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ABSTRACT

Objective To conduct a systematic review to identify and critically appraise clinical practice guidelines on the assessment, diagnosis and management of childhood glaucoma.

Methods and analysis A systematic literature search of databases and professional websites for clinical practice guidelines published on eye conditions between 2010 and April 2020 in English was conducted. Identified guidelines were screened for relevance to childhood glaucoma and exclusion criteria applied. Guidelines that passed the screening and quality appraisal with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool and, if they achieved a mean score of ≥45 and ≥3 on subsets of 9 and 5 AGREE II items, respectively, were selected for inclusion and data extracted using a standardised form.

Results Following screening and critical appraisal, three guidelines were included for data extraction. None of the three guidelines was specifically developed for childhood glaucoma. A consistent recommendation was that children should undergo some form of eye screening examination or a comprehensive eye assessment to detect paediatric eye disease. Children at high risk of childhood glaucoma should undergo additional screening. One clinical practice guideline recommended interventions for childhood glaucoma consisting of tube surgery and topical beta-blockers or carbonic anhydrase inhibitors. Recommended interventions for childhood glaucoma were based on low-quality to moderate-quality evidence or expert opinion.

Conclusion Based on our selection criteria, we did not identify any high-quality clinical practice guidelines specifically targeted at childhood glaucoma. This is compounded by the lack of high-quality evidence on childhood glaucoma.

Key messages

What is already known about this subject?

- Childhood glaucoma is a rare, but devastating, eye condition among children, which requires often life-long management and treatment.

What are the new findings?

- Clinical practice guidelines specifically targeting childhood glaucoma are scarce.
- This systematic review identified only three guidelines, none of which was specific to childhood glaucoma.

How might these results change the focus of research or clinical practice?

- This systematic review will inform a Package of Eye Care Interventions developed by WHO.
- There is need for a high-quality clinical practice guideline for childhood glaucoma.

INTRODUCTION

Childhood glaucoma is a rare eye condition with estimated incidence of 2.29 per 100 000 people below 20 years of age in the USA to 5.41 per 100 000 live births in the UK.[1 2] A higher incidence has been reported in Asian populations.[1 3–5] Childhood glaucoma is an important cause of vision loss and is estimated to be responsible for 10% and 3% of childhood blindness in African regions and the USA, respectively.[6] Childhood glaucoma is not a single disease entity and may arise secondary to one or more underlying congenital anatomical defects, genetic alterations, neoplastic, infectious, inflammatory or postsurgical causes. The Childhood Glaucoma Research Network defines childhood glaucoma as intraocular pressure (IOP)-related ocular damage and classifies it into primary and secondary types.[7] Primary childhood glaucoma includes primary congenital glaucoma (PCG) and juvenile open angle glaucoma. Secondary childhood glaucoma includes glaucoma associated with non-acquired ocular anomalies (eg, Axenfeld Rieger anomaly), non-acquired systemic diseases (eg, Down syndrome), acquired conditions (eg, uveitis) and previous cataract surgery.[7]

Despite several available options for management of childhood glaucoma, the prognosis is often suboptimal. People with childhood glaucoma have a reduced quality of life[8] and visual acuity is often poor with approximately 25% of children with PCG meeting the WHO's definition of blindness in one Indian cohort.[9 10] As the disease and its management essentially requires lifelong monitoring, there is also a significant impact on the caregiver quality of life, indicating that

evidence-based interventions are required at a multitude of levels to optimise patient outcomes.[11]

Childhood glaucoma has been identified as a priority eye condition for inclusion in the WHO's Package of Eye Care Interventions (PECI). The PECI is being developed in response to a recommendation from the World Report on Vision to imbed eye care into Universal Healthcare Coverage. The PECI will be an evidence-based tool that aims to improve access to, and the provision of, eye care by assisting Member States, particularly low-income and middle-income nations, with the planning, budgeting and integration of eye care interventions.[12] For example, in the context of childhood glaucoma, the PECI will provide recommendations on cost-effective, evidence-based interventions and the resources required to implement these interventions. Stage 2 of the PECI is a systematic review of clinical practice guidelines (CPGs) to identify recommended, evidence-based interventions for priority eye conditions. Later stages of the PECI development include the review and selection of recommended interventions for inclusion in the PECI by a panel of experts from low-resource, middle-resource and high-resource settings, identification of required resources and peer review of the package.[12]

This systematic literature review aims to identify CPGs for childhood glaucoma and extract data to support the development of the WHO PECI.

