ABOUT THE AUTHORS

Alanna James, MD

Dr. Alanna James is a glaucoma fellow at University of Southern California Roski Eye Institute. She completed her ophthalmology residency at Loma Linda University Eye Institute. She received her medical degree from Loma Linda University School of Medicine in Southern California. She has a Bachelor's of Science in Biochemistry from Andrews University in Southwest Michigan. She has a strong interest in the medical and surgical management of glaucoma in addition to cataract surgery and a passion for both community service and global ophthalmology.

Author Affiliations: USC Roski Eye Institute, Los Angeles, CA

Benjamin Y. Xu, MD, PhD

Dr. Benjamin Xu received his B.S. from Yale University and M.D. and Ph.D. in neuroscience from Columbia University. He then completed his ophthalmology residency at the LAC+USC Medical Center / USC Roski Eye Institute and glaucoma fellowship at the UCSD Shiley Eye Institute under the mentorship of Dr. Robert N. Weinreb. He is now Chief of the Glaucoma Service at the USC Roski Eye Institute. His NIH-funded research focuses on developing novel diagnostic tools to care for patients with glaucoma using OCT imaging and artificial intelligence (AI). He also uses epidemiological and electronic healthcare data to study the impact of glaucoma on diverse populations and devise strategies to deliver more effective glaucoma care worldwide.

Author Affiliations: USC Roski Eye Institute, Los Angeles, CA

Recent Advances in the Evaluation and Treatment of Primary Angle Closure Disease

Introduction

In the realm of ophthalmology, the clinical management of angle closure remains a disputed topic. An aging population, underperformance of gonioscopy, and a paucity of clear guidelines about management have contributed to the rising number of patients with primary angle closure glaucoma (PACG). The global prevalence of PACG based on a meta-analysis published in 2014 was 0.50%, with the highest prevalence occurring in Asian populations. This study also projected that the number of people with PACG worldwide will increase to 32 million by the year 2040.[1] PACG is a visually devastating disease; around a quarter of individuals worldwide and one out of nine individuals in the United States with newly diagnosed PACG are affected by blindness (visual acuity of 20/200 or less).[2,3] The rising burden of the visual morbidity associated with untreated PACG highlights the urgent need for more clearly defined, evidence-based practice guidelines in angle closure care.

Classification

While angle closure comprises a spectrum of disease, categorical definitions of primary angle closure disease (PACD) have been established to aid in its scientific study and clinical care. The current classification consists of the following categories: primary angle closure suspect (PACS); primary angle closure (PAC); primary angle closure glaucoma (PACG); and acute primary angle closure (APAC).[4] PACS is defined as 180 or more degrees of non-visible pigmented trabecular meshwork on gonioscopy in the absence of elevated intraocular pressure (IOP) greater than 21 mmHg and optic nerve damage (**Figure 1**). PAC shares similar findings as PACS except there is presence of peripheral anterior synechiae (PAS) and/or elevated IOP greater than 21 mmHg. PACG is defined as PAC with concurrent examination findings consistent with glaucomatous optic neuropathy. APAC is defined as an acute episode of PAC with elevated IOP greater than 21 mmHg.

Angle Closure Diagnosis

Dark-room dynamic gonioscopy remains the clinical standard for evaluating the anterior chamber angle and detecting patients at risk for PACG. The American Academy of Ophthalmology (AAO) Preferred Practice Pattern guidelines for primary open angle glaucoma (POAG) and PACG both emphasize the importance of gonioscopy in patients undergoing evaluation for glaucoma. They also note that ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) (**Figure 2**) can aid in the diagnosis.[5]

Despite its importance, gonioscopy tends to be underperformed by eyecare providers. Hertzog et al reported a gonioscopy rate of 51.3% at initial evaluations of patients with moderate to severe glaucomatous damage, a number that is supported by more recent studies on gonioscopy.[6,7,8] The rate of gonioscopy was found to be even lower (less than one-third) in patients who presented with an episode of APAC who were previously evaluated by an ophthalmologist or optometrist in the preceding two years.[9] The diagnosis of PACS prior to the diagnosis of PACG was associated with lower risk of blindness, showing that earlier detection of angle closure via gonioscopy yields more favourable outcomes.[2] Therefore, the importance of performing angle evaluations in all patients suspected of glaucoma cannot be ignored.

