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Uveitis: Rheumatology and Ophthalmology Collaboration

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Disclosure

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Faculty Disclosure

Patty Travis, CNP

- Speaker Bureau: AbbVie

Learning Objectives

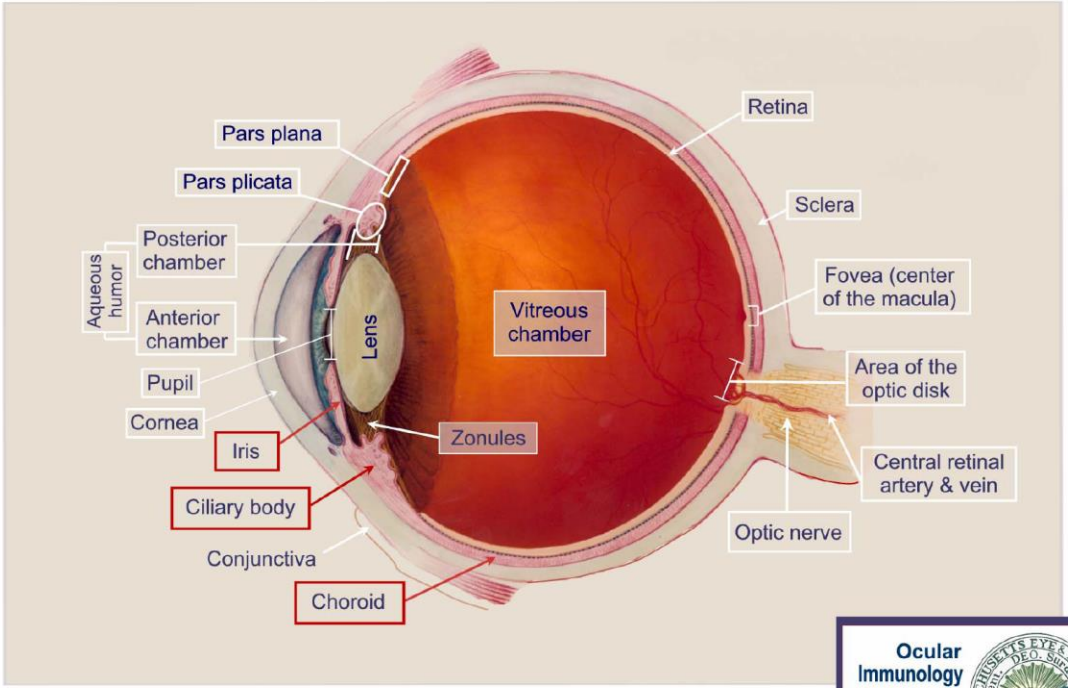
- Gain a better understanding of the anatomic and clinical classifications of uveitis
- To be familiar with the signs and symptoms that are associated with different types of uveitis
- To appreciate the extent to which uveitis can be an extra-articular manifestation of systemic disease
- To be knowledgeable in treatment options for uveitis and what ophthalmology will initiate and what rheumatology will manage specifically as it relates to systemic disease

Introduction

- Uveitis is broadly defined as inflammation of the uvea, and may be accompanied by involvement of the other ocular structures such as the retina, sclera, cornea, vitreous, and optic nerve
- The uvea consists of the middle, pigmented, vascular layer of the eye and includes:
  - Iris
  - Ciliary body
  - Choroid
- Inflammatory response: chemical mediators result in vasodilation, increased vascular permeability, and chemotaxis of inflammatory cells in the eye

Dmour, M. Uveitis in Systemic Disease Health & Medicine. 2017 Mar 20.

Anatomy of the Eye
With Special Reference to Ocular Inflammatory Disease



Uveitis (U'VE-I-TIS) is inflammation inside the eye, specifically affecting one or more of the three parts of the eye that make up the uvea: the iris, the ciliary body, and the choroid (the vascular lining tissue underneath the retina).

Ocular Immunology and Uveitis Service
www.Uveitis.org

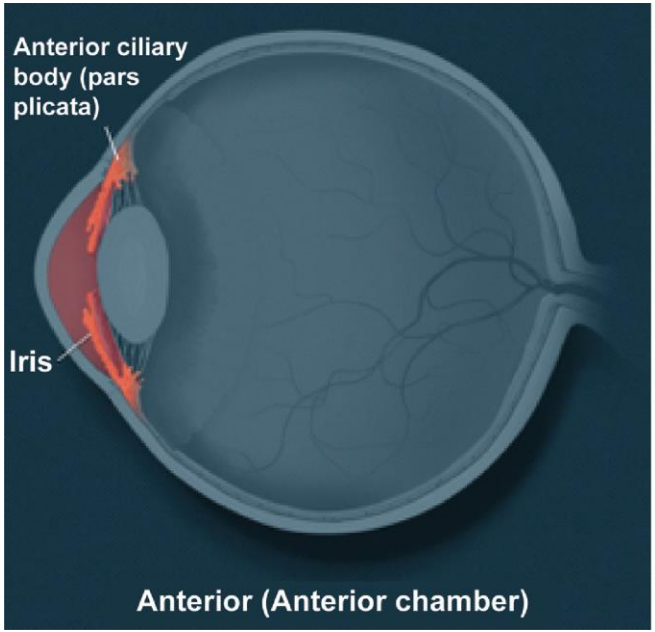
Standardization of Uveitis Nomenclature (SUN) Classification

