Title Page: Areas of agreement in the management of childhood non-infectious chronic anterior uveitis in the UK

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There are no competing interests to declare.

Synopsis/Precis

Childhood uveitis comprises a heterogenous group of rare, blinding eye diseases. High-level evidence to support practice is lacking. We report evidence of absence of consensus, amongst UK specialists, on the management of childhood anterior uveitis.

35/35

ABSTRACT

Background/Aims

There is a paucity of high-level evidence to support the management of childhood uveitis, particularly for those children without juvenile idiopathic arthritis uveitis (JIA). We undertook a modified Delphi consensus exercise to identify agreement in the management of chronic anterior uveitis (CAU), the most common manifestation of childhood disease.

Methods

A four round, two panel, process was undertaken between June and December 2017. Paediatric uveitis specialists identified through multiple sources, including a multicentre network (the Paediatric Ocular Inflammation Group, POIG), were invited to participate. They were asked whether they agreed with items derived from existing guidelines on the management of JIA-uveitis when extrapolated to the population of all children with CAU. Consensus was defined as agreement greater than or equal to 75% of respondents.

Results

26 of the 38 (68%) invited specialists participated with the exercise, and response rates were 100% for rounds one to three, and 92% for round four. Consensus was reached on 23 of the 44 items. Items for which consensus was not reached included management at presentation, use of systemic and periocular steroids for children with severe disease, and the role of conventional steroid sparing immunosuppressants beyond methotrexate.

Conclusion

The areas of management uncertainty at the level of the group, as indicated by absence of consensus, reflect the areas where the evidence base is particularly poor. Our findings identify the key areas for the future research needed to ensure better outcomes for this blinding childhood ocular inflammatory disorders.

INTRODUCTION

Paediatric uveitis, a group of rare inflammatory eye disorders, affects approximately 2-3 per 10,000 children.[1,2] The majority of childhood uveitis is chronic anterior uveitis (CAU).[1,3] Juvenile idiopathic arthritis (JIA), an umbrella term for a group of childhood arthropathies, is the most frequent systemic disorder accompanying CAU.[2,4,5] However, up to 40% of children with chronic anterior uveitis never develop JIA.[3] Prolonged uveitis activity may cause irreversible structural damage, and there is a risk of severe visual impairment in at least one eye before adulthood.[6,7] Individuals remain at risk of further visual loss in adulthood.[8,9] Management of childhood uveitis is complicated by the heterogeneity of the underlying systemic disorders, and uncertainties regarding disease natural history and the likely variation in underlying endophenotype.[1,3,7] Whilst novel therapies have emerged, the lack of molecular understanding and the rarity of the associated systemic disorders associated with childhood uveitis further complicates management by limiting the generalisability of the existing evidence. Up to a quarter of children with JIA associated uveitis (JIA-U) do not achieve disease control with adalimumab.[10 11] Moreover, high level comparative therapeutic research for other forms of paediatric uveitis is lacking.

The Delphi consensus method is a structured iterative process used to elicit or determine consensus from a defined expert opinion group when high level evidence is lacking.[12] The traditional Delphi approach uses the expert group to develop item lists. A common modification is the evidence based pre-selection of items for which consensus is sought, where such evidence is "available and useable".[12] In 2017, the Paediatric Ocular Inflammation Group (POIG, n=63 specialists) was established as a national multidisciplinary collaborative clinical research network which aimed to improve the evidence base for children with inflammatory eye disease. Within POIG sit disorder-specific groups of clinicians, the largest of which is the uveitis subgroup. We report the findings of a modified

Delphi approach, undertaken through the POIG Uveitis Group, which aimed to identify areas of national consensus in the management of childhood chronic anterior uveitis.

