

Prevalence and Severity of Blepharitis Symptoms and Signs amongst Patients with Age-Related Macular Degeneration

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Abstract

Purpose: It is recommended that prior to intravitreal injections, ophthalmologists identify and treat comorbidities that predispose a patient to endophthalmitis. Therefore, in populations that frequently receive intravitreal injections, such as patients with age-related macular degeneration (AMD), it is important to know the prevalence of these comorbidities. Blepharitis is a disease that is known to predispose to endophthalmitis, however, little is known on the rates of blepharitis within the AMD patient population. The purpose of this study was to determine the prevalence and severity of blepharitis amongst patients with age-related macular degeneration (AMD).

Methods: This IRB approved study included 50 patients (21 male, 29 female, age 78.1 ± 8.48 years) with both dry ($n = 21$) and wet ($n = 29$) AMD. Five common ocular surface symptoms and four clinical signs associated with blepharitis were evaluated. They were scored (0-4) by a self-reported survey and a blinded investigator performing a clinical examination. To compare the prevalence and severity of the symptoms and signs, total symptom and total sign scores were calculated and then normalized to the same scale of 0-10. The severity of symptoms and signs were then categorized as normal (0), mild (0.1-3.3), moderate (3.4-6.6), severe (6.7-10).

Results: In this AMD patient population, 32% had a history of dry eye or blepharitis prior to examination and 26% had a history of rosacea. Self-reported patient surveys and blinded investigator examinations both demonstrated similar-high prevalence of blepharitis. 14% of total patients reported no symptoms, and 6% had no clinical signs of blepharitis. Most patients had mild to moderate disease. The incidences were 50% and 36% for mild grade, 32% and 50% for moderate grade, and only 4% and 8% for severe grade, for the symptoms and signs of blepharitis, respectively. Self-reported symptom scores were generally lower than clinical examination scores.

Conclusions: Both the rate and severity of signs and symptoms of blepharitis are increased in the AMD patient population. Implications of these findings should be further studied in a larger series to determine its impact on endophthalmitis occurrence.

Introduction

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in adults in the developed world. AMD affected over 1.7 million people in US alone in 2004. Owing to the rapid aging of the population, the number is expected to increase to 3 million by the year of 2020 [1]. AMD is classified as either dry (nonexudative, atrophic) or wet (exudative, neovascular) form. Individuals with dry AMD typically experience a gradual visual reduction, while those with wet AMD often suffer a more precipitous and profound visual loss. Although most AMD patients (about 90%) have the dry form of disease, the wet form accounts for 80 – 90% of legal blindness rendered by AMD. [2]. The recent introduction of anti-vascular endothelial growth factor (VEGF) therapies, i.e. pegaptanib, ranibizumab and bevacizumab, has revolutionized the management of wet AMD. About 95% patients treated with ranibizumab showed visual improvement and stabilization [3,4]. However, in order to maintain the therapeutic effect, those patients may require frequent intravitreal injection, often monthly, over an extended period of time.

This tremendously increased frequency in intravitreal administration of therapeutic agents will likely result in a rise of its associated complications. Endophthalmitis is one of the devastating complications that physicians should actively avoid. It has been recommended that prior to intravitreal injections; the ophthalmologist should identify and treat patients with comorbidities that predispose to endophthalmitis, specifically patients with active blepharitis. These recommendations

originated from panel discussions to establish guidelines for intravitreal injections, and are followed in many randomized multicenter clinical trials, which notably include blepharitis as a contraindication to trial enrollment or treatment [5,6].

Blepharitis is an inflammation of the eyelid margins which can result in patient discomfort, decline in visual function and cosmetic distress. It is also known to be commonly associated with dry eye syndrome and rosacea. The etiology of blepharitis can be infectious (commonly caused by *Staphylococcus aureus*) or inflammatory. It is categorized as anterior or posterior. The former is most often a product of bacterial growth or sebaceous gland malfunction, whereas the latter is almost always associated with dysfunction of the meibomian glands (MGD). According to a 2008 Canadian consensus statement on the identification and management of blepharitis, staphylococcal bacteria

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were involved in both anterior and posterior blepharitis [7]. Physicians are aware that blepharitis is one of the most common disorders encountered in eyecare practice. [8] However; there is extremely little literature about the prevalence or incidence of blepharitis.

