maculogix
the AMD experts

Practical Guidelines for the Treatment of Nonexudative AMD

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A Comment on These Guidelines

Over the past fifteen years, tremendous advances have been made in the detection and treatment of age-related macular degeneration (AMD). Numerous peer-reviewed scientific papers are published every month, covering a broad range of topics ranging from epidemiology to treatment. Although the expanded knowledge is welcome news, the information overload has made it difficult for clinicians to keep up with the science, much less understand the implications for patient care. To address this need, MacuLogix assembled a clinical advisory board that includes leading educators and private practice clinicians with large AMD practices. The advisory board was charged with the task of developing practical, evidence-based guidelines that can be implemented in a medically-oriented practice.

The following recommendations represent a consensus opinion and are not exclusionary of different approaches. The goal here was to develop a treatment algorithm that would be beneficial to all patients and was broadly agreed upon by all clinicians because it is evidence-based.

Goal of AMD Management

The goal of managing AMD is to preserve visual function, including but not limited to visual acuity.

To achieve this goal, proper early detection, diagnosis, monitoring, and treatment must be practiced. Currently, doctors are too passive when diagnosing and treating nonexudative AMD.[1–3] Nonexudative AMD is often not diagnosed until the patient presents with drusen and visual acuity loss. By this criterion, the patient likely has had the disease for years. The patient has lost some of the potential benefits of treatment. The patient is at higher risk of central visual loss, especially in the first eye that progresses to choroidal neovascularization (CNV).[4,5] Because there is no cure for AMD, the goal is to halt or slow the disease progression. Earlier detection allows earlier treatment, which leads to better patient outcomes. With proper care, significant visual acuity loss may be prevented in many patients.

The Importance of Visual Function in Nonexudative AMD Diagnosis

AMD is often missed upon routine clinical examination. A recent study found that 25% of patients referred to a clinical study as having normal retinal health, in fact, had clinically evident AMD based upon fundus photography that was not identified by the primary care provider.[6] As previously mentioned, many doctors will not diagnose nonexudative AMD until there is visual acuity loss. Drusen may be found and documented on clinical examination, but the diagnosis of AMD is often not made.

Why is there hesitation to diagnose AMD? One cause of indecision stems from the understanding that not all drusen are caused by AMD, while others are based on assumptions about what the patient will do after the diagnosis is made. For example, if a patient is told that she has AMD but she has no symptoms, will the patient be compliant with care? Perhaps she won't. However, we can easily assume that if a patient is not told that she has AMD, then she surely will not make changes or take steps to be compliant with her care. We have witnessed a similar challenge in the management of glaucoma, because the patients do not generally experience symptoms, such as visual function loss, until very late in the disease.

Most doctors find that when they can point to a symptom of disease, patients are more motivated to be compliant. Consider the following examples:

1. **"Mrs. Smith, you have age-related macular degeneration. Fortunately, it is not affecting your vision. My treatment plan is …"**
2. **"Mrs. Smith, the reason that you are having difficulty reading is because you have age-related macular degeneration. My treatment plan is…"**

The second option is superior and will more likely result in better patient compliance. The measurement of dark adaptation speed can further address these issues. Dark adaptation impairment has been found to be highly sensitive and specific for the detection of AMD. The accuracy of using impaired dark adaptation to identify AMD is 90%.[7] Thus, dark adaptation can be used as part of the differential diagnosis to understand whether the drusen noted are likely caused by AMD.

This characteristic dark adaptation impairment occurs very early in the disease process. Dark adaptation impairment can be present up to three years before the disease can be detected by clinical examination or retinal imaging.[8] This provides the clinician the opportunity to treat the disease earlier and increase the probability of halting or slowing progression of the disease. Because the patient's dark adaptation is abnormal, the frequent complaint of difficulty with night vision may be used to enhance compliance to care. For example:

3. **"Mrs. Smith, the reason that you have difficulty driving at night is because you have age-related macular degeneration. Our goal now is to prevent central vision loss or other visual function deficits. My treatment plan for you is…"**

Patients with AMD express difficulty with their night vision and specifically driving at night.[9,10] Patients understand that they have a functional deficit or symptom caused by AMD and are eager to save their central vision.

Subclinical AMD

A new stage of AMD has been identified, named subclinical AMD. Subclinical AMD was identified by histopathological and clinical research, which found that AMD has structural and functional consequences before drusen are clinically evident. Histopathological studies have shown that the retinal pigment epithelium (RPE) cells deposit locally generated cholesterol beneath the RPE cell layer and in Bruch's membrane before drusen are formed.[11] These lesions were first identified in donor eyes using an electron microscope. With disease progression, cholesterol continues to accumulate, resulting in focal areas that are sufficiently thickened to be identified as drusen. Thus, drusen caused by AMD are the tip of an iceberg of the earliest lesions caused by AMD. More dysfunction is present than would be concluded simply on the appearance of drusen.