MATERIALS AND METHODS

We undertook a four round modified Delphi process between June and December 2017, involving two specialist panels (fig 1) selected on the basis of the following criteria:

Panel one: Paediatric Ophthalmologists or Uveitis Specialists managing uveitis in children (individuals aged under 18 years) within UK specialist regional centres. Within the UK, anti-TNF alpha immunomodulation treatments are commissioned and funded by NHS England through designated specialist regional centres. These centres were also the recruiting centres for the SYCAMORE study[10] and have particular experience in the management of complex or refractory childhood uveitis.

Panel two: Consultant Paediatric Ophthalmologists or Uveitis Specialists managing uveitis in children at other UK tertiary care centres. Tertiary care centres were identified through POIG membership and via membership lists for two existing national paediatric ophthalmology clinical collaborative research networks (the British Childhood Visual Impairment and Blindness Study Group, and the British Isles Congenital Cataract Interest Group).[13]

Panel members were asked to agree or disagree with items derived from existing international guidelines on the management of JIA-U. These comprised, firstly, interdisciplinary guidelines developed by the German Ophthalmological Society and based on a systematic review of the available evidence undertaken in 2009.[14] Secondly, a survey undertaken in 2013 through an international network of uveitis specialists.[15] Thirdly, the treatment algorithm within the SYCAMORE randomised controlled trial, which were based on a systematic review of the evidence and a multi-centre consensus process undertaken in 2013.[10] Lastly, a management algorithm developed in 2013 by a national interdisciplinary panel of

European specialists.[16] The items selected for this consensus exercise was limited to those within these four papers, with, for example, absence of items on investigation of infectious uveitis, or use of intravitreal drugs.

The items within the guidelines were circulated amongst the core group (ALS, CE, JSR, AR, ADD) for refinement, specifically removal of duplicate items and clarification of item wording, and examination of consistency with the existing evidence from randomised controlled trials in childhood uveitis, as identified through a concurrent systematic review of childhood uveitis studies within the International Committee of Medical Journal Editors Clinical Trials Registration system.[17] There were 44 items extracted (Supplemental file).

The items were distributed to the panels with accompanying item metadata (links to the originating literature, and the Oxford Centre of Evidence Based Medicine (OCEBM) level of the relevant supporting evidence for each item as cited in the originating guideline literature). Panel members were invited to use an electronic survey form (SurveyMonkey®) to state whether they agreed or disagreed with each item (figure 1). Summated responses (percentage of agreement and anonymised collated free text comments) were redistributed to the group as described in figure 1. For each round, panel members were given six weeks to reply, with a reminder email sent four weeks after initial contact.

Analysis

Consensus was reached when at least 75% of respondents agreed, or disagreed with an item.

RESULTS

Of the 15 specialists invited to join panel one, 12 (80%) replied. These comprised eight uveitis specialists (seven ophthalmologists, one rheumatologist) who treated adults and / or children, and four paediatric ophthalmologists who managed childhood uveitis services. Response rates for rounds one and two were 100%.

Of the 23 ophthalmologists invited to join second panel 19 (83%) replied. Five of these respondents described themselves as adult uveitis specialists, and declined to participate in the consensus exercise. Of the remaining 14 ophthalmologists, eight were uveitis specialists, and six paediatric ophthalmologists. Overall, 16/26 respondents (67%) submitted responses to all 44 items, and respondents abstained on a median of two items (range 0-8) which they felt were outside their area of expertise. One panel member changed their responses in round two, and one changed their responses in round four. Response rate for the last round was 92% (24/26). Consensus was reached on 23 of the 44 items.

Initial investigations

The majority of the Delphi group agreed with undertaking full blood count, liver function, urea and electrolyte, anti-nuclear antibody, human leucocyte antigen-B27, angiotensin converting enzyme, and erthrocyte sedimentation rate testing on children with chronic anterior uveitis without a diagnosis of JIA. However, the predefined threshold of 75% for group consensus was not reached for these items (table 1).. There was also absence of consensus on whether asymptomatic children should be referred for a paediatric rheumatology consultation), with respondents commenting that their investigations and referrals would be guided by the child's history. Group consensus was reached on the absence of an indication for complete HLA sequencing or Borrelia serology for these children (table 2).

