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OCULAR Infection & Inflammation

Uveitis

A continuing education newsletter for physicians, pharmacists, and nurses interested in infection & inflammation of the eye

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Activity Title

OCULAR Infection & Inflammation

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Objectives

At the conclusion of this activity, participants should be able to:

- Compare & contrast the immunology of the anterior eye & pathophysiology of uveitis
- Describe the types of uveitis
- Identify appropriate clinical tests to correctly diagnosis uveitis
- Review the rationale for current and new treatments for uveitis

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Pharmacists
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INTRODUCTION

Uveitis refers to inflammation of the uveal tract, which includes the iris, ciliary body, and choroid.[1] The uveal tract represents the vascular organ of the eye. In addition to providing most of the blood supply to the intraocular structures, it acts as a conduit for immune cells, particularly lymphocytes, to enter the eye. The uveal tract is consequently represented in many intraocular inflammatory processes. Many forms of uveitis are chronic in nature and often require continuous treatment. Of people under 65 who are registered legally blind, 10% are visually impaired because of uveitis and its complications.[2,3]

The portrait of patients diagnosed with uveitis is changing. Recent studies highlight the need to treat the disease aggressively while monitoring potential effects to avoid lengthy recurrences and complications. New treatment modalities offer hope for improved outcomes in pediatric and adult patients with uveitis.

EPIDEMIOLOGY

Uveitis has an estimated prevalence of about 38 cases per 100,000 population, and an incidence of 15 cases per 100,000 population. Approximately 2.4 million people in the world suffer from uveitis.[4] In the United States it is estimated that uveitis affects more than 280,000 people each year.[5] The vast majority of these patients are cared for by comprehensive ophthalmologists rather than uveitis specialists.

In the general population, the estimated prevalence and annual incidence of chronic uveitis associated with juvenile arthritis is as high as 11 per 100,000 and 1.5 per 100,000, respectively.[6]

The largest population-based uveitis study in the U.S. reviewed 2,070 people in Northern California in a cross-sectional study using retrospective database and medical record review. Researchers found the incidence was 52 per 100,000 person-years – nearly 3 times that of previous U.S. estimates. The same Northern California Epidemiology of Uveitis Study found a prevalence of 115 per 100,000 persons, a higher prevalence among women and a higher prevalence of ongoing uveitis in older age groups. [7]

PATHOPHYSIOLOGY

In order to understand the pathophysiology of uveitis, it is imperative to understand the immunology of the eye, and its differences, similarities, and relationship to systemic immunity. The immunologic properties of the anterior eye are affected by the composition of the circulating aqueous fluid. The aqueous fluid has a significantly lower protein composition compared to serum. However, there are circulating proteins such as immunomodulatory cytokines, neuropeptides and complement inhibitors that influence the immunologic events within the eye. There is a size dependent gradient in the capillaries of the ciliary body that allow some plasma macromolecules to be incorporated into the aqueous fluid. These, as well as the tight junctions between the pigmented and the nonpigmented ciliary epithelium, are responsible for the existence of the blood-ocular barrier.

The clearance of aqueous proteins is dependent on aqueous outflow channels, which ultimately drain into the systemic venous system. This provides antigenic communication between the eye and the body's systemic immune system. The iris and the ciliary body contain a large reservoir of antigen presenting cells (APCs). The APCs are able to carry antigenic stimuli through the trabecular meshwork, and ultimately to the lymph nodes and spleen where immune processing occurs. The anterior uvea does contain some T-cells and mast cells, but does not have any B cells, eosinophils, or neutrophils under normal conditions. The vitreous has not been as closely studied, but is thought to possess similar immunologic properties as the anterior eye.[8]

The anterior uvea is immune privileged, sharing this property with other sites such as the retina, the brain, and the testes. In looking at the affector arc of the immune response of the anterior uvea to antigenic stimuli, we see a form of deviant immunity triggered, termed *anterior chamber-associated immune deviation* (ACAID). This is characterized by inhibition of delayed hypersensitivity and complement-fixing antibody production, though there is preservation of other immune effector modalities. This effector blockade is influenced by complement inhibitors in the aqueous fluid, as well as immunomodulatory cytokines and neuropeptides produced by ocular tissues.[9]

The blood-ocular barrier in the retina is essentially maintained by the tight junctions at the level of the retinal pigment epithelium, providing a physiologic barrier from the highly permeable choroid. The retina and choroid are both rich in APCs. The density of lymphocytes in the retina is low, and there is no evidence for the presence of neutrophils or eosinophils. Cytokines are produced by the RPE as well as various other cell types in the retina and choroid.

The development of intraocular inflammation is dependent on the underlying etiology. Thus, the variety of mechanisms for uveitis is as broad as the range of etiologies. Whether it is secondary to foreign or autoantigenic stimuli, intraocular inflammation is secondary to innate and adaptive immune responses in the eye. Innate responses may result from infectious triggers, or nonspecific soluble molecules, such as mechanical irritation of the iris or ciliary epithelium by an intraocular lens (IOL).[8] Innate immune responses initiate a cascade of events including recruitment of neutrophils and macrophages, and this serves to potentiate adaptive immunity. Adaptive immune responses in the eye can be divided into predominately antibody-mediated soluble effectors, and predominately lymphocyte-mediated cellular effectors.[10]

For many years there has been a well recognized association between *human leukocyte antigen* (HLA) molecules and several forms of uveitis. A few examples of such are the association between acute anterior uveitis and HLA-B27, juvenile rheumatoid arthritis and HLA-DR4, Adamantiades-Behçet and HLA-B51, and birdshot chorioretinitis and HLA-A29. Unfortunately, the exact nature of this relationship remains elusive. There are several theories that exist that may explain the pathophysiology of HLA-associated uveitis. One theory suggests that expression of certain forms of HLA molecules may increase the processing of certain antigens that would not be processed if that certain HLA molecule were not expressed. Another theory proposes molecular mimicry as the mechanism, in which a bacterial antigen may share an epitope similar to an HLA molecule. Thus, when a bacterial antigen is introduced, an antibacterial effector response is triggered initiating a cross reaction effector response with the epitope of the HLA molecule. A third theory suggests that presence of a certain HLA molecule, may simply lead to an exaggerated innate immune response.[10]

