Guidelines for the Collaborative Management of Persons with Age-Related Macular Degeneration by Health- and Eye-Care Professionals

BACKGROUND

Age-related macular degeneration (AMD) is the most common cause of severe visual impairment in adults in the developed world. Statistics released by the CNIB report that AMD now represents more than 50% of new referrals to their organization.[1] Considered in light of the growing incidence and prevalence of this disease and an aging population, AMD poses a major public health challenge.

As its name suggests, AMD is an age-related degenerative disease affecting approximately 1.5% of Canadians by age 40 years, rising to affect a full 25% of society by age 75. It begins with the development of drusen, yellowish deposits of waste material within the macula. This gradually progresses with advancing age and may result in the loss of central (detail) vision. Such progression ultimately affects a person's ability to read, drive, and perform many other activities of daily living.[2] AMD is typically divided into two forms:

1. Non-exudative or dry AMD, which affects approximately 85% of patients with AMD, but typically progresses slowly and causes less visual impairment.

2. Exudative or wet AMD affects approximately 15% of patients with AMD, but is responsible for greater visual impairment that can occur within weeks or months of development.

The Age-Related Eye Disease Study (AREDS) defined four categories of AMD, summarized as follows [3]:

AMD CLASSIFICATION AS PER AREDS

AREDS category 1 – no AMD

AREDS category 2 – early AMD: small and intermediate drusen, little or no pigment epithelial abnormalities, generally normal central visual acuity

AREDS category 3 – intermediate AMD: extensive intermediate drusen or ≥1 large drusen, geographic atrophy (GA) not involving the center of the macula

AREDS category 4 – advanced AMD: neovascular (wet) AMD or GA involving the center of the macula, visual acuity is usually affected, may have one or more zones of well-defined retinal pigment epithelium atrophy, drusen and other pigmentary abnormalities surrounding atrophic areas, choroidal neovascularization (CNV), serous and/or hemorrhagic detachment of the retinal pigment epithelium (RPED), disciform scarring

AMD has been clearly shown to have a strong genetic component.[4] This confers higher risk upon individuals with first-degree relatives who have AMD.[5,6] Several genotypes have been detected that result in a significantly higher risk for the development of late-stage dry and wet AMD.[7] In addition, several studies have shown a clear relation between smoking and the progression of AMD to the exudative form.[8,9]

In the Beaver Dam Eye Study, approximately 22% of patients with advanced wet or dry AMD in one eye developed advanced wet or dry AMD in the fellow eye within five years, while in the Age-Related Eye Disease Study, subjects with advanced AMD in one eye or vision loss due to non-advanced AMD in one eye had a 43% probability of progressing to advanced AMD in the fellow eye at five years.[10] The AREDS data also indicate that the probability of intermediate AMD progressing to advanced AMD is approximately 18% within five years.

Although visual loss from dry AMD cannot be prevented at this time, clear evidence for the benefits of early detection and intervention exists. [11-14] AREDS showed a modest but statistically significant benefit (20–25% risk reduction) to patients with intermediate AMD in one or both eyes who received high daily doses of supplements containing a combination of antioxidant vitamins and minerals (see Appendix 1A). In doing so, this landmark study provided the foundation for early intervention.[12–14]

AREDS2 examined the benefit of omega-3 fatty acid supplementation, the effect of lutein and zeaxanthin, and the impact of reducing zinc in the original AREDS formulation.[12,13] Results of this study were comparable to the original study, showing that no additional benefit was realized in adding lutein and zeaxanthin or omega-3 fatty acids to the original formulation, but that lutein and zeaxanthin could be substituted for beta carotene (which may increase the risk of lung cancer in smokers or recent ex-smokers), with no loss of effectiveness. Effects (and side effects) of low- and high-dose zinc were similar (see Appendix 1B).

