CLINICAL PRACTICE

The 2021 Portuguese Society of Ophthalmology joint guidelines with Paediatric Rheumatology on the screening, monitoring and medical treatment of juvenile idiopathic arthritis-associated uveitis

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ABSTRACT

Aim: To develop the first Ophthalmology joint guidelines with Paediatric Rheumatology with recommendations on the screening, monitoring and medical treatment of juvenile idiopathic arthritis-associated uveitis (JIA-U), endorsed by the Portuguese Society of Ophthalmology (SPO).

Methods: A systematic literature review was conducted to include publications up to July 14th 2020, with no language restrictions, in order to include all the international position papers/guidelines concerning the medical management of JIA-U and randomised clinical trials assessing the efficacy and safety of medical treatment in this field. We searched through MEDLINE (PubMed), Scopus, Web of Science and Cochrane Library. The Delphi modified technique to generate consensus was used. Preliminary evidence statements were subject to an anonymous agreement assessment and discussion process using an online survey, followed by further discussion and update at a national meeting. A draft of the manuscript with all recommendations was then circulated among all participants and suggestions were incorporated. The final version was again circulated before publication.

Results: Twenty-six recommendations were developed focusing on the following topics: general management (3), screening and follow-up of uveitis (4), treatment (17) and health education in JIA-U among patients and families (2).

Conclusion: These guidelines were designed to support the shared medical management of patients with JIA-U and emphasize the need for a multidisciplinary approach between Ophthalmology and Paediatric Rheumatology regarding the comprehensive care of JIA-U. We acknowledge that updating these recommendations will be warranted in the future, as more evidence becomes available.

Keywords: Juvenile idiopathic arthritis; Uveitis; Biological treatment; Conventional immunosuppressive treatment; Multidisciplinary management; Guidelines; Consensus; Review; Delphi Technique.

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INTRODUCTION

Juvenile-idiopathic arthritis (JIA) is by far the most common chronic inflammatory rheumatic condition of childhood and adolescence and the most frequently associated systemic condition in paediatric uveitis[1–10]. It is a heterogeneous group of clinically distinct chronic non-infectious idiopathic arthritides that, by definition, starts before the age of 16 and lasts for at least 6 weeks[5,11–15].

Uveitis is the most frequent and potentially one of the most devastating extra-articular manifestations of JIA[13,16–18]. JIA-associated uveitis (JIA-U) usually presents as an asymptomatic bilateral anterior non-granulomatous chronic uveitis, of insidious onset[1,12,19,20]. However, acute anterior unilateral or alternating uveitis presenting with a red and painful eye is the most common manifestation in enthesitis-related arthritis (ERA), a subtype of JIA[13]. Arthritis generally precedes the occurrence of uveitis but, in about 10% of cases, uveitis can present first. In an ophthalmology practice, this entity represents a great burden as up to 80% of paediatric uveitides are secondary to JIA; and also because all JIA patients without uveitis require regular ophthalmological screening for many years[14]. Known risk factors for the occurrence of uveitis in a patient with JIA are younger age at diagnosis of JIA, shorter duration of disease, female gender, oligoarticular subtype of disease and anti-nuclear antibody (ANA) positivity[1–3,21,22]. A recent study has shown that an elevated erythrocyte sedimentation rate is a predictive factor for the development of uveitis[23,24]. Regarding the clinical course, identified risk factors for worse prognosis are male gender, diagnosis of uveitis prior to arthritis and presence of ocular structural complications at first ophthalmological screening[25,26].

The fact that uveitis can develop before the onset of arthritis, together with the insidious and asymptomatic nature of the ocular inflammation, can contribute to the development of significant ocular sequelae which may be present at the time of first ophthalmological screening. The most common ocular complications of JIA-U encompass cataract, band keratopathy, posterior synechiae, macular and optic nerve oedema, secondary glaucoma and hypotony, which can ultimately lead to profound and irreversible visual loss and affect the emotional well-being of patients and their families[2,9,14,16,19,22]. Complications have been reported to be present at diagnosis in up to 20-40% of patients[3], with a higher risk of complications among patients with severe disease at presentation[19]. Up to 10-15% of children with JIA-U may develop bilateral visual impairment and become legally blind[20,27]. However, in the era of biological therapy, more optimistic outcomes have been reported[9]. Therefore, in this clinically silent disease, early and regular ophthalmological screening by slit-lamp examination is absolutely crucial to avoid irreversible and devastating visual loss[1,4,13,14].

The main goals of treatment are to completely suppress inflammation, preserve vision, manage complications and prevent recurrences, while avoiding adverse drug reactions[1,12]. JIA-U has been traditionally treated with topical steroids and conventional immunosuppression. Early treatment with immunosuppressive therapy has been associated with lower risk of visual loss, blindness and structural ocular sequelae. In past decades, stricter screening programs and the advent of biologics has positively changed the visual prognosis[28–30].

Besides the medical management of JIA-U, surgical care is essential to address potential structural complications such as cataract and glaucoma[11,12]. However, the scope of these recommendations is limited to screening, follow-up strategies and medical management. Also, in these guidelines we do not include recommendations about paediatric non-infectious non-JIA-U.

In general, uveitis is less common than many other eye diseases, such as glaucoma, cataract or diabetic retinopathy, which poses significant challenges for clinical research and may explain why there is no standardised treatment in several ocular inflammatory conditions[31]. Specifically in JIA, it has been recognised that management is based on clinicians' personal experience and training, and that follow-up and treatment strategies can vary substantially according to clinical practice[16,32]. The aim of this guideline project is to provide the first Portuguese multidisciplinary recommendations, developed in a joint effort between Uveitis and Paediatric Rheumatology experts, in order to support decision-making in the management of JIA-U for the paediatric population, sustained by updated international data and taking into account the Portuguese national reality.

