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# Temporal Trends in Childhood Uveitis: Using Administrative Health Data to Investigate the Impact of Health Policy and Clinical Practice

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**ABSTRACT**

**Background:** We describe an investigation of temporal trends in the incidence of childhood uveitis-related hospital admissions, hospitalization being a robust indicator of disease severity.

**Methods:** A population-based retrospective study using a hospitalization database, the Hospital Episode Statistics (HES) dataset, capturing data on care between 2013 and 2020. Primary outcomes were rates of pediatric hospital admissions for uveitis-related disorders.

**Results:** During the study period, there were 3,258 reported uveitis-related hospital admissions of children aged 0 to 14 years, comprising 19% of all-age uveitis-related admissions. Anterior uveitis was the most common diagnosis. The annual incidence of childhood uveitis-related hospitalizations declined year on year from a peak incidence of 5.4 per 100,000 children (95% confidence interval 5.0–5.9) in 2015–2016 to 3.3 per 100,000 (95% CI 3.0–3.6) in 2019–2020. Over the same period, the national incidence of juvenile arthropathy-related admissions stayed stable.

**Conclusion:** The decline in admissions nationally may reflect reduced incidence of uveitis complications with increasing use of immunosuppressive therapies.

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Uveitis; child; epidemiology; outcome assessment; health care

Childhood uveitis is a potentially blinding, uncommon disorder with reported annual incidence of 4–7 per 100,000.[1–3] Approximately half of all children with uveitis also have juvenile idiopathic arthritis (JIA),[2–4] with uveitis being the most common extra-articular manifestation of JIA.[5] Uncontrolled ocular inflammation can result in visually impactful ocular structural complications,[1,5] which carry significant risk of visual disability and negative impact on quality of life.[5,6] Structural sequelae typically occur as a consequence of uncontrolled intraocular inflammation.[1] Sequelae such as cataract or detachment of the retina are treated surgically, and others, such as macular edema or glaucoma, may require surgical intervention following failure to respond to medical treatment.[1] Children may also require 'ambulatory' hospital-based care for delivery of systemic treatment. An admission for a uveitis-related procedure is therefore a strong indicator of disease severity.

Over the last decade, there have been significant changes in the management of childhood uveitis, with increased recognition of the importance of long-term disease control for children with and without JIA,[7] increased use of steroid sparing disease modifying agents such as methotrexate and mycophenolate,[7,8] the availability, and demonstrated effectiveness of monoclonal antibody 'biologic' therapeutics, such as adalimumab, for use in refractory childhood uveitis,[9] and international commissioning and adoption of the use of biologics for affected children.[7,10] An understanding of the temporal trends of outcomes for children affected by uveitis would enable some assessment of the impact of these changes.

The United Kingdom's National Health Service England Hospital Episodes Statistics (NHS HES) administrative database holds information on day case and overnight admissions, outpatient appointments and emergency attendances in NHS hospitals. The freely available HES datasets do not carry individual level details such as length of stay, or the specific procedure for which admission is warranted. They do, however, provide information on the primary diagnosis for the hospitalization. The aim of this study was to use NHS HES data in a retrospective study to estimate the annual incidence of pediatric hospitalizations for non-infectious uveitis in England from 2013 to 2020, in order to investigate the distribution and temporal trends of disease.

## Materials and methods

### *Data source*

NHS HES data are accrued on an ongoing basis across all 151 healthcare Trusts (providing primary and secondary care and specialized services) in England. The diagnostic information for each 'episode' (attendance as an outpatient, inpatient, or in emergency care) is documented by clinical coders in the reporting

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hospitals and catalogued using the World Health Organization's International Classification of Diseases, 10th revision (ICD-10) classification system. Freely available, anonymized and aggregated data on the primary diagnosis for hospital admissions, and patient age at admission, were extracted from the HES databases.

