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Chapter

Childhood Glaucoma and Medical Treatment: An Up to Date

Antonio Greco, Marco Giuseppe Leto, Andrea Greco, Riccardo Merli and Agostino Salvatore Vaiano

Abstract

Successful treatment of paediatric glaucoma presents many challenges, with IOP control as the first but not the only priority. In paediatric cases medical therapy may play different roles: it could be an important tool for preparing patients for surgical intervention by clearing the cornea, it may help control IOP post-operatively or it may be the initial and often the mainstay pillar for clinical management. Besides inadequate IOP reduction, multiple factors conspire against the success of long-term medical therapy in paediatric glaucoma: the difficulties with long term adherence, more than in adults, adequate ascertainment of drug-induced side effects and potential adverse systemic effect of protracted therapy among others. Many medications are available for glaucoma management but many of them still carry a warning that “safety and efficacy in paediatric patients have not been established”. An “Up to date” of medical options for childhood glaucoma is the core aim of this chapter, hoping it could be useful for the daily clinical decision process.

Keywords: juvenile glaucoma, childhood glaucoma, glaucoma, paediatric glaucoma, therapeutic management, primary congenital glaucoma

1. Introduction

Treatment of paediatric glaucoma presents many challenges, with IOP control being the first but not the only priority. In paediatric cases, medical therapy may play different roles: it could be an important tool for preparing patients for surgical intervention by clearing the cornea, it may help control IOP post-operatively or it may be the initial step and often the mainstay of clinical management. In addition to inadequate IOP reduction, multiple factors conspire against the success of long-term medical therapy in paediatric glaucoma: these include, among other things, the difficulty of ensuring long-term patient compliance, which is a problem in children more so than in adults, and inadequate assessment of drug-induced side effects and potential adverse systemic effects of protracted therapy. Indeed, as pointed out in a review by Samant et al. in 2016 “the goal of medical therapy for glaucoma in children should be to achieve target IOP while minimizing side effects and maximizing compliance” [1]. The core aim of this chapter is to provide an “update” of medical options for childhood glaucoma, in the hope that it might be useful for everyday clinical decision making.
2. Definition, classification and epidemiology

Childhood glaucoma is a rare, heterogeneous group of diseases characterised by progressive ganglion cell loss, as in adult forms. Often vision-threatening, these diseases present special challenges in terms of diagnosis and management: the clinical presentation of glaucoma varies with the age of onset and the severity of IOP elevation and clinical examination, as well as the administration of drugs, may be exceedingly difficult. Several classifications of paediatric glaucoma have been proposed: differences are based on the chosen criteria, such as anatomical parameters, the age of onset, the presence/absence of associated systemic disorders and hereditary factors. Most classifications distinguish between primary and secondary glaucoma. Although this classification system is far from ideal, it is the one most commonly used, also because our somewhat limited knowledge today precludes a more meaningful conceptual classification.

The classification approved by the European Glaucoma Society is the following:

- **Primary glaucoma**: this category comprises cases in which a developmental abnormality of the structures of the anterior chamber angle leads to obstruction of normal aqueous outflow. Depending on the age of onset, a distinction can be made between primary congenital/infantile glaucoma (PCG) and juvenile open-angle glaucoma (JOAG). Three years of age is generally taken as the threshold between PCG and JOAG. It is common to distinguish among different forms of PCG: newborn (age of onset 0–1 month), infantile (age of onset 1–24 months) and, finally, late onset (age of onset 24–36 months) [2].

- **Secondary glaucoma**: this category includes glaucoma in which the outflow obstruction arises from multiple causes, including trauma, intraocular neoplasia, inflammation, lens-induced disorders, surgical interventions and so on. Within this group, the conditions may be divided into the following sub-groups: glaucoma associated with non-acquired ocular anomalies, glaucoma associated with non-acquired systemic disorders or syndromes, glaucoma associated with acquired conditions and Glaucoma following childhood cataract surgery.

According to a US population-based survey published in 2013, the incidence of paediatric glaucoma was 2.29 per 100,000 residents, and secondary glaucoma was the predominant type [3].

PCG occurs more frequently (1:1250–1:70,000) in Eastern Europe, in the Middle East, within the Roma population and in southern India, where parental consanguinity may play a role in the increased incidence [4–8].

There is no clear sex or racial-ethnic predisposition to PCG (except where consanguinity or a small population size may play a role).

Most PCG cases occur sporadically; only 10–40% of cases are familial, usually with autosomal recessive inheritance and variable penetrance [4–12]. Thus far, two main causative genes have been reported: the CYP1B1 gene, on the GLC3A locus, and the LTBP2 gene, possibly on the GLC3C locus [13–16].

3. Clinical features

PCG commonly presents bilaterally (65–85% of cases) [17, 18] although significant IOP elevation may occur in only one eye in 25–30% of cases. Several ocular
Childhood Glaucoma and Medical Treatment: An Up to Date
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features, with the exception probably of those emerging from gonioscopy, are not unique to PCG, as they may be a part of any childhood glaucoma occurring during the first few years of life. For example, it is common to observe, in all forms of glaucoma, an enlarged cornea (megalocornea, defined as a cornea wider than 13 mm in children) and high long axis-related myopia; these findings are attributable to the effect of an uncontrolled IOP on a more distensible eye in children than in adults. Stretching of the infant eye is not limited to the cornea and may involve the whole globe (AC angle structures, sclera, ONH) [19].