- Anatomic
  - **Anterior**
    - Intraocular inflammation in the anterior chamber
  - Intermediate
    - Inflammation of the pars plana and vitreous humor
  - Posterior
    - Inflammation of the posterior segment
  - Panuveitis
    - Involving anterior and posterior segment

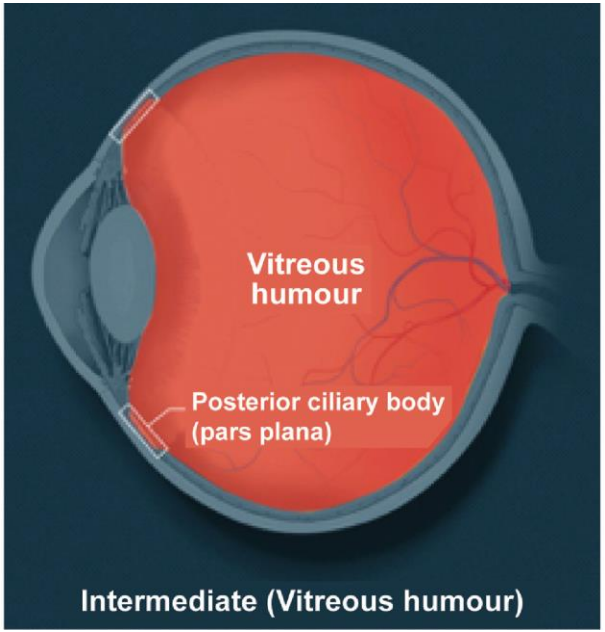
The SUN Working Group has provided additional descriptors of the disease, such as onset (sudden or insidious), duration (limited [≤3 months] or persistent [>3 months]), and course (acute, recurrent, or chronic)

Martina Biggioggero, Chiara Crotti, Andrea Becciolini, Elisabetta Miserocchi, Ennio Giulio Favalli. "The Management of Acute Anterior Uveitis Complicating Spondyloarthritis: Present and Future." *BioMed Research International.* vol. 2018, Article ID 9460187, 11 pages, 2018; James T. Rosenbaum et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Seminars in Arthritis and Rheumatism.* Volume 49, Issue 3, 2019, Pages 438-445.

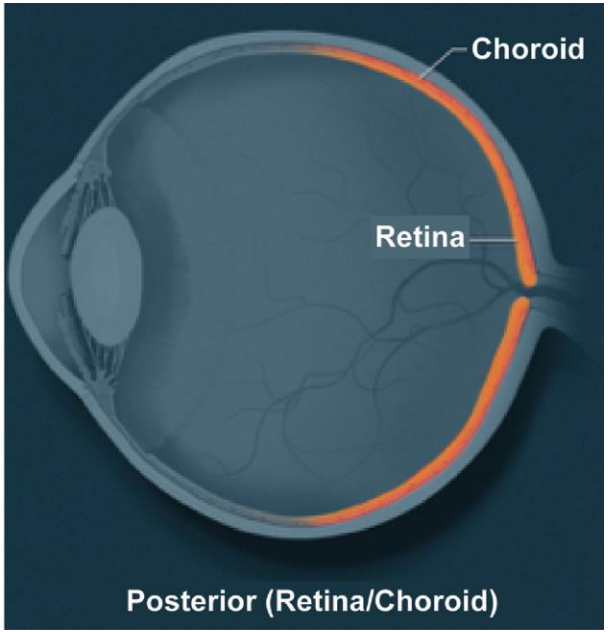
Anterior Uveitis



Intermediate Uveitis



Posterior Uveitis



James T. Rosenbaum et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Seminars in Arthritis and Rheumatism.* Volume 49, Issue 3, 2019, Pages 438-445.

Standardization of Uveitis Nomenclature (SUN) Classification

- Clinical
  - **Non-infectious**
    - Immune-mediated ocular disease that can be associated with systemic diseases
  - Infectious
    - Bacterial, viral, fungal, or parasitic
  - Masquerade
    - Heterogeneous group of eye diseases that mimic chronic intraocular inflammation, e.g. lymphoma

Martina Biggioggero, Chiara Crotti, Andrea Becciolini, Elisabetta Miserocchi, Ennio Giulio Favalli. "The Management of Acute Anterior Uveitis Complicating Spondyloarthritis: Present and Future." *BioMed Research International.* vol. 2018, Article ID 9460187, 11 pages, 2018; James T. Rosenbaum et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Seminars in Arthritis and Rheumatism*. Volume 49, Issue 3, 2019, Pages 438-445.