CLASSIFICATION OF UVEITIS

There are a variety of ways to classify uveitis. Several classification schemes have been developed to characterize uveitis based on anatomy, clinical course, etiology, and histopathology. The most widely used classification of uveitis is the one devised by the International Uveitis Study Group (IUSG) in 1987, based on the anatomical location of the inflammation. This classification includes anterior uveitis (iritis, iridocyclitis, and anterior cyclitis), intermediate uveitis (para planitis, posterior cyclitis, and hyalitis), and posterior uveitis (focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, and neuroretinitis).[11] An additional term, panuveitis (anterior chamber, vitreous, retina, and choroid), was also described. The Standardization of Uveitis Nomenclature (SUN) Working Group was an international committee that updated standardized taxonomy for uveitis in 2005.[12]

The SUN Working Group Anatomical Classification of Uveitis divides uveitis into anterior, intermediate, posterior and panuveitis based on where the primary site of inflammation is located. With anterior uveitis, the primary site of inflammation is the anterior chamber (AC). If the inflammation is confined solely to the AC, it is referred to as iritis. However, anterior uveitis can be further classified depending on what adjacent anatomical structures are inflamed. If the inflammation includes the AC and the retrolental space, it is referred to as iridocyclitis. If the cornea is involved, it is keratouveitis, and if the sclera and uveal tract are included, it is referred to as sclerouveitis. In the US, anterior uveitis is estimated to account for up to 70% of new uveitis cases.[13] The presentation of anterior uveitis may range from a subclinical, asymptomatic appearance of cell in the AC to high-grade inflammation with an injected, painful eye.

Intermediate uveitis is defined as uveitis that features the vitreous as the primary site of inflammation. Intermediate uveitis accounts for up to 2.9% of all cases of uveitis in the US.[14] Another study in France by Bodaghi et al, showed intermediate uveitis accounting for 15% of cases.[15] Patients with isolated intermediate uveitis often complain of floaters with an otherwise asymptomatic eye. Intermediate uveitis may be further classified as pars planitis, posterior cyclitis, and hyalitis. Inflammatory cells may aggregate in the anterior vitreous, forming what may be referred to as "snowballs."

Posterior uveitis is defined by the SUN Working Group as inflammation primary confined to the retina and the choroid. There can sometimes be an associated vitritis that can accompany posterior uveitis. The inflammation may be focal, multifocal, or diffuse. The inflammation may be localized solely to the choroid, solely to the retina, or may be a combination of chorioretinitis. Furthermore, depending on the etiology and the clinical course of inflammation, there may be an associated vasculitis and/or neuritis.[16]

Panuveitis is characterized as having the primary sites of inflammation include the anterior chamber, vitreous, and retina or choroid. Panuveitis may often begin as an isolated anterior or posterior inflammatory process that may progress to involve all portions of the eye. Gritz et al. found panuveitis to be responsible for 5.0% of new uveitis cases.[13]

The SUN Working Group also identified further descriptors in uveitis nomenclature characterized by the onset, duration, and course of the inflammation. The onset may be characterized as sudden or insidious. Uveitis is considered limited if the duration of inflammation is less than or equal to three months, and persistent if the duration lasts greater than three months. Uveitis may also be characterized by its clinical course, being divided into acute, recurrent, or chronic uveitis. Acute uveitis is defined as an episode characterized by sudden onset and limited duration. Recurrent uveitis is characterized by repeated episodes separated by periods of inactivity without treatment greater than or equal to three months' duration. Chronic uveitis is defined as persistent uveitis with relapse in less than three months after discontinuing treatment.

The SUN Working Group also outlined ways of grading inflammation and classifying the activity of uveitis. Grading anterior chamber cells is characterized by slit lamp quantification of cells in the anterior chamber using a 1 x 1 mm slit beam:

Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field
0	< 1
0.5+	1-5
1+	5-16
2+	16-25
3+	25-50
4+	> 50

Grading Scheme for Anterior Chamber Flare

Grade	Cells in Field
0	none
1+	faint
2+	Moderate (iris & lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plasmoid aqueous)

Grading Scheme for Vitreous Cells

Grade	Cells in Field
0	No cells
0.5+	1-10
1+	10-20
2+	20-30
3+	30-100
4+	> 100

Uveitis is defined as inactive if 0 cells are seen in the AC. Worsening activity is defined as a 2-step increase in the level of inflammation (e.g., anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+. Improved activity is defined as a 2-step decrease in the level of inflammation or decrease to grade 0. Remission is characterized by inactive disease for greater than or equal to 3 months after discontinuing all treatments for eye disease.

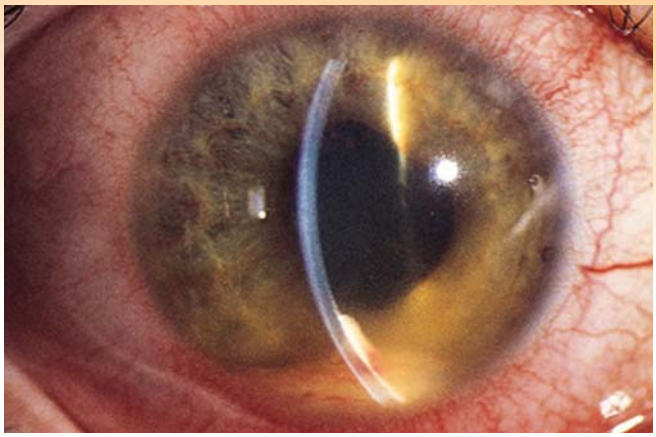
The International Uveitis Study Group (IUSG) designed a simplified classification system based on etiologic criteria in 2008.[17] The IUSG classified uveitis into three separate categories: infectious, non-infectious, and masquerade. Infectious etiologies included inflammation secondary to bacterial, viral, fungal, or parasitic origin. Herpetic uveitis was found to be the most common infectious cause of uveitis.[15] Non-infectious forms of uveitis were divided into those with known systemic associations, and those without known systemic associations. In a large retrospective study, acute anterior uveitis of undetermined origin was found to be the most common cause of uveitis, followed by Behçet disease.[18] Masquerade etiologies include neoplastic and non-neoplastic causes. Examples of non-neoplastic masquerade syndromes are retinitis pigmentosa, ocular ischemic syndrome, chronic rhegmatogenous retinal detachment, and pigment dispersion syndrome. Neoplastic syndromes include lymphoma and leukemia, as well as other malignancies such as uveal melanoma, retinoblastoma, juvenile xanthogranuloma, and metastatic tumors.