Infants with PCG usually undergo ophthalmologic evaluation because the paediatrician or the parents have noticed one or more of the following classic symptoms (triplet): epiphora, photophobia (which results from corneal oedema and is manifested by the child hiding his/her face when exposed to bright light or even just light in severe cases) and blepharospasm, which may be considered as another sign of photophobia. Other symptoms and signs that may manifest themselves include lack of eye contact, facial birthmarks, pupillary abnormalities and nystagmus, but these account for less than 2.3% of symptoms at first presentation [20]. The severity of presenting signs and symptoms varies among infants, probably as a function of the magnitude and duration of IOP elevation.

In children with glaucoma onset after 1 year of age, fewer signs and symptoms may occur due to decreased eye expansibility.

IOP measurement in an infant or child should ideally be performed in the doctor’s office so as to avoid causing trauma to the child, also because performing tonometry on an uncooperative child will invariably produce falsely elevated readings, which are not useful for the diagnosis of PCG or follow-up of an already diagnosed PCG. Handheld devices such as the Perkins, Tono-Pen and I-Care tonometers are useful in the case of babies, whereas in the case of more collaborative children older than 3 years of age a Goldmann applanation tonometer can be used. Infants with PCG commonly present with unanaesthetised IOPs in the range of 30–40 mmHg, although occasionally values above or below this range occur [9]. As in adults, the target pressures depend on the details of the particular case, although, as shown by G. Sinha et al. an IOP greater than 30 mmHg will result in a greater visual field loss. The most common visual field defect in PCG is arcuate scotoma, according to G. Sinha et al. [21, 22].

Measuring IOP under anaesthesia is sometimes necessary but should be combined, for the sake of convenience, with an overall assessment of the whole eye/eyes (optic nerve photographs, axial length and gonioscopy). When IOP is measured during general anaesthesia, account must be taken of the possible variations due to the anaesthetics used; the effect of the latter may be dose- and/or time-dependent.

Many paediatric anaesthesiologists routinely use inhalational agents (halogenated agents like isoflurane and sevoflurane) before obtaining intravenous access and placing an airway device. They are known to decrease IOP by suppressing the diencephalon, which has a direct effect on IOP [23]. Park et al. found a mild to moderate IOP decrease 3 min after administration of halogenated agents. Propofol, an intravenously administered sedative agent used commonly for maintenance, may cause a sharp IOP drop [24].

In the case of ketamine—which has been used routinely for procedural sedation in children [25]—the effects on IOP have not been so clearly determined: some suggest an increasing effect on IOP [26], probably by virtue of an increase in extraocular muscle (EOM) tone, whereas others report no effect [27, 28]. Another drug causing an IOP increase is succinylcholine; the increase is usually transient, with a peak at 20–30 s postinjection, and it is due to drug-induced EOM contraction as in the case of ketamine [29].
Midazolam is an anxiolytic and sedative often used as a preoperative medication in children. Most studies show no significant effect of midazolam on IOP [30]. Further information is given in the table below (Table 1).

In 2017 Mikhail et al. [30] identified a few rules for obtaining an accurate IOP measurement during an examination under anaesthesia (EUA):

- Midazolam should be considered for sedation, as it seems to have little or no effect on IOP;
- When inhalational agents such as sevoflurane or desflurane are used, their mild effect on IOP should be considered;
- If intubation is performed, wait at least 3–5 min before proceeding to measure the IOP (intubation stimulates the sympathetic system, resulting in an acute rise in IOP due to the increase in trabecular meshwork outflow resistance) [32];
- Applanation tonometry should be performed with a Perkins tonometer. The Tono-Pen may be used, bearing in mind that it might overestimate the IOP if the measurement is above 11 mmHg. Bordon et al. investigated the agreement between Perkins and the Tono Pen and reported comparable values in 77.8% of cases when the IOP ranged from 0 to 9.9 mmHg, in 67.5% of cases where the IOP was comprised between 10 and 20 mmHg and, finally, in 46.1% of cases in the range of 20.1–30 mmHg [33];
- Where possible, try to standardise EUAs using similar anaesthesia protocols and the same devices;
- If possible, a speculum should not be used during IOP measurement. Care must be taken while opening the eyelids to avoid undue pressure on the globe.

The role of central corneal thickness (CCT) evaluation in children as opposed to adults has yet to be determined: in several children with PCG, the CCT has shown to be smaller than in other children [34], but eyes with aniridia have a thicker central cornea than normal, as do eyes with aphakia, particularly those with aphakic glaucoma [33, 35–41].