Epidemiology of Uveitis

- **Anterior uveitis is most common.**
- **Non-infectious uveitis (NIU) is more common in developed countries than infectious uveitis.**
- Third leading cause of blindness worldwide.
- Accounts for 10-15% of all cases of total blindness in the U.S.
- From The Ocular Immunology and and Uveitis Foundation, in the U.S.
  - Prevalence of about 38 cases per 100,000 population.
  - Incidence of 15 cases per 100,000 population.
- From a 2012 claims-based analysis of a database that included 14 million privately insured individuals in 69 companies, approximately 4 million eligible adult patients and almost 1 million children were analyzed.
  - Adult prevalence of NIU was 121 cases per 100,000 and pediatric NIU prevalence was 29 cases per 100,000.
  - Anterior NIU accounted for 81% of adult NIU cases and 75% of pediatric NIU cases.
  - Prevalences of noninfectious intermediate, posterior, and panuveitis were, for adults: 1, 10, and 12 per 100,000, respectively, and for pediatric patients, 0, 3, and 4 per 100,000, respectively.

https://uveitis.org. Accessed Nov 2020;
Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, Ganguli A. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. *JAMA Ophthalmol*. 2016 Nov 1;134(11):1237-1245.

Demographics of Uveitis

- In non-infectious uveitis, generally men and women are equally affected overall
  - Male predominance in human leukocyte antigen (HLA)-B27-associated uveitis
  - Female predominance in juvenile idiopathic arthritis (JIA)-related uveitis
- Uveitis may occur at any age, but most commonly affects the working population aged between 20 and 59 years
- Childhood uveitis is relatively less common, but may cause long-term severe visual loss
- *In the 2012 claims-based analysis, prevalence of NIU increased with age and was higher among adult females than males*

Pasadhika, S., & Rosenbaum, J. T. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. *Biologics: Targets & Therapy.* 2014; 8, 67–81; Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, Ganguli A. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. *JAMA Ophthalmol.* 2016 Nov 1;134(11):1237-1245.

Classification of Uveitis by Primary Anatomic Site of Inflammation

Classification	Primary site of inflammation	Includes
Anterior	Anterior chamber	• Iritis (iris) • Iridocyclitis (iris and ciliary body)
Intermediate	Vitreous humor	• Pars planitis (pars plana)
Posterior	Retina and/or choroid	• Focal, multifocal, or diffuse choroiditis • Retinal vasculitis
Panuveitis	Anterior chamber, vitreous humor, retina, and/or choroid	• Iritis (iris) • Iridocyclitis (iris and ciliary body) • Pars planitis (pars plana) • Focal, multifocal, or diffuse choroiditis

James T. Rosenbaum et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Seminars in Arthritis and Rheumatism.* Volume 49, Issue 3, 2019, Pages 438-445;
Jab DA, et al. *Am J Ophthalmol.* 2005;140:510.

Anterior Uveitis Causes:

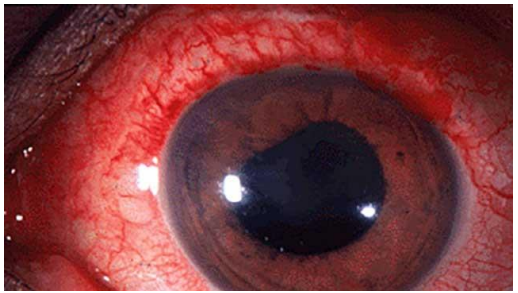
- Idiopathic (37.8%)
- **Seronegative HLA-B27-associated arthropathies (21.6%)**
- **Juvenile idiopathic arthritis (10.8%)**
- **Sarcoidosis (5.85%)**
- **Systemic lupus erythematosus (3.3%)**
- **Rheumatoid arthritis (0.9%)**
- Herpetic uveitis (9.7%), Fuchs' heterochromic iridocyclitis (5.0%), intraocular lens-induced persistent uveitis (1.2%), Posner-Schlossman syndrome (0.9%)

Syphilis, tuberculosis, phacogenic uveitis, Lyme disease, and **collagen vascular disease (Granulomatosis with Polyangiitis (formerly called Wegener's), polyarteritis nodosa, and relapsing polychondritis)** caused some cases of anterior uveitis

https://uveitis.org. Accessed Nov 2020.