TYPES OF UVEITIS

For the purposes of this discussion, we will describe the types of uveitis based on the 2005 SUN classification system.

Anterior Uveitis

Because uveitis can occur secondarily to inflammation of the cornea or sclera, a primary keratitis or scleritis should be ruled out.[19]



Acute anterior uveitis.

Rapid onset of the classic triad of pain, redness, and sensitivity to light is characteristic of this condition. Varying degrees of ciliary flush, episcleral blood vessel engorgement, and anterior chamber cells and flare are present. Hypopyon, as shown here, occurs with extreme inflammation. Admixture with erythrocytes is uncommon. Hypopyon is commonly found only in cases of acute anterior uveitis caused by HLA-B27-related diseases, Behçet's disease, and endophthalmitis. In otherwise uninflamed eyes, hypopyon may indicate leukemic infiltration.

Taken from: Janet L. Davis In Atlas of Ophthalmology: Intraocular Inflammation. Edited by Janet L. Davis. Current Medicine, Inc. 2000.

Major systemic associations with secondary anterior uveitis include:

- HLA-B27 associated spondyloarthropathies
- Ankylosing spondylitis
- Reiter syndrome
- Inflammatory bowel disease
- Psoriatic arthritis
- Reactive arthritis
- Juvenile rheumatoid arthritis

Major ophthalmic disorders causing anterior uveitis:

- Herpetic disease
- Fuch's heterochromic iridocyclitis
- Sarcoidosis
- Lupus
- Lens-associated uveitis
- Intraocular lens implant-associated
- Posner-Schlossman syndrome

Intermediate Uveitis

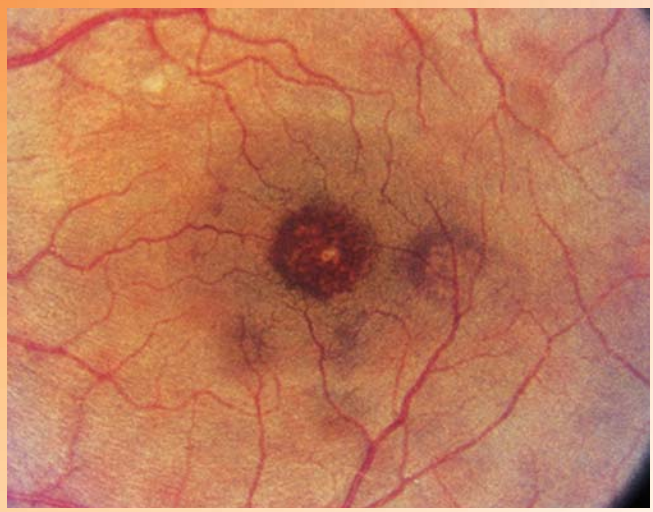
More than two thirds of intermediate uveitis is idiopathic, and this entity can be referred to as pars planitis. Pars planitis most commonly affects individuals 5 to 40 years of age, and is thought to involve autoimmune reactions against the vitreous, peripheral retina, and ciliary body.[20] Some identifiable systemic associations with intermediate uveitis include:[21]

- Multiple sclerosis
- Sarcoidosis
- Toxocariasis
- Syphilis
- Lyme disease

Posterior Uveitis

Infectious causes of posterior uveitis include:

- Acute retinal necrosis/progressive outer retinal necrosis – caused by Herpes simplex virus (HSV),
- Herpes zoster virus (HZV), Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV)
- Rubella
- Rubeola (measles)
- Subacute Sclerosing Panencephalitis virus (SSPE)
- Syphilis
- Coccidioidomycosis
- Cryptococcosis
- Candidiasis
- Toxocariasis
- Cystercosis
- Diffuse unilateral subacute neuroretinitis (DUSN)
- Toxoplasmosis



Multiple evanescent white dot syndrome (MEWDS).
This condition is a type of well-defined acute posterior uveitis. Onset is usually unilateral. The diagnosis can often be made by history if the patient reports photopsias, blurred vision, and a field defect or enlarged blind spot. The retinal "white dots" are approximately 100 to 200 µm in size and may be subtle or transient. Indocyanine green angiography of MEWDS generally shows extensive multifocal choroidal perfusion defects with indistinct borders. These defects may be distributed throughout the fundus and are more prominent and widespread than the changes visible on fluorescein angiography. The lack of a one-to-one correspondence with visible fundus lesions is helpful in discriminating MEWDS from acute posterior multifocal placoid pigment epitheliopathy.

Taken from: Janet L. Davis In Atlas of Ophthalmology: Intraocular Inflammation. Edited by Janet L. Davis. Current Medicine, Inc. 2000.

CMV is the most common cause of posterior uveitis in immune-compromised patients, affecting up to 5% of patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) receiving highly active antiretroviral therapy. Candida or herpes infections are also seen as causes of retinitis in immunodeficient patients.[22]

The toxoplasmosis intracellular parasite has worldwide distribution with an estimated 1 billion people affected.[23,24]

Noninfectious causes of posterior uveitis include:

- Lupus
- Polyarteritis nodosa (PAN)
- Wegener's granulomatosis
- Sarcoidosis
- Retinochoriodopathies:
- Acute posterior multifocal placoid pigment

epitheliopathy (APMPPE)
- Acute retinal pigment epitheliitis (ARPE) or "Krill disease"
- Acute zonal occult outer retinopathy (AZOOR)
- Birdshot retinochoroidopathy
- Multiple evanescent white dot syndrome (MEWDS)
- Punctate inner choroiditis (PIC)
- Serpiginous choroidopathy
- Subretinal fibrosis and uveitis syndrome
- Multifocal choroiditis and panuveitis syndrome (MCP)

Panuveitis

Causes of panuveitis include:[25]

- Sarcoidosis
- Syphilis
- Lyme disease
- Leptospirosis
- Vogt-Koyanagi-Harada syndrome
- Sympathetic ophthalmia
- Tuberculosis
- Onchocerciasis
- "River blindness" associated with onchocerciasis is endemic in sub-Saharan Africa

SIGNS & SYMPTOMS

Early symptoms of uveitis may be mild or severe. Time course can range from insidious to sudden, and symptoms can rapidly progress.