### Case definitions and data collection

A non-infectious uveitis-related admission was defined as an 'episode' with a primary diagnosis using uveitis ICD-10 codes. These comprise acute and subacute iridocyclitis (ICD-10 code H20.0); chronic iridocyclitis (H20.1); lens-induced iridocyclitis (H20.2); other iridocyclitis (H20.8); unspecified iridocyclitis (H20.9); iridocyclitis in other diseases classified elsewhere (H22.1); focal chorioretinal inflammation (H30.0); disseminated chorioretinal inflammation (H30.1); posterior cyclitis (H30.2); other chorioretinal inflammations (H30.8); unspecified chorioretinal inflammation (H30.9); glaucoma secondary to eye inflammation (H40.4); and other endophthalmitis (H44.1). ICD-10 codes H20.0 to H22.1, code H30.2 and codes H30.0, H30.8, H30.9 were then categorised as anterior, intermediate or posterior uveitis, respectively, to align with international consensus on uveitis nomenclature.[11] ICD codes referring to purely infectious ocular diagnoses such as tuberculosis of eye (A18.5), toxoplasma oculopathy (B58.0), or herpes viral ocular disease (B00.5), were not included. Data were also extracted on admissions due to JIA specific or aligned ICD-10 diagnoses: juvenile arthropathy related admissions, using ICD-10 M08 and M09 subcategories, comprising juvenile rheumatoid arthritis (ICD-10 code M08.0); juvenile ankylosing spondylitis (M08.1); juvenile arthritis with systemic onset (M08.2); seronegative juvenile polyarthritis (M08.3); pauciarticular juvenile arthritis (M08.4); other juvenile arthritis (M08.8); juvenile arthritis, unspecified (M08.9); and juvenile arthritis in Crohn's Disease (M09.1).

Age at admission for hospitalizations is categorised within HES as either 0–14 years, 15–59 years, or older. Thus, data on all admissions for those children aged 0–14 years were extracted for analysis.

### Analyses

Descriptive analyses of the numbers and proportions of uveitis-related admissions across different age groups and different forms of uveitis were undertaken. The Office for National Statistics (ONS) dataset was used to obtain data on childhood population numbers in England, and the population-adjusted frequencies by age group and type of uveitis were calculated. Temporal trends in the incidence of pediatric admissions for uveitis-related procedures were described using non-parametric testing (Mann-Kendall, or MK test) for trends. Data were extracted from the HES database using Microsoft Excel, and analyses were undertaken using Microsoft Excel and STATA (release version 15.0; Statacorp, College Station, TX).

This research involved re-use of robustly anonymised and aggregated data which were already in the public domain, and was not used for any purposes beyond those for which the data were originally gathered, thus ethical review was not deemed necessary by the National Health Service Health Research Authority.[12]

## Results

From April 2013 to March 2020, there were a total of 14,380,481 admissions of children aged 0–14 to NHS hospitals in England. Over this study period 3258 of all these admissions involved a primary diagnosis of uveitis (Table 1). This comprised 0.023% of all childhood admissions for any diagnosis, and 19.4% of the 16,773 uveitis related admissions for individuals of any age over this period.

From 2015 onwards (Figure 1), we observed a year on year decrease in the population adjusted annual incidence rates of uveitis-related admissions in children aged 14 and below, from an annual incidence of 5.4 per 100,000 children (95% confidence interval 5.0–5.9) to 3.3 per 100,000 (95% CI 3.0–3.6). This trend reached statistical significance (MK test, $z = -1.91$, $p < .05$). Over the same period, the national incidence of juvenile arthropathy-related admissions stayed stable (Figure 1 and supplemental tables).

During the year ending March 2016, there were 7009 childhood (0–14) hospitalizations for JIA and 580 for uveitis (a ratio of 12:1). By the year ending March 2020, the ratio of JIA admissions to uveitis admissions was 21:1, with 7766 and 378 JIA and uveitis-related pediatric hospitalizations, respectively. Amongst the 69653 pediatric hospitalizations for JIA over the study period, the most commonly reported International League of Associations for Rheumatology (ILAR) subtypes were polyarticular seronegative and pauciarticular (i.e. oligoarticular) JIA, accounting for 25% and 15% of JIA admissions (supplementary table).

### Age at admission

Approximately half of admissions involved children aged 10 years to 14 years (1695/3258, 52%). Only 244, 7%, of children were aged under 5 years on admission. There were no significant changes in the distribution of age at admission over the study period (Figure 2).