Gonioscopy provides vital anatomic information about the mechanism of glaucoma in a given eye. The structures composing the angle in a healthy infant appear slightly different from those in a healthy adult eye: Schwalbe's line is less distinct, the trabecular meshwork (TM) is less pigmented and the junction between the scleral spur and ciliary body is less clear. In PCG infants the iris usually has an insertion that is more anterior to the TM, while the angle is usually avascular; anomalous iris vessels may also be seen as loops branching from the major arterial circle (MAC) (the so-called Loch Ness monster phenomenon) and the other structures seems to be covered by a translucent veil known as the Barkan membrane [42–45].

An evaluation of the optic nerve head (ONH) is of central importance also in paediatric glaucomatous patients, not only for the purpose of diagnosis but also for assessing the response to therapy; associated fundus abnormalities may sometimes help confirm the glaucoma type (for example a stalk in persistent foetal vasculature, foveal hypoplasia in aniridia or choroidal hemangioma in Sturge Weber syndrome). Like adults with glaucoma, children with PCG have an increased cup-to-disk (CD) ratio, but unlike in the case of the former, in children the cup enlarges circumferentially [46]. Cupping proceeds more rapidly in infants than in adults and it is reversible—though there are exceptions to the rule—if the pressure is lowered...
sufficiently, thanks to the high resilience of ONH connective tissue and the elasticity of the lamina cribrosa in children [47]. An improvement in ONH appearance does not necessarily lead to a visual field gain.

**4. Medical management: general considerations**

Although childhood glaucoma often requires surgery as soon as possible, goniotomy, trabeculotomy etc., medical therapy may in any case play different roles, e.g. in preparing patients awaiting surgery—according to data from the British Infantile and Childhood Glaucoma (BIG) Eye Study, 81% of PCG subjects had medication before an operation—and aiding in the management of IOP post-operatively, and it may be the initial and often the mainstay therapy for juvenile open-angle glaucoma and other secondary forms of glaucoma, such as those occurring in aphakia or with uveitis. In children with glaucoma, medical therapy is used more often in the management of secondary glaucoma rather than the primary congenital form; however, IOP is successfully controlled (the goal being to reach a pressure less than or equal to 21 mmHg) through the administration of drugs alone in only 32% of patients with the congenital form, while the same target is reached in 86% of cases with a secondary childhood glaucoma, according to data from the BIG Eye Study [2]. Multiple factors conspire against the success of long-term medical therapy in paediatric glaucoma: the difficulty of ensuring long-term adherence to treatment protocols, a bigger problem in children than in adults, inadequate assessment of drug-induced side effects and potential adverse systemic effects of protracted therapy, among others.

A large variety of drugs are available for intraocular pressure control but little is known regarding their use in the paediatric population; there is scarce evidence, especially as regards the latest prostaglandin analogues (tafluprost), or none at all, as in the case of the newest Rho kinase inhibitors. This is partly due to the
secondary role covered by medical therapy in children and partly to greater difficulties in conducting prospective studies due both to ethical issues and to intrinsic difficulties in their evaluation. Moreover, changes in the European regulatory framework were introduced in 2007 (Official Journal of the European Union, Regulation (EU) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use) with the aim of ensuring that paediatric medicines were subject to research of high quality; this changed the clinical and pharmaceutical practice of prescribing medicines to children in Europe.

At present, few data are available from prospective clinical trials on the efficacy and safety of a defined therapeutic scheme for the medical management of paediatric glaucoma; to our best knowledge, the Glaucoma Italian Paediatric Study (GIPSy) is the only interventional study where a predefined therapeutic scheme seemed to be effective in the management of PCG (the sample included patients in whom IOP was insufficiently controlled after a single surgical procedure) [48].

This review provides an overview of the latest evidence available in the literature for every category of drug used in paediatric glaucoma treatment, as well as the more promising prospects in this field.

5. Carbonic anhydrase inhibitors

5.1 Specific Drugs: Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors reduce the secretion of the hydrogen ion and increase the excretion of bicarbonate, potassium, sodium, and water, which in turn decreases aqueous humour secretion [49].

They are metabolised in the liver by cytochrome P450 and afterwards excreted principally with urine. They are the only class of anti-glaucoma drugs available for both oral and topical administration, but to date none have been licenced for use in glaucomatous children. Oral intake also produces slight diuresis.

Systemic CAIs are usually administered in addition to a topical treatment, but their side effects limit their use. The recurrence of side effects in the paediatric population has not been clearly determined due both to the wide spectrum of their manifestations and the lack of prevalence studies in this particular group. According to Moore and Nischal, they occur in more than 40% of cases: headache, dizziness, paraesthesia, asthenia, nausea, epistaxis and hypersensitivity reactions (including urticaria, angioedema and bronchospasm), just to mention a few. Although in adults the risk of aplastic anaemia has been reported to increase with higher intakes, this does not seem to be the case in children [50]. Metabolic acidosis may occurs in infants and toddlers; its manifestations include rapid breathing, poor feeding and poor weight gain and may be somewhat ameliorated with oral sodium citrate and citric acid oral solution (Bicitra, 1 mEq/kg/day) [9].

In 2010 Sharan et al. retrospectively evaluated the weight gain in 22 patients who had been taking acetazolamide orally for three months at least; the purpose was to detect the real impact on growth of the intake of CAIs, growth retardation being the largest complaint made by several paediatric ophthalmologists. According to their results "acetazolamide does not cause significant weight changes in cases of pediatric glaucoma" [51].

