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Approach to the Diagnosis of the Uveitides

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Abstract

Purpose—To describe an approach to diagnosing the uveitides, a collection of about 30 separate diseases characterized by intraocular inflammation.

Design—Perspective.

Methods—Integration of clinical approach with a more formal, informatics-derived approach to characterization and a Bayesian approach to laboratory testing.

Results—The patient's uveitis is characterized along several dimensions: course, laterality, anatomic location of the inflammation, morphology, presence of active infection, and the host (age, presence of a systemic disease). Posterior uveitis can be characterized further by whether it is primarily a retinitis, choroiditis, or retinal vasculitis, by whether it is paucifocal or multifocal, and by the morphology of the lesions. This characterization narrows the differential diagnosis to one or, at most, a few diseases. Laboratory screening (i.e. testing all patients) should be reserved for those diseases that can present as any type of uveitis, whereas targeted testing (i.e. testing a subset with specific features) is used selectively. Laboratory testing should be used to identify an infection (which will alter therapy) or a systemic disease that will affect the patient's health. A uveitis that is not one of the established diagnoses is designated as "undifferentiated" with the course, laterality, and anatomic location (e.g. undifferentiated bilateral chronic anterior uveitis). We avoid the term "idiopathic" uveitis as most identified non-infectious uveitic diseases are idiopathic, and most systemic diseases associated with uveitis also are idiopathic (e.g. juvenile idiopathic arthritis).

Conclusion—This approach should lead to the correct diagnosis of the specific uveitic disease in the large majority of cases without overuse of laboratory testing.

Uveitis refers to a collection of about 30 diseases characterized by intraocular inflammation (Table 1). Traditionally these diseases have been grouped by the primary anatomic location

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of the inflammation as anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis.[1,2] In the past, standardized "review of system" questionnaires often have been used to identify any symptoms of a systemic disease, and a laboratory evaluation conducted to identify the "cause" of the uveitis, an approach often termed "the etiologic diagnosis of uveitis". A refinement on this approach is the "naming-meshing" approach popularized by Smith and Nozik.[3] If no underlying disease is found and a specific syndromic name cannot be given to the uveitis, it was termed "idiopathic." This approach has problems and has led to tactics such as shotgun "uveitis survey" laboratory testing (a practice deplored by uveitis experts), the idea that one should only "work up" the second attack of uveitis (because of the low yield of shotgun laboratory testing), and exhaustive searches for laboratory evidence of sarcoidosis or other systemic diseases (often using tests with a low positive predictive value) even when there is no other evident organ involvement.

Underlying these approaches is the flawed notion that uveitis typically is a manifestation of "something else" and that the "something else" must be identified regardless of cost. Also underlying this approach is the flawed concept that discovering an idiopathic systemic disease renders the uveitis not-idiopathic. For example is chronic anterior uveitis in a child without an associated systemic disease idiopathic but not idiopathic when present in a child with juvenile *idiopathic* arthritis? In fact, the etiology of most complex disorders is unknown (i.e. idiopathic). Risk factors can be identified and pathogenesis inferred, but except for infectious diseases, Mendelian genetic disorders, and drug- or foreign substance-related toxic or allergic reactions, most disorders are not amenable to a simple identification of one "etiology". Hence "the etiologic diagnosis of the uveitis" is a misleading concept.

A more modern approach is to recognize that the goal of the clinician is to make the diagnosis of a specific uveitic disease. The likely diagnosis can be derived from the history, examination, and for posterior uveitides, sometimes the imaging studies. Laboratory testing then is used to identify infectious diseases which cannot be identified by the morphologic picture and systemic diseases with an impact on the patient's health. Making the correct diagnosis of a specific uveitic entity is critical to management; each disease has its own course, treatment, and prognosis. The import of this approach is shown in Table 2, which lists selected posterior uveitides. Several are infectious (in this article infectious uveitides are those in which there are replicating infectious organisms) and require antimicrobial or antiviral treatment, some are spontaneously remitting diseases with a good prognosis, requiring no treatment, and several are presumed to be autoimmune (or auto-inflammatory), chronic, eye-limited disorders, requiring systemic immunosuppression. Even if one restricts the discussion of management decisions to non-infectious posterior uveitis, the management varies substantially depending on the specific disease diagnosed.

