Long-term perimetric stabilization with a management algorithm of set target intraocular pressure in different severities of primary angle-closure glaucoma

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Purpose: To evaluate long-term perimetric stabilization at set Target (IOPs) in primary angle-closure glaucoma with visual field defects. Methods: Two hundred forty-eight eyes, of 124 primary angle-closure glaucoma (PACG) patients on medical treatment, and 124 eyes, of 95 patients after trabeculectomy performed at least 5 years prior were evaluated. One hundred eighty-five eyes had a follow-up of ≥10 years. Target IOPs for mild, moderate, and severe glaucomatous optic neuropathy were set at ≤18, ≤15, and ≤12 mmHg, respectively. Progression was evaluated by event-based changes on guided progression analysis. Primary outcome measure was therapy required to achieve individualized Target IOP. Secondary outcome measure was assessment of perimetric change over time. Results: Mean baseline IOP was 23.34 ± 6.16 mmHg in medically treated and 36.08 ± 9.73 mmHg in surgically treated eyes (P = 0.0001). All eyes with a baseline IOP of ≤25 mmHg were on medications alone, 65.53%, of those with a baseline IOP of 25–30 mmHg were on medications, while 34.67% required trabeculectomy. In total, 91.4% of eyes with a baseline IOP of >30 mmHg underwent a trabeculectomy for achieving Target IOP. Perimetric stabilization was achieved in 98.17% of PACG eyes. “Target” IOP was achieved for mild, moderate, and severe glaucomatous optic neuropathy, medically in 90.2, 73.9, and 29.7%, and surgery was required in 9.8, 26.1, and 70.3%, respectively. Overall analysis found that percentage reduction in IOP was significantly more after trabeculectomy than medical treatment, 64.16 ± 14.91 and 43.61 ± 13.73%, P = 0.0001. Decrease in IOP was significantly greater 5–9 years after trabeculectomy, in comparison to ≥10 years, P = 0.001. Conclusion: Medications controlled IOP to “Target” in PACG eyes with mild and moderate glaucoma for over ≥10 years, when the baseline IOP off treatment was <30 mmHg. Trabeculectomy was necessary in PACG eyes having severe glaucomatous optic neuropathy, or with a baseline IOP of >30 mmHg to achieve Target IOP. These appropriate initial therapeutic interventions and Target IOPs are therefore suggested as a clinically validated algorithm of care for different severities of PACG.

Key words: Management algorithm, primary angle-closure glaucoma, Target IOP

Primary angle-closure glaucoma (PACG) is a common cause of irreversible visual loss, especially in Asians.[1,2] There have been large strides in its epidemiology and understanding of pathogenesis; however, long-term studies of response to different therapies and prognosis are few.[3,4] In primary open angle glaucoma (POAG) randomized control trials[5–7] have provided therapeutic guidelines for different stages of glaucomatous damage. The Collaborative Initial Glaucoma Treatment Study (CIGTS), Early Manifest Glaucoma Trial, and Advanced Glaucoma Intervention Study (AGIS) reports have presented an insight into the efficacy of medical, laser, and trabeculectomy in POAG.[3,4,5,6] However, long-term, clinically applicable algorithms of care for PACG are necessary.

There are some studies on “Target” intraocular pressure (IOP) or percentage reduction in IOP for different severities of PACG;[6,9] however, long-term management in PACG with medications or surgery needs further elucidation. PACG eyes have been shown to have higher IOPs than POAG and progress faster to blindness. Medical therapy alone may be unable to achieve mandated IOP in all, while trabeculectomy is feared to have an increased risk of postoperative shallow anterior chamber (AC), malignant glaucoma, or cataract formation.[10–15] Therefore, an early decision about appropriate Target IOP and initial medical versus surgical treatment is of crucial importance at different severities of PACG, which would prevent progression.

An additional IOP lowering of only 1.18 mmHg after cataract surgery has been reported by the EAGLE study,[16] as compared to iridotomy in PACG, with the authors themselves explaining that this small fall was “unlikely to be clinically relevant.” Thomas et al. found a fall in IOP of 2–6 mmHg after cataract surgery in chronic PACG, which was inadequate to

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reduce the high-baseline IOP in such eyes.\(^{[17]}\) Therefore, filtering surgery is required to control IOP to Target levels in chronic PACG having visual field defects.

