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Review article

French recommendations for the management of non-infectious chronic uveitis

Uvéites chroniques non infectieuses de l'enfant et de l'adulte

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ABSTRACT

This French National Diagnostic and Care Protocol (NDPC) includes both pediatric and adult patients with non-infectious chronic uveitis (NICU) or non-infectious recurrent uveitis (NIRU). NICU is defined

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as uveitis that persists for at least 3 months or with frequent relapses occurring less than 3 months after cessation of treatment. NIRU is repeated episodes of uveitis separated by periods of inactivity of at least 3 months in the absence of treatment. Some of these NICU and NIRU are isolated. Others are associated with diseases that may affect various organs, such as uveitis associated with certain types of juvenile idiopathic arthritis, adult spondyloarthropathies or systemic diseases in children and adults such as Behçet's disease, granulomatoses or multiple sclerosis. The differential diagnoses of pseudo-uveitis, sometimes related to neoplasia, and uveitis of infectious origin are discussed, as well as the different forms of uveitis according to their main anatomical location (anterior, intermediate, posterior or panuveitis). We also describe the symptoms, known physiopathological mechanisms, useful complementary ophthalmological and extra-ophthalmological examinations, therapeutic management, monitoring and useful information on the risks associated with the disease or treatment. Finally, this protocol presents more general information on the care pathway, the professionals involved, patient associations, adaptations in the school or professional environment and other measures that may be implemented to manage the repercussions of these chronic diseases. Because local or systemic corticosteroids are usually necessary, these treatments and the risks associated with their prolonged use are the subject of particular attention and specific recommendations. The same information is provided for systemic immunomodulatory treatments, immunosuppressive drugs, sometimes including anti-TNFα antibodies or other biotherapies. Certain particularly important recommendations for patient management are highlighted in summary tables.

Mots clés :
Uvéite
Biothérapies
Anti TNFa
Behçet
Sarcoidose
Vascularites

RÉSUMÉ

Ce protocole national de diagnostic et de soins (PNDS) français inclut les patients pédiatriques et adultes atteints d'uvéite chronique non-infectieuse (UCNI) ou d'uvéite récurrente non-infectieuse (URNI). L'uvéite chronique non infectieuse est définie comme une uvéite qui persiste pendant au moins 3 mois ou avec des rechutes fréquentes survenant moins de 3 mois après l'arrêt du traitement. L'uvéite récurrente non-infectieuse est définie par des épisodes répétés d'uvéite séparés par des périodes d'inactivité d'au moins 3 mois en l'absence de traitement. Certaines de ces UCNI et URNI sont isolées. D'autres sont associées à des maladies qui peuvent toucher différents organes, comme les uvéites associées à certains types d'arthrite juvénile idiopathique, les spondylarthropathies de l'adulte ou les maladies systémiques de l'enfant et de l'adulte comme la maladie de Behçet, les granulomatoses ou la sclérose en plaques. Les diagnostics différentiels des pseudo-uvéites, parfois liées à une néoplasie, et des uvéites d'origine infectieuse sont discutés, ainsi que les différentes formes d'uvéites en fonction de leur localisation anatomique principale (antérieure, intermédiaire, postérieure ou panuvéite). Sont également décrits les symptômes, les mécanismes physiopathologiques connus, les examens complémentaires ophtalmologiques et extra-ophtalmologiques utiles, la prise en charge thérapeutique, le suivi et les informations utiles sur les risques associés à la maladie ou au traitement. Enfin, ce protocole présente des informations plus générales sur le parcours de soins, les professionnels impliqués, les associations de patients, les adaptations de l'environnement scolaire ou professionnel et d'autres mesures qui peuvent être mises en œuvre pour gérer les répercussions de ces maladies chroniques. Les corticostéroïdes locaux ou systémiques étant généralement nécessaires, ces traitements et les risques liés à leur utilisation prolongée font l'objet d'une attention particulière et de recommandations spécifiques. Les mêmes informations sont fournies pour les traitements immunomodulateurs systémiques, les immunosuppresseurs, incluant parfois les anticorps anti-TNFα ou d'autres biothérapies. Les recommandations importantes pour la prise en charge des patients sont mises en évidence dans des tableaux récapitulatifs.

Abbreviations

ACE	Angiotensin converting enzyme
AH	Aqueous humour
ANA	Anti-Nuclear Antibodies
ARN	Acute Retinal Necrosis
ASCA	Anti-Saccharomyces cerevisiae antibody
BAL	Bronchoalveolar lavage
BAB	Blood-aqueous barrier
CAPS	Cryopyrin associated periodic syndrome
CBC	Complete Blood count
CINCA	Chronic Inflammatory Neurologic Cutaneous and Articular syndrome
CMO	Cystoid macular edema
CMV	Cytomegalovirus
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
DHDP	Departmental House for the Disabled Persons
DLCO	Diffusing capacity of carbon monoxide
DMO	Diffuse macular edema
EBV	Epstein Barr Virus
EDI	Enhanced Depth Imaging
ENT	Ear, Nose, Throat
ERG	Electro-retinogram
EULAR	European League Against Rheumatism
FDG	Fluorodeoxyglucose
NDCP	National Diagnostic and Care Protocol
GWC	Goldmann-Witmer Coefficient
HAS	French National Authority for Health
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
IBD	Inflammatory Bowel Diseases

ICG	Indocyanine green
ICGA	Indocyanine green angiography
IFN	Interferon
IGRA	Interferon-ɣ release assay
IL	Interleukin
IMP	Inosine monophosphate
IOP	Intraocular pressure (or eye tone)
IV	Intravenous
IVT	Intravitreal injections
JIA	Juvenile Idiopathic Arthritis
MA	Marketing Authorization
MEWDS	Syndrome of multiple evanescent white spots
MMF	Mycophenolate Mofetil
MTX	Methotrexate
MUI	Million Units
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
NICU	Non-infectious chronic uveitis
NIRU	Non-infectious recurrent uveitis
NOMID	Neonatal Onset Multisystem Inflammatory Disease
OCT	Optical coherence tomography
PCR	Polymerase chain reaction
PEP	Protein electrophoresis
PET	Positron emission tomography
PFT	Pulmonary function testing
POCL	Primary Oculo-cerebral lymphoma
RCP	Retro-corneal precipitates
RNFL	Retinal nerve fiber layer
RPE	Retinal pigment epithelium
RSD	Retinal serous detachment
SC	Subcutaneous
SD-OCT	Spectral Domain optical coherence tomography
SUN	Standardization of uveitis nomenclature
TINU	Tubulointerstitial nephritis and uveitis
TNF	Tumor necrosis factor
TPE	Therapeutic patient education
TST	Tuberculin skin test
VAD	Visual acuity decrease
VEGF	Vascular Endothelial Growth Factor
VKH	Vogt Koyanagi Harada
VZV	Varicella zoster virus
WB	Western blot
WHO	World Health Organization

Definitions

Immunomodulators/Immunosuppressive drugs: although it is possible to group all conventional immunosuppressive drugs and immunomodulators such as interferon-alpha and biomedicines under the term "immunomodulators", we have chosen to use the term "immunosuppressive drugs" whenever treatments other than corticosteroids or agents with a partial immunosuppressive effect are mentioned.

Biotherapy: rather than the term 'biologics', we have chosen to use the more common term 'biotherapy' for treatments that specifically antagonise certain inflammatory cytokines referred to in this document, such as anti-TNFα.

1. Introduction: non-infectious chronic uveitis in children and adults [1-15]

1.1. Definition

Uveitis is the primary inflammation of the tunica intermedia of the eye, including the iris, ciliary body, vitreous base and choroid. By extension, retinal inflammatory diseases are considered to be uveitis in their own right.

The diagnosis of non-infectious chronic uveitis (NICU) is made for any persistent uveitis or uveitis with frequent relapses that occur less than 3 months after cessation of treatment and after pseudo-uveitis or infectious uveitis has been excluded.

This French NDCP also addresses non-infectious recurrent uveitis (NIRU). These are repeated episodes of uveitis separated by periods of inactivity in the absence of treatment. The minimum duration of these periods is 3 months.

1.2. Differential diagnosis

The causes of uveitis may be inflammatory, autoimmune or infectious and are a threat to the visual prognosis. Pseudo-uveitis (or masquerade syndrome) and infectious uveitis are the main differential diagnoses of NICU and are discussed in section 4.4.4 Differential diagnosis and Table 1.

1.3. Epidemiology

Knowledge of the epidemiology of uveitis is essential because the diagnostic approach should be directed towards a search for frequent conditions or diseases whose diagnoses are useful because of their therapeutic consequences. The incidence of uveitis ranges from 17 to 52 per 100,000 and its prevalence from 38 to284 per 100,000. A recent study based on Medicare data in the United States from 4 million individuals reported a prevalence of 133 per 100,000 including a majority of non-infectious uveitis (90.7%) and anterior uveitis (80%). In France, the incidence of uveitis has only been estimated in one early study in Savoie at 17 per 100,000 inhabitants. In children, the incidence of uveitis is 4.3 per 100,000 and the prevalence is 27.9 per 100,000, often associated with chronic diseases. Non-infectious uveitis accounts for 69-95% of the cases of uveitis in children; 41-47% of these are related to juvenile idiopathic arthritis (JIA) and 28-51% are idiopathic.

Uveitis is responsible for 5% of the cases of legal blindness in France (visual acuity of the better eye $\leq 1/20$), mainly due to complications such as macular edema, retinal atrophy, uveitic glaucoma, ocular hypertonia and retinal ischemia.

About 60 causes of uveitis have been described, classified into 5 groups of unequal importance (Table 2).

Epidemiological studies vary according to genetic factors (especially for recurrent adult uveitis: HLA-B27, in the first instance), environmental factors (e.g. tuberculosis), the definition of the disease (e.g. sarcoidosis), the inclusion of certain ophthalmological entities in the group idiopathic uveitis (e.g. pars planitis), the paraclinical investigations (e.g. nuclear imaging chamber puncture for PCR. . .) and the mode of patient recruitment (e.g. tertiary centes). This explains the marked heterogeneity of these series in the literature. In Western countries, the etiological distribution, except for infectious causes, is as follows: one quarter of the cases of uveitis are related to an ophthalmological disease, one quarter are due to a systemic disease meeting consensual diagnostic criteria, one quarter to a presumed systemic disease while the origin of the last quarter is undetermined (or idiopathic).

Table 3 shows the distribution of the most frequent etiologies, based on the most recent studies in Western Europe

The etiological distribution varies geographically: for example, toxoplasmosis predominates in South America, tuberculosis in India, while sarcoidosis and Vogt-Koyanagi-Harada disease account for most uveitis in Japan.

1.4. Classification

1.4.1. Anatomical classification

The anatomical classification and criteria for uveitis disease progression were defined by the International Uveitis Research Group in 1987 and the SUN (Standardization of Uveitis Nomenclature) in

Table 1
Main etiologies of infectious uveitis in adults reported in Western European series. In bold, the most frequent etiologies (>0.5%).

Infectious etiologies	Diagnosis
Bacterial infections	
Lyme disease uveitis (*Borrelia burgdorferi*)	Antibody detection (ELISA and Western-Blot), culture, PCR on biological fluids, serum, CSF
Syphilis (*Treponema pallidum*)	CSF, serology with treponemal and non-treponemal test (RPR, VDRL)
Leptospirosis (*Leptospira interrogans*)	Serology
Tuberculosis (*Mycobacterium tuberculosis*)	TST, chest X-ray or CT scan, importance of IGRA tests and directed bacteriological samples that are exceptionally contributory
Brucellosis (*Brucella sp.*)	Serology
Rickettsiosis (*Rickettsia conorii*)	Serology
Bartonellosis (*Bartonella henselae*)	Anatomo-pathology lymph node, serology, PCR on blood and aqueous humor
Whipple's disease (*Tropheryma whipplei*)	Digestive biopsy (PAS + inclusions in macrophages), PCR or immunohistochemistry
Fungal and parasitic infections	
Candidiasis	
Cryptococcosis (*Cryptococcus neoformans*)	
Histoplasmosis (*Histoplasma neoformans*)	
Pneumocystis (*Pneumocystis jirovecii*)	
Parasitic infections	
Toxoplasmosis (*Toxoplasma gondii*)	Desmonts immune load factor, western-blot (IgG, IgA) and PCR if sufficient volume
Toxocariasis (*Toxocara cani*)	Serology (ELISA), PCA (Western-Blot, Goldman-Wittmer coefficient)
Viral infections	
HSV1 and 2, VZV, CMV	PCR, Goldman-Witmer coefficient
EBV	Serology
HIV alone or co-infections	Serology, PCR blood and aqueous humor
HTLV1	PCA, CSF: anti-HTLV1 antibodies
Chikungunya virus	Serology
West Nile virus	Serology
Arboviruses (dengue. . .)	Serology

Table 2
Main etiologies of non-infectious uveitis in adults reported in Western European series. In bold, the most frequent etiologies (>0.5%).

Inflammatory diseases	-HLA-B27 associated uveitis (psoriasis and reactive arthritis) -Chronic inflammatory bowel diseases -Sarcoidosis -Behçet's disease -Vogt-Koyanagi-Harada disease -Multiple sclerosis -Juvenile idiopathic arthritis -TINU syndrome -Celiac disease -Lupus, systemic vasculitis -Blau syndrome, cryopyrinopathies -Variable common immune deficiency
Pseudo-uveitis	-Trauma, intraocular foreign body -Tumour pathology (lymphoma, melanoma, retinoblastoma, metastases)
Ophthalmic entities	-Fuchs' heterochromic cyclitis (Fuchs' uveitis) -Pars planite -Multifocal choroiditis (and internal punctate choroiditis) -Birdshot chorioretinopathy -Possner-Schlossman syndrome -White spot syndromes (patchy epitheliopathy, serpiginous choroiditis. . .) -Sympathetic ophthalmia -Phacoantigenic uveitis
Iatrogenic uveitis	-Rifabutin -Biphosphonates -IFN-α or -β -BCG therapy -Brimonidine topical -Checkpoint inhibitors used for cancer immunotherapy

(TINU: Tubulointerstitial nephritis and uveitis).