METHODS

This systematic review of CPGs was conducted in compliance with the methodology outlined in the introductory PECI paper.[12] A CPG was defined according to the Institute of Medicine definition: 'statements that include recommendations, intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options'.[13] Exclusion criteria for each stage of screening are provided in table 1.

Systematic literature search

A systematic literature search for CPGs was conducted on 9 March 2020 in the following academic databases: MEDLINE, Embase, CINAHL and Global Index Medicus. In addition, a search of guideline databases and the websites of several optometry and ophthalmology associations were also undertaken for CPGs that met the inclusion criteria. The search terms and filters were adapted according to the search options in the specific guideline databases and websites. Guidelines were limited to publication in the last 10 years and published in English. The full search strategy and list of databases and websites searched are presented in online supplemental appendix 1.

Table 1 Exclusion criteria for screening of CPGs

	Reason for exclusion
Title and abstract screening	▶ The identified literature was not a CPG. ▶ The guideline was not published in the last 10 years. ▶ The guideline was not in English. ▶ The guideline was not developed for selected eye conditions.
Full-text screening	▶ There was commercial funding or unmanaged conflicts of interest present. ▶ Absence of affiliation of authors.
Quality appraisal	▶ The average score of the two researchers for items 4, 7, 8, 12 or 22 is below 3. ▶ The sum of the average score of the two researchers for all nine items is <45.

CPG, clinical practice guideline.

Title and abstract screening

Title and abstracts of the records identified in the searches were screened independently by two authors (GL, SS) using the semi-automated AbstrackR software.[14] The following exclusion criteria were applied: the document was not a CPG, the guideline was not published in the last 10 years, the guideline was not in English or the guideline was not developed for a priority eye condition for PECI. Discrepancies were resolved by a representative from WHO (SK) and Cochrane Eyes and Vision (CEV; JRE).

Full-text screening

CPGs identified as potentially relevant to childhood glaucoma based on title and abstract screening underwent independent full-text screening by two authors (GL, ST). Broadly, guideline relevant to paediatric populations, glaucoma or some combination of the two were selected for full-text screening and we opted to be inclusive to avoid missing eligible guidelines. CPGs were excluded if they were deemed not relevant to childhood glaucoma, did not list the affiliations of all authors, did not declare potential conflicts of interest or there were significant conflicts of interest present. Potentially significant conflicts of interest included scenarios such as a large proportion of authors having relevant conflicts of interest, the first or senior author having a direct, proprietary conflict of interest or a lack of a description for managing relevant conflicts of interest, when present. Where it was unclear whether there was a significant conflict of interest, the full-text screening team was encouraged to consult with a third (SK) and fourth author (JRE) from WHO and CEV, respectively. Other discrepancies were resolved through discussion between the two authors (GL and ST) or, in the event a consensus could not be reached, by discussion with the aforementioned third and fourth authors (SK and JRE).

Quality appraisal

The selected CPGs underwent independent quality appraisal by two authors (GL, ST) using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.[15] The AGREE II tool contains 23 items relating to 6 quality domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. Based

Table 2 Details and AGREE II ratings of clinical practice guidelines that met eligibility criteria

Organisation	Region	Included	Publication year	AGREE II ratings of each reviewer separately									
				4	7	8	10	12	13	15	22	23	Total
AAO[18]	USA	Yes	2017	7	7	3	5	6	6	5	7	7	53
				7	7	5	6	6	6	6	7	7	57
AOA[19]	USA	Yes	2017	7	4	7	6	7	7	6	7	4	55
				7	6	7	7	7	7	7	7	5	60
NHMRC[17]	AUS	Yes	2010	7	4	6	6	5	6	5	6	6	51
				7	4	6	5	5	5	5	6	6	49
Anwar *et al*[26]	USA	No	2013	4	1	1	2	5	4	4	2	6	29
				4	1	1	1	3	4	3	2	5	24
EGS[27]	EU	No	2014	7	2	2	4	5	3	5	4	4	3
				6	4	5	4	6	5	5	5	4	44
SOS[28]	SE	No	2012	6	3	6	2	5	4	5	3	5	39
				6	3	5	2	2	4	5	4	4	35