METHODS

Guideline development teams

This work involved 3 groups: 1) a Core Leadership Team, consisting of 4 uveitis specialists (IL, LF, VM and CF), with expertise in managing paediatric uveitis, that coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, led by experienced literature review consultants, that completed the literature search and data extraction; 3) a Voting Panel, including 32 uveitis specialists with expertise in managing paediatric uveitis and 3 paediatric rheumatologists. Input from practicing clinicians was valued for their empirical experience and attentiveness to the points that most contribute to the streamlining of clinical decisions, while working towards the best interest of the patient.

Systematic Review Strategy

A systematic literature review addressing JIA-U was

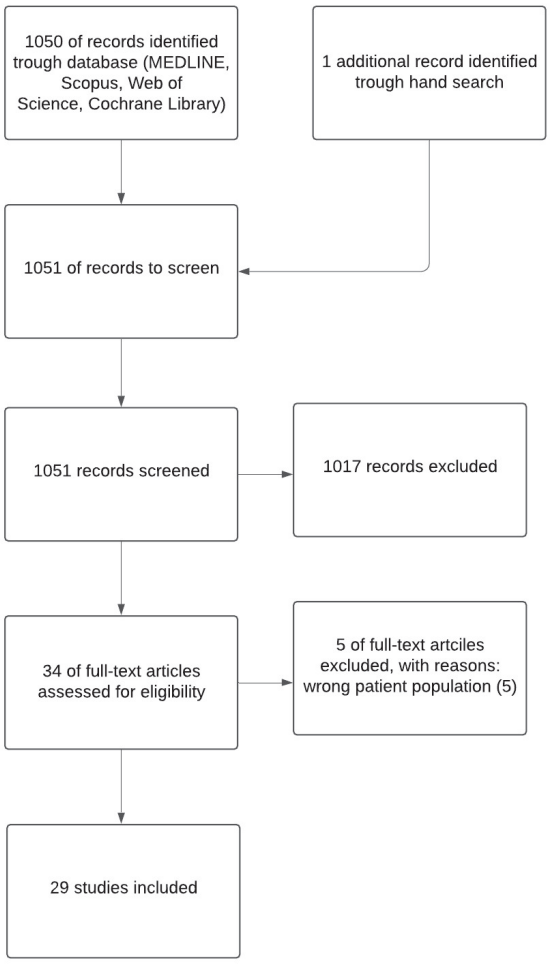

Figure 1. Flowchart of the selection of included studies

performed. Publications were included up to July 14th 2020, with no language restrictions. However, all relevant papers included were written in English. The following electronic bibliographic databases were used: MEDLINE (PubMed), Scopus, Web of Science and Cochrane Library. A restriction on date of publication was done to include only the previous 10 years due to the fast pace of changes in this field, except for the search in the Cochrane Library that was performed with no restriction. Due to the relatively small number of publications addressing specifically JIA-U, no restriction on further search terms was used. The full search strategy (including search terms, queries and number of references per database) can be found in Supplementary Appendix 1. All international position papers/guidelines on the management of JIA-related uveitis, and randomised clinical trials assessing the efficacy and safety of treatment (steroids, conventional immunosuppression and biological treatment) were included. The classifications of the International League of Associations for Rheumatology (ILAR)[16,32], and Standardization of Uveitis Nomenclature (SUN)[33] were taken into account. The initial search led to a total of 1050 references (after duplicate removal). One additional reference was added from the Royal College of Ophthalmologists[34] through hand search conducted on websites of several international societies; and abstract lists from the past ten years of relevant meetings were reviewed. Two authors (JBB and DCS) screened all the titles and abstracts independently, followed by a full-text screening independently to assess eligibility. This was done through an automated online tool called Rayyan[35]. In case of disagreement, a third author (IL) was consulted to reach consensus. Inclusion criteria included: (i) position papers, (ii) guidelines, (iii) systematic reviews; (iv) interventional clinical trials, (v) conducted in humans. We considered as exclusion criteria: (i) retrospective studies, (ii) case reports, (iii) observational studies (with no intervention), (iv) non-systematic reviews. A total of 29 references were considered to write several Key-Statements (KS) that together make up the guidelines that follow. A flowchart illustrating the selection of the included studies is presented in Figure 1.

The Delphi modified approach

The Delphi consensus method is a structured iterative process used to gather data from experts and determine consensus from a defined expert opinion group, when high-level evidence is lacking. It consists in a forecasting method based on several rounds of questionnaires sent to a panel of experts. The anonymous written responses are aggregated and shared within the group after each round. In the original Delphi approach, the expert group is responsible for developing the list of recommendations. A modified approach was used to reach consensus, using evidence-based preselection of statements and areas of agreement previously prepared by the Core Leadership Team[36].

Pre-consensus meeting survey (first round)

Preliminary evidence statements that were initially developed by the Core Leadership Team (Delphi modified approach as described above) underwent an anonymous and rigorous discussion process by the Voting Panel through a web-based remote platform (Google Surveys®). A syllabus, consisting of a summary of the literature review and existing guidelines/position papers was presented in the form of 25 KS. Afterwards, Voting Panel members were given 4 weeks to reply, with a reminder email sent 2 weeks after initial contact. In this phase, the recommendations were anonymously voted online to define the agreement rate among participants. For each recommendation, voting 1 meant total disagreement and 9 total agreement. For these guidelines,