2005. This classification distinguishes anterior, posterior, intermediate and panuveitis (Fig. 1).

1.4.2. Ophthalmological semiology

Functional symptoms vary depending on the extent of inflammation and its location. Thus, acute anterior uveitis most commonly manifests as a red, painful eye with photophobia and a decrease in visual acuity (VAD). Classically, a peri-keratotic circle is noted on inspection. Intermediate uveitis causes myodesopsias and VAD is usually moderate. Posterior uveitis may leave the eye white with a sometimes abrupt VAD if there is macular and/or papillary involvement. Peripheral retinal involvement may not affect visual acuity.

1.5. Physiopathological reminders

Autoimmune uveitis is thought to be related to the peripheral activation of lymphocytes by microbial and microenvironmental stimuli having epitopes in common with retinal tissue. Lymphocytes recognising retinal antigens play a central role and macrophages as well as antigen-presenting cells that produce cytokines and chemokines directly induce retinal lesions when they infiltrate the eye. These lesions are induced by chemotaxis during the *in situ* release of cytokines.

The intraocular release of cytokines and chemokines therefore seem to play a major role in the pathogenesis and persistence of ocular inflammation, that may even lead to blindness.

The major cytokines involved in uveitis would correspond to the Th1 lymphocyte subtype as IFN-γ producer and Th17 as IL-17A producer. The cytokines that play a mainly pathogenic or cytoprotective role are IL-6, IL-8, CCL2, IL-1β, IL-2, TNFα and IL-10. Pro-inflammatory cytokines produced by non-T cells are also critical in determining the lineage of choice for differentiated Th cells.

1.6. Progression and prognosis

1.6.1. Analysis of the course of uveitis

Uveitis is said to be limited when it lasts for less than 3 months and chronic when it lasts for more than 3 months. The term acute uveitis is reserved for uveitis with a sudden onset and a limited course. The term recurrent uveitis is used when there are episodes of uveitis separated by periods of remission of more than three months without treatment. Finally, uveitis is also considered to be chronic if it relapses less than three months after treatment is stopped. To standardize this classification the SUN group has

Table 3
Distribution of the main etiologies of uveitis reported in recent Western European series.

References	Bodaghi et al., 2001 N = 927 (France)	Cimino et al., 2010 N = 1064 (Italy)	Jakob et al., 2009 N = 1916 (Germany))	Barisani-Asenbauer *et al, 2012* N = 2619 (Austria)	Jones et al, N = 3000 (UK)	Llorenç et al., 2015 n = 1022 (Spain)	Luca et al., 2017 N = 990 (Italy)	Jamilloux N = 1000 (France)
Idiopathic	34%	26%	35.3%	39.3%	31.2%	26%	23%	37.9%
Sarcoidosis	6.4%	3%	5.2%	2.4%	9.7%	3%	4.3%	18%
HLA-B27 and spondyloarthritis	5%	7%	14%	18.3%	4.5%	10%	7.7%	11.5%
Behçet	6.1%	5.3%	2.2%	1.8%	2.7%	5%	4.8%	2.3%
Harada	2%	2.5%	NR	0.4%	0.8%	1%	4.1%	1.5%
Multiple sclerosis	1.7%	NR	3.4%	1%	0.6%	0.8%	NR	?
Birdshot disease	4.4%	NR	NR	0.4%	1.2%	3%	0.8%	4%
Pars planite	11.3%	NR	NR	NR	NR	1%	3.3%	2.2%
Fuchs cyclite	2.7%	22.7%	8.5%	3.4%	11.5%	1%	9.7%	2%
Toxoplasmosis	11.9%	6.9%	5.1%	7.5%	6.9%	7%	4.7%	1.5%
Tuberculosis	4.1%	4.5%	NR	NR	3.3%	5%	5.7%	4.2%
Herpes virus	8.2%	9.9%	6.3%	8.6%	3.5%	12%	15.6%	2.4%
Lyme	1.1%	NR	1.4%	NR	NR	NR	NR	1.2%
Syphilis	0.6%	NR	NR	NR	0.3%	NR	0.8%	1.2%

NR: Not stated.

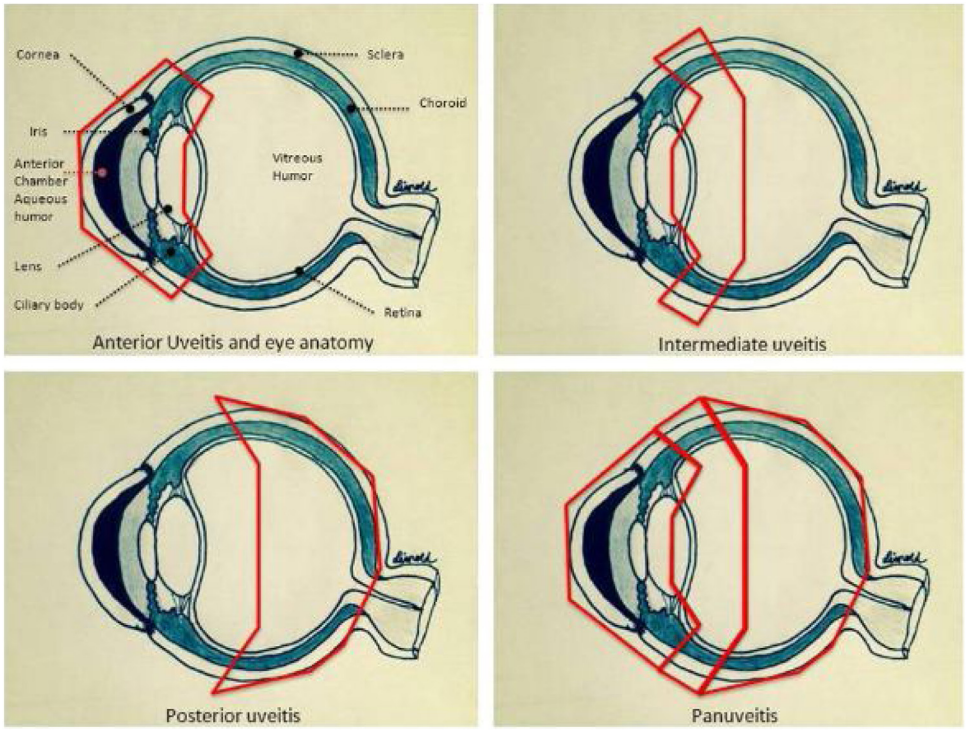

Fig. 1. Anatomy of the eye and anatomical models of uveitis. Anterior uveitis: iritis, iridocyclitis; intermediate uveitis: pars planitis, posterior cyclitis, hyalitis; posterior uveitis: focal or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis; panuveitis: involvement of all three compartments of the eye. Adapted from *Sève et al., 2015*.

proposed precise definitions of the notions of inactivity, improvement, aggravation or remission of uveitis (ANNEX).

Remission is defined as inactive disease for more than three months after cessation of any specific treatment.

1.6.2. Uni- or bilateral uveitis

The laterality of the condition is also important for the etiological diagnosis. Infectious uveitis, HLA-B27-associated uveitis and Fuchs' uveitis (or Fuchs' cyclitis) are predominantly unilateral, whereas uveitis in sarcoidosis, JIA, Behçet's disease and Vogt-Koyanagi-Harada disease are most often bilateral.

Table 4 shows the main etiologies to be considered according to the ophthalmological findings.

2. Objectives of the French National Diagnostic and Care Protocol

The aim of this French National Diagnostic and Care Protocol (NDCP) is to explain the current optimal management of a pediatric or adult patient with non-infectious chronic uveitis (NICU) to healthcare professionals.

The goal is to optimize and harmonize the management and follow-up of rare diseases throughout the country. It also makes it possible to identify pharmaceutical agents used in an indication not provided for in the Marketing Authorization (MA) as well as agents, products or services necessary for the care of patients but not usually covered or reimbursed.

Table 4
Etiological orientation according to the anatomical-clinical type of uveitis.

Anatomical type		
Unilateral acute anterior uveitis		-Uveitis HLA-B27 -Uveitis related to herpes viruses (HSV, VZV, CMV)
Bilateral acute anterior uveitis		-Drugs, infections (including post-streptococcal), Interstitial and tubular nephritis with uveitis (TINU), Kawasaki
Chronic anterior uveitis	Granulomatous Non-granulomatous	-Sarcoidosis, tuberculosis, syphilis, herpes virus -idem + spondyloarthritis, juvenile idiopathic arthritis, Behçet, Fuchs' heterochromic cyclitis
Intermediate uveitis		-Sarcoidosis, multiple sclerosis -Oculo-cerebral lymphoma (>40 years) -Lyme, syphilis
Posterior uveitis	Chorioretinitis in foci Associated choroiditis Retinal vasculitis	-Toxoplasmosis and other infections -Sarcoidosis, birdshot disease, syphilis, tuberculosis, Vogt-Koyanagi-Harada, sympathetic ophthalmia - Behçet, sarcoidosis, tuberculosis, syphilis, multiple sclerosis, Susac, IRVAN, birdshot, sympathetic ophthalmia, connectivites. . . - Infections
Panuveitis		- Sarcoidosis, Behçet's disease - Bacterial infections, syphilis, herpes virus, toxoplasmosis - Vogt-Koyanagi-Harada, sympathetic ophthalmia Systemic granulomatoses

TINU: Tubulointerstitial nephritis and uveitis; IRVAN syndrome: Idiopathic Retinal, Vasculitis, Aneurysms and Neuro-retinitis.

This NDCP can be used as a reference by the general practitioner (the physician designated by the patient to the French national health insurance) in consultation with the specialist physician, particularly when drawing up the treatment protocol in collaboration with the consulting physician and the patient, in the case of a request for exemption from co-payment for an off-list condition.

However, the NDCP cannot consider all specific cases, all comorbidities or complications, all therapeutic particularities or all hospital care protocols. It does not claim to cover all possible management approaches or replace the individual responsibility of the doctor towards his patient. However, the protocol describes the standard reference management of a pediatric or adult patient with NICU. It should be updated according to new validated data.

3. Methods

This NDCP has been drafted according to the "Method for drafting a national diagnosis and care protocol for rare diseases" published by the French National Authority for Health (Haute Autorité de Santé, HAS) in 2012 (methodological guide available on the HAS website: www.has-sante.fr) using a one-round Delphi type consensus method.

A first versions of the management proposals were submitted to the multidisciplinary working group for a vote. The relevance of the proposals was rated by all members by individual electronic vote. Consensus was assessed using the HAS method for developing good practice recommendations (2010). Proposals with an insufficient degree of agreement between the voters were discussed again during a physical meeting until a consensus was reached.

4. Diagnosis and initial assessment[16-112]

4.1. Objectives

- Establish the diagnosis of NICU in relation to a systemic disease, if any, after ruling out any differential diagnoses.
- Announce the diagnosis and present the different aspects of management.
- Establish the therapeutic indications.

4.2. Professionals involved (and coordination)

The initial diagnosis of NICU in a child should be made in collaboration with a center experienced in pediatric ophthalmology and should involve ophthalmologist(s) and pediatrician(s) or pediatric rheumatologist(s).

The initial diagnosis of NICU in an adult should be made in collaboration with an experienced ophthalmology center and should involve ophthalmologist(s) and internist(s)/rheumatologist(s).

When an underlying rare disease is suspected in association with NICU the expertise of a specialist pediatric/internist/rheumatology center is needed to perform the appropriate investigations.

4.3. Differential diagnoses

The causes of uveitis can be inflammatory, autoimmune or infectious and are a threat to the visual prognosis.

Pseudo-uveitis (or masquerade syndrome) can mimic uveitis and includes exogenous (post-ocular surgery or post-traumatic infection) or endogenous (hematogenous) endophthalmitis, vitreoretinal lymphoma (primary or secondary to central nervous system lymphoma) and other tumoral conditions including paraneoplastic syndromes, retinoblastomas and leukemias. Hereditary retinal dystrophies and some rarer entities (such as autoimmune retinopathies, vitreoretinopathies, amyloidosis. . .) should be considered in this group. Intraocular foreign bodies are another differential diagnosis.

Suspected pseudouveitis should be rapidly diagnosed by performing a diagnostic anterior chamber puncture and/or a vitreous biopsy. Microbiological and/or fungal research is performed using PCR for endophthalmitis, cytology for lymphoma with determination of IL10 and IL6 and calculation of the IL10/IL6 ratio, immunophenotyping and molecular analysis.

Paraneoplastic retinopathy is an eye condition associated with the presence of an extraocular malignancy and circulating autoantibodies to retinal proteins. An electroretinogram (decrease or loss of cone and rod responses) and a clinical/radiological examination guided by the internist or oncologist's assessment are useful in this differential diagnosis for carcinoma, CAR (Cancer-Associated Retinopathy) and MAR (Melanoma-Associated Retinopathy) syndromes.

Infectious uveitis may be viral, bacterial, parasitic or, more rarely, fungal in origin. An infectious origin must be suspected from the outset on the basis of the symptoms of the uveitis, which are nevertheless rarely specific, and the concomitant infectious extra-ophthalmological signs. Any uveitis that is resistant to anti

-inflammatory and/or immunomodulatory/ immunosuppressive therapy should be re-considered for an infectious origin (Table 1).