This cholesterol accumulation causes three primary insults to the retina — inflammation, oxidative stress, and disruption of oxygen and nutrition supplied to the outer retina. One functional aspect of the role of nutrients in AMD that has been proven to be disrupted is vitamin A transport.[10] Vitamin A is critical for rod-mediated dark adaptation. Disruption of vitamin A availability dramatically slows dark adaptation. Increased disease severity is correlated with increased dark adaptation impairment.[12,13] It has been shown that the dark adaptation impairment can be detected before AMD is clinically evident.[8] If histopathology were to be performed on a patient over the age of 50 years with no other comorbid diseases and impaired dark adaptation, subclinical lesions associated with AMD would likely be found. Thus, dark adaptation is a functional marker of subclinical AMD.

Improved understanding of the histopathology of the disease, combined with a thorough understanding of its functional consequences provide several clinically useful observations. First, AMD manifests itself before drusen are visible through impaired dark adaptation, which is expressed by the patient as night vision difficulties. Thus, impaired dark adaptation is the first detectable consequence of AMD and can be used to identify patients with subclinical disease. Patients with impaired dark adaptation and small drusen have AMD because the appearance of any drusen is a consequence of previously undetectable lesions revealing themselves. Dark adaptation can be used to evaluate whether small drusen are focal deposits or the visible tips of the lesions caused by AMD. Evaluating structure and function together provides the clinician with improved diagnostic accuracy and the opportunity to treat the disease earlier than by use of structure alone.

Nonexudative AMD Diagnosis and Staging

The gold standard for the diagnosis and staging of nonexudative AMD is the use of a grading system developed for epidemiological studies and clinical trials. These grading systems rely on careful inspection of three-field stereo-fundus photographs to grade the presence of drusen and/or pigmentary changes. For a variety of reasons, these systems have not been widely adopted in primary eye care. A thorough understanding of AMD pathogenesis suggests that diagnosing and staging AMD should rely on both structure and function. Thus, the Practical Guidelines use structure and function to assist with AMD diagnosis and staging.

The Beckman Initiative for Macular Research published a classification system designed for use in a primary care setting.[14] The Practical Guidelines presented here are a modification of the Beckman system. The Beckman system is based solely upon structural findings; whereas the Practical Guidelines are based upon the structural findings and augmented by functional findings such as the dark adaptation status. The Practical Guidelines differ from the Beckman system in the following ways: (1) The system defines a disease stage named subclinical AMD, which is the stage at which abnormal dark adaptation is present in the absence of drusen and/or RPE pigmentary changes. (2) The definition of early AMD is expanded. The Beckman system requires medium drusen for a diagnosis of AMD; whereas, the Practical Guidelines includes small drusen when the dark adaptation impairment is present. In addition, the Practical Guidelines include RPE pigmentary abnormalities in the presence of dark adaptation impairment, whereas the Beckman system does not consider pigmentary abnormalities for the definition of early AMD. The two systems have identical definitions for intermediate and advanced AMD.

AMD classification

Normal

- ☐ Absence of drusen
- ☐ Absence of RPE pigmentary abnormalities
- ☐ Normal dark adaptation

Subclinical AMD

- ☐ Absence of drusen
- ☐ Absence of RPE pigmentary abnormalities
- ☐ Abnormal dark adaptation

Early AMD

- ☐ Absence of drusen
- ☐ Presence of RPE pigmentary abnormalities
- ☐ Abnormal dark adaptation

– OR –

- ☐ Presence of small or medium drusen
- ☐ Absence of RPE pigmentary abnormalities
- ☐ Abnormal dark adaptation

– OR –

- ☐ Presence of medium drusen
- ☐ Absence of RPE pigmentary abnormalities

Intermediate AMD

- ☐ Presence of medium drusen
- ☐ Presence of RPE pigmentary abnormalities

– OR –

- ☐ Presence of large drusen

Advanced AMD

- ☐ Presence of choroidal neovascularization (CNV)

– OR –

- ☐ Presence of geographic atrophy (GA)

Notes: Retinal area to be examined: The area to be examined is roughly within a two-disk diameter radius around the fovea.