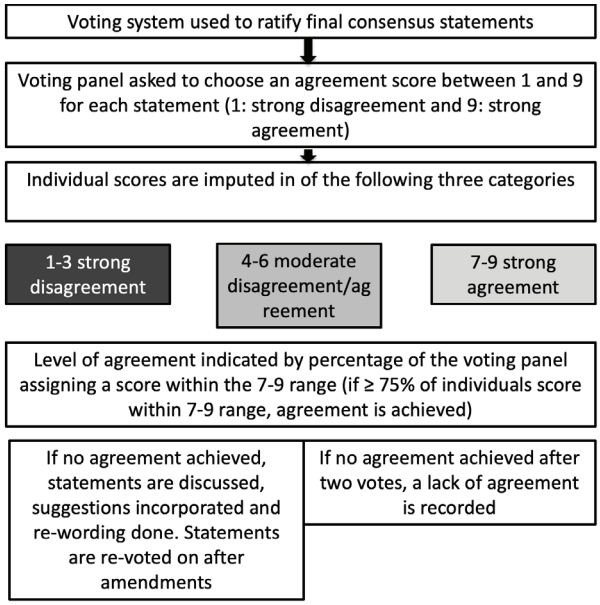

Figure 2. Key-Statements' agreement voting system

agreement was achieved if > 75% of participants scored a KS within the 7-9 range. For KS without > 75% agreement achieved during the initial vote, it was planned that the Voting Panel members would hold additional discussions before re-voting, including rewording of recommendations if needed, addition of key points or suggestions, until consensus was attained, as described elsewhere[37]. Due to the broad nature of these recommendations, the quality of evidence was not defined.

The Core Leadership Team reviewed experts' comments and incorporated suggestions and key points whenever possible into the final proposed KS. Discrete options, as well as free text items, were included. Respondents also provided input on their preferences about general management of these patients.

In total, 25 draft clinical recommendations were developed by the Core Leadership Team and an additional one was added, after the first round, by the Voting Panel and Core Leadership Team. The list of recommendations and changes proposed by the Voting Panel were circulated among the Core Leadership Team for refinement, clarification and re-wording.

The voting system used in this work is presented in Figure 2.

Consensus meeting (second round)

The results of the first round were analysed, presented and discussed during a web-based meeting. Because of social gathering restrictions related to the COVID-19 pandemic, the consensus meeting took place virtually. In this joint session, the Core Leadership Team and Voting Panel met to refine and discuss the final statements, especially changes suggested in the first round. The discussion was facilitated by a moderator (IL); the meeting was video-recorded and changes were written/added to the previous documents.

Post-consensus meeting survey (third round)

After the meeting (second round), questions for which consensus was not achieved were brought back to the Voting Panel for further analysis, discussion and decision-making. The Core Leadership Team further refined these post-consensus statements and sent them to the Voting Panel through the same web-based remote platform (Google Surveys®). Subsequently, a version of the revised manuscript, including tables and figures, was presented to the Voting Panel for final review.

Besides the main virtual meeting, workgroup interactions occurred via follow-up calls, surveys and email discussions between November 2020 and March 2021. For all recommendations, a written explanation is provided, describing the reasons for the decision and conditions under which an alternative may be preferable.

RESULTS

General management recommendations

Key-Statement 1: The follow-up and management of these patients should be handled in a multidisciplinary context, with a close working relationship and shared responsibilities between an experienced ophthalmologist and a paediatric rheumatologist.

In many clinical practices, ocular disease is assessed by the ophthalmologist, while steroid sparing systemic immunosuppression and systemic disease management is generally performed by rheumatologists[17]. Because optimal management of this disease requires collaboration between ophthalmologists and paediatric rheumatologists, these guidelines were developed through a joint effort by physicians from both specialties. Close cooperation between ophthalmologists and paediatric rheumatologists may ideally be achieved through the organization of a true multidisciplinary clinic[7,10,19,38–40].

Key-Statement 2: A comprehensive dataset of clinical information should be recorded in the patient's file.

Several data collection items should be recorded in the patients' file/notes: past medical and ophthalmic history, family medical history if relevant, details regarding JIA such as JIA category, active joints, functional status and joint damage, ANA test results, and, if justified, rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) and HLA-B27 blood results, date of onset, visual acuity, intraocular pressure (IOP), anatomical location, anterior chamber (AC) cells, ocular complications, ocular surgeries, treatment onset and stop dates, patient reported outcomes measures, school/kindergarten absence due to disease[17,40]. In Portugal, there is an electronic medical record available countrywide, uveite.pt, that has been