4.4. Ophthalmological assessment: expert recommendations 1 to 4

Initial ophthalmological assessment:

1: All non-infectious chronic uveitis must be very precisely described, including the anatomical location (anterior, intermediate, posterior, panuveitis) according to the SUN criteria (ANNEX), whether it is granulomatous or not, synechial or not, laterality and complications, as well as the existence of criteria of potential severity (papilledema, macular edema, visual acuity less than or equal to 4/10, posterior segment involvement, occlusive vasculitis, retinal foci located within the vascular arches and/or close to the optic nerve, ocular hypertonia, hypopion).

2: The complex management of non-infectious chronic uveitis requires consultations by several specialists with an ophthalmological examination including at least visual acuity measurement, biomicroscopy, and ocular tone measurement. A dilated fundus examination is essential during the initial ophthalmological visit. This is also systematic for any intermediate or posterior uveitis, or panuveitis during follow-up. It should be performed yearly for anterior uveitis, and at each visit if the inflammation persists or worsens (decrease in visual acuity, etc.).

3: Macular Optical Coherence Tomography (OCT) is recommended in the follow-up of non-infectious chronic uveitis. OCT is essential in case of decreased visual acuity or macular damage of the fundus.

4: Fluorescein and indocyanine green (ICG) angiography is recommended in posterior involvement and in some cases of non-infectious chronic intermediate uveitis.

4.4.1. Interview and clinical assessment

This initial stage of the diagnosis is necessary before any additional examinations are prescribed. The absence of a precise clinical description results in unnecessary and costly tests.

The ophthalmological examination is bilateral and comparative. Before examining the patient with a slit lamp, the patient's symptoms, the history of the disease and any prior history must be accurately recorded. The patient should be examined under white light to look for and rule out iris heterochromia, anisocoria, (epi)scleritis, or conjunctival or palpebral skin nodules (suggesting sarcoidosis). The ophthalmological examination includes measurement of the best corrected monocular visual acuity to quantify the functional impact of the uveitis. Measurement of intraocular pressure (IOP) distinguishes hypertensive (IOP > 21 mm Hg) from non-hypertensive and even hypotensive uveitis. Hypertonia may be related to damage to the iridocorneal angle (inflammation of the trabeculum, trabeculitis), to anterior synechiae, i.e. iridocorneal synechiae or to pupillary seclusion caused by the presence of posterior synechiae (or iridocrystalline synechiae), or may be iatrogenic (cortico-induced).

4.4.2. Examination of the anterior segment

The eye may be red with a perikeratitis circle, especially in certain etiologies of uveitis such as spondyloarthropathy, sarcoidosis, infections or Behçet's disease. Redness associated with pain, photophobia and sometimes a decrease in visual acuity supports a diagnosis of uveitis. In the case of a red eye, the signs of conjunctivitis include a sensation of sand grains, a foreign body, pruritus and conjunctival secretions.

The eye may remain white especially in certain etiologies, such as JIA, tumor pseudo-uveitis, or birdshot chorioretinopathies.

Slit lamp biomicroscopy is used to examine the cornea and look for the number, appearance and arrangement of any retrocorneal precipitates (RCP).

Large, thick, mutton-fat keratic precipitates are sufficient to make the diagnosis of granulomatous uveitis and suggest certain etiologies (Table 5) that may be associated with iris nodules (Koeppe's nodules and Busacca's nodules). Non-granulomatous uveitis corresponds to the presence of dusty or absent RCP. It may be plastic with the presence of fibrin in the anterior chamber and sometimes a pre-pupillary cyclitic membrane. It is synechial unless treatment is promptly instituted.

The presence of inflammation of other ocular tunics helps guide the diagnosis (e.g. keratitis and herpetic uveitis or scleritis and rheumatological pathologies such as rheumatoid arthritis and granulomatosis with polyangiitis).

Analysis of the anterior chamber can help identify and quantify the cellular and/or protein Tyndall which reflects the inflammation in this chamber. Cellular Tyndall is scored from 0 to 4 based on cellularity in a field of light measuring 1 mm x 1 mm. Flare, or protein Tyndall, is quantified from 0 to 4 according to the turbidity of the aqueous humor or can be measured objectively by a laser flare meter.

Hypopyon (inflammatory sedimentation in the anterior chamber) may be associated with Behçet's disease and HLA-B27 associated uveitis. Iris analysis looks for iridocorneal (so-called anterior) and iridocrystalline (so-called posterior) synechiae with a risk of pupillary block and acute glaucoma. Iridial heterochromia suggests Fuchs' heterochromic cyclitis while irial sectorial atrophy is suggestive of a herpes infection.

Lens analysis may reveal a cataract, usually cortico-induced but which may be part of the clinical picture of Fuchs' heterochromic cyclitis, or complicating chronic inflammation.

Table 5
Main etiologies of granulomatous uveitis.

Infectious diseases	Systemic diseases	Ophthalmic entities
Herpes	Sarcoidosis, Blau	Vogt-Koyanagi-Harada
Toxoplasmosis	Multiple sclerosis	disease
Tuberculosis	TINU syndrome	Sympathetic
Leprosy	Crohn's	ophthalmia
HTLV1		Phacoantigenic uveitis
Syphilis		
Toxocariasis		
Lyme disease		
Brucellosis		
Bartonellosis		
Fuchs		
Previous CMV uveitis including		
Posner Schlossman syndrome		

Fuchs' cyclitis sometimes has a granulomatous appearance. Topical brimonidine sometimes induces granulomatous uveitis. TINU: Tubulointerstitial nephritis and uveitis.

4.4.3. Examination of the middle and posterior segments

A fundus examination should be systematically performed to look for inflammation of the posterior segment.

Vitreous analysis searches for hyalitis or vitreous Tyndall, corresponding to vitreous cellularity, rated from 0 to 4, and an overall vitreous disorder called vitreous Haze. Pre-retinal condensations in the vitreous such as "ant eggs" or "snowballs" or even an ice pack covering the peripheral insertion of the retina (ora serrata) may be present. The presence of an ice pack indicates a specific form of intermediate uveitis called pars planite. An ice pack is more easilty

Table 6
Main etiologies of uveo-papillitis.

Inflammatory diseases	Infectious diseases
Sarcoidosis	Toxoplasmosis
Vogt-Koyanagi-Harada disease	Tuberculosis
Birdshot chorioretinopathy	Syphilis
Multiple sclerosis	Bartonellosis
Intra-ocular lymphoma (pseudo-uveitis)	Toxocariasis
	Lyme disease
	Herpes infections (retinitis, RNA)

identified by a fundus examination with a three-mirror lens with indentation.

Inflammatory retinal vascular disease or "vasculitis" is systematically looked for during the clinical evaluation and if necessary confirmed by fluorescein angiography. The vessels show whitish, usually peripheral, perivascular sheathing. Retinal venous vasculitis or "periphlebitis" is most common and retinal arterial vasculitis is rarer and restricted to certain etiologies (Behçet's disease, acute retinal necrosis (ARN), etc.). This can be complicated by macular edema, vascular occlusions and retinal ischaemia or neovascularisation.

Fundus analysis looks for retinal or choroidal foci.

Other conditions that may be seen include macular edema, vitreous inflammation (hyalitis), papillitis and the presence of neovessels. Papilledema may be part of a more general picture of optic neuropathy associated with uveitis, for example in Behçet's disease. OCT analysis assesses retinal, choroid and papillary damage. OCT-angiography visualizes the retinal, macular or peripapillary vascular network, the choriocapillaris and the choroid. Table 6 shows the main etiologies of uveo-papillitis.

4.4.4. OCT (optical coherence tomography) and uveitis

Assessment of the retinal impact may include a multimodal imaging approach, depending on the practices of the ophthalmologist.

OCT is particularly useful in the diagnosis and monitoring of macular edema (retinal thickening of the macular region due to intra- or extracellular fluid accumulation) and can exclude the associated abnormalities of epiretinal membrane, vitreo-macular traction and choroidal neovascularisation (Table 7).

4.4.5. Endocular samples

4.4.5.1. Anterior chamber puncture. Aqueous humor (AH) analysis has identified the involvement of a viral agent in several entities previously considered to be autoimmune (Fuchs, Posner-Schlossman). Depending on the clinical context, the analyses are sent to different laboratories for virological (PCR of herpes viruses (HSV1-2, CMV, EBV, Varicella zoster virus (VZV) and rubella virus), bacteriological (blood cultures, universal panbacterial PCR (ARN16S), specific PCR), mycological, parasitological (search for antibodies and fungal PCR or *Toxoplasma gondii*) and biochemical (with determination of interleukins 10 and 6) analyses.

4.5. Extra-ophthalmological assessment: expert recommendations 5 to 9

Initial assessment:

5: Non-directed investigations are not recommended for the etiological assessment of non-infectious chronic uveitis because of their very low cost-effectiveness in this situation.

6: Before making the diagnosis of non-infectious chronic uveitis in adults, in the absence of an obvious diagnostic referral, syphilis serology should be performed and tuberculosis searched for.

6bis: Before making a diagnosis of non-infectious chronic uveitis in children, in the absence of an obvious diagnostic referral (JIA), the search for tuberculosis should be discussed.

7: In non-infectious recurrent uveitis, diagnostic HLA-B27 antigen testing is useful in non-granulomatous anterior uveitis in adults and children.

8: In non-infectious chronic uveitis, lumbar puncture is recommended in case of suspected uveomeningitis (especially in the context of sarcoidosis, Behçet's disease, Vogt Koyanagi Harada (VKH) or CINCA).

9: In sarcoidosis or other systemic granulomatoses and Behçet's disease a full ophthalmological examination is recommended at diagnosis in both children and adults, even if there are no visual signs.

4.5.1. Interview and clinical examination

A full interview and a clinical examination are essential, to look for:

- a family history suggesting immune dysfunction or genetic diseases (monogenic auto-inflammatory diseases), or inflammatory bowel disease (IBD), psoriasis, spondyloarthritis;
- tuberculosis contagion, geographical origin, notion of tick bite, walks in the forest, erythema migrans, contact with animals (toxocarosis, toxoplasmosis, bartonellosis);
- weight loss, a change in the general condition suggesting an associated chronic inflammatory disease;
- arthralgia or arthritis, inflammatory spinal and/or buttock pain, recurrent single or bipolar aphthosis, fever, ENT or respiratory signs, digestive signs, skin signs, adenopathies.

4.5.2. Additional examinations

4.5.2.1. Minimum assessment before confirming the diagnosis of NICU. Any additional investigations are guided by the ophthalmological and physical examination. The latter are particularly useful for the diagnosis of intracellular bacterial infections and primary oculocerebral lymphoma (POCL).

To date, the few studies that have evaluated the value of complementary examinations for the etiological diagnosis of uveitis have focused on investigations for specific entities. Recommendations for a diagnostic approach are based on experience and retrospective studies. The recent ULISSE study (Uveitis: clinical and medico-economic evaluation of a standardized strategy for etiological diagnosis) is the first prospective study to compare a standardized three-stage strategy (oriented assessment, assessment according to the anatomical-clinical type of uveitis, and then the possibility of prescribing complementary examinations) with a so-called "free" strategy, which allows ophthalmologists the freedom of prescription. These recommendations did not include uveitis in children, immunocompromised patients, severe retinal vasculitis or ophthalmological entities whose diagnosis is based on an ophthalmological examination.

4.5.2.2. Standard biological work-up. A standard biological work-up should be performed in the presence of uveitis of undetermined etiology, including a blood count, C-reactive protein (CRP), blood ionogram with renal function, phosphocalcium and liver function tests. Lymphopenia (less than 1 Giga/l) may suggest a diagnosis of sarcoidosis.

Table 7
Main angiographic and electrophysiological features of white spot syndromes.

	ERG	FA	ICG	other explorations	complications
Birdshot	Achievement of the most sensitive full-field ERG light-adapted 30 Hz flicker peak time (cones and bipolar cells).	Vascular leakage, papillary impregnation. Deep lesions not visible	Round hypofluorescent (intermediate time), iso or hypofluorescent (late time) lesions.	HLA A-29, visual fields (Humphrey 30-2), ERG	WTO (frequent) NVC, SEA
Plaque epitheliopathy (PPE)		Early stages: hypofluorescence Late stages: hyperfluorescence (impregnation)	Extensive hypofluorescence of active lesions and heterogeneous scars (early to late stages).	OCT: hyper-reflectivity of the outer retina.	NVC (rare)
MEDWS	not mandatory, sometimes helps in diagnosis: decrease in amplitude of a-wave.	Early stages: numerous punctate "crown" lesions Late stages: hyperfluorescent lesions by impregnation	Numerous extensive, rounded hypofluorescent lesions in the late stage	OCT: interruptions of the EZ, an accumulation of hyperreflective material on the RPE with extension to the inner retina. Lesions observed in AF and ICG correlated with OCT abnormalities.[1] Visual fields: large blind spot and central scotoma	None. NVC (rare)
Multifocal Choroiditis and Internal Punctate Choroiditis (ICP)	0	Active lesions: hypofluorescence (early time), hyperfluorescence (late times). Hyperfluorescent heterogeneous chorioretinal scars	Extensive hypofluorescent lesions in the active phase		NVC (OCT-A), OMC. Scarring spots with a cookie cutter design.
Serpiginous choroiditis	Not necessary	Active lesions: hypofluorescence (early time), hyperfluorescence on the edges of the lesions (late times). Scarring: window effect and late impregnation.	-Hypofluorescent (choroidal) lesions in the active phase; -Hypofluorescent lesions in the active phase; hyperfluorescent in the healing phase and Inactive phase: hypofluorescent lesions with well-defined borders.[1]	OCT: hyperreflective active lesions and thickening of the outer retina. Increased reflectivity of the choroid . Interruption of EZ (active and inactive lesions).[1] Visual fields autofluorescence	CVN (± fibrosis subretinal_ (interest of OCT-A), OMC

RPE: retinal pigment epithelium; ERG: electroretinogram; EZ: ellipsoid zone; FA: fluorescein angiography; FO: fundus, IZ: interdigitating zone; ONL: outer nuclear layer; TB: tuberculosis; CMO/OMC: cystoid macular edema; MER: epiretinal membrane; CNV/NVC: choroidal neovascularisation.