This study was done to evaluate PACG eyes after iridotomy, for long-term stabilization of visual fields on medical therapy and/or after trabeculectomy, aimed to achieve an individualized “Target” IOP commensurate with baseline severity of glaucomatous damage.\(^{[8,18]}\) This would provide an algorithm of care in PACG eyes. A comparison of outcomes between 5 and 9 years and ≥10 years was done to identify significant time points, if any, for the rise of IOP, complications, or progression on perimetry.

**Methods**

All consecutive adult PACG patients reviewing regularly with a single glaucoma-specialist for at least 5 years were identified over 2018–2019. Institutional-Ethics-Board approval was obtained for an ambispective cohort study (Ref. No.: IECPG-395/2018), with written, informed-consent taken. The study adhered to tenets of the Declaration of Helsinki.

Baseline inclusion criteria were: phakic eyes with a chronically elevated IOP of >21 mmHg on >3 occasions, occludable angles with peripheral anterior synechiae extending over at least 180°, presence of optic nerve cupping >0.7 with NRR loss, and corresponding glaucomatous VF changes. Exclusion criteria included acute/secondary angle closure, any other retinal/optic nerve disorder causing perimetric defects, any prior ocular surgery, and those not on follow-up >5 years.

Details of a standardized baseline examination by a single consultant, best-corrected visual acuity (BCVA), gonioscopy, optic nerve head status, IOP off medication (baseline IOP), glaucoma medications used, perimetry, and ophthalmic/systemic records were noted in a uniform format from hospital records. Drug-related side effects, trabeculectomy or cataract surgery, any early/late postoperative complications, interval since trabeculectomy, and any further surgical interventions were recorded. All patients were managed as shown in Fig. 1.

The efficacy of therapy, medical or surgical, over >5 years was ascertained by a regular focus on achieving a “Target” IOP based on baseline Hodapp Parrish Anderson classification for glaucomatous severity: mild, moderate, and severe.\(^{[19]}\)

Indications for trabeculectomy were an IOP uncontrolled on maximal tolerated medical therapy or perimetric progression. A trabeculectomy with adjunctive mitomycin-C (MMC), was performed under peribulbar block. Mannitol was given 30 min before surgery. A 6–8 mm high limbus-based conjunctival flap was raised and cellulose acetate sponge soaked in MMC 0.2 mg/mL applied for 1 min subconjunctivally. The AC was maintained with air after doing paracentesis. A 4 × 4 mm superficial scleral flap and 3 × 1 mm ostium were made. A peripheral iridectomy was done and scleral flap closed with two 10-0 nylon buried sutures. Box-type releasable sutures, modified Wilson’s

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**Figure 1:** Overview of the management for primary angle-closure glaucoma patients

- **Medications**
  - Pilocarpine + PG analogue/ Timolol → Add on Brimonidine/ CAI

- **Nd YAG iridotomy**

- **Diurnal phasing/ Perimetry**

- **Target IOP:** <18, <15, <12 mmHg for mild, moderate & severe PACG

- **Target IOP achieved/ No side effects**
  - IOP review at peak times for 1 month
  - Review 3 months
  - Review 6/12 (Perimetry & tonometry)

- **Target IOP not achieved**
  - Trabeculectomy with MMC 0.02% for 1 min
  - F/u day/ 1 week/ 6-8 weeks
  - Review 3 months
  - Target IOP at diurnal peak

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technique, were used in all patients [Fig. 2]. The conjunctiva was sutured with continuous 8–0 Vicryl, hitching it to the episclera 8 mm from the limbus. Postoperatively, antibiotic-steroid and tropicamide drops were prescribed for 6–8 weeks. Both releasable sutures were removed within 3 weeks of surgery.

Perimetry was performed using 30–2 full threshold/SITA standard on Humphrey field analyzer, HFAII-i Series (Zeiss, San-Leandro, CA, USA) at baseline, 3 months and thereafter every 6 months. Reliability criteria were <20% fixation losses, <33% false-negative error, and <20% false-positive errors. Guided progression analysis, with event-based changes, confirmed on at least two consecutive VFs and a label of “likely progression” were taken as progression. Nonglaucomatous causes of VF defects were looked for clinically and recorded after thorough fundus examination by a retina specialist.

