

Anterior Uveitis: Teaching Case Reports

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Abstract

Acute anterior uveitis (AAU) is the most common form of intraocular inflammation seen by eye care professionals that affects relatively younger patients, with significant distress and potentially long-lasting sight-threatening complications. The diagnosis of AAU is relatively simple for clinicians because of multiple presenting signs and symptoms; however, the etiology is often much more difficult to elucidate. Therefore, it is critical for interns and practicing clinicians to have an extensive understanding of the pathogenesis of AAU. Judicious yet effective dosage of topical corticosteroid and cycloplegic agents are the mainstay of AAU treatment. Depending on the presentation and cause, other medications, lab tests and tertiary procedures may be necessary. Finally, coordination with other specialists (i.e., ophthalmologists, rheumatologists) may be critical in diagnosis and treatment. Eye care providers play a key role in the interdisciplinary management of the patient with AAU.

Key Words: Anterior uveitis, iritis, iridocyclitis, cells and flare, HLA-B27, corticosteroids, cycloplegics

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Background

Two cases of acute anterior uveitis (AAU) are presented; one involving a 24-year-old Caucasian female, and the other affecting a 48-year-old Hispanic female. These cases cover one of the most common forms of 'red eye' that prompts patients to seek eye care urgently, and illustrate the clinical decision-making process arriving at the diagnosis and appropriate management. The condition is relatively common, with many third- and fourth-year optometry interns encountering it at least once during their clinical rotations. Thorough case history, careful slit lamp biomicroscopy and complete posterior segment examination are essential to correctly diagnose and treat this ocular condition. In addition, lab testing, imaging and referral to an internist and/or rheumatologist are called for in some cases.

AAU is an acute intraocular inflammation of the iris and ciliary body due to a breakdown in the blood-aqueous barrier, leading to presence of "cells and flare" in the anterior chamber (AC).¹ The diagnosis of AAU is relatively simple due to the plethora of clinical symptoms, such as photobia and painful eye, and signs, such as limbal flush, posterior synechiae, and AC cells and flare observed on slit lamp biomicroscopy. In contrast, the challenge is in determining the etiology because AAU could be a result of trauma or iatrogenic sources, an infectious agent, medications, a systemic autoimmune condition or idiopathic cause. Consequently, the differentials for the etiology of AAU can be lengthy, and a thoughtful list of questions is important in narrowing the causative suspects. For instance, questions related to recent soft contact lens wear, injury or ocular surgery can rule out their corresponding association.

Whereas age-related macular degeneration and glaucoma tend to affect older patients, AAU is a condition that affects relatively younger patients more frequently, with significant distress and potentially long-lasting sight-threatening complications.² Therefore, it is critical for interns and practicing clinicians to have an extensive understanding of the pathogenesis of AAU and its prompt and appropriate treatment, including

interdisciplinary co-management as indicated.

Student Discussion Guide

Case 1 description

A 24-year-old Caucasian female presented to the University Eye Clinic on June 16, 2010 with a complaint of a red, watery and painful right eye for about a day. She also mentioned that this was the third episode she had experienced on an annual basis over the past three years, with the past two episodes lasting approximately 40 days with treatment. Her medical history was unremarkable, without any ocular injury or surgery. In addition, she had denied any joint pain or bowel disease when questioned. She reported that her sister has an 'eye turn' and had been treated with an eye patch, and that her maternal uncle was recently diagnosed with glaucoma. She currently takes multivitamins and an oral contraceptive. Her last eye exam two months ago revealed normal exam findings.

At the current visit, her distance visual acuity (VA) without correction was 20/20-1 OD and 20/20+1 OS. Both eyes showed smooth, accurate, full and equal extraocular muscle movements in all fields of gaze. No pupillary defect was observed, and no notable photophobia was reported in either eye. Finger counting confrontation visual fields were full OD and OS. Anterior segment findings, as observed with biomicroscopy, demonstrated 1+ circumlimbal flush with trace cells and flare OD (Figures 1A and 1B). Goldmann applanation tonometry was 13 mmHg OD and 14 mmHg OS at 10:48 a.m. Dilated fundus examination showed a normal retina with healthy maculae and vasculature and optic nerve cup-to-disc ratios of 0.45H /O.40V OU, with healthy optic nerve head rims and distinct disc margins in both eyes.

The patient was diagnosed with recurrent, but mild, acute anterior uveitis of her right eye and educated about her findings, prognosis and treatment options. She was treated with Pred Forte (PF; prednisolone acetate 1% ophthalmic suspension) igt q2h and homatropine 5% (H) ophthalmic solution igt qhs OD. She was recommended to return to clinic a week later, or sooner if her symptoms get worse. Since the uveitis