In patients aged 1 month to 12 years acetazolamide is well tolerated when administered orally with food or milk three or four times daily (dosage 10–20 mg/kg, maximum daily dosage 750 mg); in teenagers the recommended daily dosage is 0.5–1 g [20, 50]. According to Portellos et al., the mean IOP reduction with systemic therapy
was approximately 35%, compared with 25% for topical therapy [52]. In a series of 22 paediatric glaucoma patients aged 8 months to 15 years, a combined administration of topical and systemic CAIs was reported to reduce IOP further than when either drug was used alone [20]. Oral or intravenous CAI administration is contraindicated in patients with meiopragic kidneys, hypokalaemia or hyponatraemia or metabolic acidosis. Allergy to sulfa drugs should be evaluated due to hypersensitivity cross-reactions.

Topical CAIs, such as dorzolamide, are an effective alternative to oral acetazolamide, as they are well tolerated and have a greater IOP-lowering effect in children than in adults [20]. In one study the effectiveness of brinzolamide was compared to that of levobunolol in children with glaucoma younger than 6 years of age; both drugs were well tolerated, but a greater efficacy of brinzolamide was shown in patients with glaucoma associated with systemic disorders (e.g. Sturge-Weber syndrome) or ocular abnormalities than in patients with primary congenital glaucoma [52]. Dorzolamide should be avoided in children with a compromised cornea due to the risk of irreversible corneal decompensation [53].

5.2 Beta-adrenergic antagonists

Since the introduction of timolol in 1978, B-blockers have played a central role in glaucoma treatment. Controlling aqueous humour production is the main purpose of this class of drugs: the influence of these agents on aqueous formation may be related to inhibition of the catecholamine-stimulated synthesis of cAMP, as has been demonstrated in rabbit studies [54, 55].

The drugs belonging to this group can be split into different categories according to the presence or the absence of selectivity for a specific adrenergic sub-receptor type and the presence or the absence of an intrinsic sympathomimetic activity (ISA) [further information is shown below in Table 2].

There have been a number of studies concerning the treatment of paediatric glaucoma with timolol. In many cases, timolol was added as an adjunct to other IOP-reducing drugs the children were already taking for their glaucoma; only a few studies evaluated the effect of timolol alone [56–60]. As noted by Plager et al. in 2009, “published works were not, for the most part randomized, masked clinical studies” [61].

Timolol is commercially available at 0.1, 0.25 and 0.5% concentrations in aqueous and gel-forming solution. The drop in IOP seems to be between 20 and 25% [56, 57, 59–63], even though different types of paediatric glaucoma may respond differently (or not at all) [63, 64]: for example, in a double-masked, randomised study comparing a 0.5% levobetaxolol suspension to a 1% brinzolamide suspension, J.T. Whitson et al. found the former drug to be more efficacious in subjects with primary congenital glaucoma and less efficacious in secondary glaucomas, especially in aphakic glaucoma, which was the prevalent type in that study [54]. According to Boger and Walton, timolol provides a good or at least modest benefit in patients with several categories of glaucoma including, primary congenital glaucoma, aniridia and congenital rubella syndrome [60]. A betaxolol-based treatment was reported by Awad et al. to be a successful therapy for a patient with Sturge-Weber syndrome, especially in combination with the administration of dipivefrin or pilocarpine [65].