Primary outcome measure was therapy required for achieving Target IOP for severe, moderate, and mild glaucoma, ≥12, ≤15, and ≤18 mmHg. Additionally after trabeculectomy, the IOPs had to be >5 mmHg. Baseline IOP of medically treated eyes was significantly higher than surgically treated eyes (P = 0.0001). Baseline reliable Humphrey VFs were available for 242 of 248 medically treated eyes, categorized as 175 (72.31%) early, 34 (14.04%) moderate, and 33 (13.64%)

Figure 2: Box type releasable suture (modification of Wilson’s technique) placement (a) passage of 10-0 nylon suture from the clear cornea to scleral shelf underneath the limbus (yellow arrow). (b) Passage of suture through the partial thickness scleral flap. (c) Passage of suture back from scleral bed to clear cornea underneath the limbus (green arrow). (d) Final picture showing two box-type releasable suture (black arrow) and two 10-0 nylon fixed scleral buried sutures (blue arrow).

Figure 3: Plots of Kaplan Meier for estimates of survival in medically and surgically treated PACG eyes by using criteria A: IOP ≤12 mmHg as survival (a), criteria B: IOP ≤15 mmHg as survival (b), and criteria C: IOP ≤18 mmHg as survival (c).

Results
Records of 985 eyes of adult glaucoma patients were examined for continuous biannual review over 5 years. Three hundred seventy-two were PACG eyes and 613 had POAG/JOAG/secondary glaucomas. All 372 PACG eyes were included in the study, 248 eyes of 124 patients were on medical treatment, and 124 eyes of 95 patients had undergone trabeculectomy. One hundred eighty-five eyes had ≥10 years follow-up and 187 eyes had a 5–9-year follow-up.

Overall, the mean ages of medically controlled patients was 61.37 ± 10.37 and 60.49 ± 12.61 years in surgically treated patients, P = 0.48, with a male:female ratio of 0.82 and 0.93, P = 0.35, and a mean follow-up of 11.34 ± 5.59 and 10.88 ± 7.08 years, respectively. Baseline IOP overall ranged from 22 TO 40 mmHg. Mean baseline IOP was significantly higher in surgically treated eyes than medically treated (P = 0.0001). Baseline reliable Humphrey VFs were available for 242 of 248 medically treated eyes, categorized as 175 (72.31%) early, 34 (14.04%) moderate, and 33 (13.64%)

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Secondary outcome measure was assessment of perimetric change over time.

Statistical analysis: Kruskal–Wallis test was used for comparison of continuous variables. Post-hoc-multiple comparisons were done using the Ranksum test, with Bonferroni correction. Chi-square and Fisher’s exact tests were used to compare categorical data. STATA 12.1 was used for statistical analysis (College Station, Texas, USA).
Table 1: Clinical parameters and visual field progression in medically and surgically treated PACG eyes

| PACG eyes | Parameters | Mean age in years (95% CI) | Baseline IOP in mm Hg (95% CI) | Postoperative IOP in mm Hg (95% CI) | % reduction in IOP | Progression on guided progression analysis |
|-----------|------------|-----------------------------|---------------------------------|-------------------------------------|---------------------|---------------------------------------------|
| Overall   | Medical treatment (n=248) | 61.37±10.37 (61.82-65.92) | 23.34±6.16 (22.48-24.19) | 13.19±4.01 (12.0-13.84) | 43.61±13.73 (3/242 (1.24%)) |
| ≥5 years (n=372) | Operated trabeculectomy (n=124) | 60.49±12.61 (57.23-63.76) | 36.09±9.73 (34.35-37.91) | 12.24±2.55 (11.05-12.45) | 64.16±14.91 (2/109 (1.83%)) |
| ≥10 years (n=185) | P | 0.48 | 0.0001 | 0.39 | 0.0001 | 0.79 |
| 5-9 years (n=187) | Medical treatment (n=116) | 62.26±10.07 (60.4-64.2) | 23.87±6.93 (22.39-23.5) | 13.24±3.0 (12.68-13.79) | 44.5±16.07 (1/112 (0.89%)) |
| Operated trabeculectomy (n=71) | P | 0.08 | 0.0001 | 0.29 | 0.0001 | 0.88 |
| 5-9 years (n=187) | Medical treatment (n=116) | 59.69±11.78 (56.9-62.46) | 37.38±9.14 (35.06-39.70) | 11.15±2.88 (10.47-11.83) | 68.5±10.51 (1/63 (1.59%)) |
| Operated trabeculectomy (n=71) | P | 0.12 | 0.0001 | 0.001 | 0.0001 | 0.60 |