Titles of the AGREE II items are as follows: 4—the guideline development groups include individuals from all relevant professional groups; 7—systematic methods were used to search for evidence; 8—the criteria for selecting the evidence are clearly described; 10—the methods for formulating the recommendations are clearly described; 12—there is an explicit link between the recommendations and the supporting evidence; 13—the guidelines has been externally reviewed by experts prior to publication; 15—the recommendations are specific and unambiguous; 22—the views of the funding body do not influence the content of the guideline; 23—competing interests of guideline development group members have been recorded and addressed.
AAO, American Academy of Ophthalmology; AGREE II, Appraisal of Guidelines for Research and Evaluation II; AOA, American Optometric Association; AUS, Australia; EGS, European Glaucoma Society; EU, Europe; NHMRC, National Health and Medical Research Council; SE, Sweden; SOS, Swedish Ophthalmolgical Society.

on a consensus finding process prior to this review,[16] we only used a subset of AGREE II items to appraise CPGs, specifically items 4, 7, 8, 10, 12, 13, 15, 22 and 23 (item names provided in table 2). These items are in the domains of stakeholder involvement, rigour of development, clarity of presentation and editorial independence and were recommended for use by the WHO Guideline Review Committee Secretariat, as they were deemed most relevant to the development of packages of care. To be eligible for inclusion, the average result for items 4, 7, 8, 12 and 22 had to be ≥3, and the average sum score of items 4, 7, 8, 10, 12, 13, 15, 22 and 23 had to be >45.

Final guideline selection

To facilitate timely development of the PECI, a maximum of five CPGs were able to be selected for data extraction. Where more than five CPGs were eligible, guidelines were to be selected according to the following criteria: quality, publication date and comprehensiveness (ie, applicability to different settings).

Data extraction

Data were extracted from the selected CPGs using a standardised form that recorded information on the recommendation (type of recommendation, dosage, target group, etc), the strength of recommendation and the quality of the evidence used to inform the recommendation by the guideline development group. Data were tabulated and organised according to intervention type: screening, assessment, prevention, promotion or treatment.

Recommended eye care interventions for childhood glaucoma were extracted from CPGs by one author (GL or ST) and independently checked by a second author (GL or ST). The process was repeated for all the guidelines until agreement on the recommended eye care interventions was reached.

RESULTS

Screening, appraisal and selection of guidelines

The results of the selection process are reported in figure 1. After the initial title and abstract screening, 68 reports were identified as potentially relevant to childhood glaucoma. On review of the full-text report, 29 of these guidelines were deemed not relevant to childhood glaucoma, 27 did not report either potential conflicts of interest or affiliations of authors, 1 had significant conflicts of interest among authors and 5 did not meet the criteria of a CPG on full-text review, leaving 6 CPGs for the AGREE II appraisal.

The results of the AGREE II appraisal are shown in table 2. There was very good overall agreement between the two raters (one-way intraclass correlation=0.83). After the AGREE II appraisal, three of the six CPGs were excluded: one due to the average score of the two researchers for items 4, 7, 8, 12 or 22 being <3 and two CPGs were excluded due to the sum of the average score of the two researchers for all items being <45. Of the three CPGs that were excluded during the AGREE II appraisal, one was aimed at addressing the side effects of glaucoma therapy while the remaining two were CPGs aimed at all

