Contents lists available at ScienceDirect

Survey of Ophthalmology

journal homepage: www.elsevier.com/locate/survophthal

Causes of infectious pediatric uveitis: A review

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ARTICLE INFO

Keywords: Infectious uveitis Childhood uveitis Paediatric uveitis Congenital infection Virus Bacteria Parasite Fungi Serology Goldmann witmer coefficient Polymerase chain reaction

ABSTRACT

Infectious pediatric uveitis is a rare disease that can cause severe ocular damage if not detected rapidly and treated properly. Additionally, early identification of an infection can protect the child from life-threatening systemic infection. Infectious uveitis can be congenital or acquired and may manifest as a primary ocular infection or as a reactivation. Nevertheless, publications on infectious paediatric uveitis are usually limited to a small number of patients or a case report. So far, most studies on uveitis in children have focused primarily on noninfectious uveitis, and a systematic study on infectious uveitis is lacking. In this review, we summarize the literature on infectious uveitis in pediatric populations and report on the epidemiology, pathophysiology, clinical signs, diagnostic tests, and treatment. We will describe the different possible pathogens causing uveitis in childhood by microbiological group (i.e. parasites, viruses, bacteria, and fungi). We aim to contribute to early diagnosis and management of infectious pediatric uveitis, which in turn might improve not only visual outcome, but also the general health outcome.

1. Introduction

Uveitis is a group of inflammatory disorders affecting the uveal tissue of the eye that may lead to visual impairment causing a significant impact on quality of life. While uveitis in children comprises a small proportion (5–10%) of all uveitis cases, it is an important cause of ocular morbidity in this age group, responsible for 5–25% of blindness.^{21,39} Infectious uveitis approximately accounts for 20–35% of all pediatric uveitis cases.^{2,21,54,83,155,171,182,220} The wide variation in incidence is caused by geographic distribution, with the highest percentage of infectious causes in developing countries.¹⁸² On the contrary, noninfectious uveitis is the most common entity in the developed western world.^{39,58,83,107,152,155,182} An overview of pathogens, location of uveitis, endemic area, diagnosis, and treatment of childhood infectious uveitis is provided in Table 1. In this review, we included parasites, viruses, bacteria, and fungi. We also include the clinical diagnosis of diffuse unilateral subretinal neuroretinitis, as this is a unique ocular presentation strongly related to nematodes.

2. Epidemiology of infectious uveitis

Widely varied incidences are reported depending on the geographic area, ranging from 3.5 to 24% in the United States, 9% to 31% in Europe, 15% to 36% in Asia, and up to 58% in a single study from South America.^{2,54,58,83,107,115,155,171,182,220} *Toxoplasma gondii* has been identified as the most common infectious cause of pediatric uveitis, with reported numbers ranging from 22% to 76% of all infectious entities worldwide.^{84,115,152,154,182} The percentages of viral and bacterial

Abbreviations: AH, aqueous humour; PCR, polymerase chain reaction; GWC, Goldmann-Witmer coefficient; NGS, next-generation sequencing; CMV, cytomegalovirus; HSV, Herpes Simplex virus; LCMV, lymphocytic choriomeningitis virus; WNV, West Nile virus; ZIKV, Zika virus; OT, ocular toxoplasmosis; DUSN, diffuse unilateral subretinal neuroretinitis; VZV, Varicella Zoster virus; ARN, Acute retinal necrosis; CNS, Central nervous system; CMVR, cytomegalovirus retinitis; AIDS, acquired immunodeficiency syndrome; EBV, Epstein-Barr virus; FHS, Fuchs heterochromic uveitis; CRS, Congenital rubella syndrome; MIS-C, Multisystemic inflammatory syndrome in children; APMPPE, Acute posterior multifocal placoid pigment epitheliopathy; JIA, Juvenile idiopathic arthritis; TB, Tuberculosis; COTS, The Collaborative Ocular Tuberculosis Study; CSD, Cat-scratch disease; mNGS, Metagenomic next-generation sequencing; MAT, microscopic agglutination test; ELISA, Enzyme-linked immunosorbent assay: FE, fungal endophthalmitis.

https://doi.org/10.1016/j.survophthal.2023.12.003

Received 7 August 2023; Received in revised form 11 December 2023; Accepted 29 December 2023