Management at presentation

Although the majority of the group agreed with the items on first line topical therapy for children with uveitis (67%, 16/24) and the use of systemic corticosteroids for children with sight threatening disease (14/24, 60%), group consensus was not achieved (table 1). Eight respondents described a lower frequency of topical corticosteroid therapy (maximum four to six daily) than that suggested by published guidance (drops every one to two hours). Six respondents commented that a three month weaning period for oral steroids was too long for paediatric practice.

There was consensus concerning the follow up of stable mild and moderate disease, with agreement that 0.5+ (Standardised Uveitis Nomenclature, SUN) anterior chamber cell activity should be seen again within 12 weeks, and 1+SUN or 2+SUN AC cells activity seen within six weeks. The group did not reach a consensus on the frequency of follow up for more severe activity [>2+ AC cells], inactive disease or those starting on a new steroid sparing systemic therapy.

Definition and management of refractory disease

The group reached consensus on the existing definitions of refractory disease (table 2). There was consensus on the use of methotrexate as a first line systemic immunosuppressive agent, with prescription supported by rheumatology clinical input, and monitoring shared by the child's primary care giver (GP) or local paediatrician. Consensus was reached for adalimumab as a second line therapy for non JIA CAU (in addition to continuation of methotrexate), but not for the use of mycopenolate mofetil (MMF) or azathioprine as an alternative to methotrexate. An illustrative response to this itemstated that more evidence was needed on the relative benefit of adalimumab versus MMF as a second choice following methotrexate failure.

Consensus was reached on the use of either another anti-TNF agent (ie Infliximab) or the use of an anti-IL-6 agent (eg, Tocilizumab) as a third line agent. However, only four of the 21

respondents declared a preference between the two classes of biologic immunomodulators. Whilst a consensus was not reached on the role of MMF or azathioprine in the management of non-JIA CAU refractory to Adalimumab, the majority of the group agreed with its use. There was consensus level disagreement with the use of ciclosporin for childhood CAU refractory to methotrexate and adalimumab used in combination.

Systemic prednisolone therapy for the management of severe inflammation (chronic anterior uveitis with non-improving dense vitreous haze, macular oedema or SUN grade anterior cell activity of 4+ or worse) and pre-cataract surgery was agreed by consensus, but no consensus was reached on the use of periocular corticosteroids for severe disease. The duration of disease remission acceptable prior to cataract surgery, suggested at three months, did not reach consensus level agreement. Two respondents suggested that 6-12 months of disease remission would be more appropriate, and 2 respondents suggesting that they would undertake surgery in children with persistent low grade activity (ie +0.5 SUN ACC) activity.

Table 1: Items on which group consensus was not reached
Levels of evidence: Ia=More than 1 randomised controlled trial; 1b=1 RCT with narrow CI; II=1 RCT, or 1 single centre cohort study with clear effect, or >1 multicentre observational study; III=Case control studies, retrospective case series, multi-centre consensus agreement, IV=Expert opinion