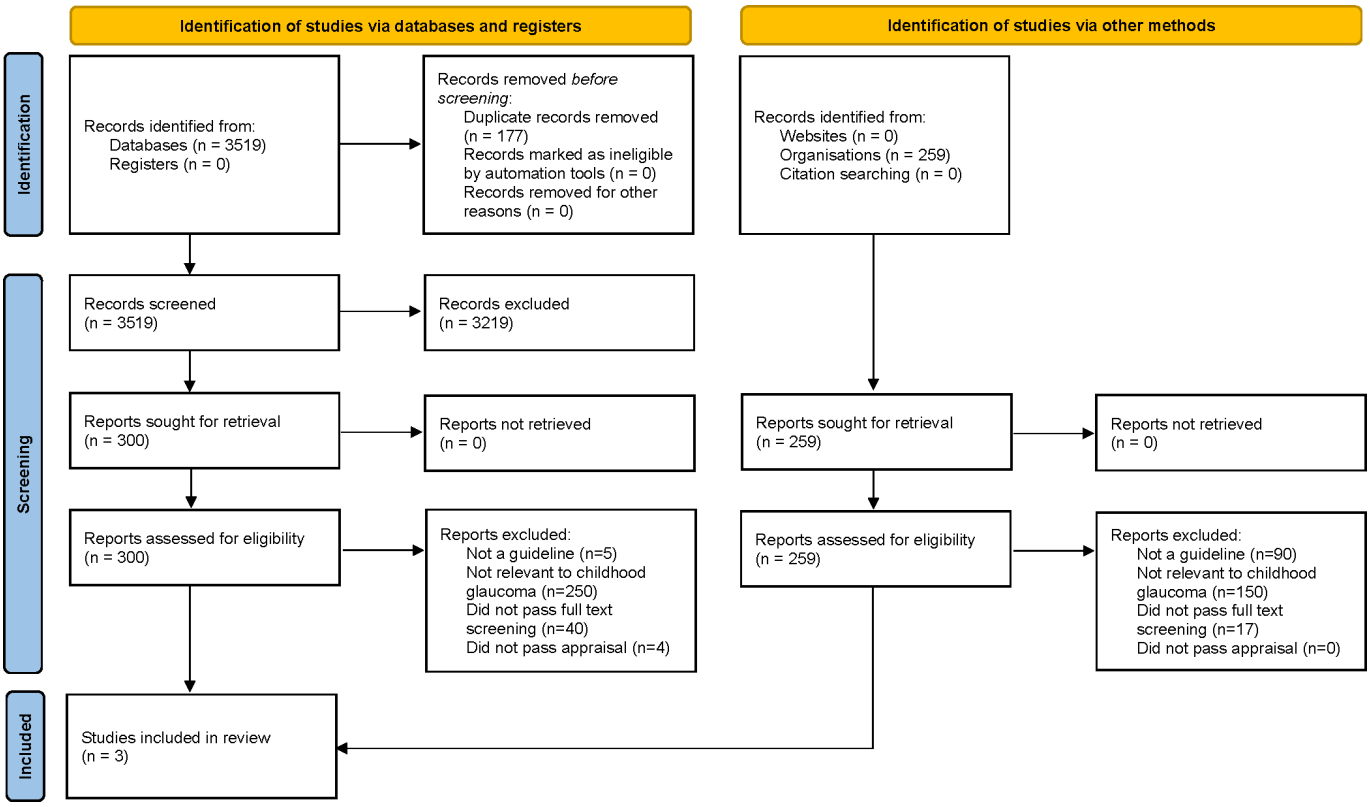

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart summarising the results of the literature review to identify clinical practice guidelines for childhood glaucoma.

types of glaucoma. These excluded guidelines performed most poorly in areas relating to reporting of systematic review methods and methods for formulating recommendations.

We ultimately selected three CPGs[17–19] for the data extraction phase. The extracted recommendations are shown in table 3. Two of the three included guidelines were published in the USA and related to the ocular assessment of children and infants and thus were not directly aimed at detection and management of childhood glaucoma. These two CPGs had the highest overall AGREE II scores. The remaining selected CPG was published in Australia in 2010 and was aimed at diagnosis and management of glaucoma at all ages and only a small part of the CPG was dedicated to childhood glaucoma. Therefore, we did not identify a CPG that specifically targeted childhood glaucoma.