Figure 1A (Case 1)
Anterior uveitis OD with fibrous deposits on the lens

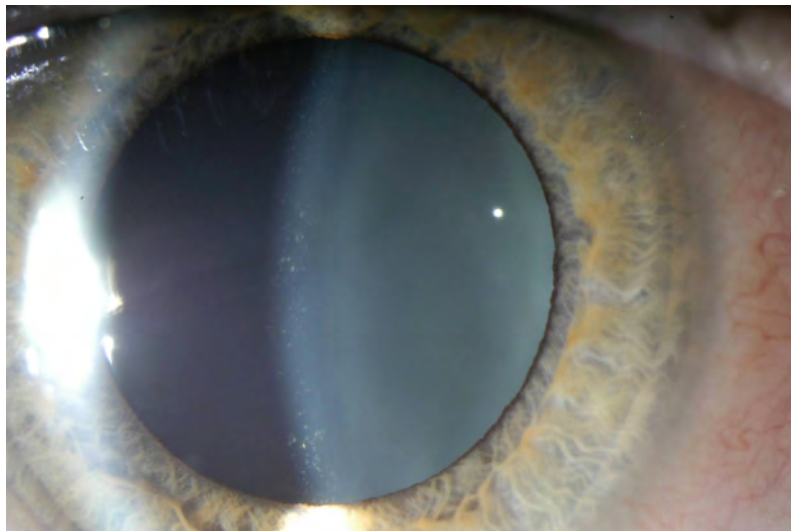
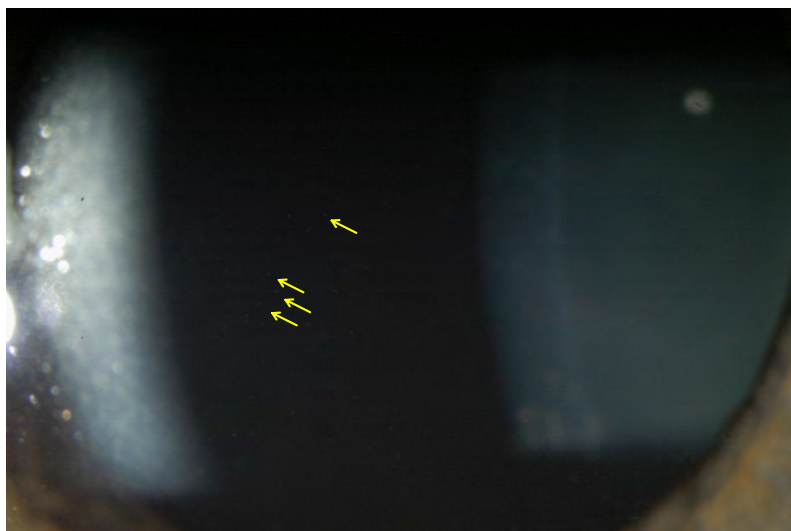


Figure 1B (Case 1)
High magnification (40X) shows cells (representative arrows) in the AC OD



was recurrent, she was also referred for blood workup, human leukocyte antigen (HLA) testing and spinal X-ray to explore a possible systemic cause. A review of her chart records revealed that her blood workup two years ago was normal.

Follow-up # 1: June 23, 2010

A week later, the patient felt that her eye condition was slightly worse, although her VA was still 20/20-1 OD and 20/20+1 OS. Moderate circumlimbal injection, 2+ cells and 2+ flare, was seen in the AC. The PF was increased to igt q1h OD and the H to igt bid OD.

She was referred to a local rheumatologist-ophthalmologist for further consultation. Her recent spinal X-ray and blood workup were normal, with the exception that she was HLA-B27 positive. The specialist concluded that the inflammation has affected only the patient's eye so far, but in the future she will have a higher risk for arthritis, and that long-term nonsteroidal anti-inflammatory drug (NSAID) treatment may be beneficial.

Case 2 description

A 48-year-old Hispanic female presented to the University Eye Clinic on Feb 2, 2010 with a chief complaint of

painful red eye, severe photophobia and tearing OD for the past few days. She had tried an over-the-counter anti-allergy drop, but it did not help. Medical history was positive for depression and hand tremors, for which she had been taking oral vitamin B6 and Flexeril (cyclobenzaprine), respectively. She reported no joint/back pain and no pain on urination or bowel movement. Her last eye exam was many years ago, and she reported no history of ocular injury or surgery. Family medical history was negative for diabetes, hypertension, glaucoma or blindness.

At the current visit, her uncorrected distance VA was 20/150 OD and 20/150 OS, with pinhole improvement to 20/60-2 OD and 20/60+1 OS. Both eyes showed smooth, accurate, full and equal extraocular muscle movements in all fields of gaze. No afferent pupillary defect was observed; however, the patient was photophobic in her right eye. Finger counting confrontation visual fields were full OD and OS. Anterior segment findings, as observed with biomicroscopy, demonstrated 2+ circumlimbal injection and 2+ cells in the AC in the right eye. No vitreal cells or haze were seen in either eye. Posterior poles appeared normal OU with healthy maculae, vasculature, and cup-to-disc ratios of O.30H/0.30V both eyes. Goldmann applanation tonometry was 16 mmHg OD and 15 mmHg OS at 5:46 p.m.

Acute anterior uveitis with posterior synechiae OD was diagnosed, and the patient was educated about her findings, prognosis and treatment options. She was treated with a prescription regimen of PF igt q1h OD and H bid OD. The patient was recommended to return to clinic the next day for follow-up.

Follow-up # 1: Feb 03, 2010

The patient reported slight improvement in her comfort after taking the drops as prescribed, but she was still tearing and photophobic in her right eye. Her uncorrected VA was worse at 20/400 OD and the same at 20/150 OS, but pinhole improved the VAs to 20/100- OD, 20/60 OS. Anterior segment findings, as observed with biomicroscopy, demonstrated 2+ circumlimbal injection, 2+ cells and 3+ flare in the AC with posterior synechiae and fibrin membrane OD (Figure 2A). Non-

contact tonometry was 10 mmHg OD and 12 mmHg OS at 9:47 a.m. One drop of phenylephrine 10% and one drop of atropine 1% were instilled in-office to attempt to break the posterior synechiae. As before, no vitreal cells or haze were seen OU. Posterior poles also were normal OU with healthy maculae, vasculature, and cup-to-disc ratios of O.30H/0.30V both eyes.

The patient was instructed to continue the PF igt q1h OD and H igt bid OD and to return to clinic in two days. A letter with request for a blood workup was sent to her primary care provider,

and a rheumatological consult was also recommended.

Follow-up # 2: Feb 05, 2010

The patient appreciated further improvement over the next two days, although she still felt some discomfort and tearing. Her VA had improved to 20/80-1 (pinhole 20/40+1) OD and was unchanged OS (20/150; pinhole 20/60). Anterior segment findings, as observed with biomicroscopy, demonstrated mild circumlimbal injection, 1+ cells and 1+ flare in the AC with posterior synechiae at 7 o'clock, and resolving fibrin membrane OD (Figure 2B).