Symptoms include:

- pain
- photophobia
- decreased vision
- red eye
- floaters
- loss of visual field

In acute **anterior uveitis**, the classic presentation is a triad of redness, pain, and photophobia[19]. Slit-lamp findings include an anterior chamber cellular response with variable flare, fibrin in the aqueous humor, keratic precipitates, and posterior synechiae. Endothelial dysfunction can lead to corneal edema. Keratic precipitates (KPs) on the corneal endothelium are indicative of uveitis. Large granular KPs indicate granulomatous uveitis, a more severe inflammatory process than the non-granulomatous type (defined by small to medium size KPs).

Floaters and blurred vision are typical in **intermediate uveitis.** Cells may be evident in the vitreous humor. Vision loss may be due to the floaters or cystoid macular edema. Inflammatory aggregates often occur over the **pars plana** (near the junction of the iris and sclera), forming "snowballs" and can cause a classic "snowbank" appearance that is often associated with neovascularization of the retinal periphery.

Patients with **posterior uveitis** exhibit decreased visual acuity, floaters, metamorphopsia, scotomata, or decreased visual field. Ocular examination reveals multifocal areas of retinitis or choroiditis.[19] Exudative retinal detachments, retinal vasculitis, and optic disc edema can be associated. In less than 5% of uveitis cases, retinal tears and rhegmatogenous retinal detachment can be associated.

SEQUELAE OF UVEITIS

Numerous sequelae can occur in patients with chronic uveitis, some as secondary manifestations of the inflammatory disease itself and others as complications of treatment. Uveitis can cause permanent damage and vision loss due to the development of glaucoma, cataract, or retinal edema. Ocular discomfort and pain is a debilitating symptom of uveitis.[19]

Cystoid macular edema (CME) is the leading cause of decreased vision leading to permanent visual loss in patients with uveitis. In rat models, endotoxin induced uveitis causes a disturbance of potassium and water homeostasis in the retina which leads to swelling of Muller cells and fluid accumulation in the outer plexiform and inner nuclear layers of the retina.[26] If the swelling is long standing, retinal pigment epithelial cells can be damaged leading to retinal atrophy and photoreceptor loss will atrophy and visual loss can be permanent. A vitrectromy may be required if the eye does not respond to medical treatment.[27]

Elevated intraocular pressure (IOP) can result from blockage of the trabecular meshwork (TM) by debris and cells, or by pupillary block in many patients with uveitis. HSV keratouveitis is associated with secondary glaucoma in nearly 30% of patients — usually when the corneal stroma is involved. The IOP elevation is typically secondary to trabeculitis or inflammatory debris clogging the TM.[28, 29] Intraocular pressure may be normal or slightly decreased in the acute phase due to decreased aqueous humor production associated with ciliary body shutdown; however, pressure may become elevated as the inflammation subsides and the ciliary body recovers. Pupillary block can result from the formation of inflammatory posterior synechiae with resultant secondary glaucoma. Intraocular pressure may also be elevated as a side effect of corticosteroid treatment.

A common complication of all forms of uveitis is cataract formation. Surgical removal of the cataract may not be safe

until the eye is free from inflammation for a minimum of 90 days. An intraocular lens implant can result in irritation and recurrent anterior uveitis. Long term topical and/or systemic corticosteroid use can increase the risk of posterior subcapsular cataract formation.[16]

Hypotony is a potentially devastating consequence of chronic uveitis, and can lead to phthisis bulbi (i.e., atrophic, scarred, and disorganized end-stage eye).[19] Hypotony results from decreased production of aqueous from the ciliary body. This can occur acutely from ciliary body inflammation and hyposecretion, or a chronic hypotony may occur from atrophy of the ciliary body.[30]

Retinal detachment is a rare and potentially devastating sequelae of uveitis.[31] Retinal detachment when seen with uveitis, is most frequently associated with posterior uveitis, panuveitis and infectious uveitis. Patients with uveitis and rhegmatogenous retinal detachments have a significantly higher proportion of proliferative vitreoretinopathy when compared to those with rhegmatogenous retinal detachments and no uveitis.[32]

Retinal and choroidal neovascularization may be a destructive complication of uveitis. This usually occurs from capillary nonperfusion or from chronic inflammation. Neovascularizatoin is particularly common in pars planitis, sarcoid panuveitis, and retinal vasculitis.[33] Choroidal neovascularization is seen in association with ocular histoplasmosis syndrome, punctuate inner choroidopathy, VKH, idiopathic multifocal choroiditis, and serpiginous choroiditis.[34]

Band keratopathy can be another visually disabling and potentially painful complication. Calcific band-shaped keratopathy results from chronic uveitis, especially in childhood-onset uveitis.[16] Calcific bands are formed by calcium deposits in the epithelial basement membrane and Bowman's layer. When the visual axis is involved, it can become visually significant.

DIAGNOSIS

A careful medical history must be taken to explore possible autoimmune, inflammatory, infectious, traumatic, or neoplastic causes of uveitis. Accurate diagnosis demands exploration of several other demographics: family history, geography/travel, social/sexual history, disease exposure and occupational exposure. Treatment should be guided by etiology, however, an etiology is often never found despite extensive diagnostic workups. Idiopathic causes are typically found in anterior uveitis and infectious causes are more common in posterior uveitis. In a study documenting etiology of uveitis in a large community-based practice, 52.1% of patients with anterior uveitis were found to have an idiopathic cause, followed by 17.4% patients with HLA-B27+/seronegative spondyloarthropathies, 7.5% patients with HSV/HZV, 1.4% patients with JRA, 0.9% patients with Fuch's heterochromic iridocyclitis, and 0.9% with sarcoidosis. IOL-related causes were found to account for 0.9% patients and trauma accounted for another 5.2% patients.[35]

Knowledge of the pathophysiology of the condition is instrumental in determining the investigation required and the possible etiology. Ophthalmoscopy, gonioscopy, tonometry, visual acuity, visual field and eye movements should all be utilized. Slit lamp microscopy will demonstrate evidence of inflammation. Fluorescein angiography provides examination of the retinal blood vasculature.[36] Ultrasound biomicroscopy can be used to assess posterior involvement when a view of the fundus is prohibited due to anterior inflammation of media opacity.[37] Polymerase chain reaction analysis of aqueous humor and vitreous specimens can assist in the diagnosis of posterior segment infectious uveitis to enhance treatment choices.[38] Polymerase chain reaction is also helpful for anterior uveitis where a viral etiology is considered. Many cases of Possner-Schlossman and Fuch's are now thought to be viral.