Drusen size: Small drusen are less than 63 microns in diameter. Large drusen are 125 microns or greater in diameter. Medium drusen fall in between. One-hundred twenty-five microns is roughly equal to the width of the central retinal vein crossing the optic disk. Thus, large drusen diameter is equal to or greater than the width of the vein. Small drusen diameter is roughly a quarter the width of the vein or smaller.

Treatment

Currently, there is no cure for AMD. Anti-VEGF therapy used for the treatment of CNV may not be durable over the long term for some patients. Patients on long-term anti-VEGF therapy have an elevated risk of vision loss caused by progression to GA.[15] Thus, the management of AMD has two primary goals, both aimed at preserving vision: (1) prevent progression to advanced AMD (GA or CNV) and (2) effectively detect and manage CNV. Achieving these goals will allow the patient to enjoy additional years of high quality central vision, enhancing the odds of a better quality of life. With increased life expectancy and earlier age of AMD disease onset, it is reasonable that a patient may have the disease for ten, twenty, or thirty years after initial diagnosis. Early diagnosis and consistent, aggressive management of the disease is required to minimize risk of vision loss.

Much of AMD treatment is based on modifying risk factors, such as smoking, diet, light exposure and other lifestyle contributors. There are, however, non-modifiable risk factors that still should be considered — namely genetics. Although we can't do anything to alter a patient's genetics currently, we need to realize that, moving forward, outcomes are largely influenced by genes. At the very least, knowing a person's family history can help influence the treatment course. For example, knowing a family member had a poor outcome may help motivate a patient to more closely follow recommendations.

Based upon our current understanding of AMD pathogenesis, the stages of subclinical, early, and intermediate AMD all represent different clinical manifestations of the same underlying disease process. Thus, the treatment of the disease should be initiated at first detection, regardless of the stage. The following treatment recommendations apply to patients with all stages of AMD.

Treatment recommendations

- Prescribe smoking cessation programs
- Prescribe nutritional supplementation
- Discuss lifestyle modifications with respect to diet and exercise
- Systemic disease management
- Prescribe blue light protection
- Prescribe UVA and UVB sunglasses protection for outdoors

Smoking cessation

Smoking is the largest modifiable risk factor for the progression of both CNV and geographic atrophy.[16] Current smokers carry a 2.5 to 4.8 times higher risk than non-smokers for late AMD.[17] Former smokers show less risk of development of late AMD than current smokers, in a dose-dependent relationship. Although this risk has been demonstrated in multiple studies worldwide, smoking cessation has not been widely emphasized by primary eye care providers. In one study, ninety percent of patients with AMD were not advised to stop smoking.[18] Fewer than half of smokers know that smoking may contribute to blindness even though this fact is an effective motivator for smoking cessation.[19] Encouraging smoking cessation is the best method to reduce risk of central vision loss.

Nutritional supplementation

No topic in the management and prevention of nonexudative AMD causes more controversy than nutritional supplementation strategies. Evidence strongly suggests that patients should be prescribed nutritional supplements because, on average, treated patients have better outcomes than untreated patients.[20–22] The reasons

for improved outcomes include both the beneficial effects of the supplements themselves as well as increased compliance with care. Based on the clinical experience of the authors, a patient who is prescribed therapeutic intervention is more likely to be compliant with their follow-up monitoring visits than a patient who is not prescribed treatment. More frequent visits provide the eye care provider with more opportunities for early detection of progression — e.g. development of CNV — and prompt intervention when indicated. The Practical Guidelines treatment protocol is designed to reduce the risk of progression of the disease, but periodic clinical examination is essential to allow detection of treatable CNV.

The Practical Guidelines recommend nutritional supplementation for all stages of AMD. There are three primary options for the selection of an appropriate nutritional supplement. The first option is to prescribe a macular pigment supplement (the xanthophylls: lutein, zeaxanthin, meso-zeaxanthin). The second option is to prescribe a supplement containing both xanthophylls and antioxidants, including zinc and vitamins E and C (e.g. an AREDS2 supplement). The third option is to prescribe a xanthophyll supplement to patients with subclinical and early AMD, and a xanthophyll-antioxidant combination supplement to patients with intermediate AMD or patients that progress to intermediate AMD. The relative merits of each option are debatable, and knowledge continues to expand about the many factors that contribute to AMD progression. However, it is reasonable to conclude that it is better to prescribe a supplement than not prescribe a supplement.