Figure 2A (Case 2)
Anterior uveitis OD with fibrous membrane and posterior synechiae

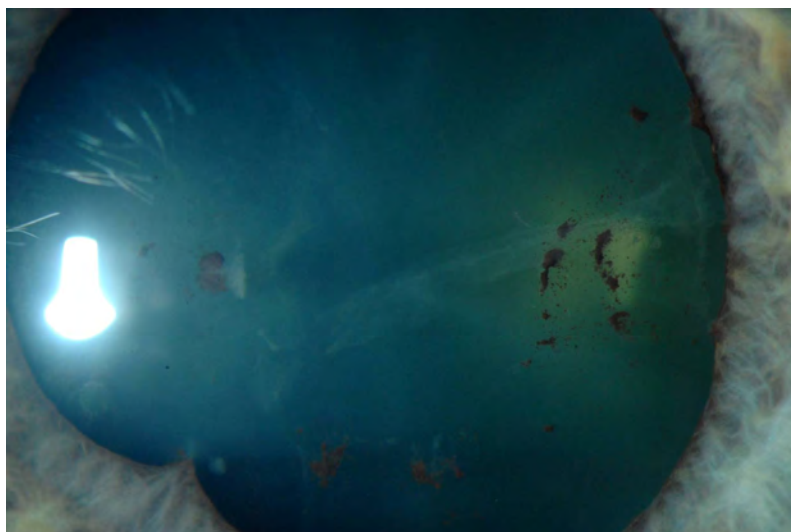
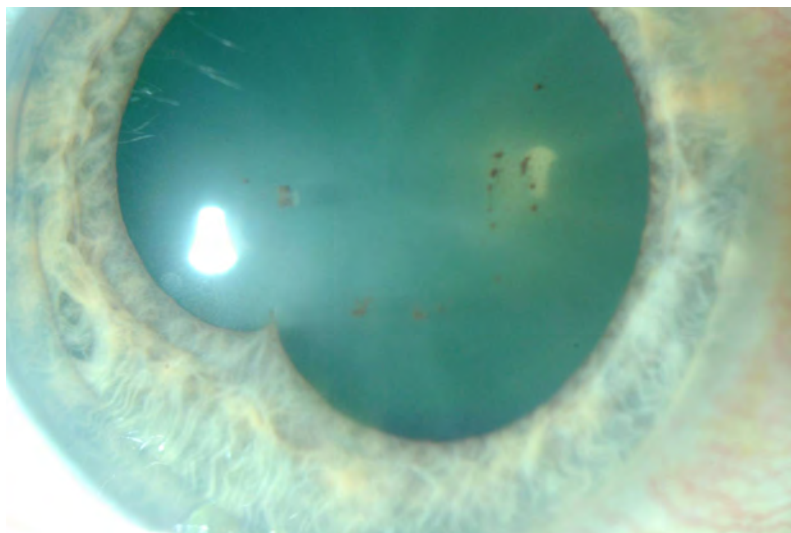


Figure 2B (Case 2)
Anterior uveitis OD. Fibrous membrane resolved with topical steroid treatment



Noncontact tonometry was 12 mmHg OD and 14 mmHg OS at 3:16 p.m.

The patient was instructed to continue the PF igt q2h OD for two days and then taper to igt q4h OD for the subsequent three days, continue H igt bid OD, and to return to the clinic in five days with her blood workup results.

Follow-up # 3: Feb 10, 2010

Five days later, the patient felt that her symptoms were worse, with more pain and photophobia. Her VA was reduced at 20/150 (pinhole 20/50) OD and 20/200 (pinhole 20/60) OS. Anterior segment findings, as observed with biomicroscopy, demonstrated moderate circumlimbal injection, 2+ cells and 1+ flare in the AC with posterior synechiae at 7 o'clock OD. Noncontact tonometry was 10 mmHg OD and 15 mmHg OS at 9:59 a.m.

The patient was advised to increase the PF to igt q2h OD and H bid OD. In addition, she was prescribed oral prednisone (60mg/day for one week). She was also promptly referred to see a local rheumatologist. Her blood workup there showed high white blood cell and platelet counts, low hematocrit and positive presence of HLA-B27.

Follow-up # 4: Feb 17, 2010

A week after the combined topical and oral steroid treatment, the patient felt much better, with only mild discomfort. Her VA was 20/80 (pinhole 20/40-) OD and 20/150 (pinhole 20/50) OS. Refraction was performed, giving -3.00 -1.00 x 164 to 20/25- OD and -2.50 -1.25 x 021 to 20/25 OS with near addition of +1.50 OU. Anterior segment findings, as observed with biomicroscopy, demonstrated mild circumlimbal injection, with no cells and trace flare in the AC OD.

The rheumatologist concluded that she has HLA-B27-associated uveitis, and maintained her on oral steroid as prescribed. She was recommended to taper off her oral and topical steroid gradually over the next two weeks and to discontinue the homatropine.

Follow-up # 5: Mar 03, 2010

At this visit (almost three weeks later), the patient was off all prescribed uveitis medication, and she felt that her eye condition had completely resolved. She

had not filled her spectacle prescription from the prior visit, and her VA was still 20/80 (pinhole 20/40-1) OD and 20/100 (pinhole 20/50) OS. She was educated on her recent uveitis condition and warned that it might recur in the future.