The incidence of systemic side effects reported in the literature varies from 0 to 18% [58–62]; the most frequently recurring ocular side effects are tearing and eye itching, whose prevalence has been determined as 2% and 4% respectively [59]. The most severe systemic adverse effects in children receiving topical B-blockers like timolol include asthma attacks, bradycardia and apnoeic spells (the latter in neonates) (cf. Figure 1) [58–62, 67]. In children, plasma timolol levels reach higher values than in adults [1], probably due to the smaller volume of distribution for the drug. That is
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Indications</th>
<th>Effect</th>
<th>Side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>First-line therapy for many</td>
<td>IOP reduction: 20–25% from baseline</td>
<td>Systemic: incidence 0–18%, include bronchospasm and bradycardia. Local: incidence 2–4% tearing and eye itching</td>
<td>Avoid in premature or tiny infants and in children with a history of reactive airways disease</td>
</tr>
<tr>
<td>Only topical</td>
<td>B.I.D. (if a solution) Q.D. (if a hydrogel formulation)</td>
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<td>Selective and non-selective, with or without ISA</td>
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<tr>
<td></td>
<td>B.I.D.</td>
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<td>Q.D.</td>
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<tr>
<td></td>
<td>Safer start with lower concentration (0.25%)</td>
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<tr>
<td><strong>Carbonic anhydrase inhibitors</strong></td>
<td>First-line therapy in young children Add well to other classes</td>
<td>IOP reduction: 35% from baseline for systemic therapy, 25% for local therapy</td>
<td>Systemic: occur in more than 40% of cases; they include headache, dizziness, paraesthesia, asthma, nausea, epistaxis and hypersensitivity reactions. Metabolic acidosis +++ in infants and toddlers → Bicitra, 1 mEq/kg/day should be considered as an antidote to poisoning Local: dorzolamide stings</td>
<td>Topical: systemically safe but is to be avoided in compromised corneas Systemic therapy is to be avoided in patients with meiopragic kidneys, hypokalaemia or hyponatremia, metabolic acidosis or allergy to sulfa drugs due to cross reaction hypersensitivity manifestations</td>
</tr>
<tr>
<td><strong>Topical</strong> (dorzolamide and brinzolamide)</td>
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<tr>
<td>B.I.D. or T.I.D. (acetazolamide) 1 month to 12 y.o. 10–20 mg/ kg [maximum daily dosage 750 mg/]; in teenagers the recommended daily dosage is 0.5–1 g</td>
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<tr>
<td><strong>Prostaglandins and prostamide</strong></td>
<td>Second or third-line therapy but the newest data from the literature suggest they may also be used as a first-line therapy</td>
<td>IOP reduction: contradictory data, from poor to no effect to more or similar to B-blockers</td>
<td>Systemic: none (just one case of heavy sweat secretion reported in the literature) Local: frequent changes in iris colour (especially in the case of mixed-colour irides), blepharitis, ocular irritation and pain, darkening, thickening and lengthening of eyelashes</td>
<td>Avoid in cases of uveitic glaucoma</td>
</tr>
<tr>
<td>Topical Q.D</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Adrenergic agonists</strong></td>
<td>Preferentially in older children as a second- or third-line therapy Helps during/after angle surgery in the short term</td>
<td>IOP reduction:</td>
<td>Systemic: hypothermia, dizziness, agitation, ataxia, coma, apnoea, hypertension, hypotension, bradycardia, respiratory depression, respiratory failure, and death Local: allergy or red eye</td>
<td>To be avoided in cases of low weight (&lt;20 kg) and a very young age (&lt;6 y.o.), do not use in addition to B-blockers</td>
</tr>
<tr>
<td><strong>Topical</strong> (apraclonidine and brimonidine)</td>
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<tr>
<td>B.I.D. or T.I.D.</td>
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why it is reasonable to begin with 0.25% drops (the lowest concentration is preferred in order to reduce systemic side effects) [68, 69], except in children with a history of asthma or bradycardia; upon the first administration on an outpatient basis, children

Table 2.
Indications, side effects and warnings for main drugs used in the management of paediatric glaucoma.

![Table 2](https://www.intechopen.com/images/doi/10.5772/intechopen.100579)

Figure 1.
Simplified scheme showing the origin of systemic effects of B-blockers after local ocular administration. CYP2D6 is a member of the cytochrome P450 superfamily and it plays a primary role in the metabolism of about 25% of the commonly prescribed drugs, including timolol and related compounds. Adapted from [66].
should be kept under observation for 1 or 2 h. Less frequent systemic side effects are hallucinations, light-headedness, depression, fatigue, diarrhoea and masking of symptoms of hypoglycaemia in children with diabetes mellitus [54, 70]. In 2007, T. Nieminen et al. reported that using a timolol hydrogel formulation in adults once daily resulted in lower plasma levels compared to when a timolol solution was used twice daily [66].

Other B-blockers available for clinical use in children are betaxolol (0.25% suspension and 0.5% solution, twice daily), levobunolol (0.5%, twice daily) and carteolol (1 and 2%, twice daily) [1].

Betaxolol, as a relatively cardioselective beta-adrenergic blocker, should be preferred in patients with a history of asthma, as it is less likely to trigger acute asthma attacks (which may also present just as coughing), although this finding has been confirmed in published studies that have investigated adults.

In children as in adults, CAI drugs, administered either orally or topically, have an additive effect when administered together with B-blockers compared to B-blockers alone [20, 61]. The two greatest limitations in using B-blockers in paediatric glaucoma seem to be the risk of apnoea developing in neonates—a life-threatening situation—and tachyphylaxis after long-term administration, which causes a loss of efficacy as in adults [46].

5.3 Adrenergic agonists

Both alpha-adrenergic and beta-adrenergic receptors, as parts of the sympathetic nervous system, play a major role in regulating aqueous humour production and dynamics. The pharmacological development of this class of drugs was based on the observation that topical administration of clonidine (an antihypertensive agent) also lowered IOP [71]. The discovery of clonidine’s ability to penetrate the blood-brain barrier, thus causing significant systemic hypotensive episodes, even after topical administration alone, limited its clinical use and led to research aimed at developing agents selective for a specific sub-receptor type (alpha 2), now available for clinical use: brimonidine and apraclonidine.

Their mechanism of action consists in reducing humour aqueous production; moreover, these agents have only a slight, if any, effect on blood-aqueous barrier permeability [72, 73]. Speculations have been made regarding a possible role played by these agents in regulating the facility of outflow through the trabecular meshwork, given the presence of alpha 2A-adrenergic receptors in the latter, but there is no supporting evidence [74, 75].

