

Age-related Macular Degeneration: Progression from Atrophic to Proliferative

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Chief Complaint: Vision changes in the left eye

History of Present Illness: A 76 year old established female patient presented to the clinic with an increase in the size of an existing central scotoma in the left eye that was discovered with home Amsler grid testing. She had a 17 year history of atrophic age-related macular degeneration (AMD) with retinal changes greater in the left than in the right eye. She denied flashes, floaters, pain, or photophobia. Her most recent eye appointment was two months ago, at which time her visual acuity measured 20/25 with correction OD and 20/160 with correction OS.

Past Medical History: Atrophic AMD, hypercholesterolemia, hypothyroidism, colon cancer treated surgically now in remission for 20 years with no recurrence. No ocular surgeries or previous eye trauma.

Family History: Mother with glaucoma

Social History: Does not smoke

Medications: Atorvastatin 20 mg, levothyroxine 88 mcg, beta carotene, calcium carbonate, latanoprost 0.005% OU qHS

Ocular examination:

- Best corrected visual acuity:
 - OD 20/25
 - OS 20/200
- Extraocular motility: Full OU
- Pupils: 4 mm → 3 mm OU, no RAPD
- IOP with applanation: OD 22 mmHg, OS 23 mmHg
- External and anterior segment examination: Normal OU
- Dilated Fundus Exam:
 - OD: Multiple large drusen, geographic atrophy, no subretinal fluid or choroidal neovascularization (CNV).
 - OS: In addition to what is seen OD, there is a larger area of atrophy and a subretinal hemorrhage indicating the presence of CNV.

Figure 1: Color fundus photos. Note the presence of subretinal hemorrhage OS.

