

## Management of pediatric uveitis

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### Abstract

Pediatric uveitis is a topic of special interest not only because of the unique diagnostic and therapeutic challenges but also because of the lifetime burden of vision loss if the problem is not adequately treated, as well as the economic and psychological toll on the family. Often, uveitis in children is discovered as part of a routine eye exam; this silent, insidious inflammation can be difficult to treat and can lead to further complications if not handled skillfully. Corticosteroids have long been the mainstay of therapy; however, the significant associated side effects mandate a corticosteroid-sparing therapeutic regimen in pursuit of remission. In this review, we cover the therapeutic options for pediatric uveitis, specifically focusing on the most common non-infectious varieties, juvenile idiopathic arthritis-associated uveitis and pars planitis.

### Introduction

While the incidence and prevalence of uveitis in children is less than that of adults [1,2], pediatric uveitis deserves special attention because of its unique diagnostic and therapeutic challenges, the lifetime burden of blindness if the problem is not cured, and the economic and psychological toll on the family. Children make up between 2.2% and 13.8% of patients in uveitis clinics [1-3]. Uveitis in children is often discovered as part of a routine eye exam, as many children do not report any symptoms, and is more likely to be chronic, recurrent, and difficult to treat. Providers may also face difficulty in getting a complete history and review of systems in uncooperative or preverbal children; general anesthesia is sometimes necessary for a complete exam in very young children.

The risk of poor visual outcomes in children may be greater than in the adult population, due to a delay in diagnosis and established ocular pathology. Between suboptimal therapy and tolerance to insidious inflammation, children are prone to complications and may silently develop cataract, glaucoma, band keratopathy, or amblyopia. Furthermore, the presence of complications

or established pathology at presentation is a significant risk factor for further complications [4,5].

Treatment options are many, and providers must be conscious of the potentially vision-threatening prognosis of uveitis in a child who is not treated quickly and appropriately. In the cases that are not resolved by initial corticosteroid therapy, providers must be keen to initiate immunomodulatory therapy early on. Extensive use of corticosteroids in children can have significant side effects; the child with recalcitrant uveitis should be co-managed with a rheumatologist or referred immediately to an ophthalmologist with the ability to adequately establish and monitor immunosuppressive therapies, such as classic immunomodulators or biologic response modifiers.

### Differential diagnosis

Uveitis in children can generally be identified as having one of three following causes: infectious; non-infectious (e.g. as part of an underlying autoimmune syndrome); or as a manifestation of a masquerade syndrome. The clinical investigation should be initiated and conducted based on a detailed family and past medical history, the

age of the child (Table 1), anatomical location, and granulomatous or non-granulomatous inflammation (Table 2) [6]. The variety of manifestations in numerous uveitic entities is broad and includes many of the same entities seen in adults. Infectious and non-infectious entities of special importance to the pediatric age group are summarized in this article by the most common causes.

#### **Infectious vs. non-infectious uveitis**

There is an estimated incidence of 4.9–6.9 per 100,000 person-years, and prevalence of 13–30 per 100,000 population, of non-infectious anterior uveitis in the North American population [7]. Juvenile idiopathic arthritis is the most common systemic association of pediatric uveitis [7].

Treatment for non-infectious pediatric uveitis is multifactorial. Topical and oral corticosteroids are used to treat acute inflammation. Corticosteroid-sparing agents should be introduced to control the inflammation. Immunomodulatory therapy has been associated with positive outcomes in non-infectious pediatric uveitis, but therapy can be limited by medication-related side effects [8].

Infectious diseases such as toxoplasmosis, toxocariasis, Lyme disease, syphilis, tuberculosis, and some viruses can be common causes of pediatric uveitis, especially in developing countries [9]. These infectious diseases can be successfully treated with specific antimicrobial interventions, and thus careful and extensive systemic work up of these causes must be performed to rule out infections prior to the institution of treatment [10].