*P<0.05 is significant; CI, Confidence interval

Table 2: Comparing medical and surgical therapy in achieving Target IOP in PACG eyes over 5-9 and >10 years

| Follow-up | PACG | Final IOP ≤12 mm Hg (Qualified success) | Final IOP ≤15 mm Hg (Qualified success) | Final IOP ≤18 mm Hg (Qualified success) |
|-----------|------|----------------------------------------|----------------------------------------|----------------------------------------|
| Overall (n=372) | Medical treatment (n=248) | 125/248 50.40% | 194/248 78.23% | 237/248 95.56% |
| Operated trabeculectomy (n=124) | P | 0.001 | 0.09 | 0.57 |
| ≥10 years (n=185) | Medical treatment (n=132) | 66/132 50.0% | 106/132 80.30% | 124/132 93.94% |
| Operated trabeculectomy (n=53) | P | 0.08 | 0.66 | 0.91 |
| 5-9 years (n=187) | Medical treatment (n=116) | 59/116 50.86% | 88/116 75.86% | 113/116 97.41% |
| Operated trabeculectomy (n=71) | P | 0.002 | 0.007 | 0.58 |

*P<0.05 is significant

Table 3: Percentage reduction in IOP required to reach Target IOP, determined by severity of glaucomatous neuropathy, in medically and surgically treated PACG eyes

| Severity of glaucoma as per Hodapp Parrish Anderson classification | Percentage reduction in IOP |
|---------------------------------------------------------------|----------------------------|
| Early HVF defect | Moderate HVF defect | Severe HVF defect |
| Follow-up | ≥10 years | 5-9 years | ≥10 years | 5-9 years | ≥10 years | 5-9 years |
| Medical treatment with HVF (n=242) | 41.69% (n=98) | 42.28% (n=77) | 42.13% (n=22) | 39.61% (n=12) | 51.33% (n=10) | 52.22% (n=23) |
| Operated trabeculectomy with HVF (n=109) | 58.90% (n=9) | 61.49% (n=10) | 59.52% (n=7) | 62.09% (n=5) | 65.29% (n=30) | 71.87% (n=48) |
| P | 0.001 | 0.0001 | 0.001 | 0.0001 | 0.001 | 0.0001 |

*P<0.05 is significant

Severe field defects and 109 surgically treated eyes were categorized as 19 (17.43%) early, 12 (11%) moderate, and 78 (71.56%) severe field defects. There were significantly more mild glaucoma eyes controlled medically and more severe glaucoma eyes surgically, P = 0.002 and 0.003, respectively. Sixteen eyes had very poor vision and the other five had repeatedly unreliable fields. The clinical data of all patients are summarized in Table 1.

Analyzing all 372 eyes for therapy needed to achieve Target IOP, with regard to baseline IOP off treatment, 100% of eyes with a baseline IOP of <25 mmHg were on medications alone over the review, while with a baseline IOP of 25–30 mmHg; 65.33% were on medications, and 34.67% required surgery. Typically, 91.4% eyes with a baseline IOP of >30 mmHg underwent a trabeculectomy for achieving Target IOP, and 8.6% were on medications, P = 0.001, P = 0.001, and P = 0.01, respectively.
There was a significantly greater number of surgeries than medical therapy over 5–9 years of follow-up to reach a Target IOP ≤ 15 mmHg, P = 0.007. [Table 2] Kaplan–Meier survival curves using Criteria ≤ 12, ≤ 15, and ≤ 18 mmHg were plotted for medically and surgically treated eyes [Fig. 3].