Guideline recommendations

Of the recommendations extracted, strongly recommended interventions largely related to the assessment of infants and children to detect eye conditions such as childhood glaucoma, as well as the assessment of IOP in the diagnosis and management of glaucoma. Screening of first-degree relatives of those with glaucoma, including those with genetic syndromes that are highly associated with childhood glaucoma, was also strongly recommended.

Tube surgery was strongly recommended for long-term IOP control in patients at high risk of trabeculectomy failure (such as in childhood glaucoma) and in glaucoma following cataract surgery. Although not formally recommended, tube surgery was noted to be an appropriate first-line treatment for some secondary causes of childhood glaucoma. Topical beta-blockers and carbonic anhydrase inhibitors were recommended with intermediate strength for the management of childhood glaucoma, although these therapies should be used with caution due to the potential for adverse events and the quality of evidence was noted to be low. Surveillance of patients on long-term steroid medication including assessment of the optic nerve head, anterior chamber and visual field was recommended with weak or intermediate strength. These recommendations, however, were targeted at all individuals with glaucoma or at risk of glaucoma and were not specific to childhood glaucoma.

The quality of evidence used for formulating recommendations varied considerably. Recommendations relating to the screening or examination of children to detect paediatric eye disease or certain ocular assessments for the diagnosis of glaucoma were generally of moderate-quality or good-quality evidence, with some exceptions. There was only low-quality evidence to support the use of topical IOP-lowering medication for the treatment of childhood glaucoma. Interestingly there was deemed to be moderate-quality evidence for the use of tube surgery; however, this recommendation was for the use of tube surgery where trabeculectomy is likely to fail including, but not limited to, some childhood glaucomas.[17] Thus,

Table 3 Extracted assessment or intervention recommendations from eligible CPGs

Assessment or intervention name	Recommendation	CPG	SoR	QoE	Remarks on recommendation
Screening to detect amblyopia or risk factors	The 2017 USPSTF report recommends vision screening for children aged 3–5 years of age to detect amblyopia or its risk factors	AAO	Strong	Good	
Examine individuals with first-degree relatives with glaucoma	…first-degree relatives of individuals diagnosed with glaucoma are considered at high risk of developing glaucoma themselves. It is recommended that they undergo a full ocular examination by a qualified healthcare provider, and receive ongoing monitoring for the development of glaucoma	NHMRC	Strong	Good	The following genetic syndromes have high associations with childhood glaucoma: Nail Patella syndrome with the LMX1B gene, Axenfeld Rieger syndrome/ anterior segment dysgenesis with the PITX2 and FOXC1 genes and Aniridia with the PAX6 gene. Patients with these syndromes or mutations are usually followed closely for glaucoma. Congenital glaucoma is associated with Cyp1B1 mutations in 17% of Australian families.
Monitor long-term users of steroids for glaucoma	…long-term users of steroids by any route of administration are at increased risk of glaucoma, and thus require surveillance.	NHMRC	Intermediate	Moderate	There is no evidence from the secondary literature regarding the risk factors for, or progression of secondary glaucoma.
Comprehensive eye and vision examination of infants (6–12 months of age)	Infants should receive an in-person comprehensive eye and vision assessment between 6 and 12 months of age for the prevention and/or early diagnosis and treatment of sight-threatening eye conditions and to evaluate visual development	AOA	Strong	Moderate	
Comprehensive eye and vision examination of children (3–5 years of age)	Preschool age children should receive an in-person comprehensive eye and vision examination at least once between the ages of 3 and 5 years to prevent and/or diagnose and treat any eye or vision conditions that may affect visual development	AOA	Strong	Moderate	
Comprehensive eye and vision examination before beginning school	School-age children should receive an in-person comprehensive eye and vision examination before beginning school to diagnose, treat and manage any eye or vision conditions	AOA	Strong	Moderate	
Annual comprehensive eye and vision examination of school-age children	School-age children should receive an in-person comprehensive eye and vision examination annually to diagnose, treat and manage eye or vision problems	AOA	Not stated	Expert opinion	
Assess intraocular pressure	…assessment of intraocular pressure in all individuals with suspected glaucoma, as it is a significant risk factor for the development of all forms of glaucoma	NHMRC	Strong	Good	
Assess optic cup:disc ratio and cup:disc ratio symmetry	Evidence supports assessment of cup:disc ratio, and cup:disc ratio asymmetry, when assessing the risk of glaucomatous damage occurring… Evidence supports the value of validated optic disc comparison techniques (simultaneous stereo photograph comparison and confocal scanning laser tomography) in order to detect longitudinal changes in the optic nerve	NHMRC	Intermediate	Moderate	
Gonioscopy of both eyes	…gonioscopic examination of both eyes is required when making a diagnosis of glaucoma	NHMRC	Weak	Expert opinion	