Available online 3 January 2024

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Review article

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Table 1

Pathogen type	Pathogen name	Common location of uveitis	Endemic	Diagnosis				Treatment	Reference
				Serology Intraocula in blood fluid		cular	Other		
				iii biood	GWC	PCR			
Parasite	Toxoplasma gondii	PU	worldwide	+	+	+	-	pyrimethamine plus sulfadiazine	24,90,97,108 130,139,153
								. 1	155,158,179 203,212,221 7,15,23,33,6
	Toxocara canis, Toxocara cati	PU, panuveitis	worldwide	+	+	+	-	steroid + /- ¹ albendazole	118,128,142 169,175,218
	Onchocerca volvulus	AU	Africa, South America	+	-	-	skin biopsy	ivermectin ²	4,28,52,113, 147,149,199
	Baylisascaris procyonis and Ancylostoma caninum	PU, DUSN	Americas, Europe, India, Chaina	$+^3$	-	+	visualization of worm	photocoagulation, albendazole	1,13,35,65,7 133,160,164 193
Virus	(neuroretinits) Herpes Simplex virus	AU, ARN	worldwide	+	+	+		aciclovir, valaciclovir	86,111,125, 157,202,204 223
	Varicella Zoster virus	AU, ARN	worldwide	+	+	+	-	aciclovir, valaciclovir	46,64,93,94, 112,125,159
	Cytomegalovirus	AU, PU	worldwide	+	+	+	-	ganciclovir, valganciclovir, foscarnet, cidofovir	16,25,85,95, 100,101,136 146,180,197 216,219,227
	Epstein-Barr virus	AU, PU, ARN	worldwide	+	+	+	-	supportive + /-aciclovir,	41,63,68,18 191
	Rubella virus	PU>AU	worldwide	+	+	+		valaciclovir supportive	20,59,70,72, 99,110,162, 188,217
	Chikungunya virus	AU	Africa, Asia, Europe, Indian, Pacific	+	-	-	-	supportive	109,114,122 163,187,210
	SARS-CoV 2	All forms	worlwide	+	-	-	nasopharynx	supportive	11,30,45,57 120,156
	Dengue virus	PU	Africa, Americas, East Mediterranean, South-East Asia West Pacific, Asia	+	-	-	-	supportive	74,98,148,13 166,198,225
	Ebola virus	AU>PU, panuvetis	west Africa	+	-	+	-	supportive	132,161,211
	Lymphocytic choriomeningitis virus	PU	Europe, Americas, Australia, Japan	+		-	-	supportive	14,137,228, 232
	West Nile virus	PU	worldwide	+	-	-	-	supportive	12,80,104,1 229
	Zika virus	PU	worldwide	+	-	-	urine	supportive	5,6,82,186, 208,213,214 224,231
Bacteria	Mycobacterium tuberculosis	choroiditis, all forms	worldwide, developing country	+	-	+	TST IGRA	Isoniazid plus rifampicin plus pyrazinamide and ethambutol	36,47,73,12 124,167,201 205,206,226
	Beta-hemolytic Streptococcus	AU, PU	worldwide	+	-	-	Anti-DNase, ASOT	supportive, immunosuppressive drug	3,8,43,62,76 173,209
	Bartonella henselae	neuroretinitis, PU	worldwide	+	-	-	Lymph node, skin	azithromycin, clarithromycin, doxycycline	40,42,60,66, 75,92,121,1 200
	Borrelia burgdorferi	all forms	worldwide	+	-	-	skin	ceftriaxone, doxycycline	19,140,184
	Brucella	all forms	worldwide	+	-	-	-	ceftriaxone, doxycline, rifampicin	117,143
	Leptospira	all forms	worldwide, heavy rain fall, flooding	+	-	-	urine, MAT	ceftriaxone, doxycycline	31,53,91,18 190,195
	Rickettsia	PU	Mediterranean countries	+	-	-	-	doxycycline	126,144
	Spiroplasma	AU	Europe	-	-	-	Lens aspiration, TEM	supportive	55,116,129

(continued on next page)

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Table 1 (continued)

Pathogen type	Pathogen name	Common location of uveitis	Endemic	Diagnosis				Treatment	References
				Serology in blood	Intraocular fluid		Other		
					GWC	PCR			
	Treponema pallidum	all forms	worldwide	+	-	$+^4$	-	penicillin G	50,61,103,135
	Tropheryma whipplei	all forms	Europe, North America	-	-	+		TMP-SMX, doxycycline	49,88,207
Fungi	Candida	chorioretinitis, endophthalitis	worldwide	-	-	+	blood culture	fluconazole, liposomal amphoteracin B	44,79,102,181, 230
	Aspergillus	chorioretinitis, endophthalmitis	worldwide	-	-	+	blood culture, serum galactomannan	voriconazole	48,79,194,222
	Coccidioides immitis, Coccidioides posadasii	granulomatous AU, PU, endophthalmitis	United States, Mexico, South America	+	-		direct microscope, culture, microbiology	fluconazole, ketoconazole, itraconazole	32,106,134, 168
Possible associated pathogen	Parvovirus B19	panuveitis	worldwide	+	-	-	-	supportive	34,69,81,87,89
	Salmonella	AU	worldwide	+	-	-	stool	supportive	9
	Yersinia enterocolitica, Yersinia pseudotuberculosis	AU	worldwide	+	-		-	Supportive	121

PCR polymerase chain reaction; *GWC* Goldmann-Witmer coefficient; *AU* anterior uveitis; *PU* posterior uveitis; DUSN diffuse unilateral subretinal neuroretinitis; AC anterior chamber; *TST* tuberculin skin test; *IGRA* interferon gamma release assay; *Anti-DNase* anti-deoxyribonuclease, *ASOT* anti-streptolysin O; *MAT* Microscopic agglutination test; *TMP-SMX* trimethoprim-sulfamethoxazole; *TEM* transmission electron microscopy

¹ trimethroprim and sulfamethoxazole is used for prophylaxis of recurrent

² doxycycline has been reported to be effective

³ serology test and PCR can be done with limited value

⁴ we experienced a positive PCR of *Treponema* from intraocular fluid in adult patients

causes, among infectious uveitis cases, varied among different studies, with herpes viruses as the main cause in developed countries, responsible for 20% to 43% of cases.^{83,152} In high-endemic areas for tuberculosis, mostly developing countries, tuberculosis is a significant and important cause of infectious uveitis, accounting for 9%– 25% of infectious childhood cases.^{171,182,201}

3. Diagnosis

Fast identification of infectious uveitis entities is crucial importance since treatment regimens are entirely different from those for noninfectious disorders. Infectious uveitis is generally suspected based on history and clinical characteristics. Unilateral posterior uveitis is the most common presentation of infectious uveitis.^{83,172,182,192} In clinical practice, the diagnosis of infectious uveitis is mainly based on a combination of specific clinical features, serological data, and aqueous humour (AH) analysis by polymerase chain reaction (PCR) and (GWC).^{56,141} coefficient Goldmann-Witmer Next-generation sequencing (NGS) testing is a new method for molecular diagnosis that can detect all DNA-based lifeforms and provide information on drug resistance; however, it is not widely available today for diagnostic purposes because it is expensive and can detect nonpathogenic organisms that might lead to misinterpretations.^{51,119} Therefore, the value of this method for detecting intraocular pathogens is currently still limited.