Blepharitis-associated staphylococcal colonization in the eyelids may pose a significant threat for endophthalmitis, a severe complication of intravitreal injections. As patients with age-related macular degeneration may be subject to frequent intravitreal injections, it is important to know how frequently this population develops blepharitis. The purpose of this study is to determine the prevalence and severity of blepharitis amongst patients with age-related macular degeneration (AMD).

Methods

This observational study was approved by the Cleveland Clinic Institutional Review Board (IRB). The clinical investigation was conducted in compliance with International Conference on Harmonization (ICH), Good Clinical Practices (GCP) guidelines, and other applicable guidelines and regulatory requirements.

The inclusion criteria were age greater than 18 years, of either sex, with either dry or active wet AMD, presenting to a retina specialist's office for routine eye evaluation. From February to July 2009, a total of 50 patients participated in the study, which included 21 male, 29 female, age 78.1 ± 8.48 years, with both dry (n = 21) and wet (n = 29) AMD. The written informed consent was obtained prior to any study related procedures were performed.

A self-reported survey was designed to evaluate and score (0-4) the frequency and severity of five common symptoms associated blepharitis reported by patients (Table 1). Subjects were also asked whether they had any history of rosacea, atopic conditions, dry eye syndrome or blepharitis. Current ophthalmic medications were also recorded. All findings were subject to the accurate recall of the participants.

Each participating patient was also seen in a clinical setting by a blinding ophthalmologist investigator, and the ocular surface signs of blepharitis (Table 2) were assessed with slit lamp biomicroscopy and the severity was scored on a range of 0-4.

Total symptom and sign scores were also calculated and normalized

Eyelid itching		
Do your eyelids feel itchy?		
(0)	None:	My eyelids do not feel itchy.
(1)	Mild:	Once in a while, my eyelids feel slightly itchy, but I do not have a desire to rub them.
(2)	Moderate:	Occasionally, my eyelids feel itchy, and I need to rub them.
(3)	Severe:	It is difficult to relieve the sensation of itchiness even when I rub my eyelids.
(4)	Very severe:	I have unbearable eyelid itching with an irresistible urge to rub my eyelids.
Foreign body sensation/sandiness, grittiness		
Do you feel like there's something sandy or gritty in your eye?		
(0)	None:	My eyes do not feel sandy or gritty.
(1)	Mild:	I am aware of the surface of my eyes once in a while.
(2)	Moderate:	My eyes feel like there is something small in them occasionally.
(3)	Severe:	My eyes feel like there is something large or gritty in them.
(4)	Very severe:	I am unable to open my eyes due to feeling of a foreign body in my eyes.
Ocular dryness		
Are your eyes feeling dry?		
(0)	None:	My eyes do not feel dry.
(1)	Mild:	I am aware of dryness to the point where I have to blink to feel better
(2)	Moderate:	I am aware of dryness to the point where I desire to use artificial tears occasionally.
(3)	Severe:	I am aware of dryness to the point where I desire to use artificial tears frequently.
(4)	Very severe:	I am aware of dryness, to the point where I always desire to use artificial tears.
Ocular burning or pain		
Are your eyes burning or painful?		
(0)	None:	My eyes do not burn or ache.
(1)	Mild:	I am aware of the surface of my eyes; they mildly burn or ache.
(2)	Moderate:	I feel my eyes are burning, but still tolerable
(3)	Severe:	My eyes feel throbbing or fiery due to burning/pain.
(4)	Very severe:	I am unable to open my eyes due to burning/pain.
Swollen/heavy eyelids		
Do you feel like your eyelids are heavy or swollen?		
(0)	Normal:	I don't feel that my eyelids are heavy/swollen.
(1)	Mild:	I feel that my eyelids are mildly heavy/swollen.
(2)	Moderate:	I feel my eyelids are heavy/swollen, but I can tolerate it.
(3)	Severe:	I feel my eyelids are heavy/swollen, I like to close my eyes for a few minutes.
(4)	Very severe:	I feel my eyelids are heavy/swollen and have to make an effort to keep my eyes open.

Table 1: Questionnaire for the Symptoms of Blepharitis.