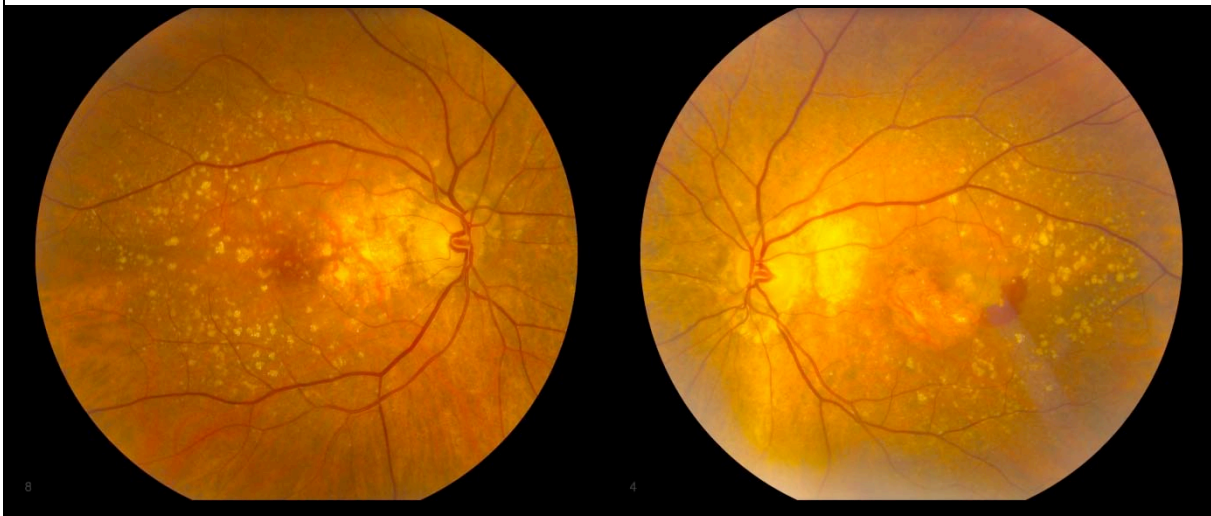


Figure 2: Optical coherence tomography