Recommendation / Guideline	Evidence Level	Agreement
Management at presentation		
Topical corticosteroid (prednisolone acetate 1 % or dexamethasone phosphate 0.1 %) used 1-2h for 1-3 days then wean, + cycloplegic	III[10,14]	17/24: 71%
Oral corticosteroid taper: tapering-off to ≤ 0.15 mg/kg within 4 weeks, and limited to 3 months	III[14]	15/23: 65%
Investigations in absence of JIA		
FBC, ANA, HLA-B27, ACE, ESR, RhF, LFT, U&Es	III[15]	16/24: 67%
VDRL (Venereal disease research laboratory) test	III[15]	9/23: 39%
Rheumatology referral	IV[15]	14/24: 58%
Follow up schedule for those on treatment without co-morbidity		
At diagnosis - weekly ophthalmological visits	III[16]	8/24: 33%
At diagnosis – see within 3 weeks	IV[15]	8/22: 36%
In grades 3+ SUN or 4+ - weekly visits until improvement	III[16]	16/24: 67%
In grades 3+ SUN or 4+ - see within 3 weeks	IV[10]	6/21: 29%
Inactive - every 3 months	III[16]	16/22: 73%
Following commencement new DMARD – at 3 weeks & 3 months	III[10,16]	9/20: 45%
Management of uveitis refractory to topical therapy		
Management of MTX transaminitis: withdraw if transaminase>3x normal upper limit until LFTs normalise	III[16]	11/17: 65%
Management of nJIA CAU refractory to MTX		
Mycophenolate mofetil 300mg/m^2 BD to 600mg/m^2 BD	III[10]	13/18: 72%
Azathioprine 1mg/kg to 3mg/kg OD	III[15]	7/18: 39%
Definition of refractory to Adalimumab		
With confirmatory drug levels / ADA antibodies measured	III[10,14,16]	9/17: 53%
Management of nJIA CAU refractory to MTX + Adalimumab		
Mycophenolate mofetil 300mg/m2 BD to 600mg/m2 BD	III[14]	14/19: 74%
Azathioprine 1mg/kg to 3mg/kg OD	III[14]	7/19: 37%
Cyclosporine-A 3 mg/kg orally	III[14]	6/19: 32%
Management of non-improving dense vitreous haze / macular oedema / 4+ SUN whilst awaiting effect of maximal dose DMARD		
Consider orbital floor steroid injections	III[14,15]	10/22: 45%
Consider subtenon steroid injection	III[15,16]	16/24: 67%
Similar management considered for post cataract surgery MO	IV[15]	16/24: 67%
Peri-cataract surgery prophylaxis		
Inflammation free for at least 12 weeks	III[15]	15/21: 71%
Maintenance duration for DMARDS		
5 years	III[15]	8/24: 33%

FBC: full blood count; ANA: anti-nuclear antibody; ACE: angiotensin converting enzyme; ESR: erythrocyte sedimentation ratio; RhF: rheumatoid factor; LFT: liver function tests; U&Es: urea and electrolytes

Table 2: Items on which group consensus was reached (≥75% group agreement with item, or ≤25% group disagreement with item)

Item / extracted guideline	Level of supportive evidence for item	Agreement (n: %)
Management at presentation		
Uveitis + comorbidity: as above plus systemic corticosteroids, oral prednisolone 1–2 mg/kg/day with wean, or IV methylprednisolone 20–30 mg/kg/day for 1–3 days	III[10,14,16]	18/24: 75%
Co-morbidity at presentation described as poor vision, hypotony, glaucoma, cataract, macular oedema, or dense vitreous body opacification	III[10,14,16]	16/19: 84%
Investigations in absence of JIA		
Complete HLA sequencing	III[15]	3/23:13%
Follow up schedule for those on treatment without co-morbidity		
In grades 1+ SUN ACC or 2+ (two successive visits) - see within 6 weeks	III[16]	18/21: 86%
In grade 0.5+ SUN (two successive visits) – see within 3 months	III[16]	18/22: 82%
Definition of refractory (to topical tx)		
Sustained non-improvement of SUN+3 or greater for 1 month	III[10,14,16]	20/22: 91%
Requiring at least 3 drops daily for more than 3 months to maintain 1+SUN	III[10,16]	21/23: 91%
No improvement of 2 grades after 1 month	III[10]	20/22: 91%
Worsening onset ocular morbidities after 3 months	III[10,14]	20/21: 95%
New onset ocular morbidities after 1 month	III[10,14,16]	19/23: 83%
Management of uveitis refractory to topical therapy		
Methotrexate 10–15 mg/m^2 (or 0.3–0.6 mg/kg) PO or SC once weekly	Ib[10]	18/22: 82%
Commencement of MTX with support of rheumatologist or CNS	III[10]	19/21: 90%
Shared care with GP / local paediatrician to facilitate regular monitoring	III[10]	16/20: 80%
Definition of uveitis refractory to Methotrexate (MTX)		
No improvement of 2 grades, worsening, >2 flares / or flare sequelae after 3 months	III[10]	18/20: 90%
Requiring at least 3 drops daily for more than 3 months to maintain 1+SUN	III[10,14]	19/21: 90%
Management of nonJIA CAU refractory to MTX		
Adalimumab 24mg/m^2 SC every 2 weeks + MTX	III[14]	18/20: 90%
Definition of refractory to Adalimumab		
Same as refractory to MTX	III[10,15]	21/21: 100%
Management of nonJIA CAU refractory to MTX + Adalimumab		
OR MTX + another anti-TNF (Infliximab)	III[14]	15/16: 94%
OR MTX + IL-6 (Tocilizumab)	III[15]	15/17: 88%
Management of non-improving dense vitreous haze / macular oedema / 4+ SUN ACC whilst awaiting effect of maximal dose DMARD		
Systemic corticosteroids, oral prednisolone 1–2 mg/kg/day with wean, or IV methylprednisolone 20–30 mg/kg/day for 1–3 days	III[10,14]	19/22: 86%
Peri-cataract surgery prophylaxis		
Systemic corticosteroids (1 mg/kg 3-5 days pre, or 2 IV infusions of 500mg for 3 days pre-op)	III[15]	19/22: 86%
Maintenance duration for DMARDS		
24 months (at grade 0 SUN)	III[10,16]	19/22: 86%