#### **Juvenile idiopathic arthritis**

Juvenile idiopathic arthritis is a systemic autoimmune disease and can be defined as a group of idiopathic arthritis diseases that occurs before the age of 16 and persists for at least 6 weeks. The peak age of onset is between the ages of 6 months and 4 years. Juvenile idiopathic arthritis affects approximately 70,000 children in the US. Its pathogenesis appears to be multifactorial; genetic predisposition has been implicated, and the onset is possibly triggered by microbial contact [6]. The most common extra-articular manifestation of juvenile idiopathic arthritis is intraocular inflammation. The prevalence of uveitis in juvenile idiopathic arthritis patients can range from 4% to 38% and varies by juvenile idiopathic arthritis subtype, the most common being oligoarticular onset [11,12]. Juvenile idiopathic arthritis patients with uveitis typically present with bilateral non-granulomatous uveitis. However, granulomatous uveitis with mutton-fat keratic precipitates can occur [13]. Rarely, the posterior segment of the eye can also be involved.

The leading cause of visual impairment in juvenile idiopathic arthritis is complicated cataract and band keratopathy. Other complications associated are secondary glaucoma, epiretinal membrane formation, macular hole, hypotony with ciliary body shutdown or atrophy. The diagnosis should include a careful review of the symptoms and general examination of patients, often with rheumatologist co-management. Early diagnosis and prompt treatment to achieve complete resolution of inflammation is the goal for the prevention of sight-threatening complications in juvenile idiopathic arthritis [6,14,15].

#### **Pars planitis**

The term “intermediate uveitis” should be used for that subset of uveitis where the vitreous is the major site of the inflammation. It is estimated that intermediate uveitis represents one-fifth of all cases of pediatric uveitis [6]. According to Standardization of Uveitis Nomenclature (SUN) criteria, the term “pars planitis” should be used only when there is intermediate uveitis with snowbank or snowball formation, in the absence of an associated infection or systemic disease [16]. Identification of vitreous cells at slit lamp examination is the *sine qua non* of this disease. Usually, patients with pars planitis present with complaints of blurry vision and floaters. Symptoms such as redness, painful eyes and tearing are less common. Children can be diagnosed with intermediate uveitis incidentally on routine ophthalmic examination because significant anterior segment inflammation is not very frequent. Children with pars planitis have worse visual acuity, both at diagnosis and at follow-up, than adults. Complications such as cataract, cystoid macular edema, secondary glaucoma, vitreous hemorrhage and retinal detachment can occur [4,17].

#### **Treatment**

##### **The stepladder approach**

The preferred treatment strategy for non-infectious uveitis is the so-called “stepladder approach”. With anterior inflammation, aggressive topical corticosteroids are initiated as the first-line treatment; if this does not quiet the inflammation, local corticosteroid injections are added to the regimen. Careful monitoring of intraocular pressure during a topical steroid regimen is important. Systemic steroid treatment can also be implemented, but in brief courses (less than three months), as there can be serious long-term side effects, including growth retardation due to adrenal suppression and premature closure of the epiphyseal plates [18]. Weight gain, hyperglycemia, infection, or osteoporosis can also occur due to extensive use of corticosteroid [18]. As topical steroids are generally ineffective at penetrating the eyeball to the posterior segment, systemic treatment or regional injections may be