Angle Closure Management

In the recent past, a few clinical studies have recommended dramatic changes to the paradigms of angle closure management. The standard of care for eyes with mild angle closure (PACS) has been laser peripheral iridotomy (LPI). The Zhongshan Angle-Closure Prevention (ZAP) Study was a landmark randomized, controlled trial

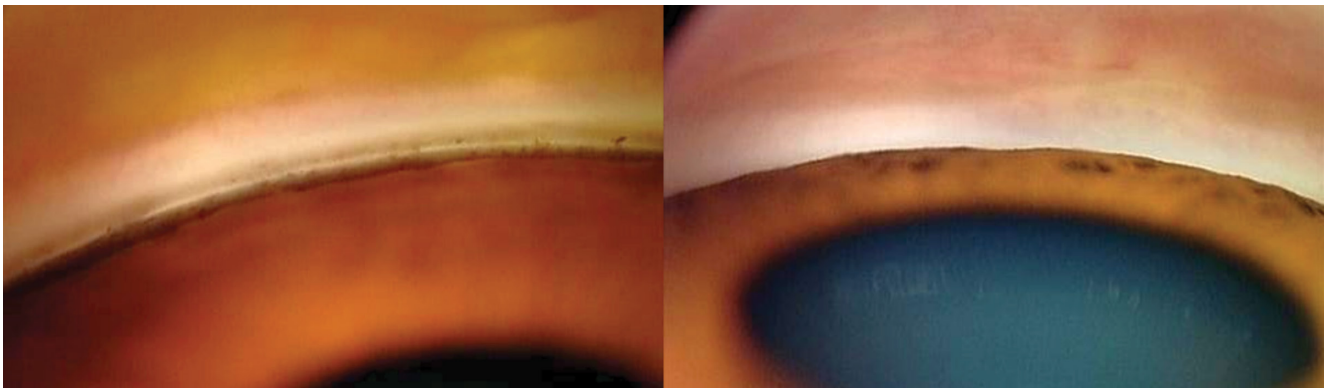

Figure 1. Gonioscopic view of the anterior chamber angle showing an open angle with visible pigmented trabecular meshwork (left) and closed angle with non-visible pigmented trabecular meshwork (right); *image courtesy of Benjamin Y. Xu, MD, PhD and Alanna James, MD.*

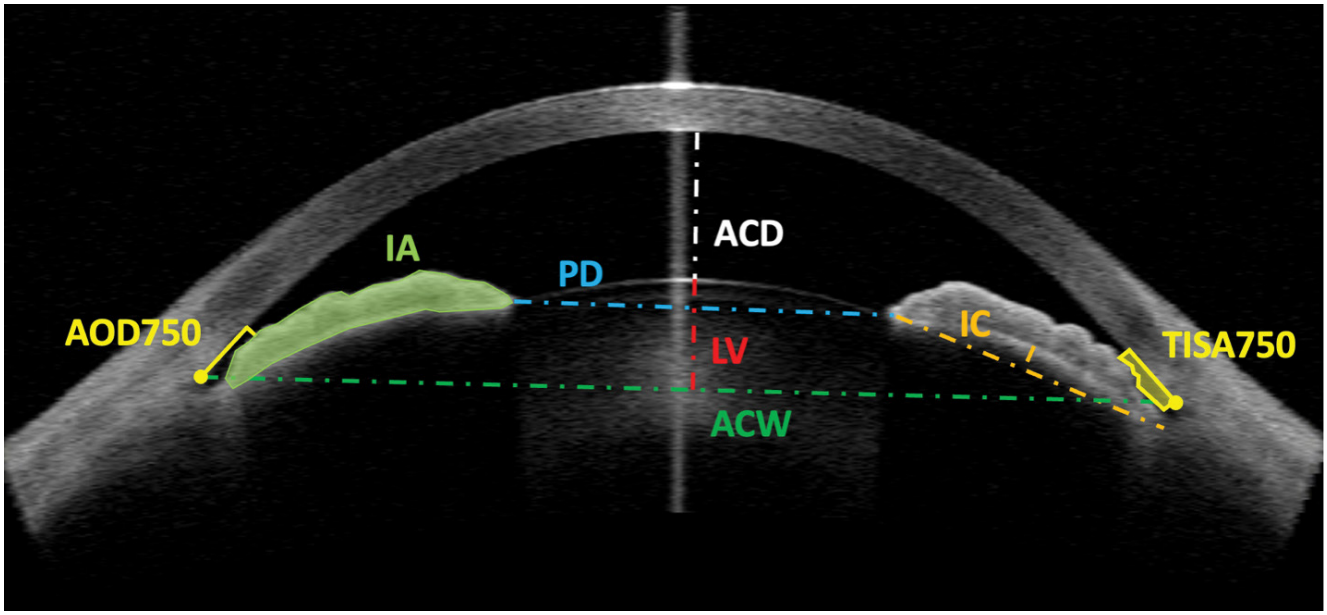

Figure 2. Representative anterior segment OCT (AS-OCT) image with ocular biometric parameters marked; *image courtesy of Benjamin Y. Xu, MD, PhD and Alanna James, MD.*
AOD: angle opening distance; **TISA:** trabecular iris space angle; **IA:** iris area; **PD:** pupillary diameter; **LV:** lens vault; **ACW:** anterior chamber width; **ACD:** anterior chamber depth; **IC**: iris curvature.