Characterization of the uveitis

The diagnosis of a uveitic entity is begun by carefully characterizing it along several dimensions (Table 3) based on the history, examination, and in selected diseases, imaging. [4,5] These dimensions have been derived from the Standardization of Uveitis Nomenclature (SUN) Project, which is developing classification criteria (criteria used for research reporting) for the major uveitic diseases,[4,5] and adapted to clinical care. The course of the disease is determined by its onset (sudden or insidious) and duration (limited or persistent). Sudden-onset disease of limited duration is considered acute disease, whereas chronic disease typically is insidious in onset but with a persistent duration. Acute disease may be monophasic with a single, limited-in-duration episode (for research purposes defined as less than 3 months), or recurrent. The key feature of recurrent acute disease is the presence of episodes of active inflammation separated by periods of no inflammation when not on therapy. Conversely, chronic disease relapses promptly when therapy is discontinued.

If these terms are used precisely, the often seen term “chronic/recurrent uveitis” has no meaning.[2] Furthermore, precise characterization will guide therapy. Recurrent acute disease may need only treatment of acute attacks, whereas chronic disease is likely to need chronic suppressive therapy.

The second dimension is the laterality. Uveitides may be unilateral, unilateral alternating, bilateral simultaneous, or bilateral asynchronous. In unilateral alternating disease, either eye may be affected by an attack, but only one eye is affected at a time, and the attacks are episodic and recurrent in nature. Conversely, in bilateral asynchronous disease, the onset in the two eyes is not simultaneous, but both eyes remain affected after involvement begins in the second eye, and the disease typically is chronic in nature.

The third dimension is the anatomic type of uveitis: anterior, intermediate, posterior, or panuveitis. The anatomic class of uveitis is based on the primary location of the inflammatory reaction, but not on the location of any structural complications, such as macular edema. In anterior uveitis, cells are seen primarily in the anterior chamber; there may be some retrolenticular cells present (iridocyclitis), but inflammation does not extend all the way posteriorly through the vitreous. Inflammation primarily in the vitreous is termed intermediate uveitis; there may be a mild anterior chamber reaction, but there should not be anterior segment structural complications, such as posterior synechiae or peripheral anterior synechiae. If there is a substantial anterior chamber reaction with structural complications, the uveitis should be classified as both an anterior and intermediate uveitis. In posterior uveitis there are chorioretinal inflammatory lesions, and in some diseases there is an accompanying vitreous inflammatory reaction. In a panuveitis, inflammation affects the anterior chamber, vitreous, and retina/choroid but no one location predominates.[2] As with any classification system, there is some arbitrariness in classification and apparent inconsistencies based on historical naming of the syndrome. Hence multifocal choroiditis with panuveitis is considered a posterior uveitis because the primary inflammation is in the choroid and the accompanying anterior chamber or vitreous reaction typically is mild.

Posterior involvement can be further subdivided based on the primary site of inflammation as a retinitis, a choroiditis, or a retinal vasculitis. Although there is some variability in the use of the term, in this context, retinal vasculitis should involve inflammation of the retinal vessels, preferably with evidence of vascular occlusion. Mere leakage should not suffice; macular edema is not retinal vasculitis, even though there is vascular leakage.[2] Retinitis and choroiditis can be further described as paucifocal (a few spots) or multifocal. Sometimes the term “focal” is used interchangeably with “paucifocal” and interpreted as distinct from “multifocal”. In immunologically normal hosts, retinitis typically is paucifocal and is nearly always infectious in nature (e.g. toxoplasmic retinitis, acute retinal necrosis). Multifocal retinitis does occur, but it occurs in immune compromised hosts and is infectious in nature. Choroiditis may be paucifocal or multifocal and may be either infectious or immune-mediated in nature. Although presumed immune-mediated multifocal choroidopathies occur in immunologically normal hosts (e.g. birdshot chorioretinitis), infectious multifocal choroiditides typically are seen in immune compromised hosts. The choroidal lesions of a multifocal choroiditis can be further described by a short phrase that leads to the likely diagnosis. For example, the lesions of serpiginous choroiditis are amoeboid or serpentine; those of acute posterior multifocal placoid pigment epitheliopathy, placoid; those of birdshot chorioretinitis, yellow-orange ovoid; those of multifocal choroiditis with panuveitis, “punched-out” atrophic; those of punctate inner choroiditis, punctate; and those of multiple evanescent white dot syndrome, evanescent and white.