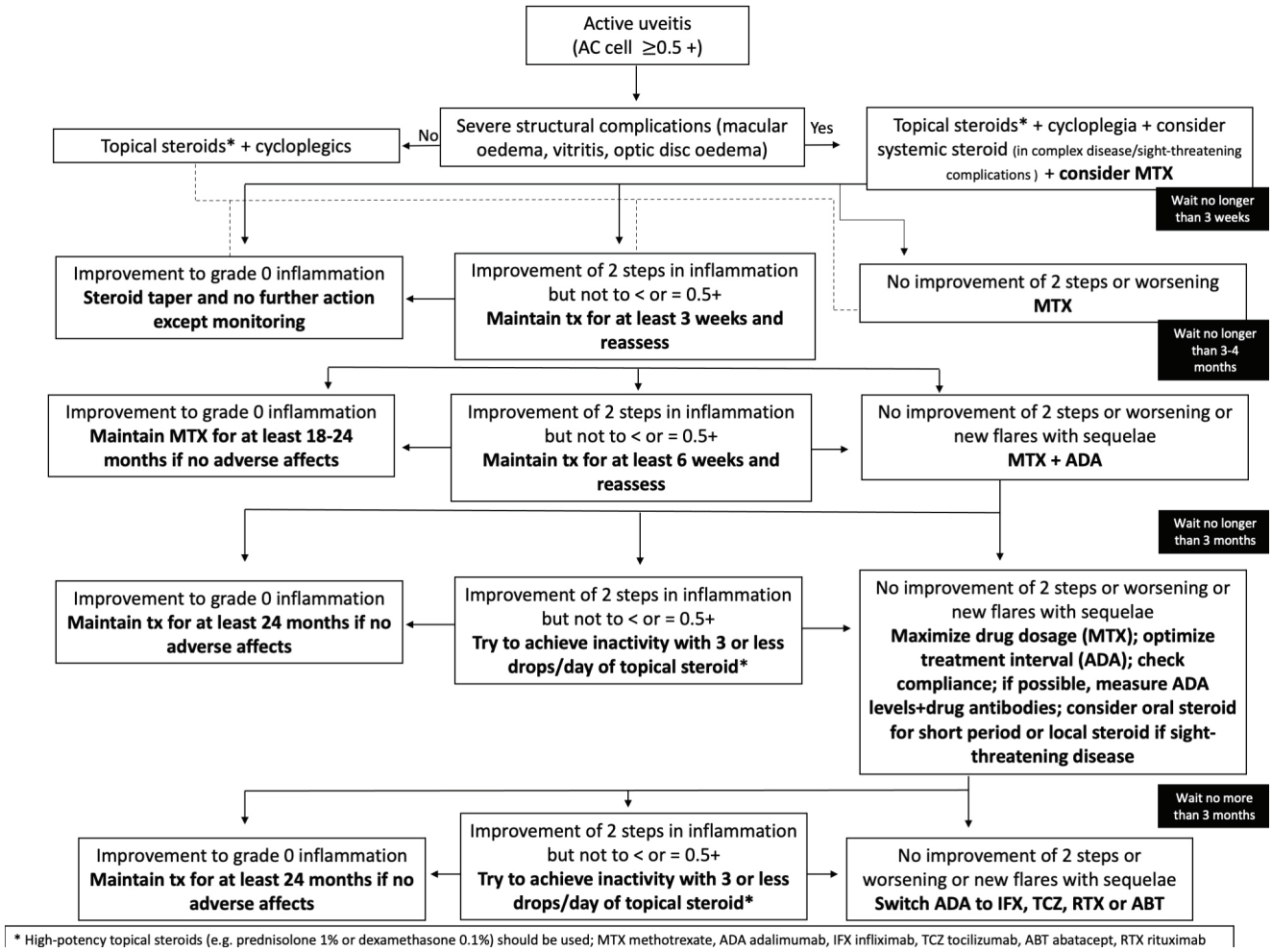

Figure 3. Medical treatment algorithm for patients with JIA-U

specifically designed to manage uveitis patients, which enables prospective data collection in a standardized system with central storage and sharing of encrypted data for research[41]. Therefore, this should be the preferred way of recording and following these patients over time[16].

Key-Statement 3: Paediatric patients with idiopathic chronic anterior uveitis and ANA-positivity, but no diagnosed JIA, should be managed in a similar way to JIA-uveitis patients.

There is enough evidence to support that ANA-positive patients with idiopathic chronic anterior uveitis and no diagnosis of JIA have a similar clinical course of disease as JIA-U patients and therefore the same treatment protocol should be followed[38,42].

RECOMMENDATIONS FOR OPHTHALMIC SCREENING AND FOLLOW-UP OF UVEITIS

Screening

Key-Statement 4: Screening for uveitis should be undertaken in all children, as soon as JIA is suspected or under investigation, rather than waiting for definitive confirmation of the disease.

Screening should occur as soon as possible and no later than 4-6 weeks from referral[39]. If patients with an initial diagnosis of JIA are symptomatic, screening should be scheduled earlier, within a week of referral. Long periods of unnoticed low-grade inflammation can explain the worse visual prognosis compared with other paediatric ocular inflammatory conditions and the high disease burden to patients and their families[1,6,39,43].

Key-Statement 5: When performing ophthalmological screening in JIA patients, slit lamp examination is mandatory.

Comprehensive screening should include recording of the following: best-corrected visual acuity (BCVA) using age-appropriate tests recorded monocularly (the assessment of VA provides a measure of both disease activity and visual damage resulting from chronic disease activity and failure/ complications of treatment); inflammatory activity graded according to the Standardization

of Uveitis Nomenclature (SUN) Working Group[33] (the SUN working group terminology is a validated instrument to grade and classify uveitis in routine clinical setting and allows for comparison and discussion of patient data among peers[44]) for anterior chamber cells and flare; complications, including IOP-related problems (hypotony, hypertension and/or glaucoma); synechiae formation; presence of cataracts; presence of band keratopathy; macular oedema (fundoscopy and/or optical coherence tomography (OCT)); epiretinal membrane formation (fundoscopy and/or OCT); papillitis; and vitreal inflammatory activity as described elsewhere[8,39,45,46].

Key-Statement 6: The screening frequency of these children should be adapted according to their risk of developing uveitis.

In the absence of uveitis, i) high-risk patients should be screened every 3 months, ii) moderate-risk patients should be screened every 6 months and low-risk patients should be screened every 12 months (these are recommended intervals for screening), according to Table I below[16,39,47].

Follow-up of active uveitis and/or inactive uveitis in remission

Key-Statement 7: Children with active uveitis and children with inactive uveitis in whom immunosuppressive treatment is being de-escalated should be screened regularly

Patients with active uveitis under treatment should be seen as follows: i) patients with +0.5 anterior chamber cell activity should be seen within 12 weeks; however, if topical steroids are started for the first time, these children should be assessed within 4-6 weeks to exclude an IOP steroid response; ii) patients with +1 or +2 anterior chamber cell activity should be seen within 6 weeks[47]. Regarding children in whom topical and immunosuppressive treatment is being de-escalated, i) children with inactive uveitis in whom topical steroids are being discontinued, should be screened within one month after each change in topical steroid dosage; ii) in children with inactive uveitis in whom immunosuppressive treatment is being de-escalated, screening should occur within 2 months after each systemic treatment de-escalation (dose reduction or increased interval between doses); iii) children with inactive uveitis under stable treatment should be screened in intervals no longer than 3 months. Longer periods between screening visits are associated with an increased risk of potentially irreversible ocular complications and visual loss[48].