Extrapolating even a modest treatment effect in a disease as common as AMD provides significant public health benefit. That being said, these treatment benefits can only be attributed to supplements identical to the AREDS or AREDS2 formulations taken at the appropriate dosages, and caution must be exercised with accruing benefit to any other (even comparable) formulations and/or dosages. Practitioners should be aware that some controversy has recently arisen around AREDS/AREDS2 supplementation and the role of tailoring treatment on the basis of individual genetic profiles. Staying abreast of the current literature is of critical importance to ensure excellence in patient care.[12,13]

Although no cure for wet AMD currently exists, several studies clearly demonstrate that visual loss from wet AMD is best prevented through early detection and intervention.[12,13] These interventions include the use of thermal laser, photodynamic therapy (PDT) with verteporfin, and intravitreal injections with agents currently including ranibizumab, bevacizumab, and aflibercept.[12–16] As the population ages and the demand for AMD screening, intervention, post-intervention monitoring, and intra- and post-intervention visual rehabilitation grows exponentially, eye care providers will face growing challenges in the management and coordination of care for patients with AMD. The delivery of eye care must provide cost-effective and efficient use of resources to minimize preventable vision loss.

Even after optimum treatment, the associated vision loss in moderate and advanced AMD leads to disability (inability to undertake desired tasks because of vision) and impacts on quality of life. Visual impairment is associated with increased risk to the individual in six main categories (National Coalition for Vision Health, 2011):

i. Functional decline (e.g., activities of daily living, driving, reading, walking)

ii. Dependency (e.g., nursing home placement, long-term care admission, being a burden on family members and caregivers, loss of employment, loss of privacy, decreased income)

iii. Injury and accidents (e.g., falls and fractures, driving accidents, pedestrian injuries)

iv. Social isolation (e.g., reduced social participation, social withdrawal, loneliness) and emotional distress (e.g., depression, grief, anger, diminished sense of control)

v. Increased morbidity (lower quality of life, increased suicide rates, increased risk of mortality, increase of comorbidities)

vi. Increased risk to others and society (public health burden, burden on family)

Vision rehabilitation reduces the disability, thereby striving to ameliorate these broad impacts. It involves a functional assessment, followed by interventions that may include low- and high-technology devices for magnification, tints, environmental modifications, training to optimize the use of eccentric vision (after central vision loss), non-optical devices for daily living skills, orientation and mobility training, counselling, and support. The aim is to enhance remaining visual function, help the patient meet their individual goals, increase independence, and optimize safety.

GOAL

The goal of these guidelines is to coordinate the services of primary health care providers, optometrists, and ophthalmologists in the management of patients with AMD, thereby ensuring the most efficient use of these professionals in the interest of patient safety, quality of care, accessibility, and cost-effectiveness.

MANAGEMENT OF AMD

Management of patients with AMD should be consistent with generally accepted protocol. The following criteria should be considered:

(A) NO AMD BUT POSITIVE FAMILY HISTORY

Generally, patients at risk for but without AMD should be monitored by their optometrist or ophthalmologist as part of a comprehensive ocular examination at intervals, consistent with current guidelines, and with specific attention paid to best-corrected visual acuity and stereoscopic examination of the retina. To date, no evidence exists suggesting benefit to early intervention with AREDS or AREDS2 supplementation. Smoking cessation is to be encouraged.

(B) EARLY DRY AMD

Patients at this stage merit disease-specific monitoring by an optometrist or ophthalmologist at least every 12 months (as described above). Patients should specifically be counselled on the merits of smoking cessation, monocular use of an Amsler grid, and specific signs and symptoms of concern that may herald the development of wet AMD. To date, no evidence exists suggesting benefit to early intervention with AREDS or AREDS2 supplementation. As soon as vision loss causes visual disability, vision rehabilitation should be initiated. Visual disability is typically found when visual acuity falls below 6/12.