The value of this approach (which is more structured and formalized but is somewhat akin to the “naming-meshing” approach) is suggested by Table 4. The proper characterization of the

uveitis along these dimensions leads to a limited differential. For example, studies of anterior uveitis have shown that although only 20% of all anterior uveitis is spondyloarthropathy-associated (also known as HLA-B27-associated), nearly 80% of a patients with recurrent acute, unilateral alternating, anterior uveitis will have a spondyloarthropathy or be HLA-B27 positive.[6] Of patients with HLA-B27-associated uveitis, about 60% to 75% will have an associated spondyloarthropathy, and of these, in about one-half, the spondyloarthropathy will be undiagnosed or misdiagnosed prior to the uveitis consultation. Hence the proper characterization of the uveitis can lead to the correct diagnosis of an associated systemic disease in about one-third of the patients with this uveitic disease.[7-9] Other features, such as the nature of the keratic precipitates, the severity of the anterior chamber inflammation (e.g. presence of an hypopyon), the presence or absence of posterior synechiae, and the presence of other iris features (e.g. atrophy, heterochromia) assist in the diagnosis of anterior uveitis (Table 5). Fuchs heterochromic iridocyclitis (also known as Fuchs uveitis syndrome) practically is defined by the features of the “stellate” keratic precipitates, the absence of posterior synechiae, and the heterochromia.[10] Although hypopyon uveitis is the classical anterior segment finding in Behçet uveitis, an hypopyon also can be seen in spondyloarthropathy-associated (HLA-B27-associated) uveitis and in certain drug reactions producing uveitis (e.g. rifabutin).[11-13] In fact, in the United States, because of the much greater prevalence of the spondyloarthropathies than of Behçet disease, a patient presenting with hypopyon uveitis is more likely to have spondyloarthropathy-associated uveitis.[11] However, in the Middle East and the Far East, the situation is reversed due to the greater prevalence of Behçet disease. A study using anterior chamber paracentesis for polymerase chamber reaction (PCR) analysis for viral DNA demonstrated that classic appearing “herpetic uveitis” with sectoral iris atrophy nearly always (>95%) was herpetic uveitis on PCR testing.[14] Hence PCR testing will have value in uncertain cases, but in typical cases the diagnosis can be made on the clinical features.

Similarly, the posterior uveitides typically can be diagnosed based on the history and examination, sometimes abetted by imaging, particularly fluorescein angiography and sometimes indocyanine green angiography. In Table 6, birdshot chorioretinitis and punctate inner choroiditis are contrasted based on their features along these dimensions.[4,15] As one can see, the nature of the spots distinguishes between the two diseases. In the case of serpiginous choroiditis, the fluorescein angiogram (lesions block early and stain late at the borders) is very helpful in diagnosis, especially if the lesions are not adjacent to the disc, as can happen with early disease. In contrast to serpiginous choroiditis, the fluorescein angiographic appearance of the lesions of acute posterior multifocal placoid pigmentary epitheliopathy is one of early blockage and late diffuse staining of the lesions. In early birdshot chorioretinitis, the indocyanine green angiogram may show many more spots than the clinical examination making the diagnosis of a multifocal choroiditis more evident.

Table 1 lists the more commonly identified uveitic diseases and classifies them based on whether they are infectious in nature, associated with a systemic disease, or are eye-limited and presumed to be immune-mediated. It is evident that certain infections, such as syphilis and Lyme disease, can cause various uveitic patterns, and need to be excluded, as their treatment is fundamentally different (antibiotics vs. anti-inflammatory medications). Similarly, as noted above, the diagnosis of a previously undiagnosed systemic disease may have import for the patient’s systemic health, even if it does not directly affect the management of the eye disease. How then should one describe a uveitis which does not fit one of the known uveitic diseases? In the past, it often would be labeled “idiopathic” uveitis, but, as noted above, that term is problematic and misleading. Our own preference is to use the term “undifferentiated” and add the descriptors related to course, laterality, and anatomic location. Hence one might diagnose an undifferentiated, bilateral, chronic anterior uveitis or

an undifferentiated, unilateral, acute anterior uveitis. The term “undifferentiated” is borrowed from rheumatology, where a connective tissue disease that cannot be characterized as one of the known rheumatic diseases or as an overlap syndrome is diagnosed as “undifferentiated connective tissue disease,” a diagnosis which has its own ICD-9 code (710.90).