**Table 1. Differential diagnosis of pediatric uveitis**

| <b>Anterior non-granulomatous</b>   | <b>Anterior granulomatous</b>   |
|---|---|
| <ul style="list-style-type: none"> <li>• Juvenile idiopathic arthritis</li> <li>• Herpetic disease</li> <li>• HLA-B27-associated disease</li> <li>• Systemic lupus erythematosus</li> <li>• Fuchs' heterochromic iridocyclitis</li> <li>• Kawasaki disease</li> <li>• Tubulointerstitial nephritis and uveitis</li> <li>• Trauma</li> <li>• Viral syndromes</li> <li>• Post bacterial infection (<i>Yersinia</i>, Streptococcal)</li> <li>• Amantiades-Behçet's disease</li> <li>• Human immunodeficiency virus</li> <li>• Leukemia</li> <li>• Drug induced</li> <li>• CINCA/NOMID</li> <li>• Juvenile xanthogranuloma</li> </ul> | <ul style="list-style-type: none"> <li>• Sarcoidosis</li> <li>• Herpetic disease</li> <li>• Inflammatory bowel disease</li> <li>• Syphilis</li> <li>• Lyme disease</li> <li>• Leprosy</li> <li>• Tuberculosis</li> <li>• Trauma</li> <li>• Sympathetic ophthalmia</li> <li>• Fungal disease</li> <li>• Multiple sclerosis</li> </ul>  |
| <b>Intermediate uveitis</b>   | <b>Panuveitis</b>   |
| <ul style="list-style-type: none"> <li>• Pars planitis</li> <li>• Juvenile idiopathic arthritis</li> <li>• Multiple sclerosis</li> <li>• Lyme disease</li> <li>• Cat-scratch disease</li> <li>• Toxocariasis</li> <li>• Masquerades</li> <li>• Sarcoidosis</li> <li>• Tubulointerstitial nephritis and uveitis</li> <li>• Syphilis</li> <li>• Familial juvenile systemic granulomatosis (Blau syndrome)</li> </ul>  | <ul style="list-style-type: none"> <li>• Amantiades-Behçet's disease</li> <li>• Sympathetic ophthalmia</li> <li>• Orbital pseudotumor</li> <li>• Vogt-Koyanagi-Harada syndrome</li> <li>• Lyme disease</li> <li>• Cat-scratch disease</li> <li>• Masquerades</li> <li>• Sarcoidosis</li> <li>• Tubulointerstitial nephritis and uveitis</li> </ul>  |
| <b>Posterior uveitis without vasculitis</b>   | <b>Posterior uveitis with vasculitis</b>  |
| <ul style="list-style-type: none"> <li>• Toxocariasis</li> <li>• Leukemia</li> <li>• Tuberculosis</li> <li>• Vogt-Koyanagi-Harada syndrome</li> <li>• Trauma (intraocular foreign body)</li> <li>• Rubella</li> <li>• Diffuse subacute unilateral neuroretinitis</li> <li>• Endophthalmitis</li> <li>• Presumed ocular histoplasmosis syndrome</li> <li>• Masquerades</li> <li>• White dot syndromes</li> </ul>   | <ul style="list-style-type: none"> <li>• Toxoplasmosis</li> <li>• Sarcoidosis</li> <li>• Syphilis</li> <li>• Lyme disease</li> <li>• Acute retinal necrosis (HSV/VZV)</li> <li>• Cytomegalovirus retinitis</li> <li>• Human immunodeficiency virus</li> <li>• Multiple sclerosis</li> <li>• Paraviral syndrome</li> <li>• Masquerades</li> <li>• Kawasaki disease</li> <li>• Amantiades-Behçet's disease</li> <li>• Polyarteritis nodosa</li> <li>• Granulomatosis with polyangiitis (Wegener's)</li> <li>• Systemic lupus erythematosus</li> <li>• Inflammatory bowel disease</li> </ul> |

HLA, human leukocyte antigen; HSV, herpes simplex viruses; NOMID, Neonatal-onset multisystem inflammatory disease; CINCA, Chronic infantile neurological, cutaneous and articular syndrome; VZV, Varicella zoster virus. Adapted with permission from Diagnosis and Treatment of Uveitis, Chapter 81 [6].