RECOMMENDATIONS FOR TREATMENT

Topical and systemic steroids and cycloplegia

Key-Statement 8: Treatment of anterior uveitis should be started when ≥0.5 AC cells.

The aim of treatment is to eliminate all active inflammation (0 cells in the anterior chamber), the ultimate goal being longstanding remission of inflammatory activity[4,10,22,33,40,49,50].

Key-Statement 9: High-potency topical steroids should be considered as first line treatment for active uveitis and should be prescribed in an initial intensive burst and progressive tapering regime.

These drugs have been shown to be effective in anterior uveitis. Topical nonsteroidal anti-inflammatory drugs play a minor role in the treatment of anterior uveitis and therefore should not be used[19,38,40,47]. High-potency steroids (e.g. prednisolone 1% or dexamethasone 0.1%;

Table I. Screening frequency of JIA children according to their risk

Oligoarticular JIA, RF – polyarticular JIA or psoriatic arthritis			Recommended time intervals for screening	
Negative ANA	≤ 6 years-old at JIA diagnosis	≤ 4 years evolution of disease	Moderate risk	6 months
		> 4 years evolution of disease	Low risk	12 months
	> 6 years at JIA diagnosis		Low risk	12 months
Positive ANA	≤ 6 years-old at JIA diagnosis	≤ 4 years evolution of disease	High risk	3 months
		4-7 years evolution of disease	Moderate risk	6 months
		> 7 years evolution of disease	Low risk	12 months
	> 6 years at JIA diagnosis	≤ 2 years evolution of disease	Moderate risk	6 months
		> 2 years evolution of disease	Low risk	12 months
Systemic-onset JIA, enthesitis-related arthritis, RF+ polyarticular JIA		**Recommended time intervals for screening**		
Low risk		12 months		

ANA: Antinuclear antibodies, RF: rheumatoid factor, JIA: juvenile idiopathic arthritis

the former presents greater bioavailability in anterior chamber, and the latter has higher potency, being both adequate choices to treat anterior inflammation) should be preferred over less potent steroids (e.g. fluorometholone and hydrocortisone), since they have been shown to be more effective than low-potency steroids in topical uveitis treatment[10,19,39,40,47]. In the first 1-3 days of treatment of a uveitis flare, topical steroids should be given frequently (at least 4-6 times a day or every 2h, but hourly instillation may be needed if 2+ or more cells are present). Because of the well-known association between chronic therapy with topical steroids and intra-ocular hypertension, every child treated with topical steroids should be regularly monitored for raised IOP, within 4-6 weeks of treatment onset of topical steroid started for the first time[10,19,38,47].

Key-Statement 10: When inflammatory activity is present (+0.5 cells or more in the anterior chamber), cycloplegics should be added.
Cycloplegics should be prescribed in the presence of anterior chamber inflammation because they are useful in preventing or breaking synechiae. The use of cycloplegics should be proportional to the degree of inflammation. In the presence of mild uveitis, cyclopentolate 0.5-1.% at night should be used[10,38,39].

Key-Statement 11: Systemic steroids should be considered in complex disease/sight-threatening complications to achieve rapid control of inflammation.
Systemic steroids should not be considered in the conventional stepladder approach for all patients. However, in complex disease (e.g. patients presenting with significant AC cell activity (e.g.: ≥2+ AC cells), macular oedema or optic disc oedema) systemic steroids may be warranted, dosage PO initially 1-2 mg/kg/day or single IV pulse with methylprednisolone 10-30 mg/kg (max. 1g) in particularly severe cases, at the discretion of the clinician and co-managed with paediatric rheumatology. In these sight-threatening situations the rationale is to use systemic steroids in the first phase of treatment to achieve rapid control of disease and/or as bridging while the effect of systemic steroid-sparing drugs kicks-in[19,39,40,42,50].

Key-Statement 12: Prolonged treatment with systemic steroids should be avoided due to the likelihood of adverse effects
In case oral steroids are used, tapering should begin no longer than 2 weeks after starting steroid sparing drugs and should be tapered-off to ≤ 0.15 mg/kg within 4 weeks and limited to a total duration of 3 months[19]. However, in severe cases at presentation, it may be necessary to extend the steroid taper a little longer since methotrexate (MTX) takes around 6-8 weeks to kick-in. Long-term use of systemic steroids can cause well-known complications such as increased intraocular pressure, cataract development, osteoporosis, weight gain, diabetes, high blood pressure and, specifically in children, growth retardation[47,50].

Immunosuppressive treatment and stepladder escalation and de-escalation regimes

Key-Statement 13: In children with inadequate/insufficient response to topical steroids and/or presenting with significant structural complications, initiation of immunosuppressive treatment should not be delayed
Reasons to escalate treatment from topical steroids are the following: i) if after 3 months (or sooner if uveitis is severe according to clinical judgement) on topical steroids, persistent inflammatory activity (i.e. at least +0.5 anterior chamber cells according to SUN criteria[33]) is present; ii) if more than 3 drops/day of steroid are necessary to control ocular inflammation; iii) if repeated and/or sustained course of topical steroids are required to control the uveitis; iv) if patients present with uveitis and significant structural complications such as cataract, ocular hypertension/glaucoma, hypotony, significant synechiae, vitreous opacities, macula oedema, epiretinal membrane, optic disc oedema and/or vision loss[19,40,50]. Nevertheless, in patients with no cataract, normal IOP and frequent ophthalmic monitoring, monotherapy with 1-3 drops a day of steroids may be a reasonable option if it achieves complete control of uveitis[48].