Lid Debris (collarettes, clumps/strands) – upper and lower eyelids		
(0)	Normal:	Clear eyelid margin
(1)	Mild:	Occasional fragment, 1-5 collarettes
(2)	Moderate:	Few fragments, 6-20 collarettes
(3)	Severe:	Many fragments, 21-40 collarettes
(4)	Very severe:	Clumps/strands, >40 collarettes
Eyelid Margin Erythema (lower eyelid)		
(0)	Normal:	Normal age-related redness and vasculature.
(1)	Mild:	Slightly dilated blood vessels; vessels colored pink; present in the middle 2/3 section of the lower eyelid margin.
(2)	Moderate:	More apparent dilation of blood vessels; vessel color more intense, whole margin of the eyelid is involved.
(3)	Severe:	Increased vascularity of the eyelid margin, numerous and obvious dilated blood vessels, deep red in color, whole margin of the eyelid is involved.
(4)	Very severe:	Clearly increased confluent vascularity of the eyelid margin; large, numerous dilated blood vessels characterized by deep red color, whole margin of the eyelid is involved.
Plugging of the Meibomian Gland (in the middle part of lower lid, n=10)		
(0)	Normal:	Clear orifices of meibomian glands in the middle part of lower lid (n=0)
(1)	Mild:	Less than 1/3 of orifices but at least one contain turbid secretions (n=1-3)
(2)	Moderate:	Between 1/3 and 2/3 of orifices contain turbid secretions (n=4-6)
(3)	Severe:	More than 2/3 of orifices but not all contain turbid secretions (n=7-9)
(4)	Very severe:	All orifices plugged with turbid or coagulated secretions (n=10)
Secretion Expressed from the Meibomian Gland (lower eyelid)		
(0)	Normal:	Minimal clear, oily secretion
(1)	Mild:	Cloudy secretion
(2)	Moderate:	Granular secretion
(3)	Severe:	Paste-like secretion
(4)	Obstructed:	No expressible secretion

Table 2: Investigator-rated Assessment of Blepharitis Signs.

Ophthalmic Medications Used	Number of Patients
None	29
Artificial Tears	18
Glaucoma Drops	4
Over The Counter Allergy Drops	1

Table 3: Usage of ophthalmic medications during the study.

to a scale of 0-10. Severity of symptoms and signs were then categorized as normal (0), mild (0.1-3.3), moderate (3.4-6.6), severe (6.7-10). The incidence and severity of blepharitis symptoms and signs were calculated and compared.

Results

In this patient population with AMD, 32% had a history of dry eye or blepharitis prior to examination and 26% had a history of rosacea or atopic conditions. During the period of study, 29 patients (58%) were not on any kind of topical ophthalmic medications. Eighteen patients (36%) were using artificial tears, and four patients were using no more than two kinds of topical glaucoma drops. And only one patient was using over-the-counter allergy eye drops (Table 3).