**Table 2. Differential diagnosis of intermediate and posterior pediatric uveitis: age at presentation**

| Infants (age 0-2 years)   | Children (age 2-10 years)   |
|---|---|
| <ul style="list-style-type: none"> <li>• Toxoplasmosis</li> <li>• Lymphocytic choriomeningitis virus</li> <li>• HSV retinitis</li> <li>• Retinoblastoma</li> <li>• Rubella</li> <li>• Congenital syphilis</li> </ul>  | <ul style="list-style-type: none"> <li>• Toxoplasmosis</li> <li>• Toxocariasis</li> <li>• Leukemia</li> <li>• Juvenile idiopathic arthritis</li> <li>• Cat-scratch disease</li> <li>• Subacute sclerosing panencephalitis</li> <li>• CINCA/NOMID syndrome</li> <li>• Familial juvenile systemic granulomatosis (Blau syndrome)</li> </ul>   |
| Adolescents (10-20 years)   | Any childhood age   |
| <ul style="list-style-type: none"> <li>• Juvenile idiopathic arthritis</li> <li>• Pars planitis</li> <li>• HLA-B27 associated disease</li> <li>• Toxoplasmosis</li> <li>• Acute posterior multifocal placoid pigment epitheliopathy</li> <li>• Presumed ocular histoplasmosis syndrome</li> <li>• Diffuse subacute unilateral neuroretinitis</li> <li>• Leukemia</li> </ul> | <ul style="list-style-type: none"> <li>• HIV retinopathy</li> <li>• CMV retinitis</li> <li>• Acute retinal necrosis</li> <li>• Endophthalmitis</li> <li>• Sarcoidosis</li> <li>• Lyme disease</li> <li>• Cat-scratch disease</li> <li>• Tubulointerstitial nephritis and uveitis syndrome</li> <li>• Tuberculosis</li> <li>• Vogt-Koyanagi-Harada syndrome</li> <li>• Sympathetic ophthalmia</li> <li>• Amantades-Behçet's disease</li> <li>• Traumatic (intraocular foreign body)</li> </ul> |

HLA, human leukocyte antigen; NOMID, Neonatal-onset multisystem inflammatory disease; CINCA, Chronic infantile neurological, cutaneous and articular syndrome. Adapted with permission from Diagnosis and Treatment of Uveitis, Chapter 81 [6].

the first-line therapy in cases of intermediate or posterior uveitis.

When tapering the corticosteroids leads to a recurrence of inflammation, the second step in the ladder involves systemic non-steroidal anti-inflammatory medications (NSAIDs). Naproxen and tolmentin have the longest history of successful use among pediatric rheumatologists [19]. Celecoxib and diflunisal, in our experience, proved to be useful in controlling human leukocyte antigen (HLA)-B27-associated anterior uveitis such as that seen in ankylosing spondylitis and the other spondyloarthropathies [20]. However, should these therapies prove to be insufficient, early initiation of immunomodulatory therapy is key. Methotrexate is generally the first choice, as it has a well-established safety and efficacy profile in children and does not appear to increase the risk of cancer [21]. We typically begin treatment of a child at 0.15 mg/kg

orally once a week, and increase the dosage every 6-8 weeks until stable quiescence, entirely without corticosteroids, is observed. In juvenile idiopathic arthritis-associated uveitis, the dose required to keep uveitis in remission is typically higher than that required to relieve joint symptoms, but children generally tolerate higher doses well [19]. Additionally, dosage of methotrexate is based on weight, so dose adjustments must be made carefully as the child grows. If uveitis persists after several dose increases, it is advisable to switch to the subcutaneous dosage form, as the bioavailability after oral administration can be variable. If the dose exceeds 17.5 mg, we typically switch to the subcutaneous form. Significant potential side effects of methotrexate include bone marrow suppression, hepatotoxicity, and interstitial pneumonitis, which is why it is crucial that a provider must be an expert in the prescribing and monitoring of methotrexate therapy, or work with a rheumatologist. As methotrexate is a folic acid analogue, adding a regimen of 1 mg of folic acid every day of the week except the day that the medication is taken, or 5 mg of leukovorin once a week, reduces the risk of side effects.

Approximately three-quarters of juvenile idiopathic arthritis patients experience improvement in inflammation with methotrexate as monotherapy [21]. In those that do not improve, the other classic immunomodulators should be explored: azathioprine, mycophenolate mofetil, or cyclosporine can be substituted. Azathioprine is moderately effective in both children and adults [22], but is less commonly prescribed in children, as gastrointestinal side effects are more common than in the other antimetabolites [23]. Mycophenolate mofetil may be effective in quieting inflammation in over half of those cases refractory to methotrexate [24] and, in non-juvenile idiopathic arthritis uveitis, is sometimes used instead of methotrexate as a first-line corticosteroid-sparing agent [8].