Key-Statement 14: MTX should be used as first line therapy in patients refractory to topical steroids and/or in patients presenting with significant structural complications, and regular monitoring for adverse effects should be performed.
Drug selection should be done according to current local/international guidelines and adapted to the experience of each team of clinicians[50]. Methotrexate (MTX) should be used as first line therapy in patients with insufficient response to topical steroids (see KS 13), if there are no contra-indications to its use, starting at 10 mg/m^2/week. It can be used either orally or subcutaneously. This dose should be increased at monthly intervals to 15 mg/m^2/week and then until 20 mg/m^2/week, if necessary, with clinical and laboratorial monitoring for toxicity. Although we share the clinical experience that subcutaneous administration of MTX has been associated with more effective uveitis control and less gastrointestinal upset, there is a lack of strong data to formally recommend this route over oral administration. Pa-

tients' and families' preferences, as well as the clinicians' experience should be taken into account when choosing the route of administration. Several studies have shown that MTX is effective and safe to treat both uveitis and arthritis in JIA, enabling the treatment of the underlying disease and ophthalmic manifestations with the same drug[10,17,52,19,20,22,40,42,47,50,51]. To prevent folate deficiency, folic acid should be administered alongside with MTX, at least 5mg/weekly, on a different day to MTX[19,39].

Other conventional immunosuppressants (e.g. mycophenolate mofetil, azathioprine or cyclosporine) may be useful when in the presence of contraindication, intolerance or toxicity with MTX, but there is not enough evidence to support any of these drugs as established second line treatment to rescue MTX-refractory patients. Moreover, these drugs are generally not effective to control joint manifestations in these children[10,17,52,19,20,22,40,42,47,50,51].

Key-Statement 15: JIA-U children refractory to MTX or with insufficient/inadequate response to MTX should be started on biological treatment with a tumour necrosis factor-inhibitor (TNF-i).

Reasons to escalate to/initiate biological treatment are as follows: i) uncontrolled ocular inflammation despite 3-4 months of treatment with MTX and topical steroid at up to 3 drops/day; ii) patients requiring systemic immunosuppression but with contraindications to anti-metabolites or unable to tolerate MTX[19]. Previous publications show that a significant percentage of children will require treatment escalation[17,50,52]. The preferred TNF-i is adalimumab (ADA), as detailed below. Despite this established stepladder approach (topical steroid → MTX → ADA), prompt treatment with TNF-i in MTX-naïve patients, can be considered in the presence of severe disease (e.g. structural complications and or complications related to the topical steroid) at the clinician's discretion[17,40].

Key-Statement 16: Adalimumab (ADA) should be the first choice of biologic drug in JIA-U.

ADA has been shown to be effective and safe in JIA-U in several prospective and retrospective studies; it has been shown to reduce the incidence of further uveitis flares, the rate of complications and need for ocular surgeries. Moreover, it is capable of treating both ocular and joint disease, being formally approved for JIA. The SYCAMORE trial (a randomized, multicenter, placebo-controlled, double-masked trial, involving 17 UK centers), showed a clear therapeutic benefit of ADA in JIA-U and has led to formal licensing of this drug for the treatment of JIA-U in Europe[9,20,37,42,46,47,50,53,54]. The ADJUVITE trial[19,46] (a double-blind, randomised, placebo-controlled trial of ADA in JIA-U during 2 months followed by an open-label period where all patients were followed up under ADA for 10 months) further confirmed the efficacy of ADA in JIA-U with inadequate response to topical therapy and MTX. ADA should be administered subcutaneously at doses of 20 mg every other week in children weighing 10-30 kg and 40 mg every other week in children weighing more than 30 kg.

Key-Statement 17: When escalating treatment to ADA, MTX should be maintained in the absence of contraindications/adverse effects.

The use of MTX in combination with anti-TNF agents reduces the occurrence of anti-TNF neutralizing antibodies and therefore, ADA should be added to, rather than administered in substitution of, MTX. However, monotherapy with ADA can be considered when patients do not tolerate or present toxicity or contraindication to MTX[17,50].

Key-Statement 18: Long term treatment with MTX and ADA should be regularly monitored by a paediatric rheumatologist.

Because of potential MTX-associated toxicity (particularly liver and bone marrow dysfunction), patients on this drug require regular clinical assessment and blood tests (complete blood count, transaminases and creatinine), and management by a clinician who is familiar with these drugs, preferably a paediatric rheumatologist[19,39]. Similar to MTX, ADA treatment requires regular clinical assessments and blood work-up (complete blood count, transaminases and creatinine) to detect possible adverse effects, and monitoring by a clinician who has experience with these drugs, preferably a paediatric rheumatologist. Common side effects of ADA include local reactions at the site of injection and an increased risk of infection. Testing for latent tuberculosis before starting ADA is mandatory because of the risk of reactivation of this infection during treatment with ADA[19,39]. All vaccines should be regularly done as planned for each age group while on ADA/MTX, except for live vaccines.

Key-Statement 19: Etanercept should be not be used in children with JIA-U and should be avoided in the treatment of articular manifestations of JIA when there is a history of uveitis.

A growing body of literature is showing that etanercept is less effective in controlling uveitis than other TNF-i and the possibility of this drug eliciting paradoxical uveitis in patients with JIA has been suggested. Moreover, there are studies suggesting that patients under treatment with etanercept should be closely monitored for the possible development of uveitis. There is evidence to suggest that the first flare of uveitis in a JIA patient treated with etanercept should prompt the clinician to consider discontinuation of treatment and switching to

another TNF-i drug, preferably ADA[10,17,19,22,39,40,50,55].

Key-Statement 20: When secondary failure to ADA is suspected (if there is no optimal control of inflammation or repeated courses of topical steroid are necessary to control recurrent/persistent uveitis), the serum concentration of ADA should be measured, the presence of neutralizing antibodies should be determined, and the treatment strategy should be revised.

If there is a suboptimal control of inflammation and the patient presents anti-drug antibodies, the biological drug should be changed. If the patient has no antibodies, but has low drug levels, ADA dose should be escalated. There is not enough evidence to support dose escalation by shortening intervals between administrations over increasing the dose in each administration and therefore, the choice should be guided by the experience of each centre. Although common in clinical practice, weekly administration of ADA is an off-label use of this drug and patients and families should be informed of this, as well as of the associated risks[39,47,56].