However, there are few published data suggesting optimal dosing schedules for paediatric patients and, as observed by M. Lai Becker et al. in 2009: “because these drugs are instilled into the eye, dosing is uncontrolled, and a child may inadvertently receive a higher-than-intended dose per unit body weight. In addition, systemic absorption through the conjunctiva may be more rapid and complete in children than adults” [76]. So despite their greater selectivity or their effectiveness, shown in adults, in bringing about an IOP reduction, these drugs are relegated to a secondary (second- or third-line) role in paediatric glaucoma control because of their potential systemic side effects, including hypothermia, dizziness, agitation, ataxia, drowsiness, coma, apnoea, hypotension, hypertension, bradycardia, respiratory depression, respiratory failure, and even death, especially when combined with topical beta-blockers [77–82]. Ocular side effects like irritation, reactive hyperaemia, adrenochrome deposits, stinging/burning, eye itching/rubbing, conjunctival follicles and eye discharge have been reported, just to name a few. Most of the time, the adverse events occur within a few hours of administration of the drops. There has been a great deal of speculation about the reasons for the increased sensitivity to brimonidine in infants; their small
size, their lesser ability to metabolise and excrete drugs, their immature blood-brain barrier or their increased receptor sensitivity seem to be the most likely [81, 83, 84].

According to data collected from different studies, it seems that the frequency of side effects increases with low weight (<20 kg) and very young age (<6 y.o.) [81, 85, 86].

Neither of the two commercially available alpha2-adrenergic agonists, apraclonidine and brimonidine, have been approved by the U.S. FDA.

There has been much speculation about naloxone, an opiate antagonist, and its role in treating alpha2-adrenergic agonist poisoning; the data in the literature are contradictory: some authors have reported efficacy [87–89], whereas others were disappointed with the results [90, 91].

In 2009 M. Lai Becker et al. conducted an interesting retrospective study in order to determine the recurrence of and trends in side effects and the actual role of naloxone as an antidote in cases of poisoning by brimonidine. They retrieved and examined data on all brimonidine exposures in children aged 0–5 years between 1997 and 2005 from the American Association of Poison Control Centers’ Toxic Exposure Surveillance System (TESS) database and the US Food and Drug Administration’s Medwatch Adverse Events Reporting System (AERS). Out of 753 reports to both authorities, they selected 200 cases involving children aged 5 years or younger, 185 from the TESS database and 15 from the AERS; there was no overlapping among the selected cases. Of 176 unintentional paediatric poisonings recorded in the TESS database, 73 children were observed at home and 103 were seen at a health care facility; 28 were hospitalised and 11 received naloxone; of the reports included in the AERS database, all the children concerned were hospitalised. In the latter system 13 (86.7%) of 15 cases involved ocular exposures and presumably adverse events occurred during therapeutic use of the drug. By contrast, only 17 (9.2%) cases from the former database involved ocular exposures. According to TESS data, 2-year-old children were most vulnerable to brimonidine poisoning.

The authors concluded that “Infants and children aged 5 years and younger can experience serious cardiovascular and neurologic toxicity after inadvertent exposure to brimonidine-containing eye drops, and medical evaluation of such cases seems prudent. Although naloxone was recommended in 10% of serious brimonidine intoxications, its role and efficacy remain unclear” [76].

5.4 Cholinergic stimulators

The use of these drugs, often called simply miotics, has been largely supplanted by the administration of other medications and their use in the treatment of childhood glaucoma, as in the adult form, have a limited value. The IOP reduction they bring about is generally poor, probably due to the abnormal insertion of the ciliary muscle into the trabecular meshwork, a frequent finding in paediatric glaucomatous patients [92, 93]. Pilocarpine is used to achieve and maintain miosis before and after surgical procedures (in goniotomy or trabeculotomy, miosis is important for keeping the angle wide and thereby aiding in protecting the crystalline lens from injury during the procedure) except in cases of uveitic glaucoma [94].

Ecothiopate iodide (EI or phospholine iodide) is a “stronger” miotic than pilocarpine, because it is a long-acting cholinesterase inhibitor; in children it may be used in the management of accommodative esotropia [95]. In 2016 M. Samant et al. mentioned a recent study where EI was used in aphakic glaucoma patients and determined a significant reduction in IOP [2, 96]. In most of the patients in the cited study, this drug was given as an additional IOP-lowering agent and the mean duration of treatment was 3.5 years. In their review M. Samant et al. noted that the study failed to discuss the significant side effects of EI in both children and adults;
the most recurrent side effects are ocular pemphigoid—induced with long-term use of this drug (minimum 6 years)—bronchospasm, cystoid macular oedema, and prolongation of anaesthetic agents, specifically succinylcholine, which have been reported to cause post-anaesthesia apnoea [2].

5.5 Prostaglandin analogues

Prostaglandin analogues (PGA) are prodrugs that become biologically active after being hydrolysed by corneal esterase. These drugs lower IOP by increasing outflow via the uveoscleral pathway and, to a variable extent, decreasing outflow resistance through a mechanism that has not been fully determined. It is thought that the ocular hypotensive prostaglandin analogues bind to various prostaglandin receptors, triggering a cascade of events that leads to matrix metalloproteinase activation. The increase in the volume of aqueous flow is probably due to the remodelling of the ciliary body, trabecular meshwork and probably also of the scleral extracellular matrix, as a result of the action of the metalloproteinases. Several studies have shown that a topical prostaglandin analogue-based therapy results in an increase in the space between the muscle fascicles within the human ciliary body, which is thought to be the primary location of uveoscleral outflow [97–100].