Continued

Table 3 Continued

Assessment or intervention name	Recommendation	CPG	SoR	QoE	Remarks on recommendation
Visual field testing	…visual field testing is invaluable to diagnose glaucoma…advancing age, visual acuity, patient capability, concurrent ocular conditions, oculo-facial anatomy and spectacle scotomata all impact on the results and interpretation of visual field testing	NHMRC	Weak	Expert opinion	
Assess target intraocular and reduce if glaucomatous progression identified	…assess target intraocular pressure at each ocular review, within the context of glaucomatous progression and quality of life. Evidence strongly supports a further 20% reduction in target intraocular pressure when glaucomatous progression is identified	NHMRC	Strong	Good	
Topical beta-blockers	Evidence supports using beta-blockers in infants and children where necessary	NHMRC	Intermediate	Low	To limit potential adverse effects, it is important to adhere to dosage times, use nasolacrimal system occlusion (if at all possible in small children) and use the minimum dose or limit the number of medications required.
Topical beta-blockers—precautions	Evidence suggests using beta-blockers with caution in premature and small infants, as bradycardia, bronchospasm and hypoglycaemia have been reported	NHMRC	Intermediate	Low	To limit potential adverse effects, it is important to adhere to dosage times, use nasolacrimal system occlusion (if at all possible in small children) and use the minimum dose or limit the number of medications required.
Carbonic anhydrase inhibitors	Evidence indicates caution when using topical and systemic carbonic anhydrase inhibitors in children, in situations where glaucoma is resistant to other treatment and/or prior to surgery	NHMRC	Intermediate	Low	To limit potential adverse effects, it is important to adhere to dosage times, use nasolacrimal system occlusion (if at all possible in small children) and use the minimum dose or limit the number of medications required.
Tube surgery	▶ Evidence strongly supports using tube surgery for long-term intraocular pressure control. This is an appropriate first-choice surgery in patients: – with eyes at higher risk of failure from trabeculectomy; – who have failed trabeculectomy; – with iridocorneal endothelial syndrome; – with various forms of uveitic (inflammatory) glaucoma. ▶ With aphakic glaucoma.	NHMRC	Strong	Moderate	Tube surgery should be considered for the primary procedure in patients in whom trabeculectomy is likely to fail, such situations include some severely traumatised eyes and secondary paediatric glaucomas.

AAO, American Academy of Ophthalmology; AOA, American Optometric Association; CPG, clinical practice guideline; NHMRC, National Health and Medical Research Council; QoE, quality of evidence (good, moderate, low expert opinion); SoR, strength of recommendation (strong, intermediate, weak); USPSTF, United States Preventive Services Task Force.

this recommendation could also be based on evidence of the effectiveness of tube surgery in adult populations.

DISCUSSION

The findings of this systematic review demonstrate that there is a lack of high-quality CPGs aimed at childhood glaucoma. The evidence to formulate recommendations for childhood glaucoma varied substantially, with recommendations related to interventions for the treatment of childhood glaucoma generally of lower-quality evidence compared with recommendations for assessments to detect childhood glaucoma (and other paediatric eye disease). In 2013, The World Glaucoma Association (WGA) formulated consensus guidelines that define childhood glaucoma and bring a more uniform set of terminology to the childhood glaucoma landscape.[7] While extremely valuable for the field, the WGA consensus document did not pass the PECI inclusion criteria as no formal systematic review was conducted.

Our review indicates much work still needs to be done to develop strong evidence to inform the development of CPGs.