Lifestyle modifications with respect to diet and exercise

Following a healthy diet, exercising regularly and maintaining overall health are sound goals for all patients.[22] These lifestyle choices may act synergistically to prevent or delay onset or progression of AMD. One study found that women who followed a healthy diet, engaged in physical exercise, and avoided smoking had substantially lower risk of early AMD compared with women who did not follow these healthy lifestyles.[23] Epidemiological evidence supports the following risk-reduction recommendations:

Omega-fatty acids: Epidemiological studies have found substantial benefit from higher dietary intake of essential fatty acid-rich foods, especially DHA, found in many species of fish.[24] Doctors should recommend that patients consume fish rich in DHA and/or supplement with high quality, highly bioavailable omega-fatty acid products.

Mediterranean diet: This diet includes high intake of fruits, legumes, vegetables, nuts, seeds, and other grains; olive oil as the main source of monounsaturated fat; dairy products, fish, poultry, and wine in moderate amounts; and limited intake of red and processed meats. Studies suggest that subjects who regularly consume a Mediterranean-like diet carry an overall lower risk of development of advanced AMD as compared to those who regularly consume a traditionally Western diet.[25] A recommendation should be made that patients avoid traditionally "Western" dietary pitfalls (high glycemic index foods, high fat dairy products, fried foods, and processed meats), and instead, follow healthier eating styles like the Mediterranean diet.

Exercise: An active lifestyle has been shown to reduce the risk of progression to CNV.[26–28] For those who participated in cardiovascular exercise of any intensity three or more times per week, the incidence of CNV was reduced by 33 percent. For individuals who walked one or more blocks per day, the incidence of CNV was half compared with those who walked less than one block per day.[27] These levels of physical activity are achievable by almost all patients.

Treatment (continued)

Systemic disease management

Several systemic conditions carry an increased risk of the development of AMD, based on epidemiological studies. Cardiovascular disease, diabetes, hypocholesteremia, and obesity have all been associated with increased risk of AMD and/or progression of AMD.[26,29–31] Body mass index and abdominal obesity are independent risk factors for progression to advanced AMD.[26] Unquestionably, good clinical practice mandates management of systemic disease for all patients, which at a minimum includes screening and subsequent referral to appropriate health care professionals. Discussion with your patient regarding the connection between risk of vision loss and any comorbid systemic diseases may enhance adherence to prescribed care regimens.

Retinal light protection

Epidemiological evidence suggests that chronic sunlight exposure increases the risk of incident AMD and its progression.[32] Randomized clinical trials are impractical to evaluate the efficacy of protective lenses. High energy visible light (HEVL) blocking (sometimes referred to as Blue-light blocking) intraocular lenses have been widely implanted for over a decade even though the protective properties of these lenses have not been systematically evaluated. One interesting observational study found reduced progression of geographic atrophy in patients who had blue-blocking intraocular lenses implanted.[33] Likewise, there may be a potential benefit of protective eyewear. Protective eyewear has a couple of advantages over blue-blocking intraocular lenses. First, the amount of tint can be made task appropriate (e.g. a darker tint for driving), and second, eyewear is removable should the patient choose to discontinue use. Prescribe full spectrum UV protection for patients and consider HEVL-blocking eyeglass lenses, which are becoming more widely available and affordable.

Monitoring

For a patient with AMD, more frequent retinal examinations are recommended. Moving from a twelve-month follow-up interval to a six-month follow-up interval may be useful for monitoring disease progression.[34] More frequent visits provide the clinician increased opportunity to detect CNV before visual acuity loss. Often, home monitoring by Amsler grid is ineffective or the patient defers reporting symptoms between office visits. The follow-up visit interval may be shortened to every three or four months for patients who are progressing rapidly or are at high risk of CNV.

Concluding Remarks

These recommendations form a solid foundation for caring for patients with AMD. These practical guidelines also may be augmented in practices where personalized medicine or more complex approaches to supplementation are routinely employed. However, the advisory board concluded that such methods are still being researched in clinics and require more evidence before a consensus opinion can be reached.

The guidelines will be periodically reviewed and updated as warranted by new evidence that clarifies best practices for the treatment of nonexudative AMD.

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MacuLogix is the only company to equip eye care professionals with the instrument, tools and education needed to effectively manage patients with AMD. By leveraging the science of dark adaptation through its AdaptDx, MacuLogix is working to eliminate preventable blindness caused by AMD, a chronic, progressive disease that impacts over 170 million people worldwide and goes undiagnosed in 25 percent of patients. Through its AdaptDx dark adaptation biomarker, MacuLogix enables eye care professionals to detect, monitor and treat AMD three years before it can be seen clinically. MacuLogix provides in-practice training and treatment best practices to support the implementation and optimization of the AdaptDx.