Use of the Laboratory

Although the history and examination generally lead to the diagnosis, there is a need for laboratory testing. In the use of the laboratory, one should distinguish between “screening”, in which all patients (or perhaps all patients in a given class of uveitis) are routinely tested, and more targeted testing, in which the laboratory tests are used in a subset of patients with specific features. Screening is appropriate for certain infections, such as syphilis and Lyme disease, as they require laboratory testing to make the diagnosis, can present as nearly any type of uveitis, and have a treatment that is markedly different: antibiotics vs. anti-inflammatory medications. Hence, even though syphilitic uveitis accounts for only about 1% of uveitic cases, testing is performed on nearly every case of adolescent and adult uveitis. Because in syphilitic uveitis the specific test (e.g. fluorescent treponemal antibody [FTA], microhemagglutination, *Treponema pallidum* [MHA-TP], or syphilis immunoglobulin G [IgG] antibody) is positive and the non-specific test (e.g. rapid plasma regain [RPR] or venereal disease research laboratory [VDRL]) negative in about one-third of cases of ocular syphilis, screening should be performed with a specific test.[16] It should be noted that the frequency of specific-test-positive, non-specific-test-negative cases in syphilitic uveitis is similar to that in late latent and tertiary syphilis.[17] Lyme disease testing should be performed in endemic areas and in exposed persons, but in areas without Lyme disease, screening for it may not be necessary. Typically Lyme disease testing consists of antibody screening and Western Blot confirmation.[18] Routing screening with serologic testing for other infections is of limited value due to the high prevalence of antibodies in the general population. For example, approximately 25% of the general population will have antibodies to *Toxoplasma gondii*, indicating previous exposure, but not disease, and over 70% will have antibodies to herpes simplex virus.[19,20] Conversely, targeted testing, such as testing for *Bartonella* antibodies in patients with neuroretinitis, has a high yield and has value. [21]

Tuberculosis testing depends on the prevalence of the tuberculosis in the general population, previous tuberculosis exposure, and the disease being evaluated. A key concept in the decision to employ a test is the positive predictive value, i.e. the likelihood that a person with a positive test has the disease. Unlike sensitivity and specificity, which are characteristics of the test, the positive predictive value is a function of the test and of the disease prevalence in the population being tested. If the disease prevalence is low, screening all patients likely will result in substantial diagnostic errors. Conversely, a higher *a priori* probability of the disease will result in a much better performance of the test (i.e. better positive predictive value). In the United States, tuberculosis accounts for 0.2% to 0.5% of uveitis cases. The sensitivity and specificity of the PPD are 75% and 85%, respectively, and of the Quantiferon-gold test are 76% and 97%, respectively.[22,23] If all patients with uveitis are screened for tuberculosis, the positive predictive value of a positive PPD is 1% and of a Quantiferon-gold test is 11%.[22,23] As such, routine screening of all patients with uveitis will be misleading in the overwhelming majority of cases. There are, however, situations where tuberculosis is much more likely, and testing is appropriate. These situations include Eales’ disease, a potential choroidal tuberculoma, and serpiginous-like tuberculous choroiditis.[24] For example, in a patient in whom the differential diagnosis is serpiginous choroiditis vs. serpiginous-like tuberculous choroiditis (an *a priori* 50% chance of either disease), the positive predictive value of the of the PPD and Quantiferon-gold are 82% and 96%, respectively. Furthermore, tuberculosis testing is warranted prior to immunosuppression in a

tuberculosis-exposed patient or someone from a country with high rates of tuberculosis and in all patients prior to the use of a TNF-α inhibitor, such are infliximab or adalimumab.

It also is important to distinguish between infectious uveitides, in which there are replicating organisms, and in which antiviral or antimicrobial agents have a therapeutic role to play (e.g. syphilis), and post-infectious diseases, in which the infection has triggered a (typically) auto-inflammatory reaction. In the latter situation, the infection itself has cleared, and antimicrobial agents have little value (except for prevention of reinfection, as in the case of rheumatic fever). An example of a post-infectious disease is epidemic reactive arthritis. In this situation a gastrointestinal infection due to a limited number of infectious agents triggers an arthritic disease (often with anterior uveitis) after clearing of the gastroenteritis. The treatment is suppression of the inflammatory reaction (e.g. topical corticosteroids for the uveitis), as the uveitis is not infectious in nature.[25] In this case, identification of the inciting organism will have epidemiologic and research value, but not diagnostic or therapeutic value to the individual patient.