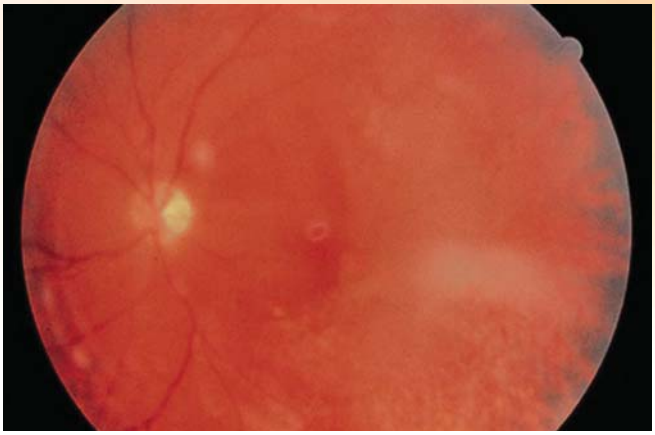
Blood tests may further assist in the investigation for underlying causes of uveitis.

An exhaustive list of tests includes: [39, 40]

Specific Clinical Laboratory Tests

- Bacterial antibody testing (toxocariasis, toxoplasmosis, *B henselae*, brucellosis)
- Viral antibody testing (HSV, CMV, VZV, EBV, hepatitis, HIV, human T-lymphotrophic virus)
- Luetic serology - Treponemal tests (fluorescent treponemal antibody absorption, microhem agglutination-*Treponema pallidum*) and nontre ponemal tests (rapid plasma reagin, Venereal Disease Research Laboratory)
- Lyme disease testing - Serology and polymerase chain reaction
- Leptospirosis serology
- Fungal serology - Blastomycosis, coccidioidomy cosis, histoplasmosis serum antibodies
- Connective tissue disease - Rheumatoid factor, antinuclear antibody, lupus anticoagulant, complement, protein electrophoresis, antineutrophil cytoplasmic antibody, and specific antinuclear antibodies (single stranded DNA, double stranded DNA, Smith, ribonucleoprotein)
- Nonspecific inflammation - Erythrocyte sedimentation rate, C-reactive protein
- Feces for parasites *(Ascaris, Entamoeba histolytica, Escherichia coli, Endolimax nana, Giardia lamblia)*
- Angiotensin-converting enzyme (sarcoidosis)
- Lysozyme (sarcoidosis, tuberculosis)

- Major histocompatibility antigens (HLA-B27 syndromes, HLA-A29 in birdshot chorioretinopathy, and HLA-B51 in Behçet disease)
- Standard tests - CBC count, differential, clotting factors, chemistry, urinalysis
- Cryoglobulins (myeloma and other myeloproliferative neoplasms, rheumatoid arthritis, Sjögren syndrome, lupus erythematosus, Waldenström macroglobulinemia, hepatitis, CMV infections, infective endocarditis, mononucleosis, leprosy)
- Complement levels, interleukin levels, circulating immune complexes
- Chlamydial complement-fixation test
- HIV testing (ELISA, Western Blot) and CD4 count



Immune reconstitution uveitis/vitreitis secondary to cytomegalovirus infection.

Immune reconstitution uveitis/vitreitis secondary to cytomegalovirus infection in an HIV-infected patient started on highly active antiretroviral therapy. (courtesy of F. Torriani, MD)

Taken from: Harold A. Kessler, Laurie A. Proia In Atlas of Infectious Diseases: AIDS. Edited by Donna Mildvan. Current Medicine, Inc. 2000.

Diagnostic Imaging

- Chest x-ray and spiral thin-cut CT scan (tuberculosis, sarcoidosis, histoplasmosis, tumor)
- Sacroiliac films (HLA-B27, reactive arthritis, ankylosing spondylitis)
- Orbital films, CT scan, or MRI (tumor, foreign body, thyroid, scleritis)
- Skull films (congenital toxoplasmosis)
- Joint films (rheumatoid arthritis, HLA-B27, JIA, lupus, gonorrhea)
- Gallium scan (sarcoidosis)

TREATMENT

Despite various classification criteria and treatment algorithms, therapies for uveitis are not universally accepted.[12] Treatment will depend upon the underlying cause, type, symptoms and severity of the disease. Therapy may be delivered locally or systemically. When a non-ocular disease is the underlying cause of uveitis, a priority will be to control that disease process. Ocular treatment directly reduces eye inflammation. Local ophthalmic treatment modalities for uveitis include corticosteroids and nonsteroidal anti-inflammatories.

Corticosteroids

Ophthalmic steroid treatment must be managed by an ophthalmologist. Intraocular pressure (IOP) must be monitored. A variety of co-morbid conditions contraindicate corticosteroid use in patients with uveitis, including viral diseases of the cornea and conjunctiva, and fungal or mycobacterial infections of the ocular structures. Herpes keratitis must be ruled out before topical steroid application begins.[41]

Some patients on steroid treatment can develop secondary glaucoma due to increased IOP. Topical steroid therapy presents the potential adverse effect of posterior subcapsular cataract formation. Children with JIA-induced uveitis must be monitored very closely.[6]

Corticosteroid treatment can include topical, periocular, intraocular, and oral routes of administration. Each will be discussed.