(C) MODERATE TO SEVERE DRY AMD

These patients have more extensive and/or larger macular drusen, often associated with changes in the RPE, and therefore represent a higher risk for progression to visual loss from advanced dry AMD (geographic atrophy, GA) or wet AMD. Patients with this level of disease should initiate, and be encouraged to continue daily use of, ocular vitamin supplementation as per AREDS/AREDS2. Regular monitoring at least every 6 to 12 months by an optometrist or ophthalmologist (as described above) is suggested. In some cases, particularly if visual changes

have occurred, ancillary testing (including but not limited to optical coherence tomography [OCT] and fundus autofluorescence [FAF]) may be considered to further assess risk of progression to wet AMD. Vigilant self-monitoring for visual changes suggestive of the development of wet AMD should be emphasized at each visit. At this and more advanced levels, vision loss is present and the eye care professional should provide vision rehabilitation or refer to other eye care professionals who do provide this service.

(D) SUSPECTED OR ESTABLISHED WET AMD

In a patient with moderate or severe dry AMD, development of any of the following necessitates immediate referral to an ophthalmologist or retinal specialist for further evaluation and possible treatment:

1. Subretinal or intraretinal fluid evident on OCT

2. New onset macular blood

3. New onset central or paracentral visual loss or distortion

Therapy may involve thermal laser for small extra-foveal lesions, albeit rarely, but usually involves intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents. Photodynamic therapy or combination therapy is sometimes used in recalcitrant disease. Immediate implementation of anti-VEGF therapy has been shown to limit the occurrence of moderate visual loss in 95% of patients and may provide improvement of visual acuity in 30% of cases. Benefit of treatment is sustained only through regular monitoring and retreatment through the remainder of the patient's life, imposing a significant burden on patients and providers.

Several anti-VEGF agents have been employed in the treatment of AMD, including pegaptanib, ranibizumab, bevacizumab, and aflibercept. The largest body of randomized clinical trial (RCT) evidence surrounds the use of monthly ranibizumab; however, aflibercept has been shown to be non-inferior when used every two months. The Comparison of AMD Treatment Trials (CATT) demonstrated that the off-label use of bevacizumab monthly is non-inferior to monthly ranibizumab; however, this equivalence was not shown for as-needed (PRN) dosing.[12,13] Whether monthly use accelerates the development of GA remains to be seen. As the evidence evolves, treatment paradigms will continue to change. Please see Appendix 3 for the current Retina Quality-Based Procedures recommendations for the use of anti-VEGF injections.

ROLES

PRIMARY HEALTH CARE PROVIDER

Primary health care providers (PCPs, including family physicians and nurse practitioners) should make every effort to ensure all patients aged over 60 years obtain a yearly eye examination from an optometrist or ophthalmologist, allowing a risk assessment of both AMD and glaucoma, a silent and similarly blinding eye condition that increases in prevalence with advancing age. PCPs should be knowledgeable about AMD and its common symptoms, including sudden-onset blurred central vision, central visual loss, and/or distortion of vision that may signify the progression of dry AMD to wet AMD. *PCPs must recognize the urgency of referring patients who present with any of these symptoms for an immediate ocular examination.* Delay in the diagnosis and treatment of wet AMD often results in significant and permanent visual loss and must be avoided. Patients should be counselled on the benefits of smoking cessation and maintaining a healthy diet.

It is important to note that OHIP insures patients of any age if they have a medical condition that their PCP or eye-care provider identifies as needing regular monitoring, such as AMD.

OPTOMETRIST

Optometrists should assess patients at risk of developing AMD with a dilated fundus examination at least annually for any clinical manifestations of the disease. In patients with several intermediate-sized drusen or extensive small drusen, the negligible risk of developing advanced AMD (1.3%) does not justify preventative treatment. Optometrists should provide counselling to patients within higher risk categories on the benefits of AREDS/AREDS2 supplementation and to all patients with dry AMD on the benefit of smoking cessation and maintaining a healthy diet. The importance of home monitoring with regular monocular use of an Amsler grid should be emphasized (see Appendix 2). Patients should be made aware of symptoms for which they should seek additional care and reassessment.

The optometrist may monitor patients with dry AMD on an annual or semi-annual basis, as long as visual acuities remain stable and dilated fundus examination does not suggest the presence of wet AMD. Supplementary evaluation with OCT might be considered for patients within higher risk categories when wet AMD is suspected. In cases where wet AMD is strongly suspected or confirmed, optometrists should promptly refer the patient to a general ophthalmologist or retinal specialist. The referral should include a clear and concise report outlining the nature of their concern and the urgency for evaluation by the ophthalmologist. The referral should be copied to the PCP.