conducted in Guangzhou, China that enrolled 889 bilateral primary angle-closure suspects. Participants received an LPI in one eye and the contralateral eye served as a control. The primary outcome measure was progression to PAC, which was defined as an IOP greater than 24 mmHg, the formation of at least one clock hour of PAS, or an episode of acute angle closure crisis (AACC). The initial study, published in 2019, presented the six-year data.[10] A follow-up study reported the 14-year progression rates from the ZAP trial.[11] Overall, LPI significantly lowered the risk of progression (largely due to development of PAS), which was three times lower in treated versus control eyes (hazard ratio = 0.31) after 14 years. The risk of progression after 14 years was low (1.4% per eye year), although it was slightly higher than in the primary six-year ZAP trial analysis (0.8% per eye year). The ZAP trial authors recommended against wide-spread LPI for PACS

due to the low overall risk of progression to PAC in both the six- and 14-year studies. Although this overall risk is low, there are still patients who developed PAC, which is associated with higher risk for PACG and risk of severe vision loss.[9] Therefore, a system of risk stratification for PACS is crucial to identify patients who would benefit from earlier LPI or other interventions.

More recent work has focused on identifying high-risk cases of PACS. Using data from the six-year ZAP trial, Xu et al proposed a method of risk stratification for untreated PACS eyes using ocular biometric measurements.[12] AS-OCT and A-scan ultrasound data from 643 subjects were analyzed, of whom 609 were non-progressors and 34 were progressors. The authors found narrower angle width and flatter iris curvature measured by AS-OCT; older age at baseline were significant predictors of progression to PAC (**Figure 1**). Interestingly, a smaller cumulative gonioscopy score (a sum of gonioscopy grades from all four quadrants) was not associated with progression, which highlights the limitations of gonioscopy in risk stratifying untreated PACS eyes.

While significantly fewer PACS eyes that received LPI progressed to PAC in the ZAP trial, it remains important to identify treated eyes at higher risk that may benefit from closer monitoring. Therefore, Bao et al recently used gonioscopy and AS-OCT data from the ZAP trial to characterize the anatomic effects of LPI on PACS eyes and identify biometric risk factors for angle closure in treated PACS eyes.[13] The authors found only around a quarter of treated PACS eyes still fit the definition of PACS after LPI treatment. They also found that persistent PACS despite LPI and narrower angle width measured by AS-OCT were both predictive of progression to PAC.

One limitation of current discoveries in the field of angle closure is their reliance on measurements obtained by AS-OCT imaging, a technology that is not as widely available as other forms of testing used in the diagnosis and monitoring of glaucoma, such as visual fields and posterior segment OCT. However, AS-OCT technology is becoming more commonplace as it is incorporated into modern biometers for intraocular lens calculations. In addition, recent advances using artificial intelligence (AI) have automated the biometric measurement process in modern AS-OCT devices, such as the ANTERION OCT System (Heidelberg Engineering, Heidelberg, Germany). These AI algorithms approximate expert-level measurements of biometric parameters, making biometric analysis of AS-OCT images accurate and convenient.[14]

Recent advances in angle closure diagnosis and evaluation have been accompanied by similar advances in treatment paradigms. Treatment options for angle closure include LPI and lens extraction; and, in the setting of elevated IOP or glaucoma, other glaucoma procedures such as trabeculectomy and glaucoma drainage implants. The AAO Preferred Practice Pattern guidelines on PACD recommend medical treatment and LPI in the setting of APAC, but also note that pupillary block, which is alleviated by LPI, plays a role in most cases of chronic angle closure. These guidelines also mention that lens extraction could be considered in some patients with PAC and PACG prior to traditional glaucoma surgery.[5]

Several studies have shown that removal of the crystalline lens widens the anterior chamber angle in eyes with angle closure, which is often accompanied by a decrease in IOP.[15,16,17] However, while lens extraction is an obvious first-line treatment for angle closure eyes with visually significant cataracts, its role in eyes with clear lens or non-visually significant cataracts is less apparent. This topic was explored by the EAGLE trial, a landmark randomized, controlled trial published in 2016 in which participants with clear lenses (VA better than 20/40) and PAC with elevated IOP (>30 mmHg) or PACG were randomized to either clear lens extraction or LPI with topical medical treatment.