Anterior Uveitis

(Includes iritis and iridocyclitis)



Anterior chamber is the primary site of inflammation

- Clinical signs and symptoms can include:
  - Corneal findings (such as keratic precipitates)
  - Pupillary changes
  - Anterior and posterior synechiae
  - Redness, pain, blurred vision, photophobia, and floaters

Representative associated systemic diseases include juvenile idiopathic arthritis (JIA), ankylosing spondylitis, Behçet's disease, sarcoidosis, tubulointerstitial nephritis and uveitis (TINU), and inflammatory bowel disease

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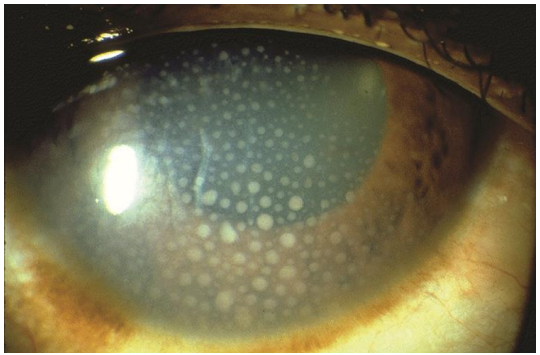
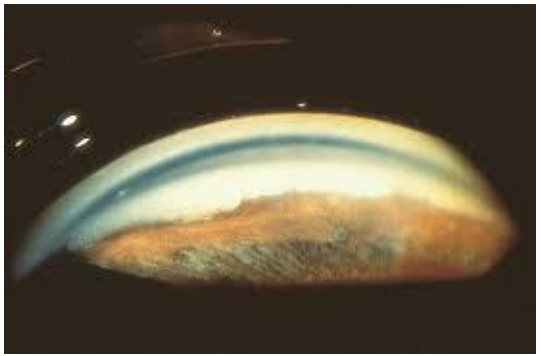
Keratic Precipitates



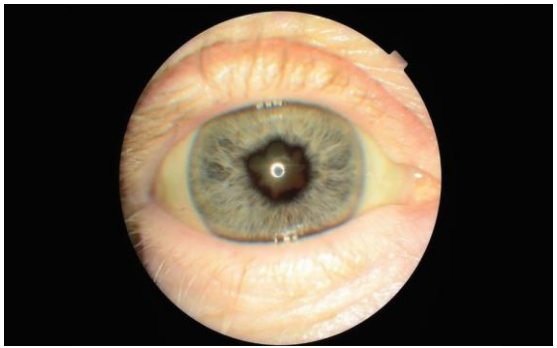
KP are collections of inflammatory cells on the corneal endothelium. When these coalesce and become large with a yellowish color, they are described as **mutton-fat KP**. These are typically associated with granulomatous inflammation

Peripheral Anterior Synechiae



When the iris adheres to the cornea this is anterior synechiae and can occur centrally or peripherally.

Posterior Synechiae (and cataract)



Posterior synchiae are more common and occur when the iris adheres to the lens capsule.

https://www.aao.org/image/keratic-precipitates-3 Accessed Nov 2020; https://webeye.ophth.uiowa.edu/eyeforum/atlas/

Intermediate Uveitis Causes:

- Idiopathic (69.1%)
- **Sarcoidosis (22.2%)**
- Multiple sclerosis (8.0%)
- Lyme disease (0.6%)

Of note:

Ocular involvement in sarcoidosis is present in up to 80 percent of patients and is frequently manifested before diagnosis of the underlying systemic disease.

https://uveitis.org. Accessed Nov 2020; Yang, S. J., Salek, S., & Rosenbaum, J. T. Ocular sarcoidosis: new diagnostic modalities and treatment. *Current Opinion in Pulmonary Medicine.* 2017; 23(5), 458–467.

Intermediate Uveitis

Primary site of inflammation is the vitreous humor

- Clinical symptoms include:
  - Blurry vision
  - Floaters
  - Photophobia

Representative origins include sarcoidosis, malignancies, and multiple sclerosis. Pars planitis corresponds to the idiopathic form of intermediate uveitis and is characterized by the presence of “snowbanks” (white exudates over the pars plana and ora serrata) and “snowballs” (aggregates of inflammatory cells in the vitreous).

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Yang, S. J., Salek, S., & Rosenbaum, J. T. Ocular sarcoidosis: new diagnostic modalities and treatment. *Current Opinion in Pulmonary Medicine.* 2017; 23(5), 458–467.

Intermediate Uveitis

Dr. Bipin Bista. NMCTH Health & Medicine. Mar 28, 2018.

Posterior Uveitis Causes:

- **Systemic lupus erythematosus (7.9%)**
- **Birdshot retinochoroidopathy (7.9%)**
- **Sarcoidosis (7.5%)**
- **Bechet's disease (2.0%)**
- **Serpiginous choroidopathy (1.65%)**
- Idiopathic (12.3%)
- Toxoplasmosis (24.6%), cytomegalovirus retinitis (11.6%), acute retinal necrosis syndrome (5.5%), Epstein-Barr virus retinochoroiditis (2.9%), toxocariasis (2.5%), syphilis (2.0%), acute posterior multifocal placoid pigment epitheliopathy (2.0%)

Other causes of posterior uveitis include punctate inner choroidopathy, multiple evanescent white-dot syndrome, multiple sclerosis, **temporal arteritis**, presumed ocular histoplasmosis, fungal retinitis, and leukemia

https://uveitis.org. Accessed Nov 2020.