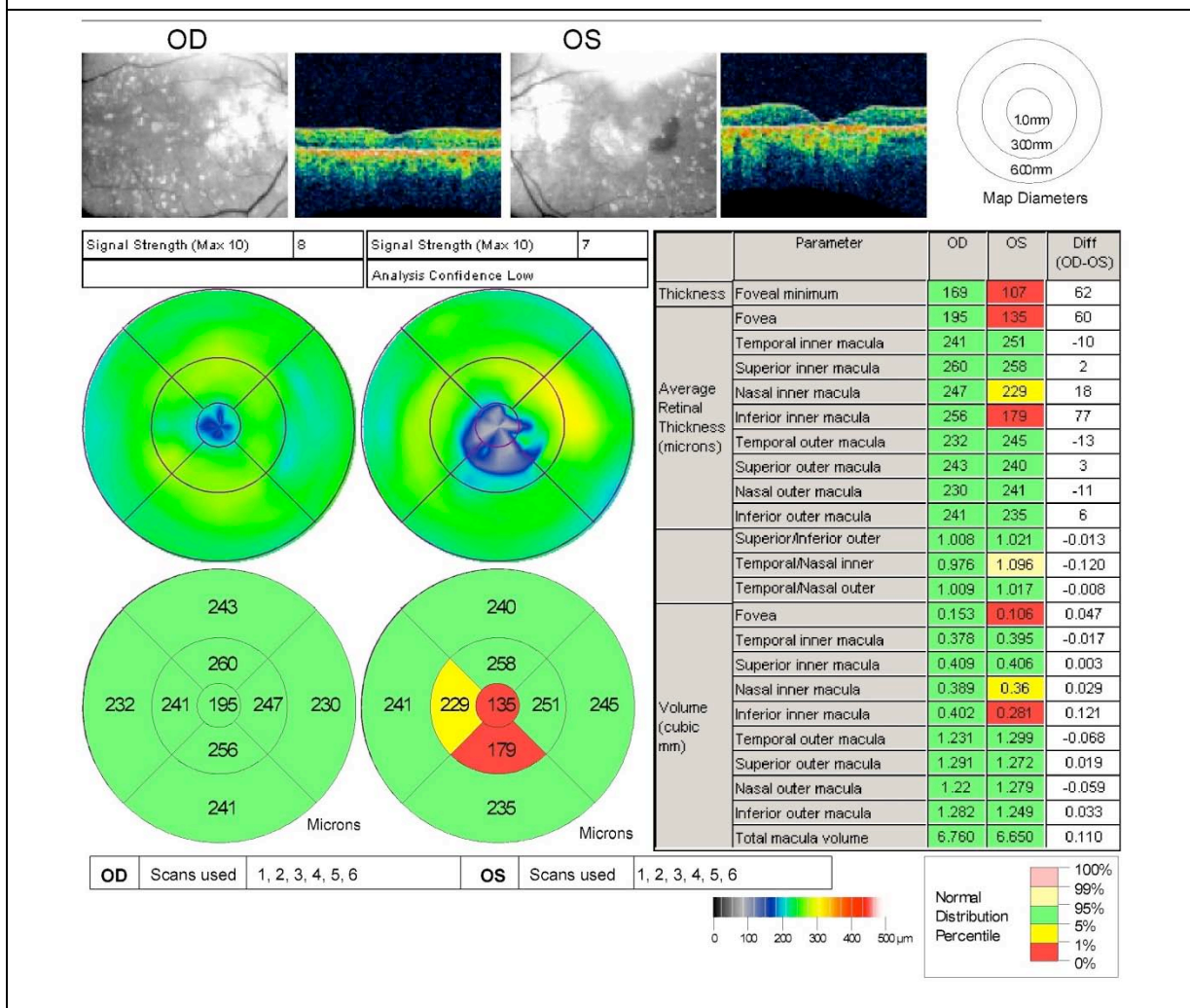
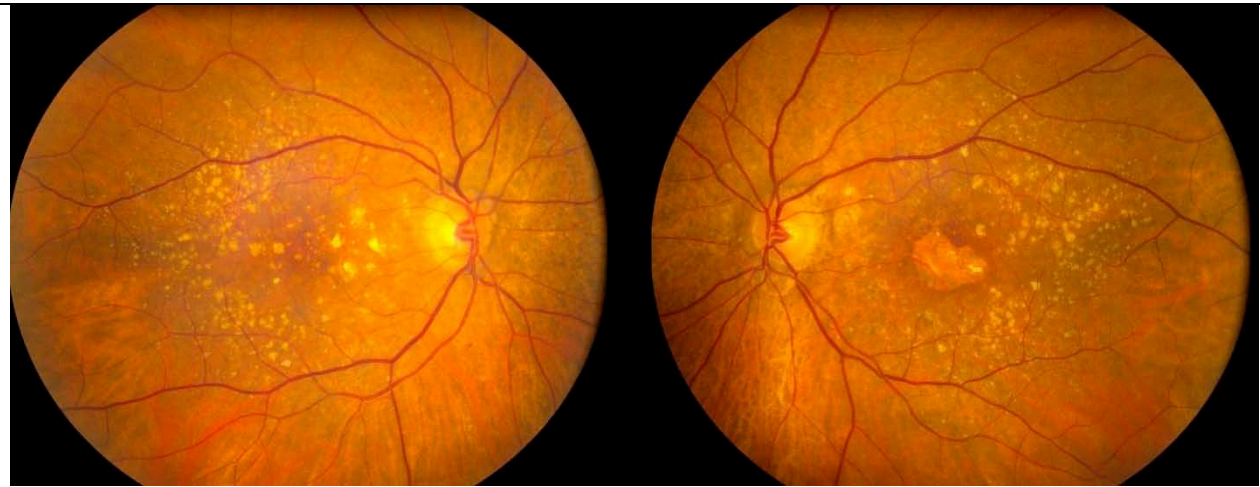