These agents are all administered once daily, preferably in the evening; another undoubtable advantage is represented by the extremely rare occurrence of systemic side effects [101, 102]: there is only one case report in the literature, as observed by Samant et al. in 2016, of abundant sweat secretion over the entire body in a child with coexisting glaucoma and aniridia within 1–2 h of latanoprost application [103]. However, prostaglandin analogues have numerous local side effects including a possible change in iris colour (particularly in patients with mixed-colour irides) [104], blepharitis, ocular irritation and pain, darkening, thickening and lengthening of eyelashes and transient punctate epithelial erosion. Less common are eyelid oedema and rash and, more rarely, darkening of palpebral skin has been reported [105].

The relationship between prostaglandin analogues and development of cystoid macular oedema (CME) in adults is still a matter of debate: several authors did not find any causative connection [106, 107], also after an uncomplicated phacoemulsification [108, 109], but there are also many important studies providing evidence of a role of a prostaglandin-based therapy in altering the blood-retinal barrier [110, 111] and consequently in CME determination. There is ample evidence in the literature of an already existing impairment of the blood-aqueous barrier in patients with glaucoma [112–116], suggesting that being glaucomatous is in itself likely to represent a risk factor for developing CME, especially after interventions like phacoemulsification [117]. As long as there is a lack of prospective studies, the debate on prostaglandin and the connection with CME in adults will continue. To the best of our knowledge, no prevalence or incidence studies analysing this connection in paediatric samples have been carried out.

Strong evidence based on reproducible data from challenge-dechallenge-rechallenge studies has attested to a connection between anterior uveitis and prostaglandin analogue use [118, 119]. Interestingly, patients with glaucoma and previous anterior uveitis do not seem to be at risk of topical prostaglandin-induced uveitis [120]. In a recent review focusing on drug-induced uveitis, the authors associate the concomitant use of corticosteroids and/or other immunomodulatory agents with the reduction in the risk of side effects from prostaglandins [121].

In a review published in 2007, Moore and Nischal [50] wrote: “[…] it is suggested that they [prostaglandin analogues—ed.] should not be used within 5 min of the use of thimerosal-containing preparations.” However, a search in the literature
database reveals nothing about a possible bad interaction between thimerosal and prostaglandin analogues.

Various different types of prostaglandins are available for clinical use: latanoprost, travoprost, bimatoprost and tafluprost; despite this variety, latanoprost still accounts for more than 65% of prostaglandin analogue prescriptions [2].

The authors of several studies evaluating the effectiveness of prostaglandin analogues and prostadime medications judged them to be less effective in children than in adults with open-angle glaucoma [65, 122–126]. But not all data are in agreement with this assessment: in the Glaucoma Italian Paediatric Study (GIPSy), the authors found, in a relatively long-term follow-up (3 years), that PGA was efficacious in 57.6% of cases, with a mean IOP reduction of 9.7 mmHg with latanoprost as a monotherapy [46]. In 2013 L. Chang et al., who analysed the database of the Paediatric Glaucoma Service of Moorfields Eye Hospital, observed that PGA and prostadime were as effective in lowering IOP as beta-blockers (the median percentage IOP-lowering effect of PGA and beta-blockers used in monotherapy was −17.2% and −17.7%, respectively) [127, 128]. A prospective, randomised, double-masked multicentre study was conducted in 2011 by T. Maeda-Chubachi et al., who compared the efficacy of latanoprost 0.005% and timolol 0.5% (0.25% for patients aged <3 years) in a sample of children with glaucoma (both primary and non-primary forms were included); they found the former drug to be either more effective than the latter or similarly effective (mean IOP reduction 7.2 mmHg for latanoprost and 5.7 for timolol), with a greater effectiveness of latanoprost in patients with a non-primary congenital form of glaucoma [129].

These contradictions in the data probably arise because the IOP-lowering effect of glaucoma drugs might sometimes be masked in patients with a more aggressive form of the disease, but they might also be due to the fact that a wide spectrum of clinical pictures is included under the heading of paediatric glaucoma and different glaucomas may respond to treatment in different ways.

Latanoprost has been the subject of several studies and has shown excellent results in lowering IOP in JOAG and aphakic glaucoma, while poorer efficacy has been found in paediatric glaucoma associated with other ocular disorders or in the primary form [129–131].

In 2017 Journal of AAPOS published a study comparing the efficacy of travoprost and timolol in a paediatric population (age range 2 months to less than 18 years) with different forms of glaucoma or ocular hypertension. Out of the 157 patients included in the study (mean age 9.6 years), 77 received travoprost and 75 timolol; the patients were evaluated at 2 weeks, 6 weeks, and 3 months after treatment. The efficacy of both drugs showed to be comparable, with a mean IOP drop of −5.4 mmHg for travoprost and −5.3 mmHg for timolol [132, 133].