Posterior Uveitis

Primary sites of inflammation are the retina and/or choroid and include focal, multifocal, or diffuse presentations of choroiditis

- Clinical symptoms include:
  - Floaters
  - Usually no pain or redness

Representative associated diseases include autoimmune disorders, Behçet's disease, and sarcoidosis

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Yang, S. J., Salek, S., & Rosenbaum, J. T. Ocular sarcoidosis: new diagnostic modalities and treatment. *Current opinion in Pulmonary Medicine.* 2017; 23(5), 458–467.

Panuveitis Causes:

- Idiopathic (22.2%)
- **Sarcoidosis (14.1%)**
- **Multifocal choroiditis and panuveitis (12.1%)**
- **Bechet's disease (11.6%)**
- **Systemic lupus erythematosus (9.1%)**
- **HLA-B72 associated (4.5%)**
- **Vogt-Koyanagi-Harada syndrome (5.5%)**
- Syphilis (5.5%), sympathetic ophthalmia (4.0%), tuberculosis (2.0%), fungal retinitis (2.0%)

Other causes of panuveitis include bacterial panophthalmitis, intraocular lymphoma, **relapsing polychondritis, polyarteritis nodosa**, leprosy, **dermatomyositis,** and **progressive systemic scelerosis**

https://uveitis.org. Accessed Nov 2020.

Panuveitis

- Sites of inflammation include:
  - The anterior chamber
  - Vitreous humor
  - Retina and/or choroid are involved
- Clinical symptoms include:
  - Floaters
  - Pain
  - Redness
  - Photophobia

Representative associated diseases include autoimmune disorders, sarcoidosis, Vogt-Koyanagi-Harada syndrome, and Behçet's disease

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Differential Diagnosis:

- Differential diagnosis of NIU is affected by various factors:
  - Geographic
  - Environmental
  - Demographic

Differential diagnosis also depends on the recognition that uveitis is not a single disease but is considered a group of syndromes based on its potential associations with primary ocular conditions as well as systemic inflammatory diseases

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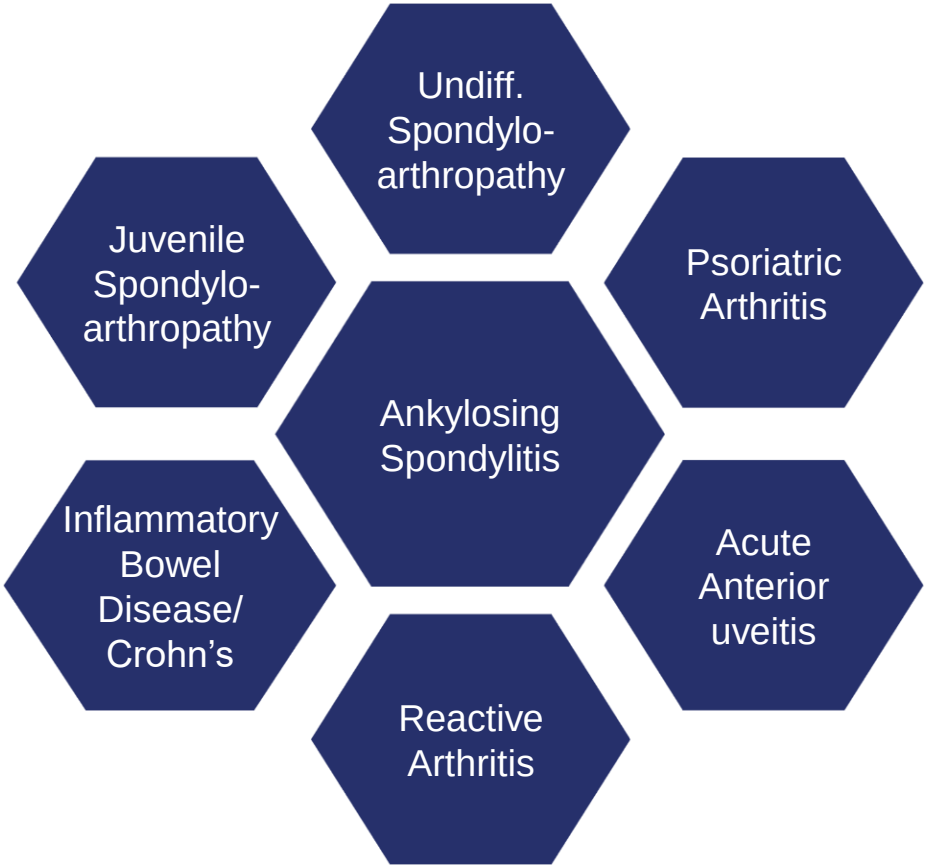
Spondyloarthropathies