Prevalence and severity of subjective symptoms of blepharitis

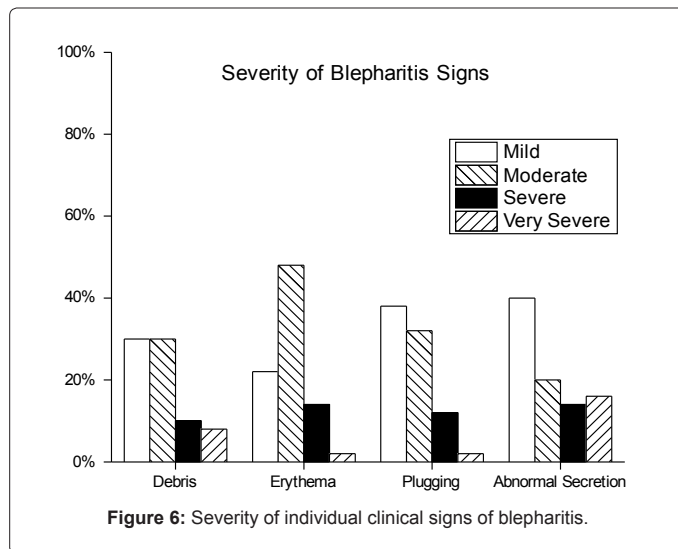
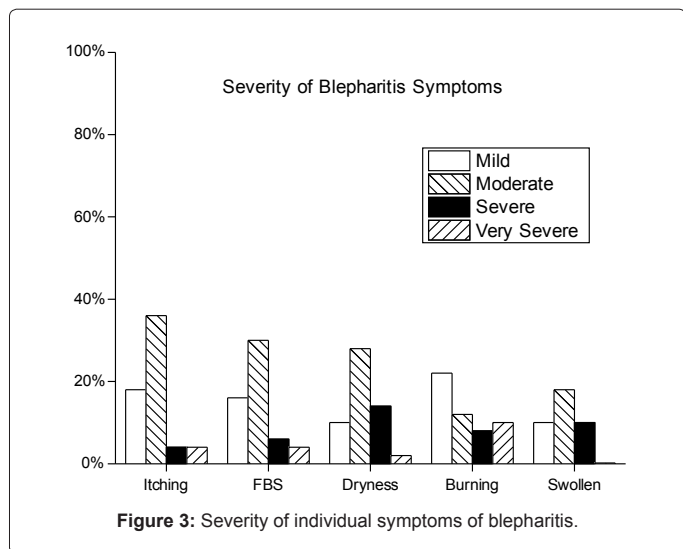
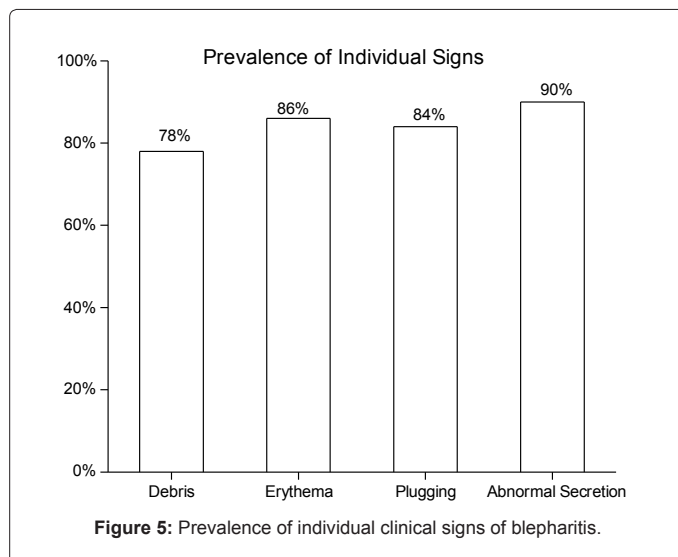
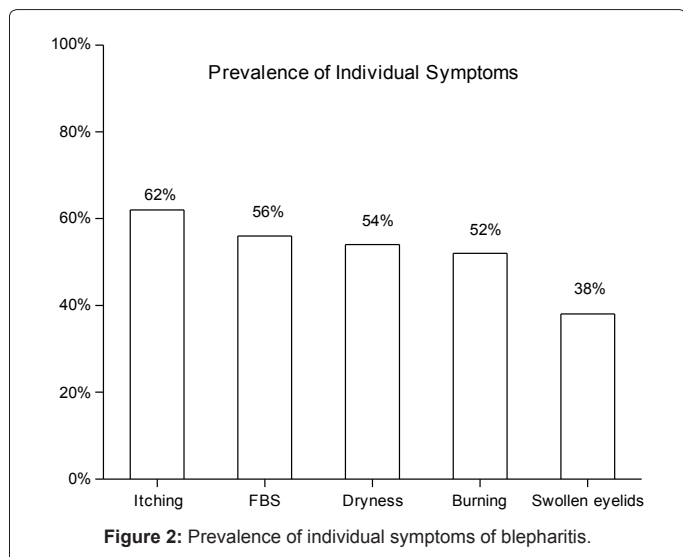
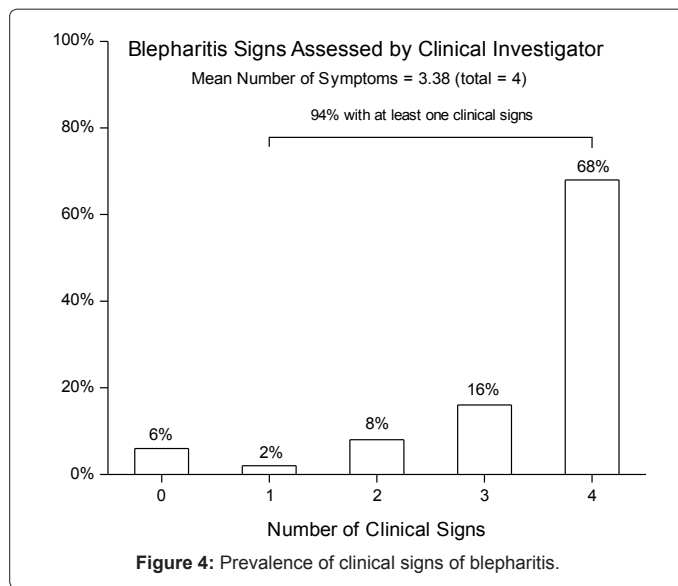
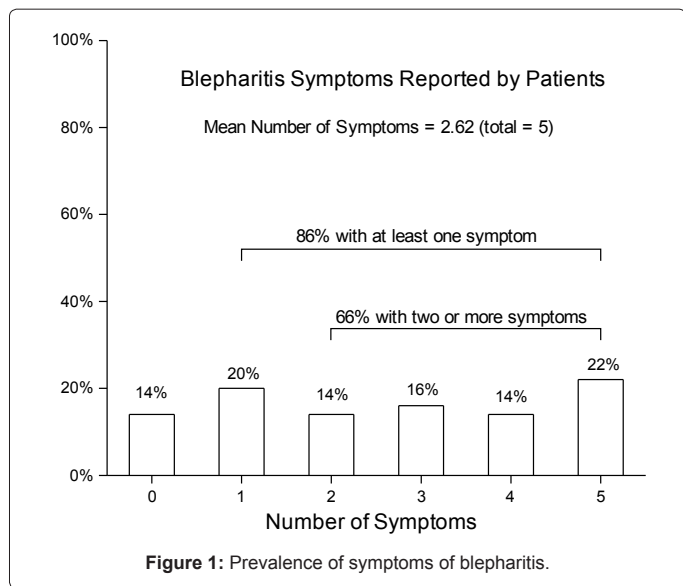
Self-reported patient surveys showed that among respondents, 86% reported experiencing at least one of the symptoms and 66% reported more than one symptom (Figure 1) at the investigation time. Mean number of symptoms experienced is 2.62 out of a total of 5 symptoms. The most commonly reported symptom was eyelid itching, and the least common symptom was swollen or heavy eyelids (Figure 2). The severity of individual blepharitis symptom was usually in the mild to moderate range (Figure 3).

