vision-related quality of life, adherence to treatment and thereby efficacy of the IOP-lowering therapy, and outcome of filtering surgery. The proposed clinical recommendations should facilitate the diagnosis of OSI not only in patients with pre-existing OSD, but in all glaucoma patients. The most effective preventive measure to limit OSI is to eliminate preserved medications, especially BAK-containing eye drops, where possible. In general, a subtractive rather than additive treatment strategy is effective in restoring ocular surface health while preserving or improving IOP control, and should be adopted. The proposed recommendations should help ophthalmologists in their practice.

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