Age-related macular degeneration: update

**Background**
Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment in people over 50, in the developed world. As of 2009, 49% of the current blind foundation registrations in New Zealand were for AMD. The incidence, prevalence and progression of AMD increases with age and varies by ethnicity. In the Beaver Dam Eye Study, a primarily Caucasian population, the prevalence of Age-related Macular Degeneration increased from 1.3% in those aged 55 to 64 year rising to 46% for those aged ≥ 75.

The prevalence of AMD in Asians over 55 is estimated at 1%, which is probably due to the Asian subcontinent and Hispanic populations and is virtually unknown in African, Maori and Polynesian people. The subtype of AMD that is seen clearly differs between ethnics. Whilst classical AMD is seen more commonly in Caucasians, 6% of Asians who are poor smokers have a risk of AMD to be 184,000, numbers which are projected to increase markedly to 208,200 by 2065. With the increasing demographic shift in the Asia Pacific region, billions of people are at risk of AMD. AMD represents a significant and increasing burden on the health care provision in New Zealand in coming years.

**Risk factors and pathophysiology**
It has been recognised that the likelihood of an individual developing AMD is the result of a complex interplay of genetic and environmental risk factors which are probably cumulative with respect to the risk of developing the disease. Whilst the genetics of AMD are beyond the scope of this article, it is clear that certain genetic anomalies can carry a significant risk for affected individuals, the classic example being complement factor H polymorphisms. Gene products for CHF play an important role in the regulation of the host immune system and individuals who carry a CCH polymorphism therefore possess a dysfunctional and “over active” immune system. This risk is not insignificant, for example, an early finding in the Blue Mountain Eye Study was that the Y420H risk allele of CHF are known to be Tx markers for AMD. In order to counteract this conventional wisdom, studies have identified significant interactions in the development of AMD. Smoking significantly increases AMD risk in a dose response relationship with the relative increase in risk rising to the number of pack years. Smoking cessation reduces the risk of progression and thus smoking cessation remains an important and effective population intervention to reduce the burden that AMD represents.

There is widespread consensus for the development of AMD holds that the primary event in the development of AMD is dysfunction of the choriocapillaris, a network of capillaries serving the retina and choroid and is characterised by the presence of one or more of the following features of AMD: large drusen (>63 microns or larger in diameter), retinal pigment epithelium (RPE) abnormalities, reticular pseudodrusen and/or of geographical atrophy (GA) of RPE. Wet AMD is characterised by the development of subretinal and intraretinal neovascularisation. Soft drusen and pigmentary abnormalities increase with age and strongly predict progression towards advanced AMD. The risk of progression of AMD also seems to accelerate the more advanced the disease becomes. Whilst approximately 15% of patients with early AMD developed large drusen at 10 years the risk of advanced AMD developing over this time period was low. A patient who has intermediate AMD the five year risk of developing advanced AMD increases steeply to near 20%. It is also worth noting that patients with reticular pseudodrusen have a particularly high propensity to develop advanced AMD. The risk of a patient who has advanced AMD in one eye, developing AMD in the other is approximately 50%. In all cases the risk of progression to advanced AMD, is inversely associated with choroidal thickness.

**Prevention**
By far and away the most effective preventive strategy for the development of advanced AMD is to stop smoking. The large and hugely influential AREDS studies demonstrated that antioxidant supplements may slow the progression of moderate AMD (soft drusen and pigmentary changes) to wet AMD but the therapeutic effects are sometimes unverifiable. Although the relative risk reduction for patients taking antioxidant supplements was around 25% in results the more important absolute risk reduction was smaller at around 8%. There have also been concerns raised by some that, in a small sub-set of patients, antioxidant supplements may actually accelerate AMD. However, generally one would still advocate antioxidant supplements in patients who are likely to develop AMD. The reported ability of lithium, xanthan and mesoxanthine supplementation to increase the density of macular pigments is interesting and the results emerging from the clinical trials with subjects on these supplements report better subjective and objective measures of visual functioning compared to controls. However, whether such interventions actually reduce the risk of the development of AMD remains uncertain and at the present time one can only say that their role is unknown.

The drug treatment of dry AMD remains an exciting area of research with a number of neuroprotective and inflammatory modulating agents the subject of large clinical trials. The technologies underpinning stem cell transplants also continue to improve and show great promise, but at the time of writing the drug treatment of dry AMD remains a story of unfulfilled promises.

**Wet AMD treatment**
It is perhaps not too much of an exaggeration to say that the use of antiVEGF agents in ophthalmology has been one of the single greatest advances in modern medicine. Certainly the advent of the antiVEGF era has transformed the outcome of wet AMD with the improvement in visual acuity observed in the key note ANCHOR and MARINA trials extending out to five years and beyond. The question now is that this antiVEGF agent to use (Lucentis, Eylea or Eylea) remains the subject of debate and the choice of which drug is used in which circumstance can have as much to do with the political and economic as it does evidence. The key note trials demonstrated that regardless of the drug used, most patients with classical wet AMD did well and, at a population level at least, there was little to choose between the agents. However as always there are nuances; not every patient responds equally well. In these cases the treating clinician needs to be prepared to switch drugs early if the agent proved to be ineffective. One exception is that AFIB promotes is more effective than the other two agents at treating patients who have the FCB variant of AMD. Currently in New Zealand avastin is the first line treatment for wet AMD, Lucentis being the second line agent. In November, Pharmax will announce the results of their long awaited review of avastin and afib which are anticipated that they will add Eylea to this list. The drug treatment of wet AMD continues to evolve at a fast pace and whilst it is not possible to make a winner at this time, what is certain is that new, longer-acting treatments enter the market over the coming years.

Putting the excitement of emerging drug treatments to one side, current treatments for AMD remain the best option for patients, particularly those in the public sector, to provide the treatment patients need. Despite innovations such as utilising trained nursing staff to deliver injections, most public eye clinics are struggling to provide the treatments their patients need. In Auckland alone, there are over 20,000 appointments annually to treat wAMD, a growth in demand that has not been matched by increased resources. It is widely accepted that under treatment of wet AMD is associated with worse outcomes and MDNZ and others continue to lobby central government and local DHBS for more resources.

In summary the outlook for our patients with AMD has never looked better. Challenges do however remain. Early diagnosis and treatment is crucial and MDNZ and others continue to work hard raising awareness of AMD. Once diagnosed patients, optometrists and general practitioners need an easy accessible “fast track” referral procedure to ensure treatment is delivered promptly. The availability of these “fast track” services are patchy and patients often have to rely on the private sector in the first instance to get prompt treatment. Therefore, eye clinicians need the resource to provide capacity for the ongoing review and treatment of what is a chronic disease. Our score card for the management of wet AMD in New Zealand remains “heading in the right direction, but could do better”.

**References**

**Figures**
Fig. 1. (a) Colour photograph, (b) fluorescein angiogram and (c) OCT of patient with classic wet AMD.
Fig. 2. OCT image of patient with retinal pseudodrusen. Note there are very few drusen seen on fundoscopy but marked changes are seen on the OCT image. The OCT image is characteristic of focal subretinal deposits.
Fig. 3. Five year outcome data from the CATT trial reveals that patients maintain their vision into year 5 with appropriate and timely treatment.

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