Key concepts

1. Common etiologies of acute anterior uveitis
2. Thorough case history for patients with acute anterior uveitis
3. The use of epidemiology in differentiating possible causes
4. Clinical findings in differential diagnosis of acute anterior uveitis
5. Treatment of acute anterior uveitis
4. The importance of patient education and regular follow-up
5. The essentials of appropriate systemic workup and specialist consultations

Learning objectives

1. To ask intelligent questions in helping with differential diagnoses
2. To understand the signs and symptoms of ocular inflammation
3. To relate patient demographics to known epidemiology of the AAU
4. To rule out posterior segment involvement of ocular inflammation
5. To provide appropriate patient education and optimal medical management
6. To collaborate with other health care professionals in management of possible systemic cause

Discussion questions

- A. Knowledge, concepts, facts, information required for critical review of the cases
1. Describe the signs and symptoms of anterior uveitis vs. other inflammation/injury
 2. Describe the different types of uveitis based on anatomy
 3. Discuss the cause of cells and flare in the anterior chamber
 4. Discuss the risk factors for uveitis
 5. Determine causality based on patient case history, risk factors

and demographics

6. Discuss the importance of the presence of HLA-B27
 7. Discuss systemic inflammatory diseases that have high association with AAU
 8. Describe the mechanisms of action of drugs used in management of AAU
 9. Discuss the potential side-effects of steroid use
- B. Generating questions, hypothesis, and diagnosis
1. What are important questions relevant to AAU?
 2. How is AAU diagnosed?
 3. What age group does AAU tend to affect?
 4. What are the potential differential diagnoses?
 5. Why is pupil dilation necessary?
 6. What laboratory tests are helpful in identifying the etiology?
 7. Is the diagnosis valid?
- C. Management
1. What are the different topical corticosteroids available for ocular inflammation? How are they ranked in terms of potency?
 2. Why are cycloplegics needed?
 3. Should oral NSAIDs be used?
 4. When is laboratory workup advised?
 5. What is the follow-up schedule?
 6. What course of action is necessary when symptoms get worse with treatment?
 7. When should the patient be referred to a specialist?
 8. What specialists are indicated?
 9. Why is it necessary to taper the steroid?
- D. Critically assessing implications, patient management and psychosocial issues
1. What are the implications of standard treatment vs. modified/no treatment? Consider

cost, time, side-effects, convenience effect and quality of life.

2. What are the consequences associated with noncompliance to the treatment plan?
3. What pertinent information should be used to educate the patient about the condition?
4. Discuss ways to respond to the anxiety of the patient towards future recurrence and prognosis with respect to the patient and the patient's family members.

Educator's Guide

The educator's guide includes the necessary information to discuss the case.

Literature review

The breakdown of blood-aqueous barrier in the iris and ciliary body leads to clinical signs and symptoms of acute anterior uveitis. It is the most common form of intraocular inflammation seen by eye care professionals.¹ The leakage of vascular contents into the anterior chamber can be seen as "cells" and "flare" via slit lamp biomicroscopy. A grading system was established by the Standardization of Uveitis Nomenclature (SUN) for clinical use (Table 1).² Cells are predominantly white blood cells (leukocytes) released in response to inflammation. Flare is comprised of serum proteins: pro-inflammatory cytokines and chemokines that selectively recruit inflammatory white blood cells. Furthermore, flare can coalesce to form fibrin, while white blood cells can precipitate in the corneal endothelium in certain forms of uveitis to form keratic precipitates (KPs). Therefore, the diagnosis of AAU is relatively simple for clinicians because of multiple presenting signs and symptoms. However, the etiology is often much more difficult to elucidate.

The annual incidence of uveitis has been estimated to be about 35 per 100,000 in the general population with a prevalence of 0.5%.¹ Of the uveitides categorized by anatomical location (anterior, intermediate, posterior, panuveitis) anterior uveitis accounts for most of the cases seen clinically.³ The lifetime incidence of AAU may be as high as 0.2 %

Table 1
Standardization of Uveitis Nomenclature (SUN) grading system for AC cell and flare severity.² The presence or absence of a hypopyon should be noted separately in addition to the AC cellular activity grade.

Grade	AC Cells (1 mm x 1 mm beam)	AC Flare
0	None	None
0.5+	1-5 cells	-
1+	6-15 cells	Faint
2+	16-25 cells	Moderate (clear iris & lens)
3+	26-50 cells	Marked (hazy iris & lens)
4+	>50 cells	Intense (fibrin or plasmoid aqueous)

of the population.⁴ HLA-B27, a Class I major histocompatibility complex (MHC), is a strong risk factor and associated with up to half of all cases of AAU.⁵ HLA-B27-positive AAU tends to be more severe in presentation and earlier in onset than HLA-B27-negative uveitis, affecting primarily younger patients between 20 and 40 years of age.³ In addition, males are affected 2.5 times more frequently than females in HLA-B27-positive uveitis. The prevalence of the HLA-B27 gene varies among populations, as high as 8% in Caucasians, and as low as 0.5% in Japan.^{1,3}

A number of systemic inflammatory diseases, such as ankylosing spondylitis (AS), Reiter's syndrome and psoriatic arthritis, have been known for decades to associate with HLA-B27 and AAU. Particularly, 90% of patients with AS possess the HLA-B27 antigen.^{2,6}

Clinical features

Acute anterior uveitis typically presents with the patient experiencing hallmark symptoms of recent onset eye pain (often dull, aching pain) and photophobia. Secondary symptoms include blurred vision, a watery/tearing eye, redness and headache. One or both eyes may be affected. Visual acuities may or may not be reduced depending on severity of the uveitis. Pupillary testing may show a sluggish pupillary constriction response to light, usually due to iris inflammation and/or iris synechial adhesions. A direct and consensual eye pain to light is highly specific to anterior uveitis, even when other signs are not as