4. Congenital infections

Infections can be congenitally obtained from an infected mother by transplacental transmission or during birth. TORCH (*Toxoplasma*, rubella virus, cytomegalovirus (CMV), herpes simplex virus (HSV), and *Treponema pallidum* (syphilis)) are the most common causes of congenital infections causing ocular morbidity.¹³⁸ In endemic areas, lymphocytic choriomeningitis virus (LCMV), West Nile virus (WNV), and Zika virus (ZIKV) are also associated with congenital infection as posterior

uveitis.^{14,17,215,231,2712} In contrast, *Spiroplasma* is reported to present as granulomatous anterior uveitis.^{55,116,129}

If a congenital infection is suspected, the presence of specific IgG/ IgM in the peripheral blood of both the mother and child can be tested. PCR on umbilical cord blood is also a beneficial diagnostic tool. Analysis of the Guthrie card can be employed in neonates and older children suspected of congenital infection.^{37,78,196} The congenital infections with their clinical signs are summarized in Table 2.

Table 2

Reported ocular manifestations of congenital infection.

Pathogen name	Ocular manifestations	References
Toxoplasma	Chorioretinal scars (macula or	108,138,139,
<u>I</u>	periphery)	221
Varicella zoster virus and	Retinitis (retinal lesions), acute retinal	138
Herpes simplex virus	necrosis	
Cytomegalovirus	Retinitis (retinal lesions)	78,138
Rubella virus	Nuclear cataract, micropthalmos, iris	72,138,188
	hypoplasia, cloudy cornea, glaucoma,	
	salt and pepper retina, nystagmus,	
	strabismus, primary optic atrophy	
Lymphocytic	Chorioretinal scars (resembling	14,27,138
choriomeningitis virus	toxoplasmosis)	
West Nile virus	Macular and peripheral chorioretinal	12,138
	scar, macular granularity	
Zika virus	Retinal (macular) lesions, optic	17,213,214,
	atrophy	231
Spiroplasma	Granulomatous anterior uveitis,	55,116,129
	cataract	
Treponema pallidum	Bilateral cataract and granulomatous	138
	uveitis, salt and pepper retina,	
	interstitial keratitis	

5. Pediatric uveitis categorized by group of pathogens

5.1. Parasites

5.1.1. Toxoplasmosis

Toxoplasmic retinochoroiditis is the most common cause of posterior uveitis in children and may be a part of a congenital infection or acquired after birth.¹³⁹ It has been shown that the frequency of ocular toxoplasmosis increases with age from 13% between the ages of 6 and 10 years to 23% between the ages of 11 till 16 years.^{155,221} Congenital toxoplasmosis is frequently observed as an atrophic hyperpigmented scar at the macula, described as a "wagon wheel". A study from Brazil in 2020 showed that, if the lesions occurred during the first year of life, they were usually in the central area, whereas if they presented later in life, new lesions predominately were found in the peripheral retina.¹⁰⁸

The presentation of acquired ocular toxoplasmos (OT) in children is focal retinitis, sometimes with overlying severe vitreous inflammation described as "headlight in the fog", and is frequently closely located to hyperpigmented scarring similar as in adults. OT is also a rare cause of high intraocular pressure in uveitis.²⁰³

The diagnosis of OT is generally based on the characteristics of the chorioretinal scar and serological testing.^{24,130} Seroprevalence to *T* gondii rises with increasing age, reaching 60% positivity in the general adult population (IgG).^{153,212} In the first 3 weeks, immunoblotting of aqueous humor has been shown to have a more significant sensitivity than GWC (64.7% vs. 23.5%).¹³⁰ PCR has been found positive in only 35.9% of cases and even lower, 24.3%, in immunocompetent patients.²⁴ Prenatal screening and information campaigns on congenital toxoplasmosis can be beneficial in terms of reducing the risk of infection during pregnancy and developing severe neurological and ocular morbidity.^{158, 179}

In children the indications for treatment are similar to those in adults (optic nerve head involvement, posterior pole involvement, immunocompromised patients, dense vitreous opacities, or lesions larger than 3 disc diameters). Neonates with congenital OT require long term therapy, regardless of specific findings, to prevent neurological and ocular recurrences.^{97,139,158} Parents should be informed that, despite complete treatment, recurrence or relapse can still occur later in life.¹⁰⁸ A long term intermittent regimen with trimethroprim and sulfamethoxazole (co-trimoxazole) could reduce the rate of recurrent infection.⁹⁰ Consultation with a pediatrician for diagnosing systemic infection and treatment is mandatory.

5.1.2. Toxocara canis and Toxocara cati

Ocular toxocariasis has a prevalence of approximately 5% of the world's population, with remarkable differences between regions, with the highest prevalence in Africa.¹⁵ Children aged between 5 and 10 years of age are affected most often, and 80% of patients are diagnosed before the age of 16.^{15,33,118} Humans are predominantly infected by ingesting infective eggs from soil or contact with affected animals. Clinical manifestations range from mostly asymptomatic to severe organ injury and are categorized into 4 types: visceral larva migrans, ocular toxocariasis, covert toxocariasis, and neurotoxocariasis.^{23,33}

The most common ocular symptoms in children are unilateral decreased vision, strabismus, leukocoria, and red eye.¹²⁸ The clinical ophthalmological presentation has 3 major forms comprised of diffuse nematode endophthalmitis, peripheral inflammatory mass, and posterior pole granuloma.^{33,128}