The second use of laboratory testing in evaluating patients is to look for a systemic disease that will affect the patient's health. As noted above, patients with acute anterior uveitis, particularly recurrent acute unilateral or unilateral alternating, anterior uveitis, have a high rate of an underlying spondyloarthropathy.[7-9] Because as many as one-third of these patients' spondyloarthropathy will be undiagnosed or misdiagnosed, testing these patients for HLA-B27 has value in that it may affect the management of the patient's systemic health.[7] The same issues with screening and targeted testing arise in the use of the laboratory for identification of a systemic rheumatic disease. Screening all patients with uveitis with an antinuclear antibody test has a positive predictive value of 0.6% (i.e. is wrong in over 99% of cases), but does have value among patients with juvenile idiopathic arthritis, as it identifies those patients at high risk for chronic anterior uveitis.[22] For other diseases, such as Behçet disease and Vogt-Koyanagi-Harada syndrome, the diagnosis is a clinical one, and there is no specific laboratory testing.[26,27]

Sarcoidosis deserves special mention. It accounts for 5-10% of all cases of uveitis in large surveys.[28-32] However, it can produce any type of uveitis, so it typically there is routine screening for its presence. Unfortunately, the screening for sarcoidosis often is performed with tests with a low positive predictive value and focuses on laboratory testing, rather than disease testing. The organs most often affected by sarcoidosis are the lungs (~90%), skin (~20%), and reticuloendothelial system (liver, spleen, and lymph nodes, collectively ~25-33%). Central nervous system sarcoidosis is potentially serious but less common (~5%).[32] As such, screening should be guided by detecting organ involvement that will affect health, particularly pulmonary and hepatic organ involvement. A chest radiograph, liver enzymes, and query about skin lesions would appear to be a reasonable approach. There are some data to suggest that a chest computed tomogram may be superior to the chest radiograph for detection of pulmonary sarcoidosis,[33] but the data quality are such that it remains unclear if the chest computed tomogram should replace the chest radiograph for routine screening or just be used in cases with equivocal results on chest radiograph. Although traditionally often recommended, screening with the angiotensin converting enzyme (ACE) is not warranted. The sensitivity and specificity of the ACE are 73% and 83%, respectively, and those of the gallium scan are 91% and 84%, respectively.[34] Therefore, the positive predictive value of the ACE, when used for routine screening (as opposed to those with known sarcoidosis) is 18%. Similarly the gallium scan, when used for routine screening has a positive predictive value of 22%. Furthermore, the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and other Granulomatous Diseases have issued a statement that sarcoidosis is a multisystem disease characterized by granuloma formation and a predilection for pulmonary

involvement and that the "presence of non-caseating granuloma in a single organ … does not establish the diagnosis of sarcoidosis."[35] Therefore, a patient with chronic anterior uveitis with mutton fat keratic precipitates and a positive ACE but with no other organ involvement has an 18% chance of having sarcoidosis and should not be classified as having "limited ocular sarcoidosis". The International Workshop on Ocular Sarcoidosis addressed this problem by developing levels of certainty for ocular sarcoidosis based on systemic features and laboratory testing: definite sarcoidosis (compatible disease and biopsy confirmation), presumed sarcoidosis (uveitis and bilateral hilar adenopathy but no biopsy performed [biopsies on these patients nearly always show sarcoidosis]), and probable (uveitis, clear lungs, biopsy not done, but other compatible features and laboratory tests). Historically this last group has a 60% chance of having a positive biopsy if one is performed (and therefore of having sarcoidosis).[36] Although it is useful for research and epidemiologic studies, this last category has little therapeutic import if there is no evident organ involvement other than the eye.