4.5.2.3. Angiotensin converting enzyme (ACE) and lysozyme. Increased serum ACE and lysozyme help in the diagnosis of sarcoid uveitis. Depending on the study, sensitivity ranges from 58-84% and 60-78% for ACE and lysozyme, respectively, and specificity from 83-95% and 76-95%, respectively. These values may also be high in other systemic granulomatoses (*Mycobacterium tuberculosis*, Lyme, etc.). ACE activity is highest from birth to adolescence, which makes the interpretation more difficult (false positives) in pediatric patients.

4.5.2.4. Tuberculin skin test and IGRA (IFN-ɣ release assay) tests. Tuberculosis uveitis, which is determined by the presence of *M. tuberculosis* in the eye (culture, PCR or biopsy), is rarely diagnosed in low-endemic countries. In the absence of direct evidence, the diagnosis is based on a range of clinical, radiological and biological arguments, the exclusion of differential diagnoses and the response to anti-tuberculosis treatment. Tests include:

Chest imaging, which is significantly different depending on the epidemiological characteristics of the region. In highly endemic areas chest imaging is often abnormal (76% of cases). In contrast, radiological abnormalities are rarely observed in low endemic areas (14%).

The tuberculin skin test (TST) remains relevant in countries where BCG vaccination is not practiced, with a sensitivity and specificity for the diagnosis of tuberculous uveitis of 92% to 95% and 72% to 90%, respectively. In France, where BCG vaccination was compulsory until 2013, the TST is relevant in case of a phlyctenular reaction (prompting treatment), tuberculin anergy (suggesting sarcoidosis) and in unvaccinated patients from highly endemic countries.

Several studies have compared the different available IGRA tests (Quantiferon TB-Gold®, Quantiferon TB gold-in tube®, Quantiplus® and Elispot®), with the TST. Their use is proposed in association with TST: the negative predictive value of the IGRA/TST combination varies from 79% to 84%. A recent study in a highly endemic country showed that the combination is the most cost-effective strategy compared to their use in alone or successively. Discrepancies between IGRA and TST vary from 25% to 49%. Serpiginous choroiditis and retinal vasculitis are the most common conditions associated with a positive IGRA test.

The threshold of 1 IU/ml appears to be the most discriminant for the diagnosis of presumptive tuberculous uveitis for Quantiferon tests. This threshold concerns 90% of patients with presumptive tuberculous uveitis in highly endemic areas. The contribution of IGRA tests varies according to local epidemiology. The sensitivity varies from 77% to 93% in highly endemic areas for the diagnosis of tuberculous uveitis and is higher than that of the Elispot (T-SPOT.TB). The latter is even less sensitive than the TST (53% vs. 70%, respectively), but has a better positive predictive value than the TST (88% vs. 76%).

4.5.2.5. Autoimmune testing. Autoimmune testing is useful in rare cases for the etiological diagnosis of uveitis. Thus, testing for antinuclear antibodies should be limited to uveitis in children with suspected JIA(anterior, non-granulomatous, synechial, hypertensive, insidious white eye uveitis) or in cases of peripheral polyarthritis and sclero-uveitis.

4.5.2.6. Serology. Few studies have evaluated the cost-effectiveness of non-directed diagnostic serologies in uveitis.

Because of the therapeutic consequences, syphilis is the only serology analyzed in uveitis, whatever the anatomical or clinical type. Toxoplasmosis serology is indicated in the presence of chorioretinal lesions and HSV, VZV and CMV serologies can help manage anterior uveitis, kerato-uveitis or retinitis, prior to ocular sampling.

4.5.2.7. HLA grouping. HLA B27 typing is only of interest in acute non-granulomatous anterior uveitis, as 50% of these cases are associated with this histocompatibility antigen. Eight to 10% of Caucasians carry the HLA B27 antigen. A diagnosis of spondyloarthritis is made in 21-40% of patients with acute anterior uveitis. This test is not indicated in intermediate and posterior uveitis. HLA B27 status and a radiological work-up should be obtained in patients with anterior uveitis and the presence of insidious, inflammatory spinal pain. Radiography or even MRI of the spine and sacroiliac joints should be performed. MRI may show active inflammatory lesions (subchondral edema) and structural changes (bone erosions, sclerosis, fatty infiltration). In rare cases uveitis with an HLA B27 negative status may be associated with spondyloarthropathy.

The diagnostic value of HLA B51 grouping, which is present in 60% of patients with a diagnosis of Behçet's disease and 20% of individuals in the general population, is limited.

HLA A29 is present in 98-100% of birdshot retinochoroidopathies and is of interest for its negative predictive value. Conversely, the positive predictive value of this test in posterior uveitis is low as it is present in 5 to 7% of the general population.

4.5.2.8. Other. Although protein electrophoresis reveals polyclonal hypergammaglobulinemia which is not very specific, it provides indirect evidence of sarcoidosis or tuberculosis.

Beta2microglobulinuria on voiding is the best diagnostic test for renal involvement in sarcoidosis or TINU, or other tubular involvement.

4.5.2.9. Imaging tests. Imaging of the spine and sacroiliac joints is of no value in the absence of clinical findings. Chest radiography can be useful in the diagnosis by showing hilar adenopathies and pulmonary parenchymal involvement suggesting sarcoidosis, or sequelae from tuberculosis.

- Chest CT scan

The sensitivity of standard radiography ranges from 41% to 69% for histologically proven pulmonary sarcoidosis, while CT has a sensitivity of 91% to 100%. Chest CT is of particular interest in patients over 50 or 60 years old as conventional radiography is not contributory in half the cases. Chest CT is suggestive of sarcoidosis if it shows bilateral hilar and/or mediastinal adenopathies defined by a small axis diameter >1 cm, pulmonary micronodules of perilymphatic distribution or other parenchymal abnormalities. Chest CT may also show sequelae from pulmonary tuberculosis in the form of scarring of the apices, pleural/pericardial/parenchymal calcifications or unilateral hilar or mediastinal calcified adenopathy.

- Brain MRI

Very few studies have evaluated the value of systematic brain MRI. Several studies have shown a prevalence of multiple sclerosis (MS) ranging from 7 to 30% in patients with intermediate uveitis, which has led authors to propose systematic brain MRI in these patients. This examination is recommended before prescribing an anti-TNFα monoclonal antibody for intermediate or posterior uveitis due to the risk of aggravating demyelinating disease.

- Positron emission tomography

In patients with unexplained uveitis or sarcoidosis-like disease, 18FDG-PET-CT can reveal fixations suggesting sarcoidosis (particularly lymph nodes) or tumors and thus guide biopsies. However, the value of mediastinal cytopuncture in patients with 18FDG-PET-CT fixations has not been demonstrated.

4.5.2.10. Other tests.

- Biopsy of the accessory salivary glands

Two studies have recently reported the value of an accessory salivary gland biopsy for the histological diagnosis of sarcoidosis in patients with uveitis. The positivity rate in these series was 5.2% and 3%, respectively. The sensitivity of this biopsy in patients with proven sarcoidosis was 18% and 41%, respectively. Limiting this test to patients with abnormal chest image results, elevated ACE or granulomatous uveitis could increase the sensitivity without altering the specificity. However a positive test does not exclude tuberculosis.

- Bronchial fibroscopy and bronchoalveolar lavage (BAL)

Several studies have reported the value of BAL for the diagnosis of sarcoid uveitis. BAL is considered to be contributory when there is a predominantly CD4 alveolar lymphocytosis of >15% (CD4/CD8 ratio >3.5). The estimated sensitivity and specificity of BAL in patients with uveitis in histologically-proven sarcoidosis is 63% and 75%, respectively.

The cost-effectiveness of bronchial biopsies varies from 42% to 61% for radiological stage 0 and 43% to 84% for stage I. Echo-guided cytopuncture of mediastinal adenopathies via the endobronchial or endoesophageal route may prevent the need for mediastinoscopy. These methods have been shown to be safe and provide a diagnostic gain of 22.5% to 41.4% in patients with suspected sarcoidosis compared to conventional bronchial biopsies.

A bronchial fibroscopy combined with a microbiological analysis with a search for mycobacteria (direct examination, culture) will be proposed in case of suspected pulmonary tuberculosis and the absence of acid-fast bacilli on the sputum or the gastric tube.

- Lumbar puncture

There are no studies evaluating the cost-effectiveness of cerebrospinal fluid (CSF) analysis. Intrathecal immunoglobulin synthesis can be demonstrated in patients with idiopathic intermediate uveitis in the absence of inflammatory signs on brain and spinal cord MRI.

A lumbar puncture may be suggested in the following situations:

- suspected uveo-meningitis (Vogt-Koyanagi-Harada disease, sarcoidosis, Behçet. . .) (cytochemistry),
- bilateral papilledema (after brain imaging) (look for meningitis and elevated CSF outlet pressure),
- suspected MS (search for intrathecal immunoglobulin synthesis),

- suspected POCL (cytology, immunophenotyping and interleukin 6 and 10 assays),
- syphilitic uveitis with posterior segment or neuro-ophthalmological involvement (cytochemistry and serology). This indication is a subject of debate in the absence of therapeutic consequences, but retained by several authors,
- suspected neuro-Lyme (cytochemistry and serology).

4.6. Prescription strategy for examinations

Non-directed complementary examinations are not recommended for the etiological assessment of uveitis, due to their very low profitability in this situation. The aim of examinations is to eliminate any differential diagnosis of NICU, particularly infectious, to confirm and characterise the NICU as well as its repercussions and potentially associated disorders, and to complete the pre-therapeutic assessment if necessary. In infants and young children, particularly before the age of 2, the question of a fetopathy should be considered and the differential diagnosis (toxoplasmosis, etc.) must be oriented in this direction.

If the interview and examination are normal, tests should be systematically performed for follow-up and to help with therapeutic decisions. Although anti-nuclear autoantibodies are not an essential examination for patient management, they are important for disease classification. It should be kept in mind that a positive test in young children is associated with an increased risk of uveitis, like a very young age of onset or biological results showing inflammation.

According to the history and the clinical assessment of uveitis:

- syphilis serology (if pubescent);
- discuss tuberculin test, quantiferon and chest imaging (socio-professional context);
- discuss HLA B27 if symptomatic and/or acute anterior uveitis;
- Lyme (if notion of tick bite, erythema migrans, exposure in a Borreliosis endemic area), Toxocarosis, Toxoplasmosis, Bartonellosis.

4.6.1. Granulomatous uveitis

Systematic assessment of:

- *Mycobacterium tuberculosis*: tubertest and/or Quantiferon, if possible;
- CBC, CRP, ACE, lysozyme, blood ionogram, blood calcium, calciuria/creatinuria, protein electrophoresis (PEP), ASAT, ALAT, γGT, chest X-ray or chest CT scan (at clinician's discretion).

Focused assessment, depending on the context:

- Herpes (if the patient has never had herpes: do a serology rather than an intraocular swab which is less invasive);
- Genetic research for NOD2 mutation if Blau syndrome;
- GI endoscopies, ASCA DEFINE for IBD.

4.6.2. Intermediate uveitis

Systematic assessment:

- Sarcoidosis: ACE, CBC, EPP, lysosyme, blood ionogram, calcemia, calciuria (+ creatinuria on sample), tubertest and/or quantiferon (if living in endemic area).
- Focused assessment, depending on the context:

- Lyme according to questioning, ELISA and confirmation by Western Blot if in doubt;
- Neurological examination, brain or spinal cord MRI;
- Lumbar puncture if papillitis;
- Syphilis if pubescent or congenital syphilis,
- Whipple if adult or suggestive signs (arthralgias, malabsorption, fever, neurological signs).

For the diagnostic management of certain diseases such as Lyme disease or sarcoidosis, refer to the French NDCP or current recommendations.

4.6.3. Posterior uveitis

Isolated posterior uveitis is rare and diagnostic tests should be determined by the ophthalmologist based on the interview and the symptoms of the disease.

4.6.4. Pre-therapeutic assessment

This includes the clinical and biological assessment of contraindications to the introduction of corticosteroid/immunomodulator/biotherapy treatment. This assessment evaluates the infectious (*Mycobacterium tuberculosis*))/carcinological risk (in particular the presence of *nevi*) and the initial biological work-up according to the chosen treatment.

4.7. Assessment of the impact of the disease

Schematically, a distinction is made between the functional impact of the disease (visual acuity, visual field, colour vision) and the anatomical impact (iridocrystalline synechiae, strip keratitis during chronic and/or prolonged uveitis, glaucoma or hypotonia, chronic rupture of the blood-aqueous barrier, epiretinal membrane, macular hole, retinochoroidal scars, choroidal neovessels, retinal detachment, etc.).

The decrease in visual acuity may be related to environmental disturbances, which may be reversible after medical and surgical treatment, or to more severe and permanent macular retinal or optic nerve damage. Alterations in the visual field are related to damage to the optic nerve, the retina or the visual pathways. Accurate measurement of visual acuity and automated visual field analysis are necessary during the initial evaluation. Normal results should not delay therapeutic management as certain chronic uveitis such as birdshot retinochoroidopathy can develop insidiously. In the case of severe and sequential damage to the visual acuity or visual field the role of therapeutic management should be discussed on a case-by-case basis, taking into account the benefit-risk ratio.