The diagnosis is based on the clinical presentation in combination with positive serology for *Toxocara*; however, *Toxocara* serology in the blood may be low or even seronegative in ocular toxocariasis.^{175,218} Therefore, the GWC and PCR analysis can be of value for a definitive diagnosis of Toxocara.^{142,218} Eosinophilia was found in only 52% of ocular toxocariasis patients.¹²⁸ Ultrasonography can assist in differentiating between granuloma and calcification to make the important distinction from retinoblastoma.¹⁶⁹ The mainstays of treatment are

anthelmintic drugs and corticosteroids (systemic and regional); however, due to massive death of the larvae, the treatment may cause severe inflammation in the eye.⁷ Other ocular treatment modalities include laser photocoagulation if the larvae are visible in the retina.^{7,67}

5.1.3. Onchocerca volvulus

Onchocerciasis, also known as river blindness, is a zoonotic disease caused by the *Onchocerca volvulus* parasite.⁴ Infected blackflies introduce the parasites by biting humans and infecting them with the larvae, which typically occurs during the wet season.²⁸ The larvae grow into adult worms and produce a large quantity of microfilariae, which are the major cause of the disease.¹⁴⁹ Clinical symptoms in affected children are photophobia, conjunctival nodules, limbal sclerokeratitis, anterior chamber microfilarias (70.3%) and anterior uveitis (3,7%).¹⁴⁷ Diagnosis is based on the presence of microfilariae, mostly from skin snips, or PCR.¹¹³ Microfilariae may be found in the anterior chamber during slit lamp examination in 70.3% of infected children.¹⁴⁷ Ivermectin is administered in order to decrease the number of intraocular microfilariae and reduce inflammatory activity.^{52,199}

5.1.4. Diffuse unilateral subacute neuroretinitis caused by nematodes

Diffuse unilateral subacute neuroretinitis (DUSN) is an ocular presentation caused by various mobile nematodes; the most common are Baylisascaris procyonis and Ancylostoma caninum.^{133,160} DUSN affects mainly healthy children and young adults.^{13,35,165} Unilateral disease with a single or unidentified nematode is common; however, bilateral eye disease with 2 worms has been reported.^{38,77} Ocular presentations in the early stage include mild to moderate vitritis, papillitis, retinal vasculitis, retinal edema, recurrent yellow-white or grey-white lesions, and macular star. The worm may or may not be visualized.^{1,13,35} In the late stage, ocular manifestations are mainly subretinal tracks, RPE alteration, white spots, vitritis, disc atrophy, and vascular attenuation.^{1,} ^{13,35,133,164} A diagnosis of DUSN is made by identification of a subretinal worm or clinical suspicion from ocular presentation. The serology test can be done, but its utility is limited if the nematodes are not identified by fundus examination because there are various causative nematodes and antibodies may wane over time.^{133,160,218} Laser photocoagulation of the worm is the gold standard treatment. Antihelminthic therapy is effective, and steroids may be administered.^{13,35,133,164,193} In general, the prognosis in the late stage is poor.^{13,35,65,193}

5.2. Viruses

5.2.1. Herpes simplex virus and varicella zoster virus (VZV)

Herpetic infections are the most common infectious cause of anterior uveitis in children in developed countries.^{96,154} In general, as in adults, clinical differentiation between VZV and HSV infections is difficult, since both can present with similar clinical features. HSV and VZV can cause a broad spectrum of ocular inflammation in children, but most commonly they present as unilateral anterior uveitis.

Herpetic anterior uveitis is usually accompanied by stromal or endothelial keratitis, high intraocular pressure, and the characteristic iris atrophy in a later stage. ^{111,223} Anterior uveitis rarely develops during primary chickenpox but has been described in primary infection if the eyelids are affected and usually has a good visual prognosis. ^{93,94} PCR and GWC are helpful for the diagnosis. Oral antiviral medications are used for the treatment of HSV and VZV anterior uveitis. ^{46,112} Topical steroids should be administered to reduce inflammation. ⁴⁶

The most severe ocular manifestation of both HSV and VZV is acute retinal necrosis (ARN), which can also occur in children. ARN can affect healthy as well as immunocompromised children of all ages, even neonates.^{64,86,125,159,202,204} Over 50% of ARN-infected children had red eye, and 30% of patients had a history of herpesvirus infection, including central nervous system (CNS) involvement.^{125,157} The diagnosis of ARN is based on a clinical presentation with rapid progressive circumferential peripheral retinal necrosis, occlusive vasculopathy, and marked anterior

and vitreous inflammation.¹²⁵ PCR for herpesviruses and serological testing with GWC in intraocular fluid is also necessary to confirm the diagnosis. Intravenous and intravitreal antiviral medication and systemic steroids in severe inflammatory cases are the mainstays of treatment.¹²⁵

5.2.2. Cytomegalovirus

Cytomegalovirus retinitis (CMVR) in children can be congenital or postnatally acquired in immunocompromised patients. In rare cases, CMV can cause hypertensive anterior uveitis (Posner Schlossman-like anterior uveitis) in immunocompetent children.²⁵ The incidence of cytomegalovirus retinitis in acquired immunodeficiency syndrome (AIDS) patients appears to be much lower in the pediatric population than in the adult population.^{136,146} Pediatric patients with secondary immunodeficiency, such as solid organ transplantation or, hematologic malignancy, are also at risk of developing CMV infection. While the recommendation for CMVR screening in secondary immunodeficiency patients is not yet established, it is generally considered beneficial for those in high-risk groups.^{85,101} For congenital CMV, apart from retinal involvement clinical manifestations also include sensorineural deafness, thrombocytopenia purpura, microcephaly, and hepatosplenomegaly.¹³⁸ Clinical features of acquired CMV retinitis do not differ from those in adults with retinal necrosis with granular white opacification of the retina, hard exudates, and hemorrhages, but they are more likely to be bilateral and located in the central area.¹⁶