Topical Corticosteroids

Prednisolone acetate 1% (Pred Forte, OmniPred, EconoPred, and generics) is the most commonly used topical corticosteroid in the treatment of uveitis. Dosing can vary for acute uveitic flares and be quite frequent with gradually reduced dosing for most long-term use applications. Prednisolone decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

Loteprednol etabonate 0.5% (Lotemax) is a structurally similar compound to prednisolone, the difference being the lack of a ketone group on the number 20 carbon. Clinical trials have found loteprednol to be effective in the treatment of anterior chamber inflammation. Seventy-two percent of patients treated with loteprednol compared to 87% patients treated with prednisolone demonstrated resolution of anterior chamber cell and flare; however the loteprednol-treated patients experienced a lower incidence of significant IOP increase (1% in loteprednol group compared to 6% in prednisolone group.) There was no statistically significant difference in reducing cells or flare on any visit day during the 4-week study between the loteprednol group compared to the prednisolone group.[42]

Dexamethasone sodium phosphate 0.1% (Maxidex and generics) is another topical steroid option with higher risks of IOP elevation.
Fluorometholone 0.1% (FML) is a less potent steroid with less IOP elevating effects.
Rimexolone ophthalmic suspension 1% (Vexol) is FDA-approved for anterior segment uveitis. Vexol is a lower potency steroid and may have a decreased likelihood of inducing steroid response glaucoma. It is a suitable choice to consider for first-line therapy for mild to moderate anterior segment uveitis.
Difluprednate 0.05% (Durezol) is a difluorinated prednisolone derivative that has potent anti-inflammatory activity effective in reducing symptoms of anterior ocular inflammation - pain & ocular discomfort, photobia, blurred vision, and lacrimation. Difluprednate ophthalmic emulsion, 0.05% is a topical ophthalmic corticosteroid approved in the U.S. for the treatment of inflammation and pain associated with ocular surgery. Difluprednate has the advantage of less frequent dosing (four times a day compared to hourly or more in severe cases) than prednisolone acetate. In addition, difluprednate ophthalmic emulsion, does not contain benzalkonium chloride, a common preservative found in many ocular treatments that is known to cause corneal toxicity with long-term use. The difluprednate emulsion does not require shaking prior to instillation.

Periocular Corticisteroids

Periocular corticosteroids are generally given as depot injections when a more posterior effect is required (e.g., as with cystoid macular edema) or when patient is either unresponsive to topical or systemic treatment or noncompliant. A sub-Tenon's approach with a 25 gauge needle is typically used for periocular injection.[16]

A commonly used agent for periocular corticosteroid injections is **triamcinolone acetonide (Kenalog).** This product is not FDA-approved for ophthalmic use. On November 30, 2007, Alcon announced that the United States Food and Drug Administration approved **Triescence (triamcinolone acetonide injectable suspension)** 40 mg/mL, a preservative-free synthetic corticosteroid for visualization during vitrectomy and treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.[43]

Intravitreal Corticosteroid Injections

In severe cases of uveitis, intravitreal injections of corticosteroids (e.g., Kenalog and Triescence) can be used. Increased IOP, cataract progression and endophthalmitis have been noted.[44]

Intravitreal Corticosteroid Implants

Based on the Multi-center Uveitis Steroid Treatment (MUST) study in the US, the Food and Drug Administration approved an **intravitreal fluocinolone acetonide (FA) steroid implant (Retisert)** in 2005 for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. This implant is surgically introduced through the pars plana into the back of the eye and the drug reservoir releases steady amounts of corticosteroids into the vitreous cavity over a period of up to two and a half years. During clinical trials, the recurrence rate of uveitis fell from 40-54% to 7-14%.[45]

Three-year clinical trial results for treatment of posterior uveitis with a fluocinolone acetonide implant randomized 278 patients to receive either the 0.59-mg FA implant (N = 110) or the 2.1-mg FA implant (N = 168) after a scleral opening was created at the pars plana. The recurrence rate of uveitis was reduced from 62% to 4%, 10%, and 20% during the 1-, 2-, and 3-year post-implantation periods, respectively, for the 0.59-mg dose. Reductions with 2.1-mg dose were similar. Incidence of intraocular pressure elevation of eyes implanted with FA had a higher rate compared with eyes that were not implanted. Filtering surgery was required in 40% of FA implanted eyes compared with 2% of non-implanted eyes. Cataract surgery was performed in 93% of phakic implanted eyes compared with 20% of phakic non-implanted eyes. Visual acuity remained stable or improved over baseline in most eyes during the 3-year study period.

Elevated IOP is a significant complication with the FA intravitreal implant but may be controlled with medication and surgery. During the 3-year follow-up, topical IOP-lowering medication was administered in 74.8% of implanted eyes, and IOP-lowering surgeries, most of which were trabeculectomies (76.2%), were performed on 36.6% of implanted eyes. IOP–lowering surgeries were considered a success (postoperative IOP of 6-21 mm Hg with or without additional IOP-lowering medication) in 85% of eyes at 1 year. The rate of hypotony (IOP ≤ 5 mm Hg) following IOP-lowering surgery (42.5%) was not different from that of implanted eyes not subjected to surgery (35.4%) (P = .09). Fluocinolone acetonide reimplantation for chronic noninfectious posterior uveitis offers similar control of ocular inflammation and coplications profile as the first implantation.[46,47,48]

Oral Corticosteroids

The typical starting dose for oral corticosteroids is 1.0 to 1.5 mg/kg/day of prednisone. There are a variety of systemic risks of oral corticosteroids. Short-term risks include exacerbation of diabetes, electrolyte alterations, weight gain and psychiatric disturbances. Risks of long-term administration include osteoporosis or avascular necrosis of bone, suppression of the hypopituitary-pituitary-adrenal axis and Cushinoid fat redistribution. Ophthalmic side effects, including cataract formation and steroid-induced glaucoma, can occur with systemic administration. Systemic steroids should be administered in

consultation with a primary care physician or endocrinologist.[49]

NSAIDS

Non-steroidal anti-inflammatory drugs (NSAIDs) are not usually used in uveitis. Oral NSAIDs may have some benefit in reducing the severity and frequency of episodes of recurrent anterior uveitis. They can be a reasonable choice in some select clinical situations, such as mild anterior uveitis in a known steroid responder.

Topical NSAIDs such as ketorolac 0.5% (Acular) are more frequently utilized for mild traumatic uveitis or for postoperative inflammation following cataract surgery. There is minimal evidence supporting their efficacy in uveitis, and most trials regarding topical NSAIDS are restricted to the surgical literature.