The laser tyndallometer is used to assess the degree of blood-aqueous barrier (BAB) disruption. This may be reversible in acute forms, but persistent breakdown is indicative of chronic BAB breakdown. Ocular complications are more likely to occur in cases of major chronic BAB disruption. The identification of the flare floor is of interest for therapeutic management and allows highly precise adaptation of corticosteroid therapy.

Macular OCT, ganglion cell complex, peripapillary retinal nerve fibre layer thickness (RNFL), OCT-angiography, autofluorescence and fluorescein or indocyanine green angiographies help determine the origin of abnormalities and the degree of severity. These multimodal imaging tools have made it possible to analyze the various macular lesions in a minimally invasive manner.

5. Therapeutic management [113-142]

5.1. Objectives expert recommendation 10

Objectives of therapeutic management:

10: In non-infectious chronic anterior uveitis, one of the goals of therapeutic management is to significantly reduce ocular inflammation within the first 3 months.

The objectives of anti-inflammatory treatment strategies for uveitis are as follows:

- Rapid control of ocular inflammation to limit irreversible structural damage and preserve visual function. This rapid action is necessary in cases of macular threat and/or inflammatory optic neuropathy. Treatment is considered effective, according to the SUN criteria, if it reduces the anterior chamber cell Tyndall by two crosses and/or reduces vitreous inflammation or if complete quiescence of uveitis is achieved.
- Prevent inflammatory recurrence, which can lead to uveitic complications (e.g. glaucoma due to chronic trabeculitis) and comorbidities.
- Effectively manage both ophthalmic and extra-ophthalmic manifestations in cases of uveitis associated with autoimmune or auto-inflammatory disease with systemic involvement.
- Limit the use of long-term systemic corticosteroids because of the metabolic, cardiovascular and infectious effects and, in children, their consequences on growth. Special care must be taken in very young children under age 2 due to the metabolism of corticosteroids, even when administered locally, and to certain complications such as myocardial hypertrophy.
- Optimize the benefit-risk ratio and promote compliance. The balance between the benefits of anti-inflammatory treatments (expected visual recovery, number of prior lines of treatment) and the risks must be closely assessed in collaboration with the internist, rheumatologist and/or pediatrician.
- Remission of the underlying systemic disease where applicable.
- Screening and treatment of disease complications.
- Adaptation of the treatment according to disease progression.
- Prevention of treatment side effects.
- Ensuring a good quality of life.
- Ensure good psychosocial development.

5.2. Professionals involved (and coordination arrangements): expert recommendations 11 to 17

Professionals involved in therapeutic management:

11: The management of non-infectious chronic uveitis must be multidisciplinary, involving ophthalmologist(s) in consultation with the general practitioner, paediatrician, internist, rheumatologist, or other specialties depending on referrals.

12: The management and follow-up of non-infectious chronic uveitis must involve local health care providers (ophthalmologist, pediatrician or general practitioner, if necessary school medicine, occupational medicine and, if possible, a city-hospital network).

13: An assessment must be performed by an ophthalmologist and a pediatrician from an expert center for all cases of non-infectious chronic uveitis in children during the first few months of management.

14: In the presence of complications and/or local or systemic cortico-dependence or cortico-resistance in non-infectious chronic and/or recurrent uveitis in adults, the patient should be referred to an ophthalmologist with expertise in inflammatory diseases of the eye.

15: The results of any investigations by other visual professions for the the diagnosis and follow-up of non-infectious chronic uveitis should be interpreted by the ophthalmologist.

16: In non-infectious chronic uveitis, even without associated systemic involvement, regular follow-up by an general practitioner, pediatrician or other specialist is indicated in addition to ophthalmological follow-up to monitor the tolerance to treatment whenever prolonged systemic corticosteroid therapy (adult: > 7.5 mg/d prednisone equivalent for at least 3 months; child: whatever the dose and duration) is necessary.

17: If background immunomodulatory/ immunosuppressive therapy is discussed or instituted for non-infection chronic uveitis an expert physician should be involved (pediatrician in children or adult specialist) both for the therapeutic decision and for regular monitoring of the treatment.

The management and follow-up of non-infectious chronic uveitis must involve local healthcare providers (ophthalmologist, pediatrician or general practitioner, if necessary school medicine, etc.) as well as a hospital ophthalmology department with expertise in the disease and a link to an internal medicine, rheumatology or pediatric center for the group of rare diseases concerned.

In some cases, treatment may involve orthoptists as well as visual impairment professionals.

5.3. Pharmacological treatments

5.3.1. Local treatment

5.3.1.1. Local corticosteroids. Topical corticosteroids (dexamethasone, prednisolone acetate or fluorometholone) are the basis of the treatment for anterior uveitis (Error! Reference source not found). In very young children under 2 years of age, particular attention should be paid to the possible systemic consequences of even topical corticosteroid therapy. Subconjunctival injections of dexamethasone, triamcinolone acetonide or delayed betamethasone are used in cases of severe and/or persistent previous inflammation. These local treatments are adjuvant treatments for posterior panuveitis or uveitis with marked anterior inflammation. Posterior subtenonial or peribulbar injections of triamcinolone acetonide provide direct delivery of high intraocular concentrations of corticoids. The intravitreal concentration of corticosteroids with a subconjunctival injection of 2.5 mg dexamethasone is three times higher that with 5 mg dexamethasone by peribulbar route and 12 times the oral dose of 7.5 mg dexamethasone.

If possible intra- or peri-ocular corticosteroid injections should be avoided in children and non-presbyopic adults, especially repeated injections.

Intravitreal corticosteroid injections can be used to treat persistent cystoic macular edema (CMO) despite systemic therapy and periocular injections.

The 700 μg intravitreal implant of dexamethasone (Ozurdex®) can also be used as an adjuvant anti-inflammatory therapy in combination with systemic treatments.

Cortisone hypertonia occurs in 10 to 30% of cases and is irreversible in 4% of cases. Peri-ocular or intravitreal corticosteroid treatments should therefore be avoided in patients with a history of cortisone hypertonia and/or uveitic glaucoma.

5.3.1.2. Other local treatments. Other anti-inflammatory intravitreal injections (IVT) have been or are being evaluated: IVT of methotrexate (MTX) in refractory cystoid macular edema (CMO), IVT of anti-TNFα, IVT of sirolimus (rapamycin), an anti-proliferative and anti-angiogenic agent that inhibits genes associated with inflammation (IL 8, COX 1, COX 2. . .). Suprachoroidal injections of triamcinolone are also being evaluated.

Local treatment is the first-line therapy for anterior NICU. The most frequently used molecule in children is dexamethasone 0.1%. With doses of more than 6 drops per day, compliance is considered to be poor and affects the child's schooling. Larger doses should be reserved for emergency situations and for a short period of time, with rapid reassessment of efficacy and compliance. The risk of developing cortico-induced glaucoma and cataracts is directly related to the number of eye drops administered and the degree of anterior chamber inflammation.

Local corticosteroids for previous NICU should be administered for a minimum of 6 weeks and tapered gradually under close ophthalmological supervision.

A cortisone-sparing background treatment should be discussed in the presence of any dependence on prolonged local corticosteroid therapy (as an indication, 2 drops per day per eye of dexamethasone or the equivalent for a maximum of 6 months or 3 drops for a maximum of 3 months). In children the use of local injectable intra or peri-ocular treatments requires expert advice (high risk of cataracts and ocular hypertonia or cortico-induced glaucoma). Repeated local injectable peri-ocular or intra-ocular treatment should be avoided in children because the risk of ocular hypertension increases when a second injection is administered within 6 months after the first.

If an ophthalmological complication occurs that may be related to local or systemic corticosteroid therapy, such as cataract or ocular hypertonia, the introduction of cortisone-sparing background therapy should be discussed with expert ophthalmologists and other specialists

5.3.2. Systemic treatments

5.3.2.1. Corticosteroid therapy. Disease progression. Systemic corticosteroid therapy is required in cases of severe or intermediate posterior uveitis or panuveitis, *especially if it is* bilateral, after ruling out an infectious etiology. Associated immunomodulatory/immunosuppressive therapy should be discussed and is most often indicated in children. Regardless of age, the initiation of biotherapy may be necessary for uveitis with a guarded prognosis and a high potential for progression.

An intravenous bolus treatment of methylprednisolone (500 mg in adults and 15-30 mg/kg in children, not to exceed 1 g/d) is often administered for three consecutive days if there are signs of severity (macular damage with a reduction in visual acuity <20/200, vasculitis with retinal ischaemia). An adult is then given an oral dose of prednisone of 0.5 to 1 mg/kg/day (depending on the severity of uveitis and not exceeding 80 mg/day) or the equivalent for an average of 3 to 4 weeks and then the dose is reduced in stages depending on the course of the disease.

The modalities of treatment in children following the initial treatment must be discussed with an expert center (as an indication, the reference doses are approximately 1-1.5 mg/kg without exceeding 60 mg/d).

The more severe the uveitis, the slower the therapeutic response and/or the more frequent the inflammatory rebound, the longer the tapering of corticosteroids. In the maintenance phase, if uveitis requires a dose of prednisone >7.5 to 10 mg/d (0.3 mg/kg/d in children) for more than 3 months, or in the event of disabling side effects, cortisone-sparing therapy should be discussed or adapted. In all children, and especially in adolescents, corticosteroid resistance or dependence must be confirmed after checking compliance, sometimes with hospitalization.

If the uveitis does not respond to high doses of corticosteroids (>0.5 mg/kg/d) after one month, it is said to be cortico-resistant. The diagnosis of non-infectious uveitis must then be systematically questioned. A new search must be made for an infectious cause or pseudo-uveitis, whose leading cause is vitreoretinal lymphoma, by cytological confirmation on endo-ocular samples taken in a reference center.

In the case of prolonged general corticosteroid therapy or an indication for immunosuppressive or immunomodulatory background treatment, the patient must receive optimal immunization protection. In particular the immunization schedule must be updated and influenza and pneumococcal vaccinations should be administered according to national recommendations.

If a live attenuated vaccine is indicated in a patient receiving prolonged systemic corticosteroid therapy, expert advice is required to discuss the benefit/risk ratio on a case-by-case basis, because live attenuated vaccines are normally contraindicated.

When prolonged systemic corticosteroid therapy (at any dose) is instituted in non-infectious chronic uveitis, even without associated systemic involvement, regular follow-up is indicated by a general practitioner or pediatrician or adult specialist in addition to ophthalmological follow-up to monitor tolerance to treatment.

Advice should be obtained from an expert ophthalmologist and from other specialists in the presence of any ophthalmological complications associated with local or general corticosteroid therapy, such as cataract or ocular hypertonia, to discuss the introduction of cortisone-sparing background treatment (immunosuppressants plus or minus biotherapies).

It is essential to provide clear information to patients about potential side effects, especially infectious and metabolic

5.3.2.2. Immunomodulators/immunosuppressants. Except for ciclosporin A, no conventional immunomodulators/ immunosuppressants have been approved for the treatment of non-infectious uveitis. Immunomodulatory/immunosuppressive therapy is discussed for corticosteroid-dependent uveitis, for cortisone sparing and to prevent inflammatory recurrence. Treatment should be started at the first episode if the posterior uveitis is associated with Behçet's disease because of the well-known very poor functional prognosis in the absence of effective treatment. Treatment can also be prescribed immediately for the treatment of uveitis that threatens the visual prognosis (serpiginous choroiditis, multifocal choroiditis, VKH, sympathetic ophthalmia, birdshot chorioretinopathy, etc.). Antimetabolites: azathioprine (2 to 2.5 mg/kg/d, no more than 200 mg/d), mycophenolate mofetil (2 to 3 g/d in adults and 600 mg/m^2 x 2/d in children) and methotrexate (0.3 mg/kg/week in adults, up to 0.6 mg/kg/week in children, no more than 25 mg/week), are the most commonly prescribed immunomodulators/immunosuppressants.

A recent randomized trial confirmed the non-inferiority of MTX (25 mg/week) compared to MMF (3 g/d).

Methotrexate is by far the most frequently used drug for the treatment of anterior JIA uveitis in children. It may prevent relapses, sarcoid uveitis and idiopathic uveitis.

Azathioprine is used as a first-line treatment for posterior uveitis in Behçet's disease.

These treatments are always initiated in combination with corticosteroid therapy (local in anterior uveitis) and prescribed for a minimum theoretical duration of 1 year. Regular screening for potential adverse effects and close biological monitoring is essential. An update of vaccinations, including pneumococcal vaccination, is recommended prior to beginning therapy.

When disease-modifying therapy is indicated in JIA NICU methotrexate is prescribed as the first-line therapy.

Background treatment will usually be maintained for at least 2 years in all NICUs with close ophthalmological monitoring.

- Methotrexate

It remains the gold standard immunomodulators/ immunosuppressants for the first-line treatment of sarcoidosis-related

posterior uveitis. Methotrexate remains the treatment of choice for pediatric uveitis due to its safety profile and the experience of pediatricians. As a single agent, it controls 60-82% of JIA-related uveitis. It is usually prescribed at a dose of 0.3 to 0.6 mg/kg/week in children, not exceeding 25 mg/week. Weekly folic acid supplementation, at a distance from the methotrexate, is recommended to reduce side effects.

• Ciclosporin

Ciclosporin is the only conventional immunomodulator/immunosuppressant to have a marketing authorization for the treatment of non-infectious uveitis. However, it is not extensively used because of its side effects (nephrotoxicity, arterial hypertension, etc.). The use of ciclosporin should therefore be reserved for patients without comorbidities at low doses ($\leq$ 3 mg/kg/d).

• Tacrolimus

Tacrolimus is reported to be as effective as ciclosporin for the treatment of posterior uveitis but with a better safety profile, in particular with less frequent hypertension at 3 months.