**Table 1.** Annual number of childhood hospitalizations for children aged 0–14 years.

| | | | Uveitis-related admissions | |
|---|---|---|---|---|
| Year | Total admissions for children | Total JIA-related admissions | Number of admissions | Incidence per 100,000 childhood population (95% CI) |
| 2013/14 | 2,012,905 | 7,079 | 447 | 4.3 (3.9–4.7) |
| 2014/15 | 2,028,995 | 6,971 | 565 | 5.4 (4.9–5.8) |
| 2015/16 | 2,036,839 | 7,009 | 580 | 5.4 (5.0–5.9) |
| 2016/17 | 2,080,383 | 7,782 | 474 | 4.4 (4.0–4.8) |
| 2017/18 | 2,081,789 | 7,848 | 418 | 3.8 (3.4–4.1) |
| 2018/19 | 2,100,330 | 8,131 | 396 | 3.5 (3.2–3.9) |
| 2019/20 | 2,039,240 | 7,766 | 378 | 3.3 (3.0–3.6) |

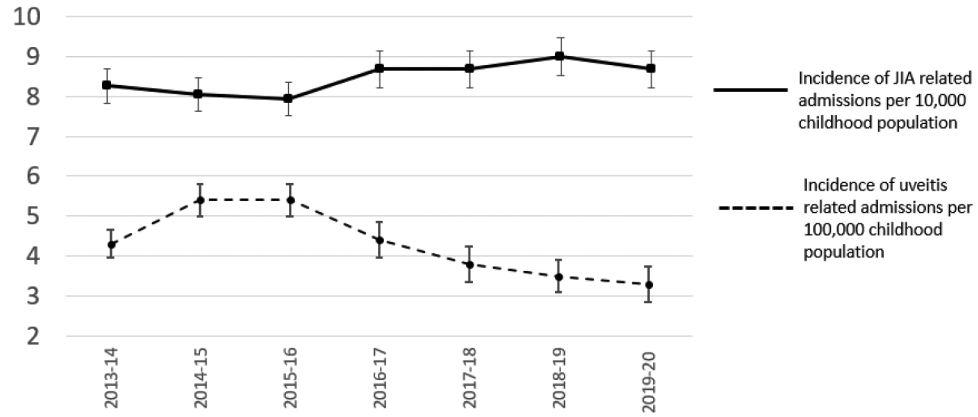


**Figure 1.** Trends in population adjusted incidence of childhood admissions for uveitis and juvenile idiopathic arthritis.

### *Type of uveitis*

Anterior uveitis was the most common disease type for uveitis-related admissions (Figure 3), accounting for 2800 of the 3202 childhood admissions (87%) for which uveitis type could be determined. Posterior uveitis was the next most common manifestation of disease responsible for hospitalizations, accounting for 383 admissions (12.6%). There were 19 reported intermediate uveitis-related admissions (supplemental tables).

## Discussion

From this population based study of administrative healthcare data, we report that childhood uveitis-related hospitalizations are uncommon. Children are over-represented in the population of all-age uveitis-related admissions. The population adjusted annual incidence rates of childhood uveitis related admissions fell from 2015 to 2019. This was largely driven by changes in anterior disease, although a similar trend was seen in hospitalisations for posterior disease. This trend was noted despite admissions for juvenile inflammatory arthropathy remaining comparatively stable over this period.

The data source for this study, the Hospital Episode Statistics (HES), is a population health dataset, but is limited by the anonymised and aggregated structure of the freely accessible version of the dataset. Without individual level data, it is not possible to describe the specific determinants of outcome. The intervention associated with each admission is not available. While some children will have been admitted for a surgical ophthalmic procedure data, some may have been admitted for ambulatory care in order to receive a course of intravenous steroids, or other immunotherapy. However, all of these indications for admissions are also indicators of disease severity. HES hospitalization episodes are 'counted' at event level rather than child level.[12] Multiple hospitalizations may be attributable to a single individual, making the determination of a true incident rate for severe disease challenging. Nevertheless, as well as the need for hospitalization remaining a strong marker of uveitis at the more severe end of the spectrum of disease, each hospitalization represents significant consumption of care resources. Despite the limitations, this trend data on the rates of these hospitalizations are valuable indicators of the burden of childhood uveitis, and this study provides previously unavailable population level estimates on the patterns of visually impactful disease through the use of an indirect measure.