HLA: Human Leukocyte Antigen; CAU: chronic anterior uveitis; PO: oral; SC: subcutaneous; IV: intravenous; SUN: standardised uveitis nomenclature; ACC: anterior chamber cells; TNF: tumour necrosis factor; IL-6: Interleukin-6; DMARD: Disease modifying anti-rheumatic drug; CNS: clinical nurse specialist

DISCUSSION

Through the use of a modified Delphi process undertaken by a national network of specialists involved in the management of childhood uveitis, a lack of consensus on several aspects of disease management was identified. These aspects comprised management at presentation, initial investigation of non-JIA CAU, the regimen of systemic steroids for children with severe disease, and the choice and sequence of conventional immunosuppressant and biologic immunomodulator in those poorly responsive to the sequence of methotrexate followed by methotrexate plus adalimumab.

The Delphi, and modified Delphi processes can be limited by the composition of the selected panel, the choice of items, and the features of the process itself, such as the absence of direct discussion within the panel.[12] Panel specialists were distributed across the UK and consisted of both uveitis specialists managing children and paediatric ophthalmologists managing complex uveitis, representing the reality of national clinical practice. In the UK specialist centres for paediatric rheumatology are characterised by registered paediatric rheumatologists who are provided prescribing rights for some treatments. The managements of paediatric ocular inflammatory disease is a registered responsibility of these centres and trials of biologics for JIA-U has been limited to such centres. There is no such restriction on those prescribing conventional immunosuppressants to children with uveitis, and no obligation to refer all cases of paediatric uveitis to specialist ophthalmologists.

The panel was split using designated specialist centre status as a marker of exposure to complex cases. Responses from these panel one members was shared with the second panel, which may have led to a ‘weighted’ response from panel two, encouraging convergence of opinion within the group, but also leading to response bias. It is however notable that most responses, and response rates, did not change from round to round, suggesting that dissenting

contributors did not disengage from the process, and that the anonymous structure of the Delphi encouraged independence of response.

The selection of a 75% agreement level, in the absence of a 'gold standard' is in keeping with the literature[12,18] and was agreed within the core group a priori. The items were pre-selected by the core group to ensure coverage of existing guidelines or treatment algorithms which were themselves evidence based and or derived through multi-centre consensus, and which covered the course of disease natural history from disease presentation to management of ocular complications.