Mydriatics & Cycloplegics

Topical mydriatics or cycloplegics are helpful in breaking or preventing the formation of posterior synechiae as well as relieving the ciliary spasm and associated photophobia. Cyclogyl, homatropine, scopolamine or atropine are commonly used drops.[19]

Surgery

Vitrectomy is sometimes necessary for the diagnosis and/or treatment of uveitis. Removing vitreous opacification or clearing a fibrotic posterior capsular opacity improves the view into the eye, which may aid in diagnosis or monitoring of choroiditis, vasculitis, or retinitis. In addition to clearing the media and treating the complications of uveitis, such as cystoid macular edema, epiretinal membranes, vitreous hemorrhage, or hypotension secondary to ciliary body traction, vitrectomy can have a diagnostic role.

Removing the vitreous from an inflamed eye permits culture and identification of the vitreous contents. Cytology and laboratory studies can sometimes assist in diagnosis characterization of uveitis or the presence of masquerade syndromes. The vitreous sample is often obtained undiluted prior to completing vitrectomy with the infusion of irrigating fluid. Vitrectomy also decreases the amount of inflammatory factors in the eye and may inhibit tissue damage or macular edema.[27]

A study of patients with chronic serous retinal detachments (SRD) associated with uveitis evaluated the anatomic and visual outcomes after surgical management. This was a retrospective, interventional, case series of patients with uveitis and controlled ocular inflammation who underwent drainage of chronic SRD at the Cole Eye Institute (1998-2006). Median time from SRD diagnosis to surgical drainage was 6 months. Retinal reattachment was achieved in all patients after a median follow-up of 55 months. Four of five patients experienced improvement in visual acuity after surgical intervention.[4]

Immunomodulation

When uveitis responds poorly to corticosteroids or becomes severe enough to threaten vision loss, cytotoxic or immunosuppressive agents may be required. Similarly, if control of disease requires 10mg/day of prednisone after a 6 month period, systemic immunomodulation may be indicated. Certain uveitic diseases (Behçet disease with posterior segment involvement, active serpiginous choroiditis, and Wegener granulomatosis) require systemic immunosuppression as part of standard treatment.[47] In these cases, collaboration between the ophthalmologist and chemotherapist are essential. Risk assessment must be made considering age, sex and social history of the patient. When used judiciously, NSAIDs and immunomodulators can cause fewer adverse events than systemic corticosteroids. Gene therapies, along with the newer therapeutic strategies, may in the future substitute modes of immunomodulation.[4,41,49,50]

Antimetabolites

Commonly used antimetabolite agents in the treatment of chronic uveitis include methotrexate, mycophenolate mofetil, and azathioprine.[48]

Methotrexate is an antimetabolite that acts by inhibiting folic acid metabolism which is required for DNA synthesis. It is typically used in a dose of 7.5 to 25mg/week, delivered orally, intramuscularly or subcutaneously. Toxicities include hepatoxicity, bone marrow suppression, pneumonitis, renal toxicity, and gastrointestinal (GI) upset. Folic acid 1mg/day is typically supplemented. Bloodwork including complete blood count (CBC) and liver function tests (LFT), and chest x-ray (CXR) and urinalysis (U/A) are monitored every 1-2 months.[48]

Mycophenolate mofetil (CellCept) inhibitis purine synthesis used in the proliferation of B and T lymphocytes. It is typically used at a dose of 1.0gm orally bid with a maximum dose of 3gm daily. Adverse side effects include GI upset in 1/3 patients, and this medication must be used with caused in patients with renal impairment. Opportunistic infections are a risk, as with all immunosuppressives. CBC and LFTs should be monitored every 3 months.[48]

Azathioprine (Imuran) is another purine synthesis inhibitor and has been used effectively to decrease recurrences of uveitis in patients with Behçet disease. It is given in doses of 1 to 3mg/kg/day. GI side effects are common and liver toxicity is a risk. Again, CBC and LFTs should be monitored every 3 months.[48]

T-cell Active Agents

Cyclosporine inhibits calcineurin which decreases interleukin release and, therefore, leads to a reduced function of effector T-cells. It can be dosed 3-5mg/kg/day and has associated side effects of retinal toxicity, hypertension, neurotoxicity, and electrolyte abnormalities. Blood pressure and renal function tests should be monitored every 3 months.[48]

Tacrolimus (FK-506) inhibits calcineurin thus inhibiting T-lymphocytes and interleukin-2 transcription. Recommended dosing is 0.15-0.30mg/kd/day. Side effects and management are similar to that of cyclosporine. In a recent randomized study, cyclosporine and tacrolimus were found to be similarly efficacious; however, tacrolimus had a slightly more favorable side effect profile.[48]

Cytotoxic Alkylating Agents

These agents are typically reserved for severe, refractory uveitis.

Cyclophosphamide forms DNA crosslinks between strands at guanine positions leading to cell death. Dosing is guided by white blood cell count (WBC) but typically is initiated at 2mg/kg/day. Side effects and risks include bone marrow suppression, GI distress, teratogenicity, hemorrhagic cystitis, bladder cancer, sterility. Opportunistic infections can be seen in as many as 70% patients. Monitoring should include a CBC and U/A monthly. Prophylaxis for pneumocystis pneumonia (PCP) with trimethoprim-sulfamethoxazole (Bactrim) should be considered.[48]

Chlorambucil also causes cytotoxicity by alkylating and cross-linking DNA during all phases of the cell cycle, resulting in disruption of DNA function and cell cycle arrest. Dosing is guided by WBC but typically begins at 0.1 mg/kg/day. Side effects and risks include bone marrow suppression, GI distress, sterility, and hepatotoxicity. CBC should be monitored.[48]

Biologic Therapies

Anti-tumor necrosis factor-[alpha] (anti-TNF α) agents are increasingly used for the treatment of pediatric uveitis and posterior uveitis associated with Behçet disease. Therapy is based on TNF-α, a pro-inflammatory cytokine in organ-specific autoimmune diseases, having been identified as a key inflammatory mediator in some models of uveitis. Current day anti-TNF α agents include etenercept (Enbrel), infliximab (Remicade), and Adalimumab (Humira).[48]

Etenercept (Enbrel) is a pseudo-receptor to TNF α. It does not appear to be as effective for the uveitic component of juvenile rheumatoid arthritis (JRA) as it is for the arthritic component.[48]