The diagnosis is based on clinical characteristics and the immune status of the patient. Aqueous humor analysis by PCR can confirm the diagnosis of ocular CMV in anterior uveitis and CMV-related retinitis in immunocompromised patients.^{25,100} The GWC may be less sensitive in immunocompromised patients due to disturbed B cell function, but it can contribute to the diagnosis of CMV anterior uveitis.^{25,180,216} There are no guidelines for the treatment of CMV anterior uveitis, topical 2% ganciclovir has been reported to be beneficial for treatment in adults.¹⁹⁷ In congenital active CMVR, systemic and/or intraocular antiviral treatment is recommended as it is likely to improve the visual outcome.⁹⁵ The visual prognosis depends on the patient's systemic immunocompetence and on the rapid institution of effective antiviral therapy.^{16,219}

5.2.3. Epstein-Barr virus

Epstein-Barr virus (EBV) or human herpes virus-4, a double-stranded DNA virus, is a common infectious agent worldwide. It is transmitted via saliva or aerosol and tends to be asymptomatic in children, but can lead to infectious mononucleosis with clinical manifestations of fever, lymphadenopathy, and pharyngitis.^{22,41} Although a link between EBV infection and ocular manifestations including hypertensive anterior uveitis, ARN, and frosted branch angiitis has been suggested, the role of EBV in the causation of uveitis remains controversial.^{10,41,63,105,1} EBV is also associated with post-transplantation lymphoproliferative disorder in organ transplant patients which can have ocular manifestations such as iris nodules, granulomatous anterior uveitis, and papillitis.41,150,170,176 The diagnosis of active EBV infection is based on serology, while aqueous humor analysis is of limited value since positive PCR for EBV has been found in patients without ocular inflammation.⁴¹, ^{68,145,191} Whether systemic antiviral therapy in EBV associated uveitis is of benefit is unclear, but some authors reported a clinical improvement.^{105,145,185}

5.2.4. Rubella virus

Ocular involvement of rubella virus infections in children consists of congenital rubella syndrome, rubella virus-associated anterior uveitis, and/or Fuchs heterochromic uveitis (FHU). Vaccination against rubella virus has resulted in less congenital rubella syndrome as well as less rubella virus-associated uveitis.^{20,110} Congenital rubella syndrome (CRS) is often a devastating disorder causing a significant lifetime burden, with a classic triad of cataract, cardiac abnormalities, and

deafness.^{72,110,188} The ocular involvement is often bilateral with nuclear cataract being the most common finding. Other findings are microphthalmos, iris hypoplasia, cloudy cornea, glaucoma, salt and pepper retinopathy, nystagmus, concomitant strabismus, and primary optic atrophy (Table 2).^{99,110,217} Rubella virus-associated anterior uveitis, as reported in non-vaccinated children, is comparable to that in adults, characterized by mild unilateral chronic anterior uveitis, iris hetero-chromia, and vitritis.^{59,70}

GWC is the preferred test for diagnosing FHU, with a positive rate of 93–100%, whereas the reported PCR sensitivity for rubella virus RNA is only 10–20%.^{70,162} Topical corticosteroids are administered briefly in symptomatic FHU. In general, the visual outcome of Rubella-associated uveitis, or FHU, is favorable but it depends on the presence of complications, such as glaucoma.

5.2.5. Chikungunya virus

Chikungunya virus is an alphavirus spreading globally through *Aedes* mosquitoes and has since recently been reported regularly in Africa, Asia, Europe, and in the Indian and Pacific ocean countries.²¹⁰ Infection can give rise to various ocular manifestations, including conjunctivitis, episcleritis, anterior uveitis, retinitis, neuritis, choroiditis, or exudative retinal detachment.^{109,122,163,210} In general, Chikungunya virus infections have a benign and self-limiting disease course in adults. In children, Chikungunya virus infection often leads to more severe clinical manifestations with neurological complications, including rarely lethal meningoencephalitis or blindness from retrobulbar neuritis.^{114,187}

5.2.6. SARS-CoV-2 (COVID-19)

COVID-19 related ocular manifestations in pediatric patients occur in 2 phases: in the acute phase as conjunctivitis and in the late phase as uveitis, part of the multisystemic inflammatory syndrome in children.^{11, 30,45,57,120} Ocular presentations of uveitis are anterior uveitis, retinitis, retinal vein occlusion, and optic neuritis.^{11,156} In general, the majority of cases of COVID-19 with ocular involvement resolved without treatment.¹²⁰

5.2.7. Dengue virus

Dengue is a viral disease caused by one of the 4 dengue virus serotypes (DENV 1–4), which are transmitted by *Aedes* mosquitoes.⁷⁴ Ocular involvement in dengue fever in children is comparable to that in adults and can be divided into 2 main mechanisms: inflammation and thrombocytopenia. Subconjunctival hemorrhage is the most common ocular manifestation.⁹⁸ The acute phase of Dengue virus infections, mainly presents as posterior uveitis, including maculopathy, macular edema, choroidal vasculopathy, retinal vasculitis, hemorrhages and yellow spots.^{148,166,198} Anterior uveitis has been reported several months after the initial infection.^{151,198} The detection of anti-dengue-virus IgM in serum, which reveals a recent infection, is the most widely used diagnostic test. At present, there is no effective drug treatment for dengue. The prognosis is favorable in most patients.¹⁵¹

5.2.8. Ebola virus

Ebola virus disease is a zoonotic virus causing hemorrhagic fever associated with high mortality. The virus is endemic in West Africa. Following the 2014–2016 outbreak, uveitis (mainly anterior) was reported in 18% of the survivors of the Ebola virus disease, 20% of which were under the age of 20 years.²¹¹ Although Ebola virus is rapidly cleared from body fluids after resolution of the acute phase, high concentrations were isolated from the aqueous humor of a patient with sight-threatening uveitis after surviving acute Ebola virus disease.^{132,161}, ²¹¹ A recently published longitudinal study of the survivors showed there were no significant differences in visual acuity between the survival and control groups.¹⁶¹

5.2.9. Lymphocytic choriomeningitis virus (LCMV)

LCMV is an enveloped RNA virus, and infection may occur through

aerosols, ingestion, or bites from rodents. Congenital infection of humans with LCMV can lead to severe neurological disease, with hydrocephalus, macro-or microcephaly, and chorioretinitis resembling toxoplasma chorioretinitis.^{14,232} Several cases of severely retarded children with chorioretinal scars related to an intrauterine infection with LCMV mimicking ocular toxoplasmosis are reported (Table 2).^{27, 137,228} Currently, there is no proven or established treatment for LCMV.