Collaboration Is the Key

- Collaboration between ophthalmology and rheumatology plays a primary role in facilitating the understanding of NIU and associated systemic immune-mediate diseases, as well as providing appropriate diagnostics methods and improving long-term outcomes in patients with NIU
- Dublin Uveitis Evaluation Tool (DUET) study, Haroon et al. found that by administering an algorithm to a validation cohort of 74 patients with idiopathic acute anterior uveitis, 40% had undiagnosed spondyloarthritis (SpA)
- Because uveitis can encompass a diverse group of syndromes, selecting appropriate disease-specific endpoints in uveitis clinical studies can be challenging
- Endpoints that assess therapeutic effectiveness need to be applicable to patients with different types of uveitis and may not fit all diagnoses equally

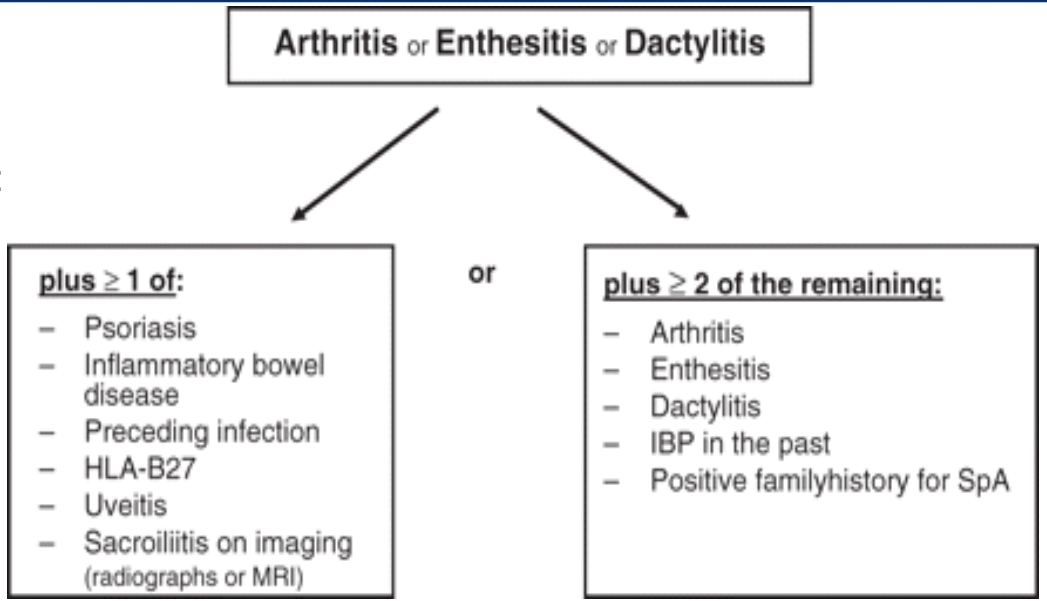
James T. Rosenbaum et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Seminars in Arthritis and Rheumatism.* Volume 49, Issue 3, 2019, Pages 438-445.

SENTINEL Study Was Initiated to Increase Collaboration, With the Aim of Improving the Management of Patients With Anterior Uveitis and Facilitating the Timely Diagnosis of Underlying SpA.

Using Assessment of SpondyloArthritis International Society criteria 798 patients with anterior uveitis were also diagnosed with:

Axial SpA = 50%

Peripheral SpA = 18%



Proportion of patients with SpA, in particular axial SpA, was higher in patients who had HLA-B27-positive anterior uveitis vs those who had recurrent HLA-B27−neg anterior uveitis (71% vs 20%).

Peripheral SpA was also more frequent in patients who were HLA-B27 pos vs HLA-B27 neg (22% vs 11%).

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Testing

- **Labs -** ANA, ENA, RF, CCP, APRs, HLAB27, and others
- **Imaging –** XR, CT, MRI; specifically SI joints
- **Skin and nail considerations** – nail pitting, punch biopsy
- **Tonometry -** measures the pressure of the eye
- **Slit-lamp examination -** magnifies and illuminates the anterior eye
- **Funduscopy** - this exam involves dilating the eye to examine the posterior ey.
- **Color photography** of the inside of the eye (retina).
- **Optical coherence tomography (OCT) imaging -** measures the thickness of the retina and choroid to reveal inflammation
- **Fluorescein angiography or indocyanine green angiography –** requires IV contrast to view the blood vessels in the eyes and allow photographs of blood vessel inflammation inside the eyes.
- **Analysis of aqueous or vitreous fluid** from the eye.