Infliximab (Remicade) is a human-murine chimeric antibody and has been well-studied for the treatment of anterior and posterior uveitis. Response is generally temporary. Side effects are uncommon and include increased risk of malignancy, tuberculosis, multiple sclerosis, optic neuritis, and drug-induced lupus. **Adalimumab (Humira)** is a fully human anti-TNF α antibody and has the advantage of being self-administered subcutaneously by the patient. Adverse events are similar to those reported for infliximab. There may be fewer adverse reactions to adalimumab than infliximab because of increased reactions to the murine component of infliximab. Efficacy of daclizumab for Behçet disease, and as maintenance therapy for non-infectious uveitic disease, are being studied in clinical trials.[51]

Other New Immunomodulating Agents

Fingolimod (FTY720) is another new immunomodulating agent used in relapsing multiple sclerosis. When administered in a short-term, high-dose, oral treatment it rapidly reduces ocular infiltrates in experimental autoimmune uveoretinitis to regain a normal myeloid cell count within the retina.[52]

IL-1 and IL-2 have been found to play key roles in posterior uveitis, providing the rationale for their use in ocular inflammatory disease. Cytokines recently linked to uveitic patients for the first time, included Interleukin (IL)-22 and IL-20. **Anakinra, a recombinant IL-1 receptor antagonist,** improves inflammation in uveitis.[41,50]

The role of Interferons (IFN) in uveitic disease is complex. **Recombinant human IFN-α** has been used with success to treat a variety of posterior uveitides, including those associated with Behçet disease and idiopathic causes. Flu-like symptoms are common with treatment. More significant adverse effects include leukopenia, elevated hepatic enzymes, alopecia, lupus, and central nervous system (CNS) effects. IFN- has been successful in the treatment of choroiditis and choroidal neovascularization (CNV) in chronic recurrent punctuate inner choroidopathy, and uveitis associated with multiple sclerosis.[41]

ANTI-VEGF Therapies

As with many current day ocular diseases in which vascular permeability may play a role in contributing to macular edema, anti-VEGF therapies are being introduced as possible components of a treatment regimen. In early studies, bevacizumab has been effective in improving acuity and reducing macular thickness in patients with uveitis-associated cystoid macular edema (CME).[41,53,54]

CONCLUSIONS

Uveitis is a complex and challenging disease that has been extensively studied, yet we still have much to learn about accurate diagnosis and appropriate treatment. The vast array of etiologies, severities, recurrences, and treatments for uveitis pose a challenge for both the clinician and the scientist. New treatment modalities, particularly some of the new biologic agents, offer hope for less toxic therapies, however, these therapies are certainly not without risks of their own. For now, the standard of care in treating uveitis patients is offering aggressive and early treatment to control inflammation, with careful consideration of side effects of such treatment plans.

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UVEITIS POST TEST

1) Classification systems of uveitis are typically based on all of the following except:
   a) clinical course
   b) etiology
   c) bacterial culture
   d) histopathology

2) The most common infectious cause of uveitis is:
   a) CMV
   b) Staphylococcus
   c) HIV
   d) HSV

3) Which one of the following is not a SUN classification of uveitis:
   a) panuveitis
   b) exterior
   c) anterior
   d) intermediate

4) A classic presentation of anterior uveitis includes all of the following except:
   a) retinal tears
   b) redness
   c) photophobia
   d) pain

5) Which of the following is not a complication of intravitreal corticosteroid injection?
   a) exotheliitis
   b) cataract progression
   c) increased IOP
   d) endophthalmitis

6) Short-term oral corticosteroids use may exacerbate all except:
   a) psychiatric disturbances
   b) weight gain
   c) electrolyte alterations
   d) reduction in corneal luster

7) Topical NSAIDs are:
   a) a common treatment for anterior uveitis
   b) used to treat recurrent uveitis
   c) appropriate for post-operative inflammation
   d) inappropriate for mild traumatic uveitis

8) Commonly used antimetabolites for chronic uveitis include all except:
   a) mycophenolate mofetil
   b) azathioprine
   c) methotrexate
   d) bevacizumab

9) Common ocular steroid treatment modalities for uveitis include all of the following except:
   a) topical
   b) subtenon's injection
   c) intravitreal injection
   d) anterior chamber injection

10) In the Unites States, uveitis affects approximately how many people annually?
   a) 88,000
   b) 160,000
   c) 280,000
   d) 520,000

OCULAR Infection & Inflammation

Evaluation/Post Test, Ocular Infection & Inflammation
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Objectives:

1) Compare & contrast the immunology of the anterior eye & pathophysiology of uveitis
2) Describe the types of uveitis
3) Identify appropriate clinical tests to correctly diagnosis uveitis
4) Review the rationale for current and new treatments for uveitis

Registration Information and Evaluation Response Form

Name: _____ Credential(s): _____

Home Address: _____

City: _____ State: _____ Zip Code: _____

Home Phone: _____ Work Phone: _____ Fax: _____

State of Licensure: _____ License #: _____ Exp. Date: _____

Type of credit desired: ❍ CME ❍ Nursing Contact Hours ❍ Pharmacist

Test response: Circle the most appropriate response matching test question number and response number.

1.	A	B	C	D	4.	A	B	C	D	7.	A	B	C	D	10. A B C D
2.	A	B	C	D	5.	A	B	C	D	8.	A	B	C	D	
3.	A	B	C	D	6.	A	B	C	D	9.	A	B	C	D	

General Evaluation: Please use the scale below to evaluate this educational activity and objectives. Circle your response.

As a result of completing this offering, I am able to meet the following objectives.	4 Strongly Agree	3 Agree	2 Disagree	1 Strongly Disagree
1. Compare & contrast the immunology of the anterior eye & pathophysiology of uveitis	4	3	2	1
2. Describe the types of uveitis	4	3	2	1
3. Identify appropriate clinical tests to correctly diagnosis uveitis	4	3	2	1
4. Review the rationale for current and new treatments for uveitis	4	3	2	1
5. Commitment to change	4	3	2	1
6. The content matches the objectives	4	3	2	1
7. Independent study was an effective teaching method	4	3	2	1
8. Is the article free of commercial bias?	4	3	2	1
9. The time required to complete this offering (in minutes) and take the test was	60	75	90	>90