5.2.10. West Nile virus

West Nile virus (WNV) is a single-stranded flavivirus transmitted by a mosquito vector (type Culex), with wild birds serving as its reservoir.⁸⁰ A typical bilateral multifocal chorioretinitis, frequently asymptomatic, is the most common ocular manifestation of WNV infection (80%).^{104, 174} Congenital infections with chorioretinal scarring have also been described (Table 2).^{12,229} There is no proven treatment for WNV.¹⁷⁴ The ocular disease itself usually has a self-limiting course, but foveal chorioretinal scarring, severe ischemic maculopathy, or optic atrophy might occur.

5.2.11. Zika

Zika virus is a flavivirus transmitted by daytime active *Aedes* mosquitoes, transplacentally, or through sexual contact. Congenital ZIKV infection can cause severe brain anomalies, microcephaly, and posterior uveitis. Brain and eye anomalies include optic nerve hypoplasia, optic nerve pallor, loss of foveal reflex, retinal pigment mottling, chorioretinal scar, and retinal vascular abnormalities.^{82,186,213,214,231} A recent study in adult patients found bilateral hypertensive non-granulomatous anterior uveitis in nearly 50% of patients with ZIKV infection and red eye; however, this has not been reported in children.²⁰⁸ The diagnosis can be confirmed by detecting viral RNA in the blood or IgM combined with a serum plaque reduction neutralization test.^{5,6,224}

5.3. Bacteria

5.3.1. Mycobacterium tuberculosis

Mycobacterium tuberculosis is mostly transmitted through aerosolized droplets and can cause latent or active tuberculosis (TB). It is endemic in developing countries.^{182,201,206} All parts in the eye can be affected in children with tuberculosis.^{36,123,205} According to the Collaborative Ocular Tuberculosis Study (COTS), posterior uveitis with choroidal involvement was the most common finding and among this group of patients, a serpiginous-like phenotype was most frequently observed.² Optic disc edema was more often observed, whereas retinal vasculitis tended to be less frequent in children compared to adults.²⁰⁵ A positive result for the tuberculin skin test without BCG vaccination or the Quantiferon-TB test is indicative of prior exposure, but the test cannot distinguish between active systemic infection and latent TB. PCR for TB in ocular fluid is not very sensitive.⁷³ For children, anti-tuberculosis treatment is given according to standard treatment regimens. 47,124,226 Rarely, paradoxical worsening due to a severe inflammatory response can be observed in children after the initiation of anti-tuberculosis treatment.167

5.3.2. Streptococcus

Beta-hemolytic streptococci are commonly responsible for respiratory tract and skin infections in children.⁴³ Post-streptococcal syndrome is believed to be caused by an autoimmune response, typically observed 7–35 days following the infection, and is diagnosed through serological tests.^{43,62,209} Post-streptococcal syndrome-related uveitis can manifest within the broad spectrum of ocular inflammation, but anterior uveitis is most commonly described in children.^{3,8,43,62,76,173,209}

5.3.3. Bartonella henselae

Cat-scratch disease (CSD) is a systemic disease caused by the gramnegative rod *Bartonella henselae*. Ocular involvement occurs in 5–10% of patients, both children and adults, and typically develops after the resolution of symptoms such as fever and malaise.¹²¹ Ocular manifestations of CSD are mainly in the posterior segment, including neuroretinitis and optic disc anomalies.^{40,42,60,66,75,121,183,200} The diagnosis of CSD is based on a history of contact with cats, along with positive serology in the blood, PCR from tissue or skin biopsy.⁹² Treatment with systemic antibiotics, possibly in combination with steroids, has been shown to improve visual acuity.^{42,60,66,75}

5.3.4. Borrelia burgdorferi

Lyme borreliosis is a tick-borne disease caused by the spirochete *Borrelia burgdorferi* that affects multiple systems. A diagnosis is typically established based on a history of a tick bite followed by erythema migrans, a positive serology, and confirmation by immunoblot.^{19,140} Ocular involvement in Lyme disease is rare, develops mainly during the late stages, and can manifest as all forms of uveitis.^{19,140,184}

5.3.5. Brucella

Brucellosis is a zoonotic disease caused by bacteria of the *Brucella* genus. Infection may occur by ingestion of infected raw milk, raw meat, or dairy products from sheep, goats, or cattle. The ocular presentations of *Brucella*- associated uveitis are anterior uveitis, posterior uveitis, and optic neuropathy.^{117,143} The diagnosis is based on a positive blood culture or PCR, a serologic test; vitreous sampling for metagenomic next-generation sequencing (mNGS), may be helpful. Treatment involves prompt antimicrobial therapy.¹¹⁷

5.3.6. Leptospira

Leptospirosis is a zoonotic infection caused by *Leptospira* bacteria. This disease can be acquired by humans through contact with contaminated urine or tissue or swimming in open water.^{91,195} Uveitis occurs between 2 weeks and 1 year after infection, with an average of 6 months, and may manifest in all forms.^{31,53,189,190} The diagnosis of leptospirosis is based on detecting spirochetes by dark field microscopy or PCR in the blood or urine.^{31,91} Other diagnostic techniques include the microscopic agglutination test (MAT) or the enzyme-linked immunosorbent assay (ELISA).^{31,91}

5.3.7. Rickettsia

Rickettsia conorii is a small coccobacillary intracellular bacterium transmitted to humans by the dog tick *Rhipicephalus sangineus*. Children in endemic areas (Mediterranean countries) present with a triad of posterior segment changes in the eye (retinitis, retinal vasculitis, optic disc abnormalities), fever, and skin rash.^{126,144} A positive result on serology tests is helpful in reaching a diagnosis.¹²⁶ Prompt antibiotic treatment can prevent complications and visual impairment.