Prevalence and severity of clinical signs of blepharitis

Blinded clinical evaluation demonstrated similar findings with a high prevalence of blepharitis in participating AMD patients. About 94% had at least one of the clinical signs blepharitis and 92% showed more than one clinical sign (Figure 4). Mean number of signs found is 3.38 out of a total of 4 signs. The most common finding was abnormal secretion expressed from the Meibomian gland, and the least common sign was lid debris (Figure 5). The severity of individual clinical sign were also usually in the mild to moderate range (Figure 6).

Comparison of the prevalence and severity of blepharitis symptoms and signs

Self-reported patient surveys and blind investigator examinations demonstrated similar-high prevalence of blepharitis (86% and 94% respectively) (Figure 1 and Figure 4). The prevalence of clinical findings was slightly higher than that of self-reported symptoms. Fourteen percent of total patients reported no symptoms, and six percent had no clinical signs of blepharitis. Normalized data demonstrated that most patients had mild to moderate disease based on both symptoms and clinical exam findings (Figure 7). The incidences were 50% and 36% for mild, 32% and 50% for moderate, and only 4% and 8% for severe symptoms and signs of blepharitis, respectively. The comparable



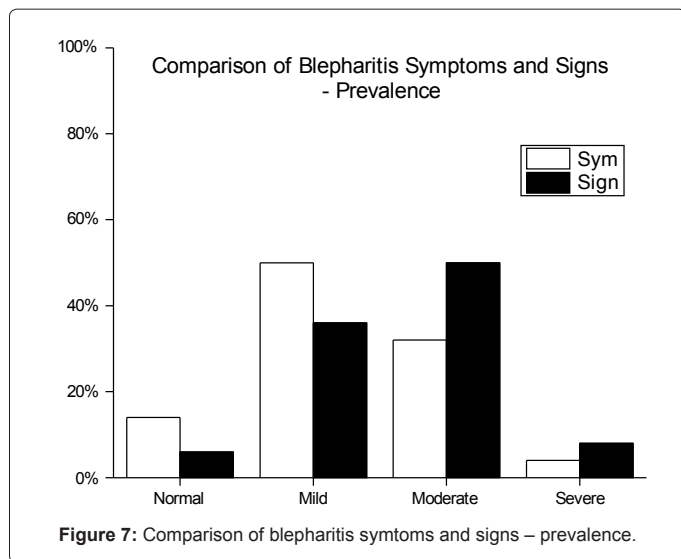


Figure 7: Comparison of blepharitis symptoms and signs – prevalence.