Figure 3: Color fundus photos from 2.5 years prior for comparison

The patient, having known atrophic AMD OU, was diagnosed with progression to neovascular AMD OS. She was treated with monthly Avastin injections OS resulting in visual acuity improvement back to her baseline of 20/160 OS at her one month follow-up appointment and 20/80 OS at her two month appointment.

Figure 4: Color fundus photos after treatment with Avastin OS

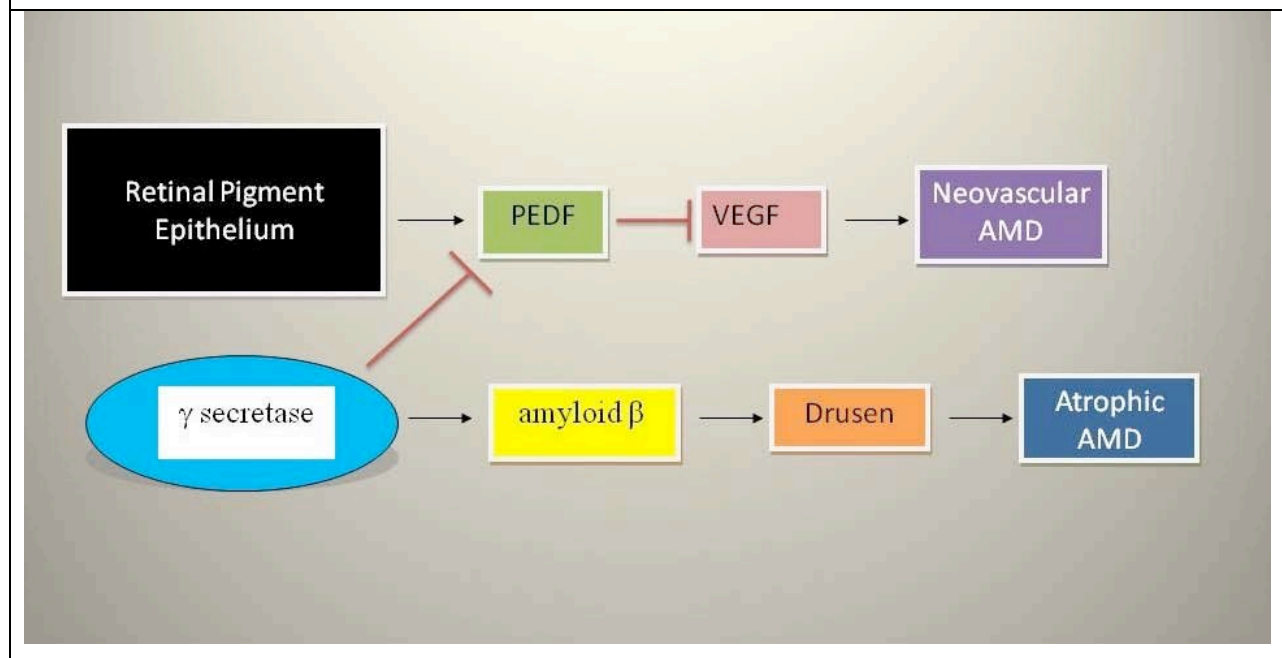
Discussion

Age-related macular degeneration (AMD) is an ocular disease affecting 35% of individuals over the age of 75 (Klein 1992). It is the leading cause of irreversible blindness in elderly people in the United States. Both forms of AMD, atrophic (dry) and neovascular (wet), are thought to be initially caused by oxidative stress to retinal pigment epithelial (RPE) cells. Atrophic macular degeneration is more common (85%) than neovascular macular degeneration, with progression from dry to wet in approximately 10% of individuals diagnosed with dry AMD. Because AMD is a complex disorder caused likely by multiple genetic variations as well as environmental factors, several mechanisms have been proposed to explain its pathophysiology.

One main cause of drusen deposition in AMD may involve activation of the complement cascade. Recently, AMD has been linked to certain genetic variations in the complement factor H gene (*HF1/CRH*), which normally produces a complement control protein (HF1) that is responsible for inactivating C3b and thus inhibiting activation of the alternative complement pathway. It is thought that in some people with these specific at-risk variations, HF1 has decreased affinity for C3b, leading to increased activation of the alternative complement cascade, especially following inflammatory stimuli or oxidative stress. This leads to complement deposition and accumulation in the form of drusen beneath the retinal pigment epithelium. Interestingly, these at-risk haplotypes were most strongly associated with exudative or neovascular AMD (Hageman 2005, Narayanan 2007).

Another theory involves the activity of γ -secretase. This enzyme plays a crucial role in the production of amyloid- β , another component of drusen in dry AMD. The enzyme is also thought to damage the protective effects of pigment epithelium derived factor (PEDF), a neurotrophic agent produced in RPE cells. PEDF is a known antagonist of VEGF. Overproduction of γ -secretase may both increase drusen formation and reduce the effect of PEDF, thereby allowing unregulated VEGF activity and progression to wet AMD (Ablonczy et al. 2009).