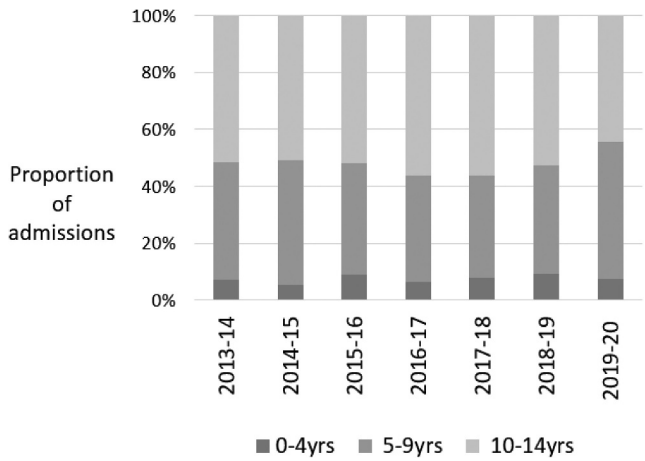


**Figure 2.** Age at admission for children hospitalized due to uveitis from 2013 to 2020 Figure 3. Trends in population adjusted incidence (per 10,000 child population) of childhood admissions for uveitis by anatomical subtype.

We aimed to capture data for cases of non-infectious uveitis, but were limited by the use of the ICD-10 disease taxonomy within this national administrative health database. ICD-10 does not allow for comprehensive classification of the uveitides. For example, whilst different forms of toxoplasma uveitis ("B58.01: toxoplasmosis chorioretinitis") and ocular tuberculosis have unique ICD-10 codes (eg: "A18.54: tuberculous iridocyclitis," or "A18.53: tuberculous chorioretinitis"), other infectious uveitides have no unique ICD-10 code (uveitis due to toxocariasis or due to Lyme disease is included within "B83.0: visceral larva migrans," and "A69.29: Other conditions associated with Lyme disease," respectively). As ICD-10 categories such as "H30.1: disseminated chorioretinal inflammation," or "H30.8: other chorioretinal inflammations" or "H44.1: other endophthalmitis" may not be limited to non-infectious uveitides, the cohort presented here may include infectious causes. However, this is expected to be relevant to only a minority of cases, and a particularly small minority within the episodes related to anterior uveitis. The incomplete mapping of ICD-10 codes to international consensus-based disease taxonomy (such as that in the standardized uveitis nomenclature) remains

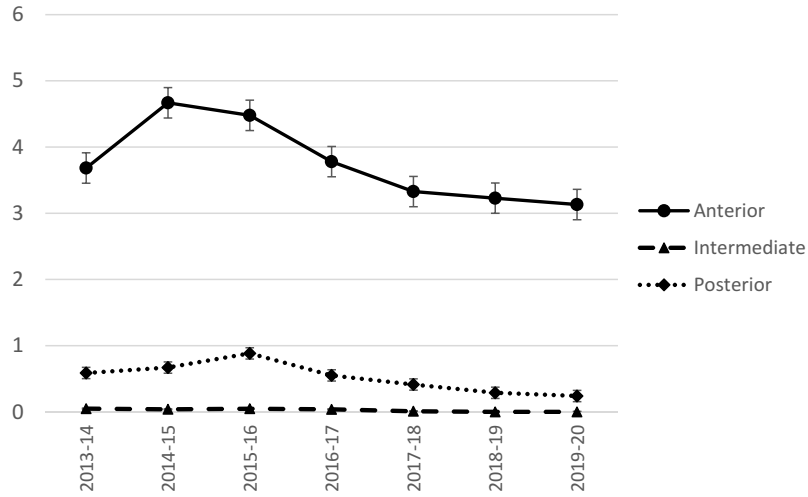


**Figure 3.** Trends in population adjusted incidence (per 10,000 child population) of childhood admissions for uveitis by anatomical subtype.

a challenge to the use of historic administrative datasets to explore trends and outcomes for the different disease phenotypes. International groups will need to continue work towards agreed supranational disease ontology.