obvious. Ocular signs include anterior chamber cells that slowly drift in the aqueous humor. These anterior chamber cells should be differentiated regionally from cells in the vitreous, which would indicate an intermediate or posterior uveitis. The clinician may often use high magnification with a relatively bright illumination upon biomicroscopy to visualize cells. The appearance of cells in the AC is similar to seeing a few to numerous dust particles floating and moving in empty space. Similarly, bright illumination and magnification is often necessary to visualize flare, with conical beam illumination revealing a Tyndall effect (light scattering) from the suspended protein particles. Severe flare and inflammatory mediators released into the anterior chamber can rarely lead to a viscous 'plasmoid' aqueous and hypopyon. The corneal endothelium may show adherent cells (both white blood cells and, less often, iris melanocytes) that predispose the inferior aspect of the cornea (Arlt's triangle). Although the eye can appear white with uveitis, circumlimbal injection is a notable sign and, less often, a more generalized conjunctival inflammation. Posterior synechiae (iris adhesions, usually at the pupillary ruff, to the anterior lens capsule) are not uncommon with anterior uveitis; one study found posterior synechiae in half of 119 patients with acute anterior uveitis, regardless if it was HLA-B27 positive or negative.⁷ A corectopia (irregularly shaped pupil) can result from posterior synechiae, as well as later adhesion of pigment to the

anterior lens capsule in a circular pattern corresponding to pupillary ruff pigment (Vossius ring). A fibrin membrane on the anterior lens capsule can often remain from longstanding synechiae. Extensive posterior synechiae can lead to circumferential adhesion to the anterior lens capsule, leading to pupillary block, a bowing forward of the iris (iris bombé) from posterior aqueous entrapment, and highly-elevated intraocular pressure (IOP). Peripheral anterior synechiae (PAS), whereby the peripheral iris tissue near the ciliary body adheres to the anterior chamber angle structures, is less common. Best observed via gonioscopy, these adhesions can block the trabecular meshwork, impeding aqueous outflow and potentially elevating the IOP.

Differential diagnoses

The common differential diagnoses for AAU are summarized in Table 2, and some of the more serious conditions are discussed.

- Intermediate/posterior/panuveitis are conditions whereby uveal inflammation has progressed beyond the iris tissue. The sign of cells and/or inflammatory exudates in the vitreous is a key finding with these uveitides, and vitreal haze is often present. Because constant fluid exchange in the vitreous does not occur as it does in the aqueous, the cells and inflammatory byproducts persist and move with gravity to settle in the inferior retina (called 'snowbanking') along the pars plana. This condition of intermediate uveitis is called pars planitis, and is more common in younger individuals, with a mean age of 30.7 years (± 15.1 years). Over two-thirds of intermediate uveitis cases are idiopathic, with sarcoidosis, multiple sclerosis (MS) and Lyme disease being the relatively less common causes.⁸ Posterior uveitis may present with macular edema, chorioretinal inflammation, retinal vasculitis and optic disc edema. Vitreal haze may also accompany posterior uveitis. While photophobia may be reduced in posterior uveitis (due to less inflammation of the irides), visual blur is usually more severe and prognosis of visual recovery poorer. Panuveitis involves all regions of

Table 2
Differential diagnoses for anterior segment inflammation

AAU (iritis, iridocyclitis)	Keratitis (infective, traumatic/toxic, contact lens acute red eye)
Episcleritis/Scleritis	Lens-related (phacolysis/phacoanaphylaxis)
Acute angle closure glaucoma	Posterior segment disease (tumor, panuveitis)
Endophthalmitis (post operation, endogenous)	

the uvea. Photophobia, eye pain and reduced vision are usually very severe, with poorer prognosis for long-term vision.

- Endophthalmitis, a true eye emergency involving inflammation of the vitreous and aqueous humor, may present with symptoms of blurred vision, eye pain and redness and light sensitivity, similar to AAU. However, history is an important differential, as endophthalmitis can be a rare endogenous (causative source is within eye) complication from ocular infection after surgical procedures such as cataract extraction and vitreoretinal surgeries.^{9,10} Exogenous (source is from outside the eye) endophthalmitis may result from infection spread from another source (i.e., endocarditis). Endophthalmitis may also occur from penetrating eye injury or ocular surgery and, in very rare instances, be due to unknown causes or present as a sterile inflammation from retained lens material after an operation or from toxic agents.¹¹ Usually along with similar symptoms, a layer of white blood cells may be seen settled in the inferior anterior chamber (hypopyon). Immediate referral for a vitreal tap and culturing/sensitivities is indicated for endophthalmitis, with subsequent pars plana vitrectomy and fortified topical, intravitreal and systemic antibiotic treatment.^{12,13}
- Keratitis can present with similar symptoms to AAU, and the causes of keratitis may be non-infective or infective in etiology. Non-infective keratitis may be due to external sources such as ultraviolet light (i.e.,

photokeratitis) from arc-weld flashes or high altitude reflection sun/snow exposure, chemical insult, or from immune conditions (i.e., Thygeson's superficial punctuate keratitis). Infective keratitis may be bacterial, viral, fungal, acanthamoebic, or chlamydial/parasitic. Light sensitivity, redness, pain, and reduced vision with any of these forms of keratitis can mimic AAU. It is also possible that an anterior uveitic response is seen accompanying an infective keratitis, so treatment of both conditions may be warranted. Treatment of the non-infective keratitis may be similar to treatment of AAU (i.e., topical steroid and cycloplegic agents). With infective keratitis, however, care must be taken to determine the specific causative organism, as topical steroids have the potential reduce wound healing and the body's immune response to fight the infection. This is especially true of herpetic epithelial keratitis, where topical steroid use may worsen the condition. Patients with herpetic keratitis (particularly herpes zoster infection) may present with acute pain, redness and light sensitivity, and the clinician must look closely for signs of dendritic lesions, pustules and rashes that may identify herpetic infection. Fluorescein sodium and rose Bengal stain assessment are critical to ruling-out herpetic lesions on the cornea. Fluorescein staining may also reveal epithelial defects, infiltrates and ulcers due to other organisms. The presence of mucopurulent discharge is a diagnostic sign of bacterial or chlamydial infection. While untreated bacterial

and chlamydial corneal infections usually worsen over several hours to a few days, fungal and certain acanthamoebic infections may progress more slowly, with progression over a week or more after initial inoculation not uncommon. History of soft contact lens wear, old makeup use, water-based activities (i.e., swimming, hot tub) and vegetative injury are important in determining the diagnosis. Treatment of infective keratitis is dependent on the causative organism, and typically involves topical antibiotics (bacterial), oral antibiotics (chlamydial), topical and oral antivirals (herpetic), antimycotics (fungal) or antiamoebics (acanthamoeba).