OPHTHALMOLOGIST

Ophthalmologists are responsible for assessing and (if necessary) treating AMD to prevent, minimize, stabilize, and/or restore vision loss. Following the clinical evaluation of suspect patients, determination of the need for supplementary evaluation with OCT and/or intravenous fluorescein angiography (IVFA) will be made. If necessary, these procedures should be provided in a timely fashion. Subsequent to any evaluation of patients with suspected wet AMD, a report to the optometrist and PCP should be provided, outlining clinical findings, treatment decisions, and follow-up plans to ensure continuity and coordination of care.

Both ophthalmologists and optometrists have a responsibility to recognize, assess, and either provide low vision rehabilitation themselves or refer to a colleague or low vision clinic where that intervention is available. All professionals share the common role of ensuring their patients are educated on AMD in general and on their specific clinical situation, including low vision rehabilitation when appropriate.

CONCLUSION

Coordination of health care resources is essential in the care and treatment of patients at risk for the ocular complications of AMD. Annual or semi-annual optometric or ophthalmologic assessment of patients will identify those with or at risk for AMD and allow for the implementation of individual home screening and AREDS/AREDS2 supplementation. Early re-evaluation on detection of signs and/or symptoms allows for intervention and treatment through appropriate and timely referral for ophthalmologic care. Such coordinated effort will assist in preserving quality vision for patients with AMD. Mutually agreed upon inter-professional guidelines and generally accepted management and referral criteria will ensure appropriate coordination of care and the most effective use of health professional resources.

APPENDIX 1. AREDS AND AREDS2 SUPPLEMENTATION

(A) The daily doses of antioxidants and zinc used in AREDS are as follows:

Beta carotene:	15 mg (25,000 I.U.)
Vitamin C:	500 mg
Vitamin E:	400 I.U.
Copper :	2 mg
Zinc oxide:	80 mg

(B) The daily doses of antioxidants, fatty acids, and zinc used in the complex AREDS2 randomization are as follows:

Lutein + zeaxanthin:	10 mg + 2 mg
EPA + DHA:	650 mg + 350 mg
Vitamin C:	500 mg
Vitamin E:	400 I.U.
Copper:	2 mg
Zinc oxide:	80 mg or 25 mg