Of all medically treated eyes, 101/248 (40.73%) required one, 93/248 (37.50%) required two, 35/248 (14.11%) required three, 15/248 (6.04%) required four, and 4/248 (1.61%) eyes required five glaucoma medications. More medications were required ≥10 years after trabeculectomy than within 5–9 years, P = 0.01. Ten years after trabeculectomy, 24 eyes (45.29%) were controlled without glaucoma medication, 22 (41.50%) required one, 4 (7.54%) required two, 2 (3.77%) required three, and 1 (1.89%) eye required four to achieve individualized “Target” IOP. None of the patients were on systemic glaucoma medication.

Overall analysis found percentage reduction in IOP was significantly more after trabeculectomy than medical treatment, 64.16 ± 14.91 and 43.61 ± 13.73%, P = 0.0001. Percentage IOP reduction was significantly greater in eyes after trabeculectomy than medical treatment in all severities of glaucoma, over review, P < 0.05 [Table 3]. The decrease in IOP was significantly greater in the 5–9 year follow-up group in comparison to ≥ 10 years follow-up after trabeculectomy, P = 0.001.

Progression by event-based guided progression analysis was seen in 3/242 (1.24%) medically treated eyes; 1/175 (0.57%) having early, 2/34 (5.88%) moderate glaucoma, but none among severe glaucoma. Two eyes were switched to four glaucoma medications and one to three medications to achieve Target IOP. After trabeculectomy, an IOP of ≥18 mmHg was noted in four (3.23%) eyes; out of which two (1.61%) had an IOP of ≥21 mmHg and showed progression; 1/12 (8.33%) eye of moderate glaucoma and 1/78 (1.28%) in severe glaucoma. One eye required a repeat trabeculectomy, and in the other, IOP was <18 mmHg after three topical medications. In total, 22/78 (28.2%) severe glaucoma eyes after trabeculectomy with an IOP of 12–15 mmHg also remained stable and were under close review.

Visual acuity was stable in both medical and surgically controlled eyes for the first 5–9 years of follow-up. Among eyes with ≥ 10 years follow-up, all patients on medical treatment maintained their baseline vision, while 2 of 53 (3.77%) eyes had a two-line drop in BCVA after trabeculectomy. One eye developed dry-ARM and one eye CNVM. In total, 19/248 (7.66%) medically treated and 8/124 (6.45%) surgically treated eyes required cataract surgery at a mean follow-up of 13.62 ± 4.77 and 11.23 ± 3.75 years, P = 0.93. The mean age of patients at the time of cataract surgery was 67.0 ± 12.39 and 64.42 ± 10.21 years. Two eyes with severe glaucoma at baseline having only perception of light and an inaccurate projection of rays preoperatively lost perception of light during the review.

A postoperative shallow AC requiring reformation was seen in six (4.83%) eyes after trabeculectomy. Three of these had an associated shallow choroidal detachment that resolved after AC reformation with air, while the others resolved on conservative management. There was no conjunctival wound leak on Seidel’s test at any time. Over 10 years, bleb-related endophthalmitis was seen in one patient and blebitis in another, managed with topical and intravitreal antibiotics. Bleb revision was required for a thin walled or swelling bleb with hypotony after a mean of 6.68 ± 2.13 years in 15 (12.09%) eyes. A repeat trabeculectomy was performed in three (2.42%) eyes after 12.67 ± 6.82 years.

**Discussion**

A review of a cohort of phakic PACG patients managed medically or by trabeculectomy for at least 5 years was undertaken to ascertain in which eyes an individualized Target IOP appropriate to their severity of glaucoma could be achieved by medication or surgery, and if this lead to stabilization on perimetry.

PACG baseline IOP in our study ranged from 22 to 40 mmHg. Medical therapy to achieve Target IOP in the long term was found to be possible in all eyes having a baseline IOP of <25 mmHg, and in 65% having 25–30 mmHg. Trabeculectomy was required for 91.4% of eyes with a higher baseline IOP. Lander et al. reported a baseline IOP of 40 mmHg, Maheshwari et al. 33.1 mmHg, Liu et al. 27.3 mmHg, and Tham et al. 24.8 mmHg in PACG undergoing trabeculectomy. There are few reports on medical management of PACG reported so far.