- Patients with acute angle closure can present similar symptoms to AAU, including pain, blurred vision, halos vision, frontal headache, nausea and vomiting. Circumlimbal flush and corneal edema is often seen. Intraocular pressure (IOP) spike is an important sign to differentiate acute angle closure from AAU; however, the patient may have an IOP spike secondary to iris bombé caused by AAU. The main approach to management of acute angle closure is to reduce the IOP as quickly as possible with topical, and often oral, glaucoma medications.

Treatment options for acute anterior uveitis

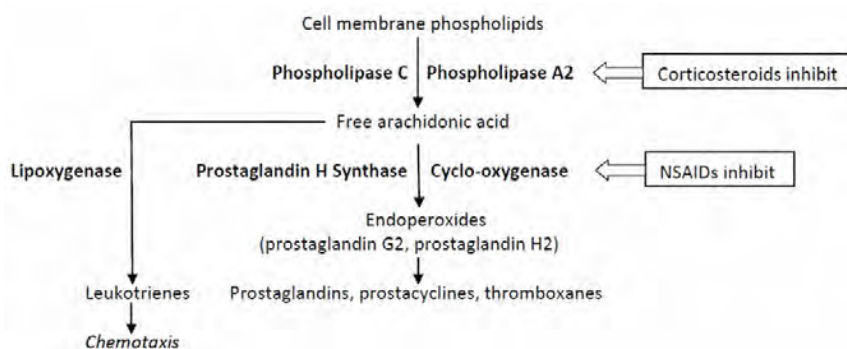
Management of AAU is focused on 1) reducing the inflammation and any associated pain, redness, photophobia and visual blur; and 2) determining the etiology. The first step is achieved by several treatments:

- Sun protection
The patient with AAU has usually determined that avoidance of bright light is to their immediate benefit. Encouragement of sunglasses, a brimmed hat, staying indoors more frequently and lowered lighting levels are good behavioral modifications during the acute symptomatic stage.
- Cycloplegics
Cycloplegic agents are important for relaxing the iris (for comfort), breaking posterior synechiae, and

Table 3
Cycloplegic agents, their concentrations, maximal effect and duration of action in healthy eyes

Cycloplegic Agent	Maximal Effect (min)	Duration of Action
Tropicamide 0.5, 1%	20-30	3 hours
Cyclopentolate 1, 2%	20-45	1 day
Homatropine 2, 5%	20-90	2-3 days
Scopolamine 0.25%	20-45	4-7 days
Atropine 0.5, 1, 2%	30-40	1-2 week(s)

Figure 3
The cellular inflammatory pathway (enzymes labeled in bold), with points of inhibition by corticosteroids and NSAIDs (nonsteroidal anti-inflammatory drugs) shown (adapted from Samiy N et al., 1996)¹⁴



stabilizing the blood-aqueous barrier by decreasing the iris surface area (preventing further cellular and exudative leakage). The main cycloplegic agents (listed from shortest maximal effect time/duration to longest) are listed in Table 3. The most popular agents used in AAU treatment are homatropine 5% (trade name: Isopto-Homatropine 5%; typical dosage igt q12hr) and scopolamine 0.25% (trade name: Isopto-Hyoscine; typical dosage igt q6hr). Atropine (trade name: Isopto-Atropine 1%; typical dosage igt q12hr) is used in more severe cases. Even though a cycloplegic's duration of action is relatively long in healthy eyes, the duration of action may be much shorter in uveitis due to the presence of increased esterases in the AC of a uveitic eye; hence more frequent dosing is needed.

- Mydriatics
Phenylephrine 2.5% or 10% (trade name: AK-Dilate) is an adrenergic

(alpha receptor) agonist used for assisting with the dilation of the pupil. It is used in-office with a cycloplegic agent for breaking recalcitrant posterior synechiae. Usually only one or two drops are instilled in the affected eye to facilitate dilation. The drug also assists in facilitating view of the vitreous and retina, to determine if there is any posterior segment inflammation.

- Corticosteroids
Corticosteroids are critical in the treatment of uveitides, including AAU. They reduce pain (including photophobia), inflammation (of most ocular tissues) and redness (of conjunctiva, episclera, limbus). Corticosteroids block the enzyme phospholipase A2 (which converts cell membrane phospholipids into inflammatory mediators such as leukotrienes and prostaglandins). This inflammatory pathway is seen in Figure 3.¹⁴ Topical ophthalmic steroid drops can be divided into 3 main cat-

egories, based on clinical potency:

Minimally effective:

- dexamethasone sodium phosphate 0.05% ointment
- loteprednol 0.2% (trade name: Alrex)

Moderately effective:

- prednisolone phosphate 0.125%, 0.5%, 1% solutions
- fluorometholone 0.1% (trade name: FML Mild), 0.25% (trade name: FML Forte)
- rimexolone 1% (trade name: Vexol)

Maximally effective:

- loteprednol 0.5% (trade name: Lotemax; combined with tobramycin in Zylet)
- dexamethasone 0.1% (combined with tobramycin in TobraDex)
- 1% prednisolone acetate (trade name: Pred Forte)
- difluprednate 0.05% emulsion (trade name: Durezol)

All topical ophthalmic steroid eye drops (except for the solution prednisolone phosphate and emulsion difluprednate) are formulated as suspensions. As such, the patient must shake the bottle vigorously before instilling the drop onto the eye, to provide a homogenous suspension of medication. The most popular steroid prescribed for AAU is Pred Forte (prednisolone 1%; igt q2hr); its generic version has been found to be less homogenous in formulation, with more shakes required for the drug to go into suspension.^{15, 16} A more recent steroid on the market, difluprednate (Durezol) was shown to be as effective as Pred Forte, yet with only half the dosage of Pred Forte.¹⁷ All steroids used over the course of a week or more are usually tapered gradually upon improvement of signs and symptoms, and then discontinued. If symptoms recur, the steroid's original dosage (or more frequent dosage) is re-initiated. Several steroid ointments (most in combina-

tion with one or more antibiotics) are also available for evening use.