The number of randomised controlled trials (RCTs) for childhood glaucoma has seen only a marginal increase in the last decade. A recent Cochrane review identified 16 RCTs or quasi-RCTs comparing various surgical interventions for PCG; however, these studies variously compared 9 different surgical interventions and generally had low sample size, making it difficult to draw definite conclusions.[20] It is also important to address the lack of long-term data on the outcomes of these interventions as childhood glaucoma has potentially lifelong consequences. Measurement of quality of life metrics in future studies with a medium-term to long-term follow-up would be of use.

The results of this review indicate that there is a consensus on the need for children to have an eye examination, conducted by either an eye care professional or as part of a screening programme, to detect paediatric eye diseases. However, these recommendations were not specifically targeted at childhood glaucoma. Limited long-term trends have shown that screening programmes such as the retinopathy of prematurity programme, now mandatory in several countries, may reduce the burden of disease and potential blindness.[21 22] As childhood glaucoma can constitute a multitude of ocular and systemic conditions, early examination of asymptomatic children in the population could potentially increase the chances of early detection and management of these conditions. However, the low incidence of childhood glaucoma means that many children would need to be examined (approximately 20 000–33 000) to detect a single case of childhood glaucoma and, from a public health perspective, the costs may not outweigh the benefits. A potential alternative to lower the cost and optimise delivery of these annual screenings would be to combine these visits with vaccination programmes or other currently implemented programmes.[23] It is also important to consider who will perform childhood eye screening or assessments. The two guidelines on paediatric eye evaluations from the USA recommends that primary care providers perform a basic eye screen of newborns and infants,[18 24] whereas it may be more appropriate for children at high risk of childhood glaucoma to be examined by an ophthalmologist in a secondary or tertiary care setting.

Tube surgery was strongly recommended by the Australian CPG for long-term IOP control of all glaucoma, including some childhood glaucomas. The remaining recommendations for management of childhood glaucoma made in this CPG were of weak or intermediate strength and generally had only low-quality evidence or were based on expert opinion. Furthermore, this Australian CPG was published 10 years ago and, based on the exclusion criteria for this review, is nearly out-of-date. Some recent evidence indicates that the IOP-lowering response to antiglaucoma drugs is often lower in children and thus surgical management is necessary.[18] It is also important to note that serious side effects can occur in children due to difference in drug pharmacodynamics and pharmacokinetics in children as compared with adults. Use of low-dose preparations, gel-based formulations, punctal occlusion during administration and frequent follow-ups can improve outcomes.[25] Notable interventions for which formal recommendations (for or against) were not made include trabeculotomy, goniotomy and topical brimonidine eye drops. These interventions were briefly and informally discussed within the Australian guidelines, but as no formal recommendation was made, did not meet the criteria for data extraction. The Australian guideline informally recommended against the use of alpha-2 agonists, such as brimonidine, in children <7 years of age due to side effects and informally suggested goniotomy or trabeculotomy as potential interventions for PCG. The absence of a formal recommendation for trabeculotomy or goniotomy may reflect uncertainty in the evidence for these interventions at the time, despite their current widespread use in clinical practice and recommended use for PCG in the WGA consensus guidelines.[7]

Childhood glaucoma is a rare, but devastating, disease. There is generally a lack of high-quality evidence to inform the management of childhood glaucoma and there are few recent, targeted CPGs. CPGs are uniquely situated to be able to combine evidence from a systematic search of the scientific literature and the opinion and experience of experts in the field. The latter is particularly important in childhood glaucoma, where the evidence is relatively sparse. The WGA consensus guidelines were an important step in providing guidance on the best-practice management of childhood glaucoma. However, there is need for a high-quality CPG, incorporating both expert consensus and a systematic search of the literature. Limitations to this study include the inclusion of only CGPs written in English in the last 10 years, which have limited the CGPs identified.

CONCLUSION

We identified three high-quality CPGs relevant to childhood glaucoma in this systematic review; however, none was specifically targeted at childhood glaucoma. There is a considerable lack of evidence-based guidelines to direct management of childhood glaucoma. A coordinated effort is needed to address this lack of quality data with standardised disease terminology and management strategies to improve outcomes for children with childhood glaucoma.

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