Key-Statement 21: When the combination of MTX and ADA is unable to control ocular inflammation, switching treatment to infliximab, tocilizumab, abatacept or rituximab should be considered.

There is insufficient data to prefer one immunosuppressant over another when uveitis is not responding to MTX combined with ADA[17,19]. We found no definitive evidence in the literature to guide the choice of biological therapy when the combination of MTX+ADA fails to achieve quiescence. A possible therapeutic second line biologic agent is infliximab, as this drug has shown good efficacy and safety in JIA-U refractory to MTX+ADA, but is not approved on label for JIA[40,50]. Angeles-Han *et al.* suggest that when the combination of MTX and ADA is unable to control ocular inflammation, switching treatment to infliximab, prior to changing to another biologic class (non-TNF-i) is recommended[17,56]. If patients are refractory to both MTX and TNF-i, tocilizumab (TCZ) (anti-IL6) may be the next therapeutic option, especially taking into account the fact that TCZ is an on-label option to treat JIA. Up to 30-40% become refractory to MTX and TNF-i, either due to primary or secondary causes, and therefore are at risk of blindness[53,57]. The multicentre, single-arm, phase 2 trial APTITUDE has shown that TCZ might be a useful adjunctive treatment in JIA-U refractory to MTX + TNF-i and there is growing evidence that TCZ is effective for uveitis with macular oedema[19,58–60]. If treatment fails with optimised treatment with MTX+ADA/IFX/TCZ, other biologics should be selected. Abatacept or rituximab are a treatment option in patients failing to respond to MTX+ ADA/IFX/TCZ. These two biologic agents have shown promising results in the treatment of refractory JIA-U but there is no solid evidence to recommend one in particular over the other[40]. Regarding the other two more recent anti-TNF agents, there is scarce evidence with golimumab (GLM) in JIA-U, with only small case series published[61,62] and no published clinical experience with certolizumab (CZP) in JIA-U. A recent systematic review and meta-analysis concluded that GLM and CZP may be proxies for ADA in the treatment of JIA-U, but with limited evidence[63].

Key-Statement 22: De-escalation/stopping immunosuppressants can be considered after 2 years of uveitis inactivity

There is no solid evidence in literature to indicate the optimal duration of treatment with ADA/MTX and any decision to stop treatment should involve an individualised risk-benefit analysis[9,37,40]. However, some expert opinions and published guidelines for JIA have suggested that reducing or suspending biologic treatment might be attempted if sustained remission of disease, i.e. no active uveitis, is achieved and maintained for more than 24 months. This decision also depends on arthritis control and should always be actively discussed with paediatric rheumatology[40,42,50,55]. Despite lack of solid evidence about de-escalation strategy, several experts agree that gradual dose reduction should be preferred over abrupt discontinuation of treatment. During dose de-escalation period, regular visits to the ophthalmologist are required to allow for an early detection of uveitis recurrence[50]. Regarding topical steroid de-escalation, in children with JIA-U inactive on systemic therapy but still on 1 to 3 drops/day of topical steroid, if there are no adverse effects from systemic immunosuppression, tapering topical steroids first is recommended over tapering systemic therapy[42].

Local treatment

Key-Statement 23: Periocular/intravitreal steroids should only be considered in JIA-U cases refractory to optimized systemic treatment and/or with sight-threatening complications.

Because JIA-U is a systemic disease in its nature and local ocular steroids present a myriad of adverse effects (cataract induction, increase in IOP and/or steroid-induced glaucoma, need for general anaesthesia to administer local steroids in many small children and toddlers), systemic and topical treatment should be preferred over periocular and intravitreal delivery of steroids. Nonetheless, local treatment can be considered as rescue therapy in patients who present with severe disease, leading to profound visual loss, and after exhaustion of the above treatment options; in these scenarios, periocular steroid

or intravitreal injection of triamcinolone or dexamethasone may be considered. Local treatment with steroids is an off-label use in JIA uveitis and the risks and benefits should be discussed with parents and patients[10,50].

Peri-surgical management

Key-Statement 24: When ocular surgery is necessary (e.g. cataract, glaucoma surgery or other) peri-operative additional treatment (systemic and topical treatment – generally steroids, to be administered before during and/or after surgery) should be carefully coordinated between the ophthalmologist and paediatric rheumatologist.

Moreover, systemic immunosuppression including biologics should not be suspended before ocular surgery[50].

RECOMMENDATION FOR PROMOTING HEALTH EDUCATION IN JIA-U (PATIENTS AND FAMILIES)

Key-Statement 25: Families and patients (if old enough) should be fully informed about the possibility of development of uveitis in JIA.

It is essential to explain that this ocular manifestation of their systemic disease is usually asymptomatic (except for enthesitis-related arthritis, in which uveitis generally causes symptoms) but still able to cause irreversible ocular complications thus requiring regular screenings[34].

Key-Statement 26: Engaging patient and family in the shared care and discussion about follow-up, treatment strategies and prognosis is crucial.