Risks of topical corticosteroids include posterior subcapsular cataract (PSC) formation and elevated IOP. Usually these risks are minimal due to the short-term use of steroids in AAU treatment. Prednisolone acetate has a higher propensity to elevate IOP. Studies have shown loteprednol 0.5% (Lotemax) to be comparable to prednisolone acetate 1% in effectively reducing anterior uveitis, yet not elevating IOP as much as prednisolone acetate.¹⁸ Other risks of topical steroid use include reduced host immunity, stromal melt, scleral thinning and herpetic epithelial infection spread.

In certain recalcitrant uveitis cases, or when the patient is unable to properly instill eyedrops or ointment, injectable steroids may be indicated. These include regional subconjunctival or sub-Tenons injections of triamcinolone or dexamethasone, as well as intravitreal injections of each drug (Triesence; Alcon Laboratories) or implants (Ozurdex; Allergan Inc.), respectively. Fluocinolone acetate intravitreal implant (Retisert; Bausch + Lomb) is also an option in recurrent uveitides unresponsive to other steroid treatments. Unfortunately, the risk of elevated IOP and cataract with these routes of administration is much higher.²¹

- Oral steroids such as prednisone (Orasone, Deltasone, Meticorten, Sterapred, other trade names) and methylprednisone (Medrol, other trade names) are indicated when an AAU is severe or when posterior ocular involvement is seen. Typical adult dosage is 1mg/kg body weight, with taper upon improvement and dependent on duration of treatment (longer tapers with longer treatments). Along with increased IOP and posterior subcapsular cataract risk, several other potential side-effects include, but are not limited to:
 - Hypertension
 - Hyperglycemia
 - Psychosis
 - Edema (Cushing's Syndrome)

- Osteoporosis
- Growth suppression
- Reduced immunity (infections)
- Hypothalamus-Pituitary-Adrenal (H-P-A) axis suppression
- Menstruation problems

Because of these risks, the use of oral steroids should be weighed with the potential side-effects.

• NSAIDs

Both oral and topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) have limited effectiveness in treating active AAU, as their mechanism of action inhibits the enzyme cyclo-oxygenase (which produces prostaglandins) but not the enzyme phospholipase A2 (which produces leukotrienes, responsible for attracting white blood cells into the anterior chamber via chemotaxis). However, one study showed a 66.8% reduction in recurrences of HLA-B27-associated uveitis over a 3-year period with chronic oral NSAID use.²⁰

• Immunomodulators

In cases of non-infectious AAU that is recalcitrant or non-responsive to steroid treatment, immunomodulation may be necessary. The effectiveness of these medications with uveitis has been demonstrated in several cases.^{21,22} These consist of immunosuppressants and biologics. The three main immunosuppressant drug categories are:

- Antimetabolites (methotrexate, mycophenolate, azathioprine)
- T-cell suppressors, aka calcineurin inhibitors (cyclosporine, voclosporin, tacrolimus)
- Cytotoxic agents, aka alkylating agents (cyclophosphamide, chlorambucil)

Biologics, a relatively newer class of drugs, are comprised of recombinant cytokines and monoclonal antibodies directed against selected cell-surface markers.²³ The main biologics are:

- Tumor necrosis factor-alpha inhibitors (infliximab, adalimumab)
- Anti-lymphocyte drugs (ritux-

imab, alemtuzumab)

- Interleukin-2 receptor blocker (daclizumab)
- Recombinant interferon-alpha

Both immunosuppressants and biologics often take several weeks to achieve efficacy.

- Surgery

Surgical treatment for AAU is rare and only indicated in severe cases where secondary complications arise. Permanent structural changes from uveitis that may require surgical management include cataract formation, secondary glaucoma due to pupillary block or angle closure, and retinal detachment. Surgical indications include restoring visual clarity, diagnostic biopsy, or removing media opacities to monitor the posterior segment. Surgical procedures include, but are not limited to: extracapsular phacoemulsification/cataract extraction, iridotomy/iridectomy, filtering surgeries, vitrectomy and other corneal and retinal procedures.

Discussion

Uveitis is an inflammatory disease of the eye, potentially responsible for up to 20% of all blindness.²⁴ The International Uveitis Study Group (IUSG) and Standardization of Uveitis nomenclature (SUN) Working Group have adopted a classification of uveitis according to anatomical location: anterior (anterior chamber), intermediate (ciliary body, vitreous), and posterior (retina, choroid), with panuveitis involving all locations.^{25,26} Acute anterior uveitis (AAU) is an ocular presentation that has many potential etiologies. Identification of the key clinical findings of AAU – cells and flare – along with the accompanying symptoms of pain and photophobia – has been documented in the literature for over half a century.²⁷ While the most common etiology of anterior uveitis is idiopathic (38-70%), the next most-common etiology is HLA-B27-positive, particularly with acute-onset forms.⁴ HLA-B27 is present in 1.4-8% of the general population; however, it can be present in between 50-60% of patients with AAU.³ Since HLA-B27-positive results are strongly related to ankylosing

Table 4
Common causes of acute and chronic anterior uveitis (adapted from McCannel et al., 1996)⁴

Acute Anterior Uveitis	Chronic Anterior Uveitis
HLA-B27 positive (uveitis only) Ankylosing spondylitis Reactive arthritis (Reiter's) Psoriatic arthropathy HLA-B27 negative (idiopathic) Sarcoidosis Behcet's disease Posner-Schlossmann Syndrome Crystalline lens-associated Syphilis Lupus Trauma	Juvenile idiopathic arthritis (JIA) Fuch's heterochromic iridocyclitis Idiopathic Sarcoidosis Syphilis Lupus Herpes (zoster/simplex)