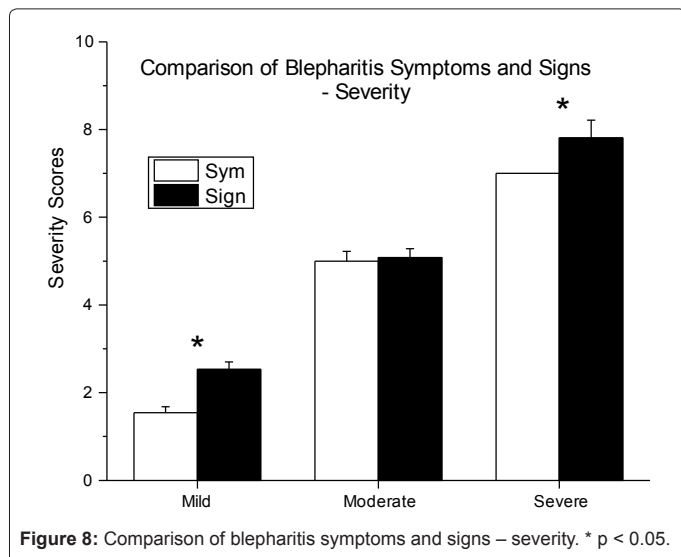


Figure 8: Comparison of blepharitis symptoms and signs – severity. * p < 0.05.

severity scores of blepharitis symptoms and signs are shown in Figure 8. Self-reported symptom scores (2.65 ± 2.16) were generally lower than clinical examination scores (4.08 ± 2.06) ($p < 0.001$, paired t-test).

Discussion

The purpose of this study was to determine the prevalence of disease in the AMD patient population, and to further determine the impact, if any, this would have on clinical trial recruitment for studies utilizing intravitreal injections. Based on self-reported findings and investigator exam findings, the prevalence of blepharitis is high in the AMD patient population. This is significant due to the frequent intravitreal injections commonly used in the management of these patients. Additionally, most of the symptoms and clinical findings were classified as mild or moderate. This is the first reported prevalence numbers for this age group and diagnosis.

Self-reported symptoms were generally less severe than clinical findings. We hypothesized that this may be partly attributed to

the acceptance of ocular insults as part of normal aging by older individuals. In addition, blepharitis and dry eye disease are chronic conditions and it is quite possible that while symptoms may remit and relapse, the clinical signs would remain even when symptoms were not prominently reported.

Regarding the prevalence of blepharitis, there is little data available on this subject despite clinical awareness that blepharitis is one of the most common disorders encountered in ophthalmologic practice. In the survey by Lemp and colleagues of 5019 adults, 79% reported at least one symptom which was verified in our patient series (86%).⁸ The percent of patients reporting two symptoms was 63%; similar to the 66% we obtained in our study. Interestingly, when stratified by age, Lemp reported lower percentage of patients manifesting symptoms as the age increased (83% in patients 18-49 years old versus 70% of patient 65 and older), but this was not found in our series (86% reported at least one symptom with average age of 78.1 years). This might partially be due to selection bias given that our patients were derived from an ophthalmology clinic while Lemp's data was derived from a randomized phone system in patients with and without ocular disorders. For the purposes of potential AMD patients requiring intravitreal injections, our population is likely more relevant for testing the hypothesis than the population tested in the Lemp study.

This is the first study to confirm that the clinical signs and symptoms of blepharitis are highly prevalent in patients with age related macular degeneration. Whether these findings lead to a higher risk of endophthalmitis following intravitreal injection cannot be confirmed in this report. Further studies utilizing a larger study population should be conducted to determine whether AMD patients with symptoms and signs of blepharitis have an associated higher risk of endophthalmitis following injections.

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