Cyclosporine A (CsA), a calcineurin inhibitor that prevents T-cell activation, can be used on its own or in conjunction with the former two antimetabolites. Cyclosporine has been observed to be particularly effective in patients with Behçet's disease-associated uveitis [25]; in children with juvenile idiopathic arthritis-associated uveitis, cyclosporine is more effective when used in combination with methotrexate [26]. Initial dosing is recommended at 3-5 mg/kg/day divided into two doses, followed by a maintenance dose of 2-3 mg/kg/day [6,27]. Less widely used T-cell inhibitors include tacrolimus and sirolimus and, although current data in children are lacking, with more research they may become options in the future. Some individuals may experience hypertension as a side effect of both cyclosporine and tacrolimus, so monitoring of blood pressure is warranted. Additionally, these drugs may have

nephrotoxic effects, and thus should not be given in tandem [27].

### **Biologic response modifiers**

The most recent additions to the treatment options of both children and adults with uveitis are the biologic therapies, which are typically monoclonal antibodies designed to halt the inflammatory cascade by binding and inhibiting proinflammatory cytokines.

The tumor necrosis factor (TNF)-alpha inhibitors infliximab and adalimumab are shown to be the most effective in their class at controlling ocular inflammation, and can be used on their own or in combination with classic immunomodulatory therapy, when one or the other is insufficient [28-31]. An expert panel of the American Uveitis Society released its recommendations on the use of infliximab and adalimumab as first-line agents in the treatment of Behçet's, as second-line in the treatment of juvenile idiopathic arthritis-associated uveitis after methotrexate, and as potential second-line agents for posterior or panuveitis, or in patients who have failed to respond to the classic immunomodulators [32]. Infliximab, a mouse/human chimeric antibody, is given by intravenous infusion at doses of 5-20 mg/kg every 4 weeks, after an induction period [28]. Low dose antimetabolite therapy is usually given in conjunction with infliximab to prevent antichimeric antibodies [33]. Adalimumab, a fully humanized monoclonal antibody, may be given at a dose of 20-40 mg every 7 to 14 days and is administered by subcutaneous injection. While infliximab has a faster onset, adalimumab has less risk of infection and greater ease of administration by subcutaneous injection. Some data suggest that adalimumab may be slightly more effective than infliximab in achieving remission [29,34], while other studies indicate no difference between the two. Trials are currently underway to evaluate the effectiveness of methotrexate and adalimumab combined therapy *versus* adalimumab monotherapy [35].

Golimumab and certolizumab pegol are two other drugs in this class that have been used to treat other autoimmune diseases such as rheumatoid arthritis. As for their effectiveness in uveitis, data are limited to case reports [36,37]. Etanercept, although effective in treating the systemic rheumatological manifestations of juvenile idiopathic arthritis, should not be used in preference to the other TNF-alpha inhibitors, as it is less effective in controlling ocular inflammation [32].

Biologics that target other immune cells may aid in the cases of uveitis that are refractory to anti-TNF therapies but the current data, especially in children, are limited.

Tocilizumab, an inhibitor of the proinflammatory cytokine interleukin (IL)-6, has been noted in several case reports to be potentially effective in the treatment of uveitis that does not respond to anti-TNF agents [38,39]. Rituximab, an anti-CD20 monoclonal antibody approved for treatment of rheumatoid arthritis, lymphomas, and leukemias, was shown to control uveitis in 7 out of 10 patients with juvenile idiopathic arthritis uncontrolled by anti-TNF or immunomodulatory agents [40]. Case reports also show that abatacept, a cytotoxic T-lymphocyte antigen (CTLA)-4 fusion protein that inhibits T-cell co-stimulation, is another agent that has been successful in controlling inflammation in refractory juvenile idiopathic arthritis-associated uveitis [41,42]. Many clinical trials are underway to assess potential biologic therapies, including sarilumab (anti-IL6), anakinra (anti-IL1), ustekinumab (anti-IL23, anti-IL12), canakinumab (anti-IL-1 $\beta$ ), and gevokizumab (anti-IL-1 $\beta$ ).