Autoimmune disease	Most commonly associated uveitis	Estimated prevalence
Spondyloarthritis	Anterior	10%–50%
Inflammatory bowel disease	Anterior and/or intermediate	2%–12%
Psoriatic arthritis	Anterior and/or intermediate	7%
Juvenile idiopathic arthritis	Anterior	10%–30%
Sarcoidosis	Anterior/intermediate/panuveitis	20% develop eye disease (30%–50% develop uveitis in bone sarcoidosis) ≤67% of patients present with anterior uveitis
Behçet's disease	Posterior and panuveitis Anterior (less common)	≤90% (ocular involvement)
Vogt-Koyanagi-Harada disease	Panuveitis Posterior uveitis (with thickening of the choroid, and serous retinal detachments)	

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Assessing Severity of Disease

SUN Working Group criteria – NIU severity can be assessed based on the graded variables corresponding to inflammation of the anterior segment of the eye and vitreous.

- Inflammation of the anterior segment of the eye (i.e., anterior chamber cell grade) is scored on a scale of 0 to 4+.
- Inflammation of the vitreous (i.e., vitreous haze grade) is scored on a scale of 0 to 4+.
- Inflammation can be seen as the number of active inflammatory lesions in the choroid or retina increase, in which a greater number of inflammatory lesions corresponds to greater disease severity.
- Visual acuity can also be a quantifiable outcome in NIU clinical studies.

Standardized Grading Scales for Uveitis[2]

SUN Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field
0	< 1
0.5+	1 – 5
1+	6 – 15
2+	16 – 25
3+	26 – 50
4+	50+

(using 1mm slit beam)

SUN Grading Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris/lens details clear)
3+	Marked (iris/lens details hazy)
4+	Intense (fibrin/plastic aqueous)

https://www.reviewofoptometry.com/article/the-many-moods-of-uveitis. Accessed Nov 2020.
James T. Rosenbaum et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Seminars in Arthritis and Rheumatism*. Volume 49, Issue 3, 2019, Pages 438-445;

Goals of Therapy

Reduce inflammation and attain complete remission, thereby mitigating or avoiding ocular complications, permanent cumulative damage, and long-term vision loss

General therapeutic progression for treating patients with non-infectious uveitis:

1. Topical corticosteroids (especially for anterior uveitis)
2. Systemic treatment with low-dose corticosteroids; or high-dose oral or intravenous corticosteroids for severe uveitis
3. Systemic immunomodulators (i.e., T-cell inhibitors or antimetabolites)
4. Biologics (i.e., adalimumab or infliximab)

The specifics of the treatment will also depend on the clinical form of non-infectious uveitis (i.e., acute episode, inter-outbreak phase, or chronic)

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Conventional Therapy

NIU typically receive first-line therapy with corticosteroids (CS) to control inflammation; oral prednisone is a commonly used systemic CS with the plan to taper once anti-inflammatory response is achieved.

- Typical maintenance dose is ≤7.5 mg/d to minimize systemic toxicity.
- Higher doses up to 60 to 80 mg/d are sometimes required (used in the acute phase and typically corresponds to the 1- to 1.5-mg/kg dose).
- High-dose methylprednisolone can be administered intravenously to deliver 1000 mg/d, usually over 3 days, when a rapid response is essential.

Ophthalmology typically writes for the prednisone and tapers it.

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Localized Therapies

Localized treatment such as intravitreal injection or intraocular implants have been developed to avoid adverse events (AEs) associated with systemic therapies.

- Intravitreal CS injections, such as triamcinolone acetate improved visual acuity in patients with uveitic cystoid macular edema; associated with an elevated intraocular pressure (IOP); ~50% required IOP-lowering medication; progression of cataract noted. Improvements in visual acuity reported to have a limited duration, and repeat injections may be needed.
- Other local therapies include CS-delivering technologies that use intravitreal sustained-release implants and inserts.
  - Retisert, fluocinolone acetonide implants that release it for up to 3 years. Reduced the rates of non-infectious posterior uveitis recurrences in the 34-week study and the 3-year follow-up, however the implants were associated with complications:
    - At least two-thirds of all eyes treated had IOP, 45% of eyes with implants had surgery to lower IOP
    - A significantly higher proportion of treated eyes required IOP-lowering medication compared with control eyes
    - Glaucoma surgery was also significantly more common
    - Almost all patients developed cataracts within 3 years after implantation

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Localized Therapies continued

A 7-year follow-up study of patients found that those who received systemic therapy had better visual acuity compared with those who received a fluocinolone acetonide implant.