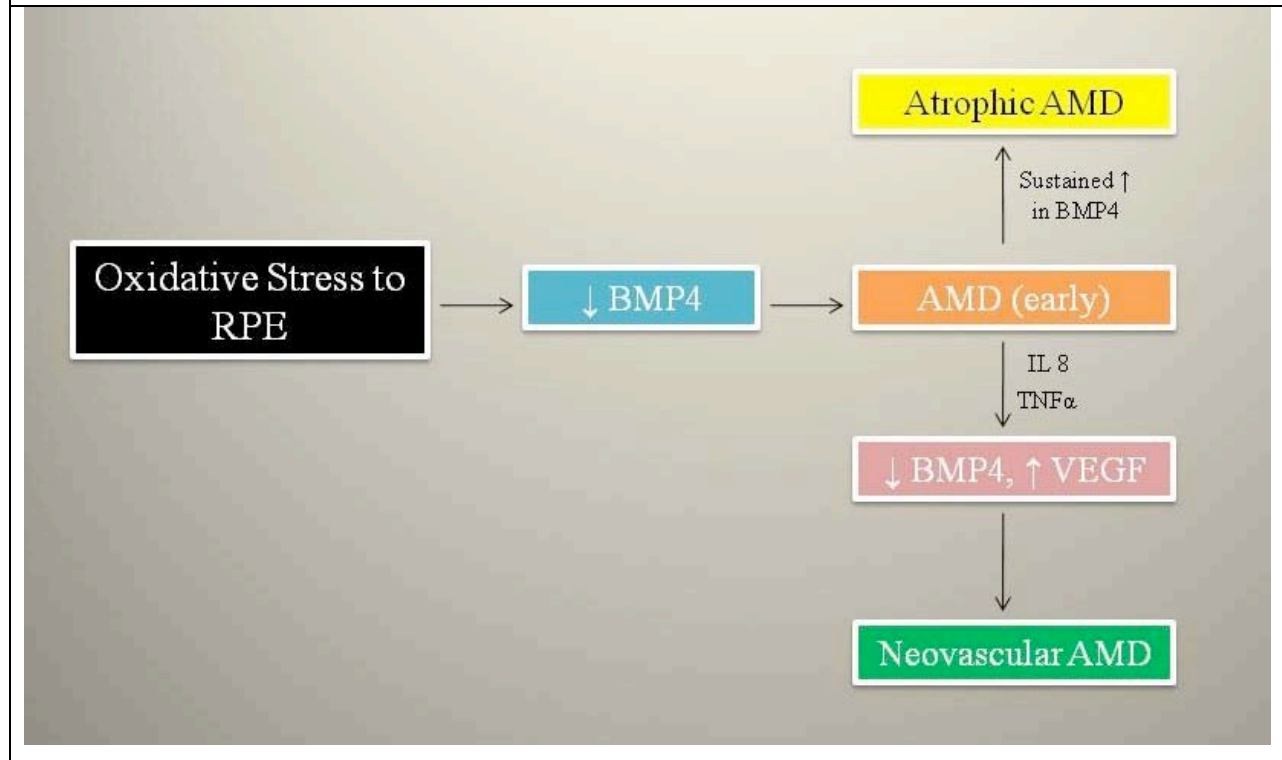
Figure 5



A third proposed mechanism involves the effects of bone morphogenetic protein 4 (BMP4), a protein responsible for senescence and apoptosis in many different cells in the body. When RPE cells undergo oxidative stress, BMP4 expression is increased. If BMP4 levels continue to increase, this can lead to atrophy of the RPE cell, causing the atrophic form of AMD. In some individuals, activation of senescence leads to release of inflammatory mediators such as IL8 and TNF α . These molecules cause a decrease in BMP4 levels and increased VEGF, leading to choroidal angiogenesis and the development of neovascular AMD. Thus, the conversion between atrophic to neovascular

AMD is thought to be due to changes in the microenvironment as RPE cells undergo senescence (Zhu 2009).