To the best of our knowledge, there do not exist any studies evaluating the effectiveness of bimatoprost or tafluprost in a paediatric sample.

5.6 Rho kinase inhibitors

The Rho kinase (ROCK) signalling pathway is involved in several cellular events (cell proliferation, cytoskeleton modulation) and in the human eye it has been identified as an important regulator of trabecular meshwork outflow.

In December 2017, the FDA approved netarsudil for the treatment of elevated intraocular pressure (IOP) caused by open-angle glaucoma or ocular hypertension. It is the first drug of this class. Approval was based on 2 phase III clinical trials (Rocket 1 and Rocket 2), with 1167 patients enrolled, where the effect of netarsudil was compared to that of timolol. Patients were randomised to receive netarsudil once daily (Rocket 1 and Rocket 2) or b.i.d. (Rocket 2 only). Treatment with
netarsudil once daily produced clinically and statistically significant reductions of IOP from the baseline value \((P < 0.001)\) and was not inferior to timolol [134].

In glaucoma patients with the primary congenital form, the trabecular meshwork is often anomalous not only in terms of its functional properties, but also in its anatomic configuration, so this class of drugs will probably not have any application in clinical practice. Their action on cell proliferation and on cytoskeleton modulation must be considered, so it is impossible to rule out in any case that Rho kinase inhibitors might properly treat these glaucoma forms. This is only a speculative consideration that does not find any support in the literature and their role in both paediatric and adult glaucoma remains to be seen.

6. Discussion

Medical therapy may play different roles in the management of paediatric glaucoma: it may be a useful instrument for preparing patients for surgical interventions—such as goniotomy, through clearing of the cornea—it may help to control IOP post-operatively and it may be the initial and often the mainstay therapy for juvenile open-angle glaucoma and other secondary forms of glaucoma such as those occurring in aphakia or with uveitis.

According to the main international guidelines, such as the World Glaucoma Association’s “Medical Management of Glaucoma in Infants and Children”, carbonic anhydrase inhibitors are considered as first-line drugs for proper IOP control in children. Their importance is also due to the fact that CAI inhibitors may be administered topically and orally, though systemic administration might give rise to some major side effects such as dizziness, paraesthesia, epistaxis and hypersensitivity reactions (including urticaria, angioedema, bronchospasm), just to mention a few, while metabolic acidosis may represent a worrying risk in toddlers. Another concern regards the influence of CAIs on weight gain and consequently subsequent growth in this latter group of patients, but there is no evidence to support this fear.

Timolol and others B-blockers play a central role in the treatment of both paediatric and adult glaucoma patients. Several pieces of evidence show that B-blocker therapy provides a good or at least modest benefit in patients with several categories of paediatric glaucoma, including the primary congenital form, aniridia and congenital rubella syndrome. In view of children’s smaller volume of distribution, it is probably advisable to use the lowest concentration solution, as severe systemic adverse effects, including asthma attacks, bradycardia and apnoeic spells—life threatening situations—may otherwise occur. That is why it is reasonable to exclude children with a history of asthma or bradycardia and to keep children under observation for 1 or 2 h children at the first administration in an outpatient setting.

Prostaglandin analogues and prostamide medications are commonly judged to be less effective in children than in adults with open-angle glaucoma and in several prominent outpatient paediatric clinics like Moorfields, they are recommended as a second-line therapy. However, several recent studies have shown an excellent result in terms of lowering IOP in JOAG and aphakic glaucoma; indeed, these drugs proved to be more effective than B-blockers or similarly effective, while the poorest efficacy was found in paediatric glaucoma associated with other ocular disorders or in the primary form.

Latanoprost is by far the most widely prescribed PGA and has also been studied in a paediatric sample; to the best of our knowledge, there do not exist any studies evaluating the efficacy of bimatoprost or tafluprost in a paediatric patient.

Brimonidine and apraclonidine, alpha-adrenergic agonists, are relegated to a secondary role in paediatric glaucoma control because of their potential severe systemic side effects, including hypothermia, coma, apnoea, hypotension,
hypertension, bradycardia, respiratory depression, respiratory failure, and even death, especially if combined with topical beta-blockers. It seems that the frequency of adverse side effects increases with low weight (<20 kg) and a very young age (<6 y.o.).

There has been much speculation surrounding the opiate antagonist naloxone and its role in treating alpha2-adrenergic agonist poisoning. The data in the literature are contradictory, and a large study on this subject conducted by M. Lai Becker et al. [76] in 2009 did not reach a definitive conclusion as to its efficacy.

Miotics occupy a marginal role in the management of paediatric glaucoma and they are primarily used to achieve and maintain miosis before and after surgical procedures in order to protect lenses from accidental injuries.

Rho kinase (ROCK) inhibitors represent the newest class of drugs used for managing glaucoma; their role in paediatric glaucoma remains to be seen.

Even children whose glaucoma is well controlled through therapy require life-long follow-up. Loss of IOP control may occur months or even decades after initial successful control and may be asymptomatic in older children or young adults; progressive myopia, progressive optic nerve cupping or an increase in corneal size constitute indirect signs of inadequate IOP control.
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