Childhood onset uveitis is thought to account for 1 in 50 of all individuals with the disorder, with the remaining having disease of adult onset.[2] In this study, childhood-onset cases are overrepresented amongst all-age uveitis hospitalizations, accounting for one in five admissions. This may be due to the comparative severity of childhood disease, or to greater problems with administration and compliance with treatment in children compared to adults and consequent higher complication rate, but may also be due to an underestimation of the number of children affected by uveitis. There are no similar population level studies of the incidence of childhood uveitis related complications or hospitalizations with which to compare our findings. Only a minority of children diagnosed with uveitis can expect to be admitted for procedures or treatments. It is notable that the annual incidence of disease related admissions reported in our study is of a similar order of magnitude to the reported incidence rates for all new cases of disease.[2,3,12] This suggests a much higher disease burden for childhood onset uveitis than that previously estimated.

It is not possible to use these HES datasets to provide estimates of the incidence of uveitis, or data on outpatient service burden. The NHS HES data on hospitalizations have been shown to be robust,[13] but there are greater limitations in the HES dataset on outpatient attendances. Unlike the hospitalization dataset, primary diagnosis is not a mandatory collection field in the outpatient attendance dataset, and of the 96,420,114 outpatient attendances within the HES database in 2018/2019, 92,080,362 are missing a primary diagnosis, making the outpatient dataset an unsuitable source from which to derive incidence rates. Thus, there are currently no other comparable databases in the UK from which to estimate the national incidence or burden of disease of all cause childhood onset non-infectious uveitis.

In 2013, following recognition of poor national coverage and data incompleteness, NHS Digital was established with a remit which included improvement in coverage, completeness and data and coding quality for the HES databases.[13] The study period for this investigation commences in 2013, in order to enable robust case ascertainment and data quality.[12] The increase in hospitalization rates seen between 2013 and 2015 may reflect further improvements in case ascertainment during the initial years of NHS digital, rather than true incidences in hospitalization burden. Improved case capture does not, however, explain the fall in admissions seen in childhood uveitis admissions from 2015 onwards, which has occurred despite steady incidence rates of juvenile arthropathy-related hospitalizations.

The most recent major change in the management of childhood uveitis is the increasing use of systemic immunosuppression in children with and without JIA, and in particular the use of the anti-tumor necrosis factor alpha (TNF-alpha) monoclonal inhibitor, adalimumab, in refractory or severe disease.[9,10,14,15] The 2014 commencement of the multi-centre SYCAMORE (randomized controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis) trial, and the premature halt of the trial in March 2015 due to superior outcomes in the treatment group (adalimumab and methotrexate) brought increased attention to the use of systemic immunosuppressive agents in childhood uveitis.[8–10,16,17] A move away from infused anti-TNF agents (such as infliximab) to subcutaneous delivery of adalimumab may explain part of the early fall in hospitalizations post 2015, but not the ongoing year on year reductions in admissions.[17] The higher proportion of children admitted aged over 5 years (versus the younger age groups) despite the peak age of onset of JIA occurring between ages 2 and 4 suggests that hospitalisations are occurring in children who have long period of untreated or undertreated ocular disease, and that the reduction seen in these admissions over time is a result of increased use of agents such as anti-TNF therapies within JIA population. However, up to half of the childhood uveitis population do not have JIA.[1,2]

Our findings support our hypothesis that population level ocular outcomes in childhood uveitis have improved alongside increasing use of systemic steroid sparing immunosuppressive agents, due to lower incidence of uveitis onset in JIA populations,[10] and improved outcomes in children affected by uveitis.[9] This probable positive clinical association is particularly important in light of the ongoing concerns about the cost-effectiveness of biologic therapies for affected children.[18]

The anonymised nature of the freely available HES data source, which does not link to disease natural history or medication datasets, is however an obstacle to inferring a direct causative relationship between hospitalization rates and the use of immunosuppressive agents. This study demonstrates the usefulness of national administrative healthcare datasets for examining distribution and patterns of disease, but population-based longitudinal datasets on natural history, outcomes, and the determinants of outcome are still needed for robust investigation of the impact of changes in practice and policy for this and other rare disorders.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

## Data availability statement

Datasets used in this study are freely available and accessible via NHS Digital: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20