5.3.8. Spiroplasma

Spiroplasma is an intracellular bacterium without a cell wall that was generally considered non-pathogenic in humans;¹²⁹ however, this organism has been reported to cause congenital spiroplasmosis presenting with ocular manifestations such as granulomatous anterior uveitis, iris synechiae, and cataract. Only 5 patients were reported in France and Germany.^{55,116,129} These babies were born to healthy mothers, except in one case where the mother had a history of *Mycoplasma* infection during pregnancy. From these babies, crystalline lens aspiration and anterior vitreous were obtained during cataract surgery. A positive PCR for *Spiroplasma* or visualization of this bacteria on the lens with transmission electron microscopy confirmed the diagnosis. There is no specific treatment, but all the cases respond well to steroids (Table 2).

5.3.9. Treponema pallidum

Syphilis, a sexually transmitted disease, is caused by the spirochete *Treponema pallidum*. In children syphilis is mostly a congenital infection, but clinicians should also be aware that sexual abuse forms a risk factor. In congenital syphilis, choroiditis with a salt and pepper fundus,

bilateral cataract and granulomatous uveitis are described.^{103,135} Also, chorioretinitis is mostly an early finding, whereas interstitial keratitis is usually seen later in the disease.^{103,135} The diagnosis is made clinically with confirmation by serological tests, such as the *Treponema pallidum* haem- or particle agglutination test, which remains positive for life even after treatment, and the Venereal Disease Research Laboratory (VDRL) test or its substitute, the rapid plasma reagin test (RPR), which is only positive during the active stages of disease.^{50,61,135} In both children and adults, treatment with intravenous penicillin is essential.¹³⁵

5.3.10. Tropheryma whipplei

Whipple disease is a rare entity caused by the *Tropheryma whipplei* bacterium that occurs mainly in Caucasians, with a strong predominance for males. Gastrointestinal symptoms and weight loss are the main clinical manifestations; however, in rare cases, uveitis occurs.^{88,207} So far, one case was reported of a 3-year-old girl with unilateral, anterior, granulomatous uveitis, possibly as a result of Whipple disease.⁴⁹ Long-term antibiotic therapy is obligatory in cases of *Tropheryma whipplei* infection.²⁰⁷

5.4. Fungi

Most of the patients infected with fungal uveitis are immunosuppressed or have a severe illness. The most common endogenous intraocular fungal infection is *Candida* and *Aspergillus* endophthalmitis; additionally, coccidioidomycosis should be considered in endemic regions.

Regarding childhood uveitis, only endophthalmitis and chorioretinis have been described for the endogenous route. Risk factors for developing disseminated fungus in children are prematurity, neutropenia, immunosuppressants, persistence of candidemia for more than three days from a centre vein catheter, and bone marrow transplants.^{48,181,230} The prevalence of fungal endophthalmitis (FE) in fungemia cases is rare, approximately 0–2.5% in the prophylactic antifungal and early treatment eras.^{48,102} Neonatal endophthalmitis from candidemia was reported in approximately 3%.¹⁸ Screening for FE in fungemia is recommended when patients report floaters or are unresponsive to antifungal treatment.^{26,48}

The diagnosis of FE can made with microbiological culture or direct microscopy of vitreous fluid; however, culture requires time, up to 2 weeks, and has a low sensitivity. Therefore, PCR from intraocular fluid is a very useful method for the diagnosis.^{44,177} Serum galactomannan is also useful for the diagnosis of aspergillosis.¹⁹⁴ Systemic anti-fungal therapy is the mainstay treatment. Intravitreal anti-fungal therapy and early vitrectomy may be needed.^{79,194}

5.4.1. Candida

Pediatric patients have similar signs and symptoms as adult patients and similar clinical findings, both in the endogenous and exogenous routes. Patients usually experience subacute onset of floaters, blurred vision, and eye discomfort. Ocular manifestations are localized fluffy creamy white retinal or subretinal nodules, string of pearls appearance, puff ball abscess, and vitreous lesions with snowball and snowbank.^{102,} ¹⁷⁸ Systemic antifungal therapy is the mainstay of fungal chorioretinitis and endogenous endophthalmitis. Vitrectomy and intravitreal antifungal may also be warranted in endophthalmitis cases.⁷⁹

5.4.2. Aspergillus

Aspergillus FE is usually more severe compared to *Candida*, with a shorter onset and worse prognosis.^{71,79} Ocular manifestations are hypopyon, fluffy white preretinal lesions with creamy white deep retinal lesions located in the macula, focal retinal hemorrhage, and retinal necrosis.^{79,102,194,222}