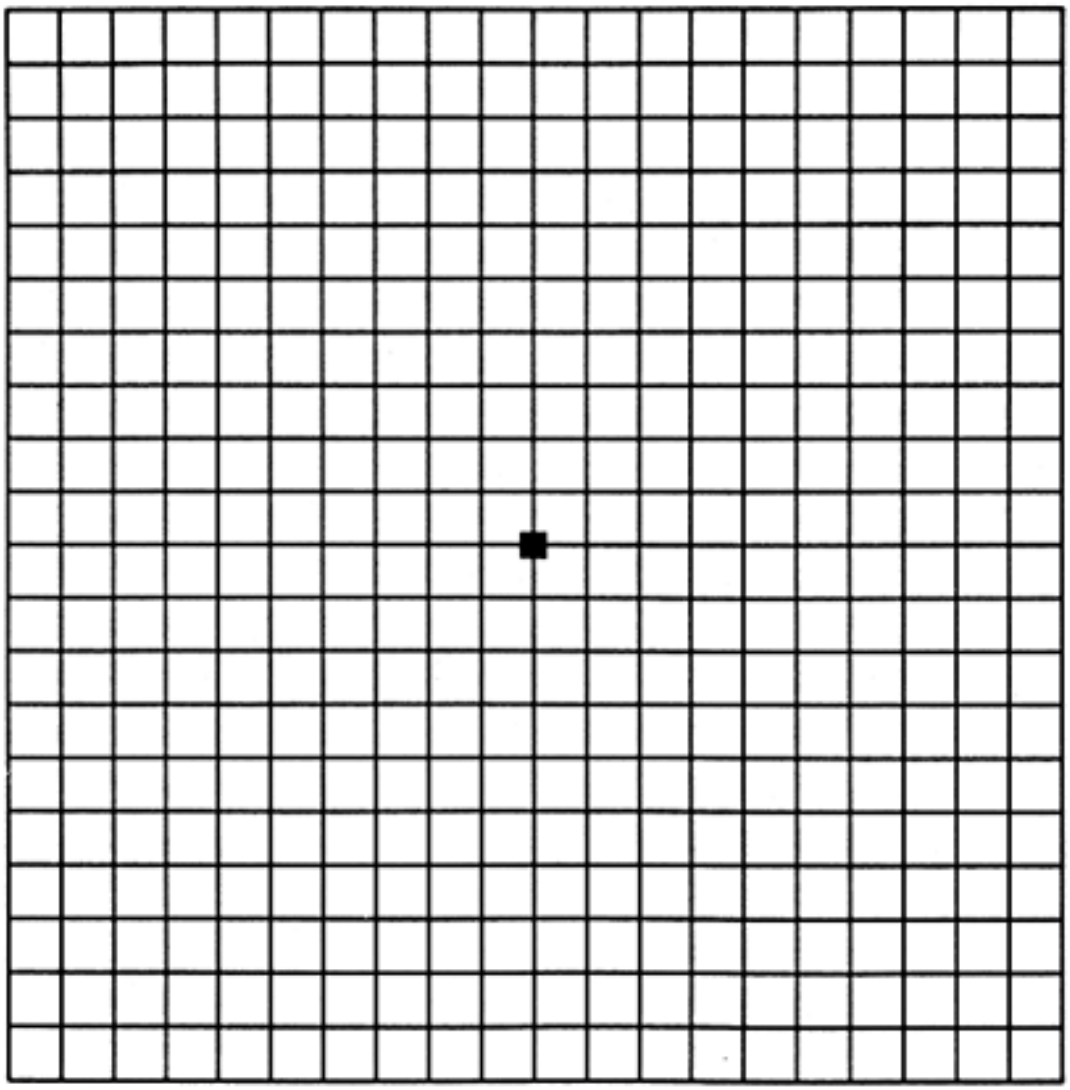
The levels of antioxidants and zinc used in AREDS/AREDS2 are much higher than what is found in standard daily multivitamins and are not achievable with diet alone. Studies have suggested, however, that diets higher in green, leafy vegetables (which are rich in antioxidants and carotenoids) reduce the risk of developing AMD.[i,ii]

AREDS/AREDS2 preparations are to be taken concurrently with any multivitamins already being used, as they do not provide a balanced supplementation. Care must be taken to ensure these combinations do not exceed the recommended maximum doses of carotenoids and zinc. The family physician should be made aware of their concurrent use; potentially serious interactions can develop when they are combined with some medications, particularly anticoagulants.

Caution must be exercised in using preparations containing beta carotene in patients with a history of smoking, due to an increased risk of developing lung cancer.[i,ii] Smoking cessation should be strongly recommended to all individuals, as the magnitude of risk reduction achieved with smoking cessation far exceeds that from other preventative measures, including antioxidant supplementation. AREDS2 results suggest that lutein and zeaxanthin may be considered appropriate substitutes for beta carotene in all populations, but should be mandatory in the cohort with a history of smoking.

Practitioners should be aware of some recent controversy around AREDS/AREDS2 supplementation and the role of tailoring treatment on the basis of individual genetic profiles.[i,ii] Staying abreast of the current literature is of critical importance to ensure excellence in patient care.

APPENDIX 2. AMSLER GRID



APPENDIX 3. RETINA QUALITY-BASED PROCEDURES RECOMMENDED APPROACH FOR INTRAOCULAR INJECTION OF VEGF INHIBITORS FOR WET AMD

Patients with wet AMD have been shown in multiple randomized controlled trials to benefit visually from treatment with intraocular injections of VEGF inhibitors. Approximately 90% of treated patients stabilize vision and 30% will show significant visual improvement. Untreated patients usually go on to lose vision that limits their independence and quality of life.