In general, HLA typing has limited diagnostic usefulness. As noted above, HLA-B27 typing often is useful in acute anterior uveitis, as it may have impact on the patient's systemic health.[6,37] However, screening all patients with a given diagnostic class of uveitis for HLA types typically has very low positive predictive values, usually less than 20%.[37] Even for HLA-A29 and birdshot chorioretinitis, where the relative odds are over 100 of a patient with HLA-A29 to develop birdshot chorioretinitis, if all patients with posterior are screened, the positive predictive value is only 47%.[37] As such, routine screening with HLA typing has limited usefulness. However, its targeted use has value. For example, in selected situations where the *a priori* risk of birdshot chorioretinitis is 50% (e.g. late-stage disease with chorioretinal scarring making morphologic diagnosis difficult), the positive predictive value goes to 92% and the negative predictive value 90%, and its use is valuable. As noted above, the diagnosis of Behçet disease is a clinical one;[26] the positive predictive value of screening patients with posterior or panuveitis for HLA-B51 is poor,[37] and its use to diagnose Behçet disease should be discouraged.

Concluding comments

In this perspective, we have addressed how to approach a patient with uveitis to identify correctly the specific disease. The discussion and tables are not exhaustive but illustrative. The approach to the uveitides recognizes that they should be approached currently as about 30 separate diseases, not as a manifestation of underlying "etiologies". The characterization of the uveitis is derived from the informatics approach used in the initial phase of the SUN Project.[4,5] The approach to the diagnosis of a systemic disease is pragmatic. It is based on the concept that if there is no evident endorgan disease and there are no implications for therapy or for the patient's systemic health, then there is no reason to pursue exhaustive laboratory searches with tests of limited positive predictive value. The approach to the use of the laboratory is Bayesian, and it avoids errors of over-diagnosis. However, as every clinician knows, there are outliers – patients with atypical presentations of a disease. It is in this situation that the "art of medicine" becomes paramount -- the skillful use of clinical judgment to select additional testing in order to make the correct diagnosis. Nevertheless, the goal of this approach is to arrive at the correct diagnosis of the specific disease in the overwhelmingly majority of patients without overuse of the laboratory resulting in misleading clinical data.

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Table 1

Major Uveitic Diseases

Anatomic location	Infectious	Systemic disease	No systemic disease
Anterior uveitis	Cytomegalovirus anterior uveitis	HLA-B27-associated uveitis	Fuchs' uveitis syndrome
	Herpes simplex anterior uveitis	Juvenile idiopathic arthritis-associated uveitis	
	Varicella zoster anterior uveitis	Behçet disease	
	Syphilis	Sarcoidosis	
Intermediate	Syphilis	Multiple sclerosis-associated uveitis	Pars planitis
	Lyme disease	Sarcoidosis	
Posterior uveitis	Toxoplasmic retinitis	Sarcoidosis	Serpiginous choroiditis
	Cytomegalovirus retinitis		Acute posterior multifocal placoid pigment epitheliopathy
	Acute retinal necrosis		Multiple evanescent white dot syndrome
	Progressive outer retinal necrosis		Birdshot chorioretinitis
	Diffuse unilateral subacute neuroretinitis		Multifocal choroiditis with panuveitis
	Syphilis		Punctate inner choroiditis
	Lyme disease		Relentless placoid choroiditis ("ampiginous")
	Tuberculosis Bartonella neuroretinitis		
Panuveitis	Syphilis	Behçet disease	Sympathetic ophthalmia
	Lyme disease	Vögt-Koyanagi-Harada disease Sarcoidosis	

Table 2
Pathogenesis, Course, and Treatment Approach of Selected Posterior Uveitides

Disease	Pathogenesis	Course	Treatment
Toxoplasmic retinitis	Parasitic infection	Recurrent acute	Antimicrobial agents
Cytomegalovirus retinitis	Viral infection	Chronic	Antiviral agents
Acute retinal necrosis	Viral infection	Monophasic acute	Antiviral agents
Serpiginous-like tuberculous choroiditis	Mycobacterial infection	Chronic	Antimicrobial agents
Acute posterior multifocal placoid pigment epitheliopathy	Unknown	Self-limited	None, good prognosis
Multiple evanescent white dot syndrome	Unknown	Self-limited	None, good prognosis
Serpiginous choroiditis	Presumed immune-mediated	Chronic	Immunosuppression
Birdshot chorioretinitis	Presumed immune-mediated	Chronic	Immunosuppression
Multifocal choroiditis with panuveitis	Presumed immune-mediated	Chronic	Immunosuppression
Punctate inner choroiditis	Presumed immune-mediated	Monophasic acute, recurrent acute, or chronic	Variable, none to immunosuppression