Overall, “Target” IOP was achieved for mild, moderate, and severe glaucoma, with medications in 95.56, 78.23, and 50.4%, and 96.77, 85.48, and 69.35% after trabeculectomy. There was a significant increase in mean IOP when reviewed ≥10 years after trabeculectomy, as compared to 5–9 years, with an increase in medications necessary to reach Target IOP. This could be due to a gradual decrease in function of the bleb or an age-related increase in trabecular dysfunction. Romero et al. reported a qualified success rate at 5 years, for IOP <18 mmHg – 72%, <15 mmHg – 59%, and <12 mmHg – 52% after trabeculectomy with MMC in PACG. They reported lower success rates than our study and suggested that trabeculectomy may not achieve low Target IOPs (≤12), especially in phakic eyes, without iridotomy, and with higher baseline IOPs. Maheshwari et al. studied 67 PACG eyes over 3 years, with success defined as final IOP of <21 mmHg, reporting complete and qualified success in 55.2 and 41.8%, and failure in 3%. Liu et al. achieved an IOP of <18 mmHg in 65.40% PACG post trabeculectomy. Chen et al. recorded a mean IOP of 14.9 ± 3.8 mmHg 1 year after trabeculectomy. Alsagoff et al. reported a 45.8% success rate in CPACG and Salmon 66.7%. Our study has shown a better success than Romero et al. at all Target IOPs.

By achieving individualized “Target” IOP with medical therapy or surgery plus tolerated medications in this study, 98.76% medically controlled and 98.17% surgically treated eyes had stable fields, 1.24 and 1.83%, respectively, progressed on GPA. Progression was seen in 0.57% early glaucoma and 5.88% of moderate glaucoma eyes after medical treatment, and 8.33% moderate and 1.28% of severe glaucoma eyes despite trabeculectomy. In POAG eyes, Beckers et al. noted 73.3% stability of VFs at 6 years with 60% having an IOP <15 mmHg. AGIS reported that IOP >17.5 mmHg lead to VF progression in POAG more often than <14 mmHg, with increasing
progression at 7 vs 2 years.\cite{18} “Target” IOP for POAG in CIGTS was formulated from baseline IOP and VF score, and 21% progressed 8 years after trabeculectomy.\cite{33} Therefore, it appears that the Target IOPs used in this cohort of PACG patients were adequate to provide stabilization of glaucoma in almost all eyes and are similar to those advocated for POAG by one study.\cite{19}

Looking specifically at severe PACG, we found an IOP of ≤12 mmHg can be achieved in some eyes by medical management if the baseline IOP is in the high 20s. However, trabeculectomy was more likely to achieve and maintain such a low IOP over ≥10 years in those with a higher baseline IOP. In total, 28.20% of severe glaucoma eyes after trabeculectomy had an IOP of 12–15 mmHg but remained stable on close review. This suggests that IOPs of 12–15 mmHg may also be acceptable in severe PACG if the percentage decrease from baseline was high, 50–60%.\cite{34}

In this study, the percentage fall in IOP from baseline over ≥10 years was 41.69, 42.13, and 51.33% in mild, moderate, and severe glaucoma for medically treated and 58.90, 59.52, and 65.29% in surgically treated eyes, with the need for escalating medications over time in the surgical group. A 55–62% fall in IOP has been reported in PACG after trabeculectomy.\cite{11,12} Tham et al. reported 8.9 mmHg or 36% fall in IOP 2 years after trabeculectomy in PACG.\cite{13} CIGTS reported mean IOPs of 14–15 mmHg with a 46% reduction after trabeculectomy in POAG.\cite{15} Cillino et al. reported a fall of 40.9 ± 14.2% at 5 years\cite{46} and TVT study a 49.5% reduction at 5 years in POAG.\cite{47} The percentage reduction of IOP from baseline values in our glaucoma patients was much higher when compared to published literature especially on POAG, probably because of higher baseline IOPs in PACG, especially in the surgical group in our study.

Phacoemulsification for a visually significant cataract was performed in 7.66% of medically and 6.45% trabeculectomy eyes over 10 years. There was no significant drop in vision among medically treated eyes. A significant drop in BCVA after trabeculectomy was attributable to ARM and diabetic neuropathy, or with a baseline IOP of >30 mmHg to achieve Target IOP. These appropriate initial therapeutic interventions and Target IOPs are therefore suggested as a clinically validated algorithm of care for different severities of PACG.

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Conflicts of interest
There are no conflicts of interest.

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