Intravenous immunoglobulin represents another option for uveitis refractory to other therapies; it is unique in that it treats autoimmune disease without suppressing the immune system. Intravenous immunoglobulin is currently used in rheumatology and ophthalmology for vasculitis, systemic lupus erythematosus (SLE), mucous membrane pemphigoid and uveitis, and is currently being studied in a wide range of other conditions [43]. Case reports show intravenous immunoglobulin as effective in treating uveitis refractory to other treatments, although more data are necessary [44,45]. Doses for immunomodulation are given at 2 grams/kg by intravenous infusion over a course of 2-3 days in 1 week, once monthly.

### **Other treatments**

The cytotoxic alkylating agents chlorambucil and cyclophosphamide are almost always effective in reducing inflammation, but are used only as a last-resort due to potential serious long-term side effects [46,47]. Prolonged use increases the risk of developing a malignancy. This risk can be mitigated by limiting the total cumulative dose and duration to one year or less. Alkylating agents are sometimes associated with significant gonadal dysfunction or infertility in post-pubescent patients, and the effects may or may not be reversible. In girls, ovarian suppression can be induced to protect ova during the course of treatment [48].

Procedural interventions, such as pars plana vitrectomy, are preferred to systemic treatments in certain cases of recurrent pars planitis in order to mechanically clear out inflammatory cells. In our retrospective medical record review of 20 pediatric patients (28 eyes) who underwent pars plana vitrectomy, quiescence of uveitis was achieved at last follow-up, with or without adjuvant therapy, in

27 of 28 eyes (96%). Mean follow-up time after surgery was 13.5 months [49]. Providers should discuss both surgical interventions and long-term immunomodulatory therapy with the family to decide on the most appropriate option.

Implantable corticosteroid-eluting intravitreal devices, such as the fluocinolone acetonide implant (Retisert<sup>®</sup>) or the dexamethasone implant (Ozurdex<sup>®</sup>), represent surgical options for the recalcitrant case. However, the data in children are quite lacking. Retisert<sup>®</sup> releases 0.59 mg of fluocinolone acetonide over 30 months [50] and Ozurdex<sup>®</sup> releases 0.7 mg of dexamethasone over 6 months [51]. Some case reports have indicated successful treatment of intermediate uveitis or panuveitis with the dexamethasone implant with minimal side effects at 3 [52] or 6 [53] months. However, with both devices, there remains a substantial risk of developing cataract and glaucoma, though the risk may be higher with the fluocinolone acetonide implant [54]. In the interest of avoiding future cataract surgery and other complications, these devices are used infrequently in children.

### Conclusion

The goal with any patient is ultimately steroid-free durable remission, in total quiescence for a minimum of two years before tapering therapies. Pediatric uveitis represents a unique challenge in both diagnosis and therapy, but it is essential that appropriate treatment be instated promptly. An ophthalmologist should still monitor children with juvenile idiopathic arthritis but without ocular symptoms so that treatment may be instated rapidly in the event that uveitis develops. The stepladder approach is the preferable method, beginning with corticosteroid therapy to quickly abolish inflammation, and then advancing to classic immunomodulators, adding biological therapies if necessary, in pursuit of steroid-free remission. Ophthalmologists not comfortable with prescribing and monitoring immunomodulatory or biologic therapies should not delay in collaborating with a rheumatologist familiar with the administration of these drugs, or referring patients to another specialist, as the long-term consequences of prolonged corticosteroid therapy are undesirable at best, not to mention the vision-threatening outcomes of recurrent inflammation.







### Abbreviations

HLA, human leukocyte antigen; IL, interleukin; TNF, tumor necrosis factor.

### Disclosures

The authors declare that they have no disclosures.

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