Two Delphi consensus exercises on CAU were completed and published whilst this study was underway. The Pan European Single Hub and Access point for paediatric Rheumatology in Europe (SHARE)[19] initiative, and the North American Childhood Arthritis and Rheumatology Research Alliance (CARRA)[20] published consensus based recommendations on the management of JIA-U (SHARE) and both JIA-U and non-JIA-U CAU(CARRA). In contrast to this study, ophthalmologists were in the minority in both of these international groups. SHARE comprised nine rheumatologists and three ophthalmologists. CARRA comprised 10 rheumatologists and two ophthalmologists. One author of this study was a member of the SHARE consensus group [CE] and one [AR] a co-author. There was considerable concordance in many areas between our findings and the SHARE and CARRA recommendation with regards to the importance of escalating to non-steroidal systemic treatment, the use of methotrexate as first line and anti-TNF biologic therapies as second line treatments. There was a significantly wider range of immunsuppressants suggested within CARRA as alternatives, reflecting international differences in drug availability and prescribing practices. In the UK funding for biologics other than adalimumab for refractory childhood uveitis requires an individualised application for funding unless there is systemic disease.[21] This will have restricted the treatment decisions of the participants of this study.

There was disagreement between CARRA and SHARE on the definition of inactive disease, specifically whether persistent low grade activity (ie +0.5 SUN activity) is sufficient criteria for escalation of systemic therapy. Our expert panel was also unable to reach consensus on this. An agreed definition of a clinically significant level of minimum activity (ie one that does not necessitates treatment escalation, and is not associated with an increased risk of relapse) remains elusive. There was, however, agreement within all three studies concerning definitions of poor treatment response.

Chronic anterior uveitis is the commonest manifestation of childhood uveitis, and has been recognised by the European Medical Agency as sufficiently unique from adulthood disease to prevent extrapolation of data from adult uveitis trials.[19,20] CAU in children with and without juvenile idiopathic arthritis may be sufficiently similar as to allow generalisability of the evidence base around JIA associated uveitis.[19,20] A key difference, however, is the possibility of an underlying inflammatory diagnosis such as sarcoidosis in children with non JIA CAU. The elicitation of systemic features of disease can be a challenge for ophthalmologists, and it can be unclear as to whether children require paediatric or paediatric rheumatological input. The local prevalence of associated disorders can also guide the diagnostic algorithm. In the UK, the most common of these disorders are the juvenile idiopathic arthritides (including the HLA-B27 and enthesitis related spondyloarthropathies). To a lesser extent, other multi-system inflammatory diseases may manifest as CAU.[1] Up to 10% of children with Behcet's disease present first with ocular features,[22] and ocular involvement may be a more common feature of paediatric sarcoidosis than that seen in adult disease.[23] Although we did not reach consensus on the investigation panel for asymptomatic children presenting with non-JIA associated CAU, ophthalmologists must remain aware that signs or symptoms of an underlying systemic disorder may not be apparent at the onset of uveitis.

Our findings are a future roadmap for essential research and the generation of the evidence base for improved future patient care. Whilst we describe consensus on many aspects of management, we are unable to use all our findings as recommendations for clinical practice in childhood uveitis. In some cases there may be a justification in taking a patient led rather than protocol based approach, for example in the decision of follow up scheduling. Further evidence on other aspects of management are awaited from studies currently underway, such as the APTITUDE phase II trial of Tocilizumab in refractory JIA-U.[24] However, at this time, the paucity of registered interventional trials suggests that an updated systematic review would not provide definitive management recommendations.

Ophthalmological involvement in study design for international prospective cohort studies of children with these rare inflammatory systemic diseases, or ophthalmology-led registers of children with rare inflammatory eye disorders, would provide the population and data needed to develop and test diagnostic algorithms for those presenting with ocular signs in the apparent absence of systemic features. Multicentre clinical rare disease networks can also provide the specialist support needed for clinical decisions on this challenging patient group. POIG, and the disorder specific groups which sit within it, aims to provide an ophthalmology led multidisciplinary clinical network to enable the further research, both observational and interventional, which is needed for better outcomes for these rare, blinding childhood ocular inflammatory disorders.

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Figure 1. The Delphi process