Table 5
Review of systems via history with uveitis-associated diseases (adapted from Cheng et al., 2005 and Gutteridge et al., 2007)^{3,27}

System	Diseases
Dermatological	Psoriasis, syphilis, sarcoidosis, lupus, herpes simplex/zoster, Behcet's disease
Gastrointestinal	Inflammatory bowel disease
Genito-urinary	Reiter's syndrome, Behcet's disease, syphilis
Respiratory	Sarcoidosis, tuberculosis
Rheumatological	Spondyloarthropathies (eg., ankylosing spondylitis)

Table 6
Systemic diseases with uveitis association and corresponding lab tests (adapted from Cheng et al., 2005)³

Diseases	Clinical Features	Laboratory tests
HLA-B27 positive	Uveitis only	HLA-B27
Ankylosing spondylitis	Lower back pain, worse in a.m.	HLA-B27, ESR, spinal X-ray
Reiter's syndrome	Triad: arthritis, urethritis and conjunctivitis	HLA-B27, ESR, ANA
Arthritis, psoriasis	joint pain, skin inflammation	HLA-B27, joint X-rays
Inflammatory bowel disease	Bloody diarrhea & abdominal cramp	HLA-B27, endoscopy
Behcet's disease	Aphthous mouth/genital ulcers	HLA-B5
Multiple sclerosis	Optic neuritis, CNS plaques	Cranial MRI, HLA-DR2
Sarcoidosis	African ethnicity, shortness of breath, skin nodules	ACE, lysozyme, chest X-ray, gallium scan, biopsy

spondylitis and other connective tissue disorders, questions regarding joint and back problems, pain on urination or stomach irritation, arthritis, or other autoimmune diseases (i.e., Reiter's syndrome, inflammatory bowel disease, psoriatic arthritis, and post-infectious arthritis) should be asked in the history, along with the patient's current medication list. Other causes of AAU may include trauma and herpetic infec-

tion. Less common potential infective etiologies include syphilis, tuberculosis, toxoplasmosis and Lyme disease.⁴ Table 4 summarizes the common causes of acute and chronic anterior uveitis.

The management of uveitis is strongly achieved through an evidence-based approach. No standard laboratory evaluation for uveitis exists, except for determining syphilis and possibly sar-

coidosis-based etiologies. In addition, many laboratory tests have false-negative or false-positive results that may potentially confuse the clinical picture and/or contribute to erroneous diagnoses, along with an additional cost burden.²⁸ Careful history and physical examination related to the review of systems (i.e., dermatologic, hematologic, respiratory, circulatory, neurological, ear/nose/throat, constitutional, etc.) often is more valuable to determining the cause of the uveitis (Table 5).²⁹ Physical signs such as the presence or absence of granulomatous nodules or keratic precipitates (KPs) also assist in discriminating autoimmune (i.e., sarcoid, systemic lupus erythematosus) from non-autoimmune-based uveitis.³⁰

When AAU is severe, unresponsive to treatment, persists or recurs, laboratory testing may be necessary (Table 6). Minimum lab tests (with key identifiable disease examples in brackets) may include: HLA-B27 (ankylosing spondylitis), urinalysis (psoriatic arthritis), angiotensin converting enzyme (ACE) (sarcoidosis), venereal disease research laboratory aka VDRL and fluorescent treponemal antibody aka FTA-ABS (syphilis) and chest X-ray (tuberculosis, sarcoidosis). In certain cases, anterior chamber or vitreal taps, culture swabs or tissue biopsies may be indicated. One clinical study made evidence-based recommendations for appropriate tests in four anterior uveitis situations:³¹

- Non-granulomatous anterior uveitis in an adult: HLA-B27
 - o If recurrent or chronic: chest X-ray, VDRL and FTA-ABS
- Granulomatous anterior uveitis in an adult: chest X-ray, purified protein derivative (PPD) tuberculin testing, serum ACE levels, VDRL and FTA-ABS
- Granulomatous anterior uveitis, suspected sarcoidosis, in an adult or child: chest X-ray, ACE
 - o If suspicion is high despite these tests normal: High-resolution computerized tomography (HRCT) scan of the chest or whole body gallium scan with or without biopsy
- Anterior uveitis in a child: Antinuclear antibody (ANA), HLA

B-27

Some lab tests, such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), and rheumatoid factor (Rf), have been regarded as too non-specific for diagnostic purposes in anterior uveitis, and only play only an adjunct role in certain cases.³² The clinician must balance the diagnostic value with cost-effectiveness when ordering laboratory tests (Table 6).

Conclusion

This article highlights two cases of acute anterior uveitis (AAU), their clinical management and course. While the hallmark signs and symptoms of AAU are highly diagnostic, the pathogenesis and etiology may be elusive. A careful evidence-based methodology, including detailed case history and review of systems, physical examination and potential laboratory testing, is necessary for effective diagnosis and management. Treatment is initially focused on reducing the inflammatory findings, with the goals of improving patient comfort and visual function. Once a more detailed etiology of the AAU is determined, treatment is then also geared towards the cause.

Throughout the care of the patient with AAU, it is important to educate the patient thoroughly regarding his/her condition, the possible causes and prognosis. Following this, discussion of the various treatment options and initiation of treatment should begin immediately, with close monitoring (i.e., daily or every few days, depending on the severity of the presentation). Judicious yet effective dosage of topical corticosteroid and cycloplegic agents are the mainstay of AAU treatment. Depending on the presentation and cause, other medications, lab tests and tertiary procedures may be necessary. Finally, coordination with other specialists (i.e., ophthalmologists, rheumatologists) may be critical in diagnosis and treatment. Eye care providers play a key role in the interdisciplinary management of the patient with AAU.

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