5.4.3. Coccidioides

Coccidioides immitis, or Coccidioides posadasii, is fungus-caused

coccidioidomycosis, also known as Valley fever, acquired by inhalation of arthroconidia.^{29,106,168} Generally, it is an asymptomatic to mild disease self-limited in a healthy patient, but it may cause disseminated disease in immunocompromised patients. Ocular involvement associated with the systemic coccidioidomycosis is rare.^{106,168} The ocular manifestations are granulomatous iridocyclitis, choroiditis, chorioretinitis, and endophthalmitis.^{32,168} The diagnosis is based on a history of visits to or living in an endemic area and evidence of systemic infection. Serology testing, culture, and histopathology from biopsy are helpful.¹³⁴ Systemic antifungal treatment should be initiated after diagnosis.^{32,168}

5.4.4. Other infectious agents associated with uveitis in adults

Other infectious agents associated with uveitis in adults are parechovirus, Human T-lymphotropic virus, HIV-infection associated uveitis, *Coxiella burnetti, Mycobacterium leprae, Chlamydia trachomatis, Histoplasma capsulatum, and Cryptococcus neoformans.* These pathogens have been described as a cause of uveitis in adults. We found no clinical reports of pediatric uveitis.

5.5. Pathogens which might be associated with pediatric uveitis

Several pathogens have been associated with uveitis, but it is unclear whether the pathogen itself directly causes the eye inflammation.

5.5.1. Parvovirus B19

Parvovirus B19 infection, known as erythema infectiosum or 'fifth disease', is a common childhood disease, with a seroprevalence of 60–80% in young adults.^{34,81} It has been associated with pediatric uveitis in a few cases.^{34,69,87,89} Interestingly, our group found local antibody production against parvo B19 in aqueous humour in a cohort of childhood uveitis. We reported that 7 of 13 children with juvenile idiopathic arthritis (JIA)-associated uveitis and 3 out of 45 children with idiopathic chronic anterior uveitis had a positive GWC for parvovirus B19.⁶⁹ The relevance of this finding for the pathogenesis of (JIA-associated or idiopathic) uveitis remains to be established.

5.5.2. Salmonella

Salmonellosis is caused by several *Salmonella* species that are divided into the typhoid group, comprising of *S. typhi* and *S. paratyphi*, which cause a generalized infection with bacteremia, and the nontyphoid Salmonellae, which cause gastroenteritis. The bacteria are usually contracted from contaminated food. One case report describes an 11-yearold girl with acute anterior uveitis in both eyes after a cultureconfirmed *Salmonella* enteritis.⁹ In this patient a transient serum antinuclear antibody positivity was found. Whether ocular manifestation was caused directly by the Salmonella bacterial infection or through a post-infection immunological phenomenon remains to be determined.

5.5.3. Yersinia

Yersinia bacteria cause enteral infections. It is widely recognized as a triggering factor for reactive arthritis. One study reported 4 cases of HLA-B27 positive children with acute nongranulomatous anterior uveitis and one case of fibrinous exudate after a systemic *Yersinia* infection. Three (sub)species were reported to be associated with reactive arthritis: *Y. enterocolitica* serotype 3 and 9, and *Y. pseudotuberculosis* serotype 1A.¹³¹ Visual acuity of all children was restored to baseline levels after anti-inflammatory treatment.¹³¹

6. Conclusion

We have conducted a literature review on infectious uveitis in the pediatric population and reported on the epidemiology, pathophysiology, clinical signs, diagnosis, and treatment. Although some of the infectious causes of uveitis are very rare, they can cause serious ocular and systemic disease if not recognized in time. In the severely ill patients, fungal infections should be considered as causative pathogen.

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Congenital infections generally present with more severe systemic, neurological, and ocular complications. Most congenital infections are diagnosed early after birth due to their associated systemic involvement. The Guthrie card test and TORCH antibody screening are useful tools for confirming a congenital infection. In cases where prenatal diagnosis is possible, especially for congenital toxoplasmosis, they should be considered.

Regarding acquired infectious uveitis in children, unilateral posterior uveitis is the most common characteristic, and ocular toxoplasmosis is the most common cause worldwide. Since most ocular infections are associated with systemic infections, it is important to gather relevant medical histories and refer the patient to a paediatrician for systemic manifestations. Early diagnosis and treatment are crucial to preventing ocular complications and preserving good visual function in many cases; however, some infections are self-limiting and only need careful monitoring. Multidisciplinary care with a pediatrician, microbiologist, and/ or virologist is essential for the optimal management of affected patients.

6.1. Method of literature search

A literature search of published data was performed using the PubMed search engine in the MEDLINE database. The last literature search was performed until August 2023. The following search terms were used: "pediatric/paediatric", "childhood", "congenital infection", "TORCH", "diffuse unilateral subacute neuroretinitis", "fungul endophthalmitis", "uveitis", "ocular", and "eye" with similar terms were used in combination with each infectious agent known to cause uveitis. Search terms of "polymerase chain reaction", "serology", "intraocular fluid", "aqueous humor", "Goldmann Witmer coefficient", "next-generation sequencing", and "guthrie card" were used for the diagnosis section.

The retrieved articles were only in English and reviewed by their title and abstract. We included papers on infectious uveitis in children (age below 18 years) and significant non-peer-reviewed publications such as guidelines. Case reports were included only if they contributed new information about the characteristics, diagnosis, or treatment of the disease, or rare diseases. Additional publications were identified from a search of studies cited within the publications identified in the literature search.

The majority of studies included in this review were performed in paediatric populations. However, general information that did not involve ocular manifestations, such as endemic area, basic knowledge of disease, diagnosis technique, other studies from adult populations, and a report from the WHO, were also considered.

CRediT authorship contribution statement

de Groot-Mijnes Jolanda Dorothea Francisca: Writing – review & editing. Hendrikse Jytte: Writing – review & editing. Ngathaweesuk Yaninsiri: Writing – original draft. Hettinga Ymkje Marije: Writing – review & editing, Writing – original draft. de Boer Joke Helena: Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Financial supports

None.

Disclosure

Authors have nothing to disclose.

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