As patients with disease in one eye have greater than a 50% risk of developing the disease in their other eye within 2 to 5 years, preservation of vision in the first eye is important, as it is not possible to predict which eye will ultimately retain better vision.

Regular follow-up and specialized diagnostic testing (OCT and sometimes IVFA) are required on an ongoing basis to detect recurrence. Data from several well-conducted studies show that, when vision worsens during treatment due to an undetected recurrence, it is unlikely to return to the previous level, despite reintroduction of therapy. Recurrences occur throughout the patient's lifetime and have the potential to cause vision loss.

Because of this ongoing need for close monitoring and treatment, treatment of this disease imposes considerable burden on patients and their families, as well as on the health care system. It is important that patients who have the greatest potential to benefit are treated rapidly, yet it is also important to modify or discontinue treatment if it is not producing the expected response.

RECOMMENDED APPROACH FOR INTRAOCULAR INJECTION OF VEGF INHIBITORS FOR WET AMD

The practices outlined below are recommended as the best way to ensure that patients with wet AMD receive the best care. These recommendations encourage re-evaluation of treatment that is failing to achieve the desired endpoint, so as to reduce the burden of potentially unnecessary or inappropriate treatment on patients, their families, and the health care system.

GUIDELINES FOR INITIATION OF THERAPY

For patients undergoing treatment of wet AMD, and in order to receive treatment for wet AMD, the following criteria should apply:

- Aged over 50 years;
- Recent onset of decreased vision or distortion of vision;
- Presence of drusen;
- Presence of subretinal haemorrhage associated with retinal thickening; and/or
- OCT evidence of intraretinal fluid and/or subretinal fluid (but not solely pigment epithelial detachment [PED]), along with subretinal changes consistent with wet AMD;
- Absence of other pathology to explain visual change;
- Absence of medical or ocular contraindications to intraocular injection;
- Absence of ocular or systemic pathology that would negate the possibility of vision benefit with treatment;
- Patient agrees to return for regular follow-up at intervals as frequently as monthly and potentially for life if treatment is successful.

Some patients may not meet the criteria listed above for wet AMD treatment, but might still benefit from treatment. Obtaining an OCT, and often an IVFA, is necessary to confirm the diagnosis in this circumstance. Once a firm diagnosis of wet AMD is established, the conduct of therapy will otherwise continue as below.

GUIDELINES FOR CONDUCT OF THERAPY

- Treatment will normally be initiated with a series of three monthly injections of a VEGF inhibitor, with a formal evaluation of treatment effect occurring at the third or fourth month.
    - To continue in this treatment pathway, patients should demonstrate significant reduction (or absence) of intraretinal fluid or significant reduction (or absence) of subretinal fluid, haemorrhage, or retinal thickening. Patients who do not demonstrate these changes should be carefully assessed to determine the reason (incorrect diagnosis, inactive disease with findings mimicking activity, disease unresponsive to treating agent).
    - If none of these apply, a review by a retinal subspecialist (or a colleague experienced in the management of wet AMD if access to a retinal specialist is limited by geography) should occur and a mutually agreed upon treatment plan established.
    - Where geography limits access to specialist care, this review may also be conducted through teleophthalmology if available.
- Beyond this point, follow-up and treatment should continue with intervals not usually greater than three months, with vision, intraocular pressure, and a fundus examination documented for each visit.
- In the absence of visible subretinal blood and retinal thickening, an OCT should be obtained at each visit to document the ongoing effectiveness of, and need for, therapy. Increase in intraretinal or subretinal fluid or development of new haemorrhage should prompt a re-evaluation of treatment and frequency.

GUIDELINES FOR DISCONTINUATION OF THERAPY

- Loss of useful vision secondary to irreversible structural change
- Development of ocular or systemic disease precluding intraocular injection
- Inability to maintain regular follow-up
- Patient desire to discontinue treatment

NOTES

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