- Iluvien insert, fluocinolone acetonide for ≥3 years and has been shown to improve visual acuity in patients with diabetic macular edema; however, a significant proportion of patients experienced elevated IOP or required cataract surgery; currently approved in UK.
- Ozurdex implant delivers dexamethasone over 6 months; studies showed that it improved vitreous haze and visual acuity in patients with NI intermediate or posterior uveitis. Elevated IOP was < 10% across all treatment groups; IOP-lowering medication was required for ≤23% of patients; cataract formation was not significantly different.
- Sirolimus, a locally injected immunosuppressant delivered intravitreally or subconjunctivally that blocks T-cell activation and proliferation; improvements in vitreous haze grade in all patients and visual acuity improvement in about 30% of patients; ocular AEs included iridocyclitis and elevated IOP. This therapy is not currently approved by the US FDA.

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Immunosuppressive Medications

Immunosuppressive agents also may be required to:

- Attain complete remission owing to disease severity or chronic flares.
- Reduce CS doses to avoid adverse effects and potential complications.

Although complete remission is the desired outcome, it is difficult to achieve, and the main use of immunosuppressants is to reduce steroid exposure.

- Immunosuppressive therapy is recommended as a CS-sparing approach when inflammation cannot be controlled with oral systemic CS ≤7.5 to 10 mg/d within 3 months.
- Immunosuppressants used to supplement systemic CS and reduce the CS burden include:
  - Antimetabolites (azathioprine, methotrexate, mycophenolate mofetil)
  - T-cell inhibitors (cyclosporine, tacrolimus)
  - Alkylating agents (cyclophosphamide, chlorambucil) – rarely used

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Biologics

The anti-tumor necrosis factor (TNF) agents provide alternative or concurrent options to immunomodulators as CS-sparing therapies to treat patients with NIU.

- Adalimumab has been approved for the treatment of non-infectious intermediate, posterior, and panuveitis and shown to be effective in patients with active and inactive uveitis. Studies show time to treatment failure due to new active inflammatory lesions, increases in anterior chamber cell grade, and increases in vitreous haze grade were numerically lower in patients receiving adalimumab.
  - The SYCAMORE trial with 90 pediatric patients receiving both methotrexate and adalimumab was shown to be highly effective in patients with JIA-associated uveitis, which is primarily an anterior uveitis. The ADJUVITE study showed adalimumab efficacy in patients with early onset idiopathic or JIA-associated chronic anterior uveitis.

- Studies have shown infliximab and adalimumab had similar efficacy, demonstrating equivalent response rates and providing CS-sparing inflammation control in patients with chronic NIU. Recent guidelines recommend infliximab therapy in patients with Behçet's disease and acute sight-threatening uveitis. A recent retrospective case series showed increased recurrence rates of inflammation after switching from originator infliximab to biosimilar infliximab-abda.

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Biologics continued

- There have been reports of uveitis exacerbations in children with JIA receiving etanercept. Additionally, etanercept has been linked with a higher number of reported uveitis cases compared with infliximab. Fundamentals Of Care for UveitiS (FOCUS) initiative reported no evidence to support etanercept.
- Other biologics that are being tested in patients with NIU include interleukin (IL)–6 receptor inhibitors such as tocilizumab, which showed improvements in visual acuity and a reduction in vitreous haze with 6 months of treatment.
- Additionally, a multicenter, randomized controlled study using filgotinib, a small molecule JAK/STAT inhibitor, to treat patients with NIU is ongoing.

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In Conclusion

- Uveitis represents a group of diseases with complex etiologic origins and clinical symptoms that may include eye pain, redness, floaters, and light sensitivity. It is a leading cause of preventable blindness.
- Collaboration among health providers, specifically, ophthalmologists and rheumatologists, is needed to improve management of patients with NIU and help identify previously undiagnosed conditions associated with uveitis, as demonstrated in the SENTINEL and DUET studies.
- Although CS have been the mainstay therapy for patients with NIU, potential serious AEs associated with long-term systemic CS use highlight the need for additional therapies allowing patients to reduce their dependence on CS.
- CS-sparing therapies that demonstrate efficacy combined with a more favorable safety profile can be used to reduce CS burden in patients with NIU.
- Adalimumab has been shown to be effective in reducing the daily CS dose in adult patients while significantly increasing TTF and enabling most patients with non-anterior NIU to achieve or maintain quiescence.

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In Conclusion

- To date, adalimumab is the only biologic approved for the treatment of NIU. However infliximab has been shown to be effective in the treatment of uveitis associated with immune-mediated systemic diseases.
- Other biologics targeting signaling molecules involved in the immune response (e.g., IL-6) may provide additional options for patients with NIU; further studies are needed to address long-term efficacy and safety of tocilizumab and sarilumab as well as JAK/STAT inhibitors. Future studies are also needed to optimize localized treatments to avoid elevated IOP and cataract associated with some intravitreal injections and intraocular implants. An appreciation of the interplay between uveitis and systemic inflammatory diseases will help ophthalmology and rheumatology to better treat their patients.

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