Figure 6



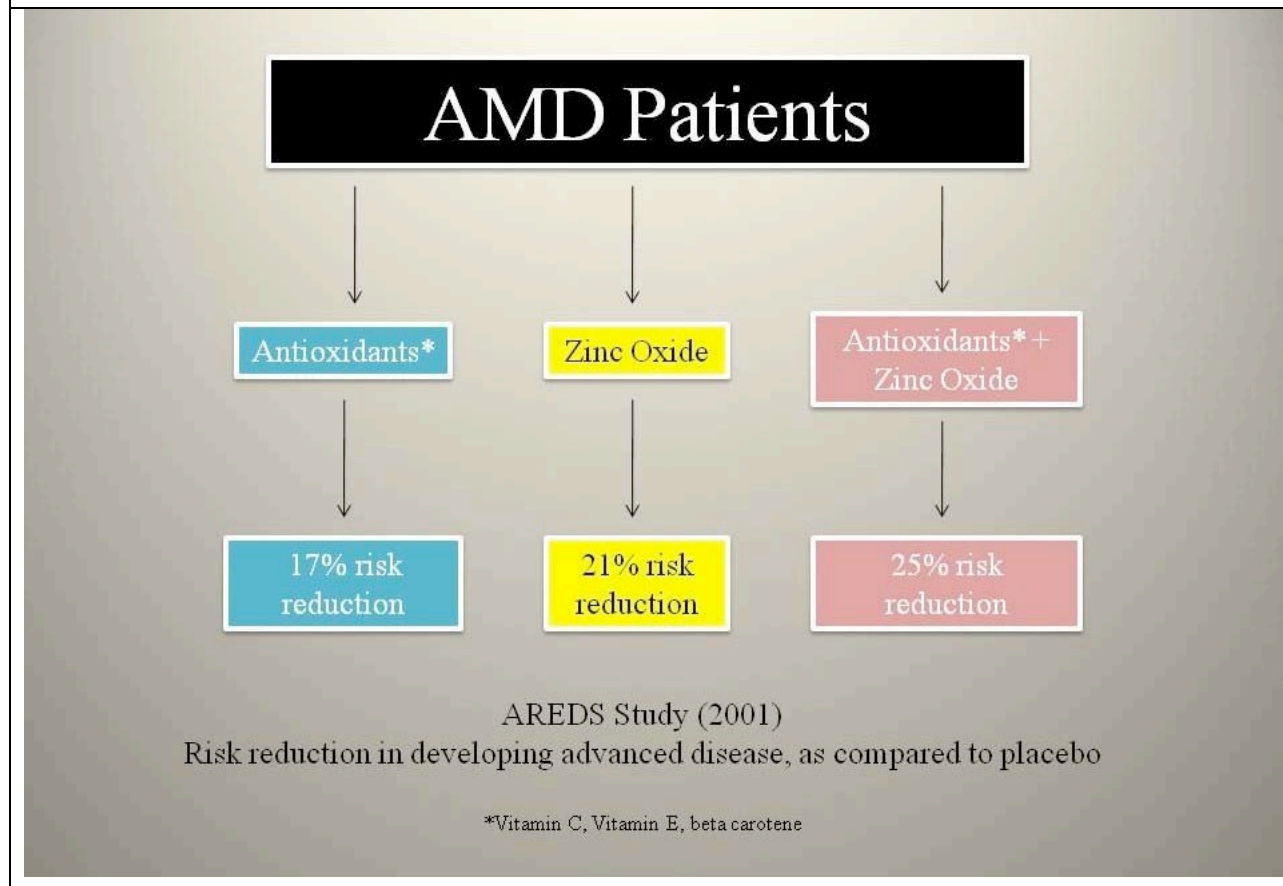
Treatment

Intravitreal bevacizumab (Avastin®)[off label] or ranabizumab (Lucentis®) injections given approximately every month over three months is currently the accepted standard of care for the initial treatment of neovascular AMD. This is usually followed with repeated injections if the patient has responded using a fixed time-to-repeat injection schedule or a regimen in which the interval between treatments is extended--the so called "treat and extend" plan (Harding 2010). The intention is to reduce the total number of injections given over a year or more. Patients are monitored by checking visual acuity, OCT, and repeating fundus fluorescein angiography only if necessary. Bevacizumab and ranabizumab are humanized monoclonal antibodies that block vascular endothelial growth factor, thereby inhibiting angiogenesis. Both drugs are also thought to decrease vascular permeability. The Comparison of Age-related Macular Degeneration Treatment Trials (CATT) is currently comparing the efficacy of the two separate treatments at various dosing schedules.

The Age-Related Eye Disease Study Research Group (AREDS) in 2001 demonstrated the effectiveness of high doses of vitamin C and E, beta carotene, zinc, and copper in slowing down the progression of AMD. One fourth of AMD patients in the study were given all of the vitamins and minerals studied (500 mg vitamin C, 400 IU of vitamin E, 15 mg beta carotene, 80 mg zinc oxide, and 2 mg copper), a quarter were given zinc oxide, a quarter were given antioxidants, and a quarter were given placebo. After following the patients for seven years, the study demonstrated that AMD

patients who took both anti-oxidants plus zinc supplements had a 25% risk reduction in developing advanced AMD. The patients who benefited most from these supplements were category 3 and 4 AMD patients, quantified by extensive intermediate drusen, large drusen, non-central geographic atrophy, or visual acuity <20/32 in at least one eye (AREDS 2001).

Figure 7



The AREDS2 study is a currently ongoing multicentered trial to evaluate effects of macular xanthophylls (lutein and zeaxanthin) and/or long-chain omega-3 fatty acids on the progression to advanced AMD. An additional goal of the study is to assess whether supplements with reduced zinc and/or no beta-carotene work as well as the original supplements. Enrollment in this study ended in 2008.

<p>Epidemiology</p> <ul style="list-style-type: none"> • AMD affects 35% of individuals over the age of 75 (85% of cases are atrophic and 15% are neovascular) 	<p>Signs</p> <ul style="list-style-type: none"> • Drusen • Degeneration of the retinal pigment epithelium • Altered macular pigmentation • Neovascularization of choroidal membranes (neovascular AMD) • Subretinal fluid accumulation
<p>Symptoms</p> <ul style="list-style-type: none"> • Central scotomas (painless loss of central vision) • Metamorphopsia • Decreased visual acuity • Decreased night vision 	<p>Treatment</p> <ul style="list-style-type: none"> • Intravitreal bevacizumab (Avastin®)[off label] or ranabizumab (Lucentis®) injections over three months (for neovascular form) • Laser photocoagulation (for neovascular form) • AREDS protocol: 500 mg vitamin C, 400 IU of vitamin E, 15 mg beta carotene, 80 mg zinc oxide, and 2 mg cupric oxide (to prevent copper deficiency from high levels of zinc)

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