• Cyclophosphamide

Cyclophosphamide is an alkylating agent that is only rarely used (0.6 g/m^2 every 4 weeks IV) in uveitis and is reserved for severe refractory uveitis with a threat to the visual prognosis, in case of failure of other therapies.

• Azathioprine

Azathioprine is an antimetabolite prescribed at a dose of 2 to 2.5 mg/kg/day in one to two doses per os (no more than 200 mg/day). Although it is well tolerated, there is a risk of hematological, hepatic and pancreatic toxicity. It should be prescribed in cases of posterior uveitis associated with Behçet's disease, in the absence of a severe form with a short-term threat to the visual prognosis (imminent visual threat from occlusive vasculitis, macular edema and/or reduced visual acuity) for which anti-TNFα is preferred.

• Mycophenolate mofetil

Mycophenolate mofetil is a pro-drug of a inosine monophosphate (IMP) dehydrogenase reverse inhibitor, that is involved in the synthesis of guanosine monophosphate necessary for DNA and RNA synthesis in rapidly proliferating cells such as B and T lymphocytes. It is administered at a dose of 2-3 g/d in adults and 600 mg/m^2 in children twice daily.

5.3.2.3. Biotherapies. The most frequently prescribed biotherapies are anti-TNFα antibodies. the use of anti-TNF antibody biotherapy (usually adalimumab, which is the only agent with a marketing authorization in this indication) is justified in non-infectious chronic uveitis associated with JIA following failure of conventional treatment (usually methotrexate) after 3 months.

Biotherapy should be discussed when conventional treatment fails in other non-infectious chronic uveitis after 3 months, and an anti-TNF antibody is the biotherapy of choice in these cases.

Biotherapy may be discussed at diagnosis in patients with an ophthalmological event involving the visual prognosis (e.g. macular edema) or significant complication(s) at diagnosis, combined with an immunomodulator/immunosuppressive treatment such as methotrexate.

Etanercept, a soluble TNF receptor, has not been shown to be effective in non-infectious chronic uveitis. Adalimumab is the first-line biologic treatment. If adalimumab fails, infliximab can be prescribed (expert recommendations) at infusions of 5-6 mg/kg on S0 and S2, followed by gradual spacing (based on expert recommendations) of injections once uveitis is controlled, and with regular ophthalmological surveillance.

In case of failure of one or more anti-TNFα antibodies in intermediate and posterior non-infectious chronic uveitis, several disease-modifying therapies can be discussed, in particular anti-IL6 (Tocilizumab), IFN-α. . .

If biotherapy is ineffective in NICU, and the assay shows a low residual level in the absence of anti-biotherapy antibodies, the dose can be increased or the interval between administrations reduced. Compliance should first be assessed. In a patient receiving conventional treatment, anti-TNFα or other biologics, a reduction or cessation of treatment should only be discussed after at least 2 years of ophthalmological remission in Behçet's disease, and at least 1 year in other NICU with prolonged ophthalmological monitoring.

5.4. Anti-TNFα: expert recommendations 18 and 19

Anti-TNFα:

18: As part of the pre-anti-TNF work-up for intermediate or posterior uveitis, a brain MRI is recommended to look for demyelinating lesions.

19: Among the anti-TNFα agents, certain monoclonal antibodies have been shown to be effective in the treatment of non-infectious chronic uveitis, but etanercept has not been shown to be effective in this indication.

TNFα is a key cytokine in the inflammatory cascade of uveitis. It is involved in the disruption of the blood-retinal barrier, and TNFα and its receptor are found at high levels in the serum and aqueous humor of patients with uveitis. The soluble and membrane forms of TNFα are active trimers that bind to TNFα receptors I and II expressed by cells of the iris, ciliary body and retina.

• Adalimumab

Adalimumab is a humanized monoclonal antibody that is administered subcutaneously. It is currently the most widely used anti-TNFα for this indication and the only one with a marketing authorization.

The recommended dosage in intermediate, posterior or panuveitis in adults is an 80 mg loading dose for the first week and then 40 mg every 15 days one week after the first dose. One randomized, double-blind multicenter, study evaluated its efficacy compared to placebo in active non-infectious, non-anterior uveitis. The failure rates in 226 patients analyzed on an intention-to-treat basis, were 39% and 55% in the adalimumab and placebo groups, respectively. Adalimumab significantly reduced the risk of relapse and visual acuity decline upon discontinuation of corticosteroid therapy, with a good short-term safety profile. In the 217 patients with active uveitis in the Visual I study, adalimumab significantly decreased the risk of treatment failure by 50% (failure was defined as increased vitreous or anterior inflammation, the development of new chorioretinal lesions vasculitis, or VAD). In the VISUAL 1 (active uveitis) and VISUAL 2 (inactive uveitis) studies, the time to relapse was doubled for adalimumab-treated patients compared to placebo. Thus, adalimumab was granted marketing authorization in 2017 for the treatment of non-infectious intermediate, posterior and panuveitis

in adults with an inadequate response to corticosteroid therapy alone, for patients requiring cortisone sparing, or for patients in whom corticosteroid therapy is contraindicated.

Adalimumab has been found to be effective in chronic anterior uveitis associated with JIA in two recent randomized trials in children compared to placebo. The SYMACORE study randomized 90 patients with uveitis inadequately controlled by corticosteroid eye drops and methotrexate (30 on placebo and 60 on adalimumab). At 3 months, 18 of the 30 patients in the placebo group had failed (failure defined according to SUN Working Group criteria), compared to only 12 of the 60 patients treated with adalimumab. The efficacy of adalimumab was confirmed at one year and safety was considered to be acceptable despite certain serious infectious events. In a smaller group of 31 patients with JIA-related uveitis unresponsive to methotrexate plus local corticosteroid therapy the ADJUVITE study showed that the number of responders was greater in the adalimumab group than in the placebo group. Improvement of at least 30% in anterior chamber inflammation assessed by laser photometry, which was the primary endpoint, was achieved after an average of two months in most adalimumab-treated patients.

Adalimumab has a marketing authorization for children in JIA NICU if local corticosteroids and MTX fail, at a dose of 40 mg every 2 weeks for children 30 kg and over, and 20 mg every 2 weeks for children under 30 kg.

- Infliximab

Infliximab, an IgG1 monoclonal antibody (human/murine) directed against the soluble and transmembrane forms of TNFα, is prescribed at an intravenous dose of 5 to 6 mg/kg. The optimal interval between infusions is not known. In practice infliximab is usually administered at S0, S2, S6 and then every 5-6 weeks in adults. In children, the infusion interval is usually more gradual. Infliximab and adalimumab have similar safety and efficacy profiles in refractory non-infectious uveitis with a response rate at 6 and 12 months of 87 and 93%, respectively. Several studies report that the association with immunomodulator/immunosuppressive treatments, azathioprine, methotrexate or ciclosporin A may be of interest for the synergistic activity to limit the risks of immunization against the biotherapy.

- Golimumab

Golimumab is a humanized monoclonal antibody directed against soluble and membrane TNFα receptors administered subcutaneously to adults at 50 mg per month. It has been found to be effective in treating refractory anterior uveitis associated with ankylosing spondylitis. It could stabilize or even improve visual acuity, CMO and inflammatory parameters and reduce the frequency of recurrence.

- Certolizumab

Certolizumab is administered subcutaneously in adults (400 mg S0, S2 then 200 mg every 15 days). It has been used to control refractory ocular inflammation in small retrospective series. This anti-TNFα has the advantage of not crossing the placental barrier and should be prescribed during a pregnancy if a patient is receiving anti-TNFα due to refractory uveitis.

- Etanercept

Etanercept, a soluble receptor that prevents the binding of TNFα to its p75 and p55 receptors, is no longer indicated for uveitis due to its poor intraocular penetration and lack of efficacy. It has been shown to be inferior to adalimumab and infliximab in the treatment of anti-TNF sensitive uveitis.

- Summary of anti-TNF alpha

Infliximab or adalimumab are fast acting.

The duration of anti-TNFα administration in non-infectious uveitis remains to be defined. Following a long-term remission and a significant reduction in ($\leq$ 5 mg/d of prednisone) or cessation of corticosteroid therapy, the spacing of infusions is progressive before final cessation according to the protocols proposed for rheumatoid arthritis. The response to anti-TNFα may diminish over time, which may be due to the development of immunogenicity against anti-TNFα, most often identified by low serum levels of this agent and the appearance of antibodies. Besides its synergistic action, the addition of a conventional immunomodulator/immunosuppressant to anti-TNFα could limit the formation of these antibodies. In the event of a poor response to treatment, a plasma and an anti-TNFα antibody assay could be useful. If the anti-drug antibody level is high and the drug concentration low, another anti-TNFα or biotherapy should be attempted.

Any latent tuberculosis should be treated and if possible anti-TNFα administration should be delayed by 3 weeks. Annual influenza and pneumococcal vaccinations are recommended. The side effects of anti-TNFα include infections, viral reactivations, anaphylactoid reactions, the development of autoimmune diseases (such as lupus or systemic vasculitis) and demyelinating pathologies. Studies in rheumatoid arthritis are reassuring in relation to an excess carcinological risk of epithelial skin tumors. The study by Kempen et al. in 7957 American patients treated for non-infectious ocular inflammation shows an increase in overall mortality (multiplied by 1.99) and cancer-related mortality (multiplied by 3.83) in patients treated with anti-TNFα compared to the general population. These data must be confirmed.

In cases of chronic intermediate uveitis, a common ophthalmic presentation of multiple sclerosis, pre-therapy brain MRI is recommended.

5.4.1.1. Immunomodulators/immunosuppressants and other biotherapies

- Interferon alpha

Interferon α 2a (Roferon 3 MU x 3/week subcutaneous or Pegasys 135 to 180 μg/week subcutaneous) may be prescribed for uveitis. The process of pegylation, which involves adding polyethylene glycol to standard IFN, decreases the clearance and increases the half-life of IFN (2 to 5 h for standard IFN), thus improving tolerance by obtaining more stable plasma concentrations. IFNα administration regimens differ among studies and the dosage of IFNα2a (Roferon) can be increased from 3 MIU x 3/week to 6 MIU x 3/week if it is ineffective and well tolerated. The prevention of an influenza-like syndrome with paracetamol is essential.

IFNα is a particularly effective treatment for macular edema, including refractory macular edema, the main cause of severe VAD, which occurs in one third of the cases of posterior uveitis.

- Tocilizumab

If conventional immunomodulators/immunosuppressants, and/or anti-TNFα fail, the use of other biological agents may be discussed for certain indications.

Interleukin 6 is a cytokine whose intraocular concentration is high in chronic inflammation due to vascular occlusion (central retinal vein occlusion, diabetes) or uveitis.

Tocilizumab is a human/murine IgG1 monoclonal antibody directed against transmembrane and soluble IL6 receptors. In

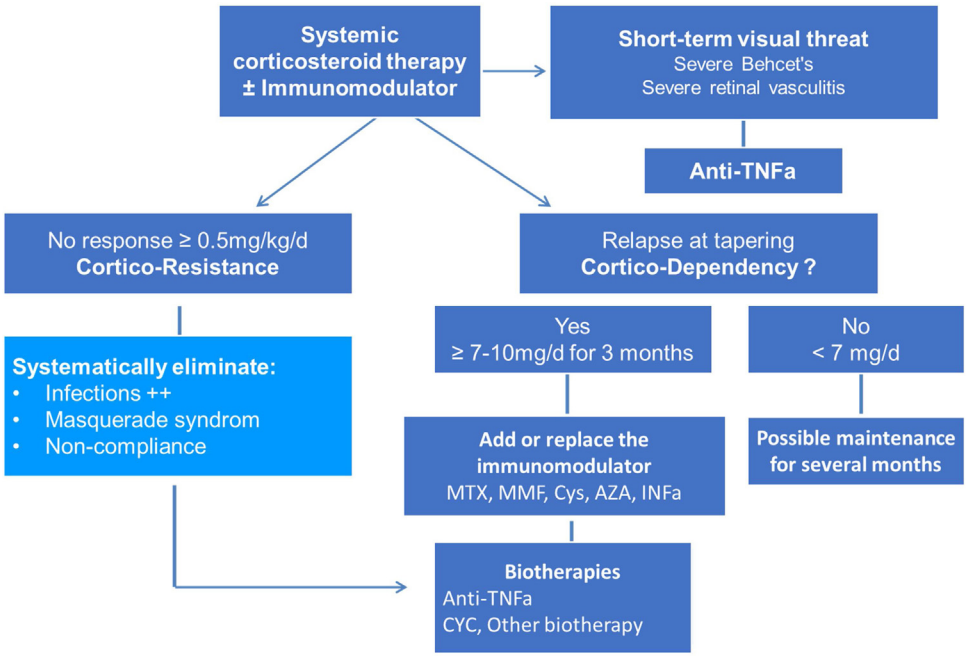

Fig. 2. Systemic treatment algorithm for severe intermediate, posterior or non-infectious panuveitis in adults.

uveitis it is usually administered intravenously at a dose of 8 mg/kg/4 weeks (10 mg/kg in children under 30 kg). Subcutaneous tocilizumab administration was studied more recently.

• Anti-IL 1

The anti-IL-1 drugs, anakinra (IL-1 receptor antagonist) and canakinumab (anti-IL-1β antibody) are rarely used in the treatment of uveitis, except for uveitis due to certain monogenic auto-inflammatory diseases such as cryopyrinopathies (CINCA/Muckle-Wells/familial cold urticaria) or even more rarely, mevalonate kinase deficiency.

These data must be confirmed in uveitis

5.4.1.2. Treatment strategy: expert recommendations 20 to 39

Treatment strategy (Fig. 2), general recommendations:

20: When non-infectious chronic uveitis is associated with active systemic disease the systemic disease must be managed.