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## References

1. Smith JA, Mackensen F, Sen HN, et al. Epidemiology and course of disease in childhood uveitis. *Ophthalmology*. 2009;116(8):1544–1551. doi:10.1016/j.ophtha.2009.05.002.
2. Paivonsalo-Hietanen T, Tuominen J, Saari KM. Uveitis in children: population-based study in Finland. *Acta Ophthalmol Scand*. 2000;78(1):84–88. doi:10.1034/j.1600-0420.2000.078001084.x.
3. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California epidemiology of uveitis study. *Ophthalmology*. 2004;111(3):491–500. doi:10.1016/j.ophtha.2003.06.014.
4. Rahman N, Petrushkin H, Solebo AL. Paediatric autoimmune and autoinflammatory conditions associated with uveitis. *Ther Adv Ophthalmol*. 2020;12:251584142096645. doi:10.12688/f1000research.26689.1.
5. Lee JJY, Duffy CM, Guzman J, et al. Prospective determination of the incidence and risk factors of new-onset uveitis in juvenile idiopathic arthritis: the research in arthritis in Canadian children emphasizing outcomes cohort. *Arthritis Care Res*. 2019;71:1436–1443. doi:10.1002/acr.23783.
6. Cassedy A, Altaye M, Andringa J, et al. Assessing the validity and reliability of the effects of youngsters' eyesight on quality of life (EYE-Q) questionnaire among children with uveitis. *Arthritis Care Res (Hoboken)*. 2020. doi:10.1002/acr.24491.
7. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American college of rheumatology/arthritis foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis–associated uveitis. *Arthritis Care Res*. 2019;71:703–716. doi:10.1002/acr.23871.
8. Solebo AL, Rahi JS, Dick AD, Ramanan AV, Ashworth J, Edelsten C. Areas of agreement in the management of childhood non-infectious chronic anterior uveitis in the UK. *Br J Ophthalmol*. 2020 Jan;104(1):11–16. doi:10.1136/bjophthalmol-2018-313789.
9. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med*. 2017;376(17):1637–1646. doi:10.1056/NEJMoa1614160.
10. Tappeiner C, Schenck S, Niewerth M, Heiligenhaus A, Minden K, Klotsche J. Impact of antiinflammatory treatment on the onset of uveitis in juvenile idiopathic arthritis: longitudinal analysis from a nationwide pediatric rheumatology database. *Arthritis Care Res (Hoboken)*. 2016;68(1):46–54. doi:10.1002/acr.22649.
11. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140:509–516.
12. Tsirouki T, Dastiridou A, Symeonidis C, et al. A focus on the epidemiology of uveitis. *Ocul Immunol Inflamm*. 2018;26(1):2–16. doi:10.1080/09273948.2016.1196713.
13. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: hospital episode statistics admitted patient care (HES APC). *Int J Epidemiol*. 2017;46(4):1093–i. doi:10.1093/ije/dyx015.
14. Rypdal V, Glerup M, Songstad NT, et al. Uveitis in juvenile idiopathic arthritis: 18-year outcome in the population-based nordic cohort study. *Ophthalmology*. 2020. doi:10.1016/j.ophtha.2020.08.024.
15. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor alpha treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. *Arthritis Care Res (Hoboken)*. 2014;66(7):1073–1084. doi:10.1002/acr.22214.
16. Roos AWW, Ayuso VK, De Vries LA, Vastert SJ, De Boer JH. Tocilizumab as an effective treatment option in children with refractory intermediate and panuveitis. *Ocul Immunol Inflamm*. 2020. doi:10.1080/09273948.2020.1712431.
17. Samra KA, Maghsoudlou A, Roohipoor R, Valdes-Navarro M, Lee S, Stephen Foster C. Current treatment modalities of JIA-associated uveitis and its complications: literature review. *Ocul Immunol Inflamm*. 2016;24(4):431–439. doi:10.3109/09273948.2015.1115878.
18. Hughes DA, Culeddu G, Plumpton CO, et al. Cost-effectiveness analysis of adalimumab for the treatment of uveitis associated with juvenile idiopathic arthritis. *Ophthalmology*. 2019 Mar;126(3):415–424. doi:10.1016/j.ophtha.2018.09.043.