Table II. Results of agreement voted of each Key-Statement

	Domain	Key Statement (KS)	Level of Agreement
General management recommendations		KS 1	8.94 (0.25)
		KS 2	8.23 (1.31)
		KS 3	8.39 (0.76)
Recommendations for ophthalmic screening and follow-up of uveitis	Screening	KS 4	8.77 (0.50)
		KS 5	8.84 (0.37)
		KS 6	8.74 (0.51)
	Follow-up of active uveitis and/or inactive uveitis in remission	KS 7	8.48 (0.77)
Recommendations for treatment	Topical and systemic steroids and cycloplegia	KS 8	8.68 (0.54)
		KS 9	8.90 (0.31)
		KS 10	8.19 (1.17)
		KS 11	8.74 (0.51)
		KS 12	8.81 (0.40)
	Immunosuppressive treatment and stepladder escalation and de-escalation regimes	KS 13	8.71 (0.53)
		KS 14	8.65 (0.67)
		KS 15	8.55 (1.15)
		KS 16	8.71 (0.64)
		KS 17	8.65 (0.75)
		KS 18	8.90 (0.40)
		KS 19	8.71 (0.53)
		KS 20	8.35 (0.91)
		KS 21	8.52 (0.72)
		KS 22	8.29 (0.78)
	Local treatment	KS23	8.26 (1.06)
	Peri-surgical management	K24	New statement: not available for voting
Recommendation for promoting health education in JIA-U (patients and families)		KS25	8.90 (0.40)
		KS26	8.97 (0.18)

KS: Key-Statement, SD: standard-deviation, JIA-U: juvenile idiopathic arthritis-uveitis

It is very important to share information about the recommended time intervals for ophthalmological screening. A shared decision process will bring the best course of treatment and follow-up[38].

Table II depicts the results of the online survey taken by 33 voting clinicians where level of agreement with each statement was selected from a scale of 1-9 (fully disagree to fully agree).

FINAL REMARKS

JIA is the most common chronic inflammatory rheumatic condition of childhood and adolescence[1–10] and uveitis is its most frequent extra-articular manifestation, with potentially deleterious consequences to the visual and general health of affected children[5,11–15]. A key aspect of management is the accurate and timely diagnosis of ocular complications, achieved only through regular and mandatory ophthalmic screenings[47].

The aforementioned twenty-six recommendations were developed in order to support ophthalmologists and paediatric rheumatologists in the medical management of paediatric JIA-U; we would like to emphasize that, although a few of these patients maintain inflammatory activity into adulthood, some of these recommendations may not apply to an adult population. Ultimately, screening and treatment decisions should be personalised, taking into account features of active disease, comorbidities and previous treatments, the clinician's personal experience, access to care, the patient's functional status and beliefs, as well as personal choices of the caregivers[47]. We took into account the latest evidence-based literature, but also but also the current management of JIA-U in the Portuguese context. Therefore, readers must keep in mind that some recommendations may contain aspects based on clinical experience and expert opinion, as robust scientific data is still lacking. Due to the broad nature and complexity of ophthalmic surgical procedures and related decision-making (mainly cataract and glaucoma surgeries)[56], this particular aspect was considered as being out of the scope of these guidelines.

We used a modified Delphi process and included a national network of ophthalmologists dedicated to uveitis, particularly in the paediatric setting, and paediatric rheumatologists, representing the reality of our national clinical practice. Statements were based on published literature, including international guidelines, after a careful systematic review. Significant lack of consensus was not identified, which may suggest an actual homogenous management of this disease at a nationwide level. Despite the absence of a gold-standard level, we decided to use a 75% agreement level, taking into account previously published literature[36,64].

Our systematic review allowed us to confirm that JIA-U is an area with a significant shortage of strong evidence. To begin with, evidence from RCTs for the use of conventional immunosuppressants, namely MTX and steroids, in uveitis is required[20]. Also, areas such as surgical management, tapering regimens for steroid-sparing drugs, role of drug antibodies, role of other promising biologics, require future research efforts. There is an urgent need for well-designed RCTs or good-quality prospective studies in order to provide solid scientific evidence concerning diagnosis, screening, and medical and surgical treatment of JIA-U.

A particular strength of these guidelines is that their development was done through a network of more than thirty ophthalmologists with a special interest in paediatric uveitis, along with the support of three experienced paediatric rheumatologists. The task of designing and writing joint guidelines, drawing on areas of agreement between two different medical specialties, brought clinicians from different backgrounds and geographic areas into contact. The resulting network may be fruitful in motivating future collaborations and lead to the development of multidisciplinary research projects in a countrywide setting.

During the writing of this article, new relevant evidence has been published, which emphasizes the need to periodically consider revision of these recommendations in order to continue to work towards a clearer decision making process even as new avenues continue to open up in this field[65–67]. A second point that we must acknowledge is the absence of the definition of the quality of evidence for the present guidelines, which is justified by the broad nature of their content.

Optimal care in JIA-U undoubtedly involves close collaboration and frequent dialogue between paediatric rheumatologists and ophthalmologists, as generally the first manage systemic immunosuppression and articular manifestations, and the latter are responsible for ocular complications' monitoring of ocular complications, and implementation of ocular medical/surgical treatment. In a disease setting where the evidence is scarce and management decisions must also rely on patients' and families' expectations and physicians' personal expertise, these recommendations should help to provide optimal care to these patients.

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APPENDIX 1
FULL SEARCH STRATEGY

A systematic literature review addressing JIA-U was performed. Publications were included up to July 14th 2020, with no language restrictions. Due to the relatively small number of publications addressing specifically JIA-U, no restriction on further search terms was used. All international position papers/guidelines on the management of JIA-related uveitis, and randomised clinical trials assessing the efficacy and safety of treatment (steroids, conventional immunosuppression and biological treatment) were included.

PubMed - 554

((((("arthritis, juvenile"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields])) OR "juvenile arthritis"[All Fields]) OR (("juvenile"[All Fields] AND "idiopathic"[All Fields]) AND "arthritis"[All Fields])) OR "juvenile idiopathic arthritis"[All Fields]) AND (("uveitis"[MeSH Terms] OR "uveitis"[All Fields]) OR "uveitides"[All Fields])

Scopus - 703

TITLE-ABS-KEY (juvenile AND idiopathic AND arthritis) AND TITLE-ABS-KEY (uveitis) AND PUBYEAR > 2009

Web of Science - 703

TS=(idiopathic juvenile arthritis) AND TS=(uveitis)

Cochrane Library – 8 reviews

juvenile idiopathic arthritis in Title Abstract Keyword