21: Treatment with local corticosteroids is the first-line therapy in anterior non-infectious chronic uveitis.

22: In anterior non-infectious chronic uveitis in adults and children, cortisone-sparing background treatment should be discussed in a multidisciplinary setting in the presence of dependence on prolonged local corticosteroid therapy (for example 2 drops per day per eye of dexamethasone or the equivalent for up to a total of 6 months or 3 drops for up to a total of 3 months)

23: Local corticosteroid therapy initiated for acute disease should be decreased slowly, in stages, under ophthalmic control.

24: An ophthalmologist specializing in inflammatory diseases and other specialists should be consulted in non-infectious chronic uveitis in the presence of corticosteroid dependence and/or ophthalmological complications, such as cataract (especially in children) to discuss introducing or intensifying cortisone-sparing background therapy.

25: Repeated injections of peri- or intraocular delayed corticosteroids should be avoided in non-presbyopic children and adults due to the risk of cataract with post-surgical loss of accommodation and ocular hypertonia.

26: Intraocular injections of delayed corticosteroids should be avoided in non-presbyopic children and young adults, except in rare cases justified by an expert center.

27:The indication and initiation of general corticosteroid therapy in non-infectious chronic uveitis in children requires multidisciplinary consultation by an ophthalmologist/pediatrician in the absence of an imminent visual threat. In adults, consultation between the ophthalmologist and the adult specialist is recommended in the first months of prolonged corticosteroid therapy.

28: Immunomodulatory/immunosuppressive therapy should be combined with systemic corticosteroid therapy, which is indicated for non-infectious chronic uveitis, either initially, especially if the patient is at risk of corticosteroid intolerance, or secondarily, if corticosteroid dependence or significant side effects of corticosteroid therapy are present.

29: The response to immunomodulatory/ immunosuppressive therapy (usually MTX, azathioprine, MMF, ciclosporin or IFNα) should be assessed regularly in non-infectious chronic uveitis. In the presence of an unsatisfactory response at 3 months or more adherence problems should be searched for and/the etiological diagnosis should be reassessed.

30: In non-infectious chronic uveitis if there is an inadequate response to conventional immunosuppressive therapy (usually MTX, azathioprine, MMF or ciclosporin), biotherapy should be discussed. Unless contraindicated, an anti-TNF antibody is the first-line biotherapy.

31: Biotherapy may be introduced from the outset in cases of severe non-infectious chronic uveitis in children and adults after receiving expert advice.

32: In HLA-B27 positive patients with recurrent (more than 3 episodes of acute anterior uveitis per year) and/or complicated uveitis, the initiation of non-biological and/or biological background treatment with anti-TNF antibodies should be discussed, even in the absence of rheumatological involvement.

33: In case of failure of one or more anti-TNF antibodies in intermediate and posterior non-infectious chronic uveitis, the choice of another line of background therapy should be discussed with an expert center, taking into account the patient, co-morbidities, associated diseases and the specificities of the ophthalmological involvement.

34: If biotherapy is not effective in non-infectious chronic uveitis the dose may be increased or the interval between administrations (without the MA) reduced, especially if the assay shows a low residual level in the absence of anti-biotherapy antibodies.

35: Some severe forms of non-infectious chronic uveitis such as Behçet's disease, which threaten the short-term visual prognosis, require the introduction of immunomodulatory/immunosuppressive treatment in association with an expert center.

36: Any posterior uveitis or panuveitis in Behçet's disease requires systemic immunomodulatory/immunosuppressive therapy.

37: Any severe posterior uveitis or panuveitis in Behçet's disease justifies a combination of systemic corticosteroid therapy and biotherapy (anti-TNFα antibodies) or interferon-alpha.

38: A reduction in background treatment should only be considered in patients with Behçet's disease receiving conventional treatment, anti-TNF or other biotherapies, after at least 2 years of ophthalmological remission and expert advice. In other NICUs, treatment is usually maintained for at least 2 years with close ophthalmological monitoring.

39: Because the duration of treatment is not well defined in other non-infectious chronic uveitis (excluding Behçet's disease) any discussion of reducing or stopping treatment must be considered in relation to ophthalmological data with a collegial discussion. Long-term ophthalmological monitoring is useful during the course of treatment in all cases, because of possible asymptomatic developments or relapses.

5.5. Main NICU with pediatric onset: expert recommendations 40 to 42

Specific recommendations for paediatric onset NICU:

40: In any patient with suspected JIA at risk of chronic uveitis, an ophthalmological assessment is essential within the first few weeks of management. In these patients, in the absence of uveitis at diagnosis, routine slit lamp examination for white eye NICU should be performed every 3 months for 5 years.

41: In non-infectious chronic JIA uveitis and non-infectious chronic idiopathic uveitis with the same ophthalmological symptoms, methotrexate is the first-line background treatment. In certain severe uveitis, the introduction of biotherapy in combination with methotrexate may be discussed based on expert advice.

42: Anti-TNFα antibody therapy should be initiated if methotrexate fails in patients with non-infectious chronic JIA uveitis or non-infectious chronic idiopathic uveitis with the same ophthalmological symptoms.

5.5.1. NICU and JIA

The occurrence of insidious uveitis is one of the most serious complications of JIA. It is the most common cause of uveitis in children. It may precede the diagnosis of juvenile arthritis in 3-7% of cases. The frequency of uveitis varies from 10 to 30% depending on the series and the insidious form mainly concerns the oligoarticular or polyarticular forms in small girls under the age of 6, frequently associated with presence of anti-nuclear antibodies (ANA). Uveitis can cause significant ocular morbidity, including permanent blindness, if it is not detected early and treated appropriately. Uveitis is most often chronic and insidious, usually with few or no symptoms and no redness of the eye. It is therefore usually only initially diagnosed by a systematic slit lamp examination which should be regularly performed during follow-up. Most of the cases observed involve anterior, synechial uveitis, most often chronic or acute recurrent. Initially a granulomatous uveitis is possible in JIA. It may be associated with posterior involvement. In 70-80% of cases, the disease may be bilateral from the outset or become bilateral.

5.5.2. NICU and juvenile spondyloarthritis

Painful red eye uveitis may occur either early or during the course of the disease. It does not require a systematic examination because the symptoms are obvious. An ophthalmological examination is urgent in the case of uveitis to confirm the diagnosis and prescribe treatment. Uveitis is usually anterior, serofibrinous, unilateral and tilted with variable intraocular pressure (IOP) depending on inflammation or sequelae. These cases of uveitis are usually non-granulomatous.

5.5.3. NICU and granulomatous diseases

In the presence of granulomatous uveitis, infectious diseases such as herpes viruses, toxoplasmosis, tuberculosis, cat scratch disease and toxocariasis should be ruled out. Granulomatous uveitis may also be associated with digestive symptoms due to IBD. The presence or absence of other granulomatous sites should suggest the much more frequent association of sarcoidosis. It may also be associated with ANA positive JIA. A very early form of granulomatous uveitis associated with a chronic skin rash and/or severe arthritis or a family history should suggest a genetic origin (Blau syndrome = *NOD2* mutation). VKH may occur children.

5.5.4. TINU syndrome

TINU (Tubulointerstitial Nephritis and Uveitis) is a rare disease that was first described in 1975 by Dobrin. These cases combined tubulointerstitial nephritis with eosinophilic infiltrate and granulomatous adenopathy in two adolescent girls. There was a female predominance (3:1). The differential diagnosis with Sjögren's syndrome or sarcoidosis is sometimes difficult. Although uveitis is anterior in 80% of cases, granulomatous, posterior uveitis and panuveitis have been reported. Uveitis involves both eyes in 77% of cases. Initially described in the pediatric population, more recent studies show that it can also affect adults. This uveitis occurs in the days, weeks or months following an episode of tubulointerstitial nephritis, justifying ophthalmological surveillance following this event. It occurs in about 20% of these cases and may be asymptomatic, so a systematic slit-lamp examination is recommended. Although these cases of uveitis are cortico-sensitive and have a relatively good prognosis, more than half will have a chronic course with

ophthalmological complications that are non-specific and include synechiae, ocular hypertension and cataract. Treatment is based on local and systemic corticosteroids and possible immunomodulators/immunosuppressants that are usually determined by the renal involvement.

5.5.5. NICU associated with other diseases

Cryopyrinopathies or cryopyrin-associated periodic syndromes (CAPS) are rare monogenic autoinflammatory diseases. that may be associated with uveitis, including in decreasing order of severity: Chronic Inflammatory Neurological Cutaneous and Articular Syndrome (CINCA) also known as Neonatal Onset Multisystem Inflammatory Disease (NOMID), Muckle-Wells syndrome and familial cold urticaria. The most typical ophthalmological involvement is papillitis associated with aseptic neutrophil meningitis. The disease is autosomal dominant and some patients carry neomutations of the *NLRP3* gene, in particular children with CINCA. In addition, somatic mutations of *NLRP3* have been described in adults with late onset disease. The diagnosis is generally based on the existence of recurrent pseudo-urticarial skin involvement triggered by cold, arthralgia and/or arthritis, with a biological inflammatory syndrome, associated in some cases with dysmorphic features, particularly facial, secondary deafness and in some forms of CINCA/NOMID with pseudo-tumour cartilage hypertrophy. Although the diagnosis is usually clinical, a mutation of *NLRP3* is found in most patients thanks to next-generation genetic sequencing.

5.5.6. NICU in adults: expert recommendations 43

Specific recommendations for adult NICU:

43: The primary treatment for chronic or recurrent idiopathic or HLA-B27-related uveitis without rheumatological manifestations is methotrexate in adults.

5.5.6.1. Posterior uveitis or panuveitis in Behçet's disease. Any patient with Behçet's disease presenting with posterior uveitis should be treated with corticosteroids and azathioprine. In case of an immediate threat to the visual prognosis (severe retinal vasculitis, existing or possible macular ischemia, unilateral involvement in a monophthalmic patient) or recurrence on azathioprine, treatment with anti-TNFα (adalimumab or infliximab) is recommended.

IFNα (Roferon 3 million units x 3 times a week SC) is an alternative to anti-TNFα, especially in cases of persistent macular edema or contraindications to anti-TNFα.

5.5.6.2. Sarcoidosis and other granulomatoses. Sarcoidosis-related uveitis is highly corticosteroid-sensitive. In cases of severe or recurrent bilateral involvement, systemic corticosteroids are often used. The dosage of corticosteroid therapy depends on the severity of ocular involvement. The prognosis of ocular sarcoidosis depends on the presence of macular edema and/or retinal involvement (extensive and/or occlusive vasculitis). In cases of corticosteroid dependence, disabling side effects from corticosteroid therapy, or severe disease, a conventional immunomodulator/immunosuppressant (most commonly methotrexate) is required.

The anti-TNFα drugs, adalimumab or infliximab, can be effective in refractory posterior sarcoid uveitis, allowing satisfactory cortisone-sparing.

Other granulomatoses may be associated with severe refractory uveitis such as Blau's syndrome, which must be managed with an experienced team.

5.5.6.3. Birdshot chorioretinopathy. Birdshot chorioretinopathy progresses with inflammatory exacerbations leading to global retinal dysfunction. Corticosteroid monotherapy is often insufficient due to a high threshold of corticosteroid dependence.

First-line immunomodulatory/immunosuppressive treatments are mycophenolate mofetil then methotrexate and azathioprine. In refractory forms, IFN, which has been shown to be effective in macular edema, and anti-TNF antibodies can be considered.

Ciclosporin (3-5 mg/kg/day) was used for many years in this indication but its prescription is now limited because of the side effects. It is still used at lower doses (1.5 to 3 mg/kg/day) alone or in combination with another immunomodulator/immunosuppressant.

5.5.6.4. Vogt Koyanagi Harada (VKH). Immunomodulatory therapy, in the form of azathioprine, methotrexate or mycophenolate mofetil is usually prescribed in case of relapse. The risk factors of relapse include: low initial visual acuity, previous inflammation >2+, extra-ophthalmological manifestations present during the acute phase of uveitis, choroidal thickening and/or the resulting presence of choroidal folds, and a too rapid decrease in corticosteroid therapy.

Case series have reported that anti-TNFα is effective in the treatment of VKH uveitis that is resistant to conventional immunomodulators/immunosuppressants.

5.5.6.5. Sympathetic ophthalmia. High-dose corticosteroid therapy is recommended in these patients and the use of a conventional immunomodulator/immunosuppressant or anti-TNFα upfront is common due to the severity of ocular involvement. Enucleation is not an option in the treatment of sympathetic ophthalmia.

5.5.6.6. Multifocal choroiditis. Multifocal choroiditis is one of the choriocapillaropathies that affects young myopic women, with a chronic course. The risk of choroidal neovascularisation is very high, 30 to 75%. Although treatment is controversial, corticosteroid therapy is the first-line choice and treatment with an immunomodulator/immunosuppressant is often necessary. Choroidal neovascularisation is treated with intravitreal anti-VEGF injections associated with anti-inflammatory drugs to prevent active lesions.

5.5.6.7. Serpiginous choroiditis. This is a serious condition with macular extension in 88% of cases if left untreated. Serpiginous choroiditis is characterized by lesions of the pigmentary epithelium and the outer retinal layers, with a peripapillary origin and a chronic and extensive progression. One of its differential diagnoses is pseudo-serpiginous choroiditis or multifocal serpiginous choroiditis, which is thought to be related to hypersensitivity to *Mycobacterium tuberculosis*. Trial anti-tuberculosis treatment should be initiated in the presence of latent tuberculosis or a poor response to immunomodulatory/immunosuppressive therapy. In the series by Gupta et al., 14% of 110 patients had paradoxical reactions to the initiation of anti-tuberculosis antibiotic therapy, however, this should not lead to the interruption of treatment. Adjuvant treatment with corticosteroids can control the inflammatory component of the disease.