Table 3

Dimensions Characterizing Uveitis*

Dimension	Examples
Course	Acute, monophasic v recurrent acute v chronic
Laterality	Unilateral vs. unilateral alternating vs. bilateral, asynchronous vs. bilateral simultaneous
Anatomic	Anterior vs. intermediate vs. posterior v panuveitis
Morphology	Retinitis vs. choroiditis Paucifocal vs. multifocal
Infection	Toxoplasmosis vs. cytomegalovirus vs. herpes simplex virus vs. varicella zoster virus vs. syphilis vs. Lyme disease vs. Bartonella
Host/systemic disease	Child vs. adult Immune compromised (e.g. AIDS, transplant) vs. immune competent

*Adapted from reference 5.

Table 4

Selected Examples of Uveitis Characterization and Uveitic Diagnoses

Course	Laterality	Anatomic location	Morphology	Host	Disease examples
Recurrent acute	Unilateral alternating	Anterior			Spondyloarthropathy-associated uveitis (HLA-B27-associated)
Chronic	Bilateral	Anterior		Child	Juvenile-idiopathic arthritis-associated uveitis
Chronic	Unilateral	Anterior	Heterochromia		Fuchs uveitis syndrome
Chronic	Bilateral	Intermediate	Snow bank formation		Pars planitis
Recurrent acute	Unilateral	Posterior	Paucifocal retinitis		Toxoplasmic retinitis
Chronic	Unilateral or bilateral	Posterior	Paucifocal retinitis	Immune compromised	Cytomegalovirus retinitis
Acute	Unilateral or bilateral	Posterior	Paucifocal peripheral retinitis	Immune competent	Acute retinal necrosis
Chronic	Bilateral	Posterior	Multifocal choroiditis	Immune competent	Birdshot chorioretinitis, multifocal choroiditis with panuveitis
Acute monophasic	Bilateral or unilateral	Posterior	Multifocal choroiditis	Immune competent	Acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent white dot syndrome

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Table 5

Comparison of Features of Selected Anterior Uveitides

Characteristic	Spondyloarthropathy-associated	Juvenile idiopathic arthritis-associated	Fuchs' uveitis syndrome	Herpetic	Sarcoidosis
Course	Recurrent acute	Chronic	Chronic	Chronic	Chronic
Laterality	Unilateral or unilateral alternating	Bilateral or unilateral	Unilateral	Unilateral	Bilateral or unilateral
Keratic precipitates	Fine	None; fine	Stellate	Fine; "mutton fat"	"Mutton fat"; fine
Anterior chamber	± Hypopyon; ± fibrinoid aqueous				
Iris	Posterior synechiae	Posterior synechiae	No posterior synechiae; heterochromia	Posterior synechiae; sectoral iris atrophy	Posterior synechiae; iris nodules
Other		Onset age ≤ 16 years		Keratitis	
Laboratory	HLA-B27	ANA *		PCR anterior chamber tap for HSV or VZV †	Chest radiograph, liver enzymes

* ANA = antinuclear antibody.

† PCR = polymerase chain reaction; HSV = herpes simplex virus; VZV = varicella zoster virus.

Table 6

Comparison of Features of Posterior Uveitides Birdshot Chorioretinitis and Punctate Inner Choroiditis

Dimension/characterization	Birdshot chorioretinitis	Punctate inner choroiditis
Onset	Insidious	Insidious or sudden
Duration	Persistent	Limited or persistent
Course	Chronic	Acute monophasic, recurrent acute, or chronic
Laterality	Bilateral	Unilateral, bilateral asynchronous, or bilateral simultaneous
Uveitis location	Posterior	Posterior
Primary site inflammation	Choroid and retinal vasculature	Choroid
Morphology	Multifocal choroiditis	Multifocal choroiditis
Descriptors of spots	Ovoid, indistinct, 50-250μm	Punctate, round, <50 μm
	Yellow-orange or cream-colored	Yellow
Fundus location (2-dimensional)	Posterior & mid-peripheral	Posterior
Other features	Vitreous cells	No vitreous cells or haze
Imaging (fluorescein angiogram)	Undetectable to faintly hyperfluorescent spots Retinal vascular leakage	Hyperfluorescent spots No retinal vascular leakage
Imaging (indocyanine green angiogram)	Hypoperfused choroidal spots	Hypoperfused choroidal spots (variable)
Systemic disease	None	None