In the absence of prospective randomized studies, the treatment of serpiginous choroiditis remains a subject of debate. To prevent recurrence and preserve visual function, oral corticosteroids (0.5-1 mg/kg/d) and a conventional immunomodulator/immunosuppressant are used as initial therapy depending on the severity of disease. IFNα has been found to be successful in a small prospective case series. Anti-TNFα can only be used in typical cases of serpiginous choroiditis and after a thorough work-up to exclude tuberculosis.

5.6. Associated management (excluding specific therapy): expert recommendations 44 to 51

Associated management:

44: Any visual disability should be anticipated when possible and managed. The patient and his or her family can receive assistance to submit a file to the DHDP (Departmental Center the Disabled) when justified, to learn Braille or receive specific aids when necessary as well as to adapt study or work conditions to the visual handicap, ideally within the framework of a care network. An ophthalmological assessment is needed to define the person's needs in relation to the disease.

45: Vaccinations are not contraindicated, even with active uveitis.

46: In the case of prolonged systemic corticosteroid therapy or an indication for background immunomodulatory/immunosuppressive therapy, care should be taken to ensure optimal immunization including updating the immunization schedule and receiving influenza and pneumococcal vaccinations according to national recommendations. Vaccination should be discussed in patients who are not immune to VZV.

47: Although there is a theoretical contraindication to live vaccines in patients receiving conventional immunosuppressant or biotherapy, in certain situations a live attenuated vaccine (measles, chickenpox, etc.) may be discussed especially if there is an epidemic, taking into account the benefit/risk ratio.

48: In non-infectious chronic uveitis, any ophthalmic surgical procedure is associated with a risk of worsening ocular inflammation. The benefit-risk ratio should be assessed in these patients by an expert ophthalmologist.

49: Control of ocular inflammation should be achieved if possible before ophthalmic surgery. Except for a therapeutic or diagnostic emergency, ophthalmological surgery should be avoided in the case of an inflammatory flare-up less than 3 months before.

50: Any intraocular surgical procedure should be closely monitored and treated to minimize the risk of inflammatory ocular flare-ups based on an expert opinion. Treatment can include local and/or general corticosteroids in temporarily high doses and, if necessary, other immunosuppressants or even biomedicines.

51: As part of the initial management of non-infectious chronic uveitis, patients and, where appropriate, their carers should be informed of the existence of patient organizations by the expert center.

5.6.1. Treatment with mydriatics and hypotonics

The development of posterior synechiae leads to adhesions between the iris and the lens. These lesions can appear very early in the course of inflammation. To prevent them from becoming permanent and deforming the pupil, making it difficult to access the fundus in the event of seclusion, ocular inflammation must be treated and mydriatics (tropicamide) or cycloplegics (atropine) must be prescribed. The latter will have no effect in the chronic synechiae. They can treat the pain associated with previous uveitis and linked to damage to the ciliary body. This option is generally used for a very short period until the inflammation is controlled.

There are many hypotonic eye drops that act by 4 different but complementary mechanisms. The aim of the treatment is to reduce the production of aqueous humor and to increase, if possible, its resorption. Prostaglandin analogues have sometimes been criticized in this indication because of their potential pro-inflammatory effect, but this has not been shown in any clinical studies. Nevertheless beta-blockers, carbonic anhydrase analogues and alpha-stimulants are the preferable first-line agents. Despite normalization of inflammation, long-term hypotonic treatment may be necessary especially in cases of cortisone glaucoma.

5.6.2. Eye surgery

In NICU, any ophthalmic surgery is associated with a risk of worsening ocular inflammation requiring a discussion between the ophthalmologist and the referring specialist to carefully assess the benefit-risk ratio. Ocular inflammation should be controlled as much as possible before any ophthalmic surgical procedure is performed.

Depending on the expert's opinion, the surgical procedure should be accompanied by close monitoring and treatment to minimize the risk of an ocular inflammatory flare. Treatment can include local and/or general corticosteroids at temporarily high doses and, if necessary, other immunomodulators/immunosuppressants.

Thus, treatment with an immunomodulator/ immunosuppressant and/or biotherapy is continued, and depending on the risk, the procedure may be associated with intraoperative corticosteroid therapy (solumedrol 10 to 15 mg/kg) and per os corticosteroid therapy of 0.5 mg/kg/day from D-7 to D0, that is gradually decreased over a month in the event of a good clinical course.

An intravitreal dexamethasone implant may be used in some cases to prevent the complications of cataract surgery. The injection is usually given one month before surgery to cover the period with the greatest risk of inflammatory recurrence. The implant has been approved for use in adults. An alternative is a subconjunctive injection of triamcinolone one week before or at the end of surgery.

5.6.3. Vaccination

If background immunomodulatory/immunosuppressive therapy is indicated, care should be taken to ensure that the patient has optimal immunization protection, including updating the immunization schedule and receiving influenza and pneumococcal vaccinations according to national recommendations.

If a live attenuated vaccine is indicated in a patient receiving prolonged systemic corticosteroid therapy and/or immunomodulatory/immunosuppressive therapy, expert advice is required to discuss the benefit/risk ratio on a case-by-case basis.

5.6.4. Therapeutic education

Therapeutic patient education (TPE) is an integral part of chronic disease management. TPE is a key element in the overall management of the patient. This approach, which must be multidisciplinary, has been defined by the WHO:

"TPE aims to help patients acquire or maintain the skills they need to manage their lives with a chronic disease as well as possible."

It is an integral and ongoing part of patient care and involves organized activities, including psychosocial support, designed to make patients aware and informed about their illness, hospital care, organization and procedures, and health- and illness-related behaviours. This aims to help them (and their families) understand their illness and treatment, work together and take responsibility for their own care in order to help them maintain and improve their quality of life.

"Oral or written information and preventive advice should be given by a health professional on various occasions; they do not amount to therapeutic patient education."

"The educational approach is participatory and person-centered, not simply the transmission of knowledge or skills."

"It is a partnership between the patient, his or her family and the healthcare team, with the aim of helping the sick person to take care of him or herself."

Thus, TPE gives patients the opportunity to be at the center of an individualized and controlled care pathway between a therapeutic standard proposed by the healthcare team and the patient's own standards based on his or her desires and projects.

Healthcare professionals have various means to obtain help to create their therapeutic education projects. The centers of reference and competence as well as the rare disease health networks have information missions and can also propose participation in TPE programs. Patient associations and websites can provide useful information (see ANNEX 2 List of useful links for health professionals and for patients).

5.6.5. Use of patient organizations

All healthcare professionals and patients should be informed of the existence of patient organizations by their doctor, reference and/or competence centers, institutional websites and Orphanet (see ANNEX 2 List of useful links for health professionals and patients).

These associations contribute to providing better overall disease management by promoting cooperation between patients, patient associations, carers, medico-social and administrative institutions.

6. Follow-up: expert recommendations 52 and 53

Follow-up:

52: For all non-infectious chronic uveitis, the patient and/or his/her parents, depending on age, must be informed of the schedule and modalities of follow-up, the rationale of the proposed treatments as well as of their objectives and risks.

53: Regular assessment of anterior chamber inflammation can be performed by laser photometry by an expert ophthalmological center in certain cases of non-infectious chronic or recurrent anterior uveitis in adults and children, generally from the age of 4 years old. This quantitative assessment is useful in particular to judge the effectiveness of local and/or systemic treatments.

6.1. Objectives

- Ensure proper control of NICU and identify and treat any relapses;
- Ensure treatment tapering in patients with controlled disease activity;
- Confirm tolerance to treatment;
- Screening for early and late disease or treatment-related complications;
- Early detection and treatment of disease or treatment-related sequelae.

6.2. Professionals involved (and coordination arrangements)

The management and follow-up of non-infectious chronic uveitis must involve local healthcare providers (ophthalmologists, pediatricians or general practitioners, if necessary school medicine, etc.) as well as hospital ophthalmology departments with expertise in the disease and associated with an internal medicine, rheumatology or pediatric centers for the group of rare diseases concerned.

Orthoptists play a central role in the frequent complementary examinations. The participation of professionals including nutritionists, psychologists and psychiatrists is often useful for successful treatment. The patient may require professional management of low vision and walking disabilities. At present a quality of life analysis is difficult. The visual handicap associated with uveitis affects the quality of life at all ages and it is important for these patients to be informed of and offered options for rehabilitation. Dieticians, psychologists and occupational therapists are important partners to help improve the quality of life in patients with a significant visual impairment.

6.3. Intervals and content of follow-up consultations

6.3.1. Ophthalmological follow-up

If NICU is diagnosed in an adult, the frequency of follow-up visits is defined by the ophthalmologist and the internist or rheumatologist.

If a child is diagnosed with NICU, the frequency of follow-up is defined by the ophthalmologist and the pediatrician, but no more than every 3 months.

The frequency of follow-up visits for the evaluation of the therapeutic response depends on the severity and the course of uveitis. The therapeutic response to induction therapy should be assessed early and disease-modifying therapy should be evaluated within three months after initiation, as recommended by the SUN Working Group (ANNEX).

Measurement of inflammation of the anterior chamber with laser tyndallometer should be repeated, if available, especially in cases of chronic BAB breakdown. This technique is particularly recommended for chronic anterior uveitis and non-granulomatous panuveitis, in JIA in children over the age of 4 and Behçet's disease.

Multimodal imaging is essential. Fluorescein angiography identifies retinal vasculitis, macular or papillary edema, as well as peripheral edematous capillaropathy and non-perfusion territories, as well as pre-retinal, pre-papillary or choroidal neovascular complications.

Ultra-wide-field fluorescein retinal angiography, can identify neovascular complications as well as areas of retinal non-perfusion for which photocoagulation may be necessary. With indocyanine green angiography (ICGA) areas of hypofluorescence may correspond to non-perfusion of the choriocapillaris in certain etiologies. An etiology of uveitis may be suggested depending on the number, arrangement, and location of these areas in the middle periphery or in the peripapillary. ICG damage is correlated with visual acuity and perimetric white spot damage. ICGA is informative for the follow-up of stromal choroiditis, VKH, sympathetic ophthalmia, sarcoidosis and birdshot chorioretinopathy. Choroidal granulomas are initially hypofluorescent and become permeated with inflammatory activity. Hyperfluorescent pinpoints (VKH, sclerites) are documented in AF with ICG.

Macular edema is monitored using spectral domain optical coherence tomography (SD-OCT). Choroidal thickness for the follow-up of stromal choroiditis is evaluated by SD-OCT in the EDI mode and in OCT Swept Source. OCT-A is performed for the diagnosis and follow-up of choroid neovascularisation, in particular to differentiate these entities from inflammatory choroid lesions (multifocal choroiditis, internal punctate choroiditis).

Analysis of the progression of the functional impact (by peripheral and central automated perimetry) and electrophysiology data (standard ERG, mERG depending on the team) are useful, particularly for insidious uveitis such as birdshot chorioretinopathy. The ophthalmological assessment should be performed at least every 3 months to achieve the remission of uveitis according to the SUN criteria. If necessary, increase in the doses of local corticosteroids followed by immunomodulators/immunosuppressants and then biotherapy should be discussed every 3 months until remission.

6.3.2. Specialized extra-ophthalmological follow-up

Follow-up in internal medicine, rheumatology or pediatrics is recommended at least every 3 to 6 months at least, depending on the underlying disease and treatment. The goal of follow-up is

to manage the systemic disease, if necessary, as well as to detect treatment complications and adapt treatment based on ophthalmological follow-up results.

6.3.3. Special case of ophthalmological follow-up in children with JIA

A slit lamp evaluation must be performed during the first few weeks of treatment to look for previous uveitis in any patient with suspected non-systemic JIA. In France, the NDCP recommendations for juvenile arthritis propose screening for white-eye NICU with systematic slit-lamp examinations every 3 months for 5 years. Screening should be continued thereafter at intervals of 6 months then 12 months for many years, because uveitis flare-ups can occur several years after the onset of JIA, even when the disease is in remission.

7. Transition

EULAR recently published recommendations for the transition of patients with rheumatological diseases. It is important that each department (pediatric and adult) has a written transition protocol and a transition-coordinating physician. Transition consultations should be planned for the adolescent to increase his/her autonomy in relation to his/her family and to address specific issues such as fertility, pregnancy, genetic counselling and treatment compliance. A group of European experts has created a checklist of issues to be addressed during the transition process to assist professionals.

The transition is prepared several years in advance by the referring pediatrician, and possibly by a therapeutic education team, with workshops for this purpose. The patient must be familiar with his or her disease and treatments. It is important to know the patient's life plan, and to help him/her to become independent by making his/her own appointments, and attending consultations and being examined without his/her parents at the consultation.

The adult physician must be identified in advance. A transition liaison form that includes a summary of the patient's history should be sent by the pediatrician to the adult physician before the consultation.

A joint pediatrician/adult physician consultation is advisable. It should be prepared in advance, and more time should be spent than usual for this meeting. If this joint consultation is not possible, then alternating consultations are an option.

The transfer should be timed at the right moment, when the disease is inactive, and the patient has no other important issues to deal with during that year.

The adult physician present at the transition consultation should be the patient's physician thereafter. The pediatrician should also remain available to the patient and family. During this period consultations should be a little more frequent than usual and the patient should be told that the pediatrician will be kept informed. The aim of this approach is to avoid repeated relapses, a patient lost to the care pathway and early mortality.

Declarations

- Ethics approval and consent to participate not applicable.
- Consent for publication: not applicable.
- Availability of data and materials: not applicable.

Competing interests

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.revmed.2023.04.002.

Further reading

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