Participants who underwent clear lens extraction had significantly lower mean IOP (by 1.2 mmHg) and higher scores on quality-of-life questionnaires. Lens extraction was also found to be more cost effective. In addition, only one patient who had clear lens extraction had irreversible loss of vision in comparison to three patients who received standard care.[18] In a separate study comparing clear lens extraction to trabeculectomy in patients with PACG, lens extraction yielded a significant reduction in synechial angle closure, and increases in anterior chamber depth and angle width in eyes without visually significant cataracts.[19] While there is significant evidence to support earlier extraction of clear lenses in angle closure eyes, there are barriers in real-world clinical practice due to insurance coverage issues, loss of accommodation in younger patients, and patient aversion to surgery.

This recent data suggests it is reasonable to perform lens extraction for patients who have PAC or PACG. However, the data does not clarify

the role of clear lens extraction for patients with PACS. Given the data from the ZAP trial, we know there is a low risk of progression from PACS to PAC; therefore, the risks and costs of clear lens extraction may not be warranted. The AAO Preferred Practice Pattern guidelines note that LPI may be considered to reduce the risk of developing PAC; alternatively, patients may be provided with education and return precautions, and followed for progression to PAC. The guidelines also list factors that may motivate a provider to consider performing LPI over observation: medication usage that could provoke APAC, symptoms suggestive of intermittent APAC, difficulty accessing prompt eye care, history of poor compliance, or the need for frequent dilated eye exams.[5] While the risks of LPI are low, possible complications include corneal edema, posterior synechiae, visual disturbances, and elevated IOP.[20]

Conclusion

There has been an abundance of high-quality research conducted in the field of angle closure focused on establishing evidence-based detection, monitoring, and treatment guidelines. While gonioscopy remains the current clinical standard for evaluating angle closure eyes, AS-OCT is a promising tool for evaluating patients with angle closure, both prior to and following treatment. These advances will enhance clinicians' ability to utilize treatments that effectively alleviate angle closure, such as LPI and lens extraction. However, further longitudinal studies on angle closure in diverse, high-risk populations are needed to determine how frequently at-risk patients should be monitored, the benefits of earlier angle closure detection, and what additional objective data may be useful to deliver more precise care to patients at risk for PACG.

Correspondence:

Dr. Benjamin Y. Xu
Email: benjamix@usc.edu

Financial support:

A.J: None declared.
B.X.: None declared.

References:

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040. Ophthalmology. 2014;121(11):2081-2090.
2. Shah SN, Zhou S, Sanvicente C et al. Prevalence and risk factors of blindness among primary angle closure glaucoma patients in the United States: An IRIS® Registry Analysis. Am J Ophthalmol. 2023; S0002-9394(23)00461-0. Advance online publication. https://doi.org/10.1016/j.ajo.2023.11.007
3. George R, Panda S, Viiaya L. Blindness in glaucoma: primary open-angle glaucoma versus primary angle-closure glaucoma-a meta-analysis. Eye. 2022;36(11):2099-2105.
4. Foster PJ, Buhrmann R, Quigley HA et al. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2022;86(2):238-242.
5. Gedd SJ, Chen PP, Muir KW, et al. Primary angle-closure disease PPP 2020. American Academy of Ophthalmology. 2022, October 5). https://www.aao.org/education/preferred-practice-pattern/primary-angle-closure-disease-ppp
6. Hertzog LH, Albrecht KG, LaBree L et al. Glaucoma Care and Conformance with Preferred Practice Patterns. Ophthalmology. 1996;103(7):1009-1013.
7. Coleman AL, Yu F, Evans SJ. Use of gonioscopy in Medicare beneficiaries before glaucoma Surgery. J Glaucoma. 2006;15(6):486-493.
8. Apolo G, Bohner A, Pardeshi AA, et al. Racial and sociodemographic disparities in the detection of narrow angles before detection of primary angle-closure glaucoma in the United States. Ophthalmology Glaucoma. 2022;5(4):388-395.
9. Wu AS, Stein JD, Shah M. Potentially missed opportunities in prevention of acute angle-closure crisis. JAMA Ophthalmology. 2022;140(6):598-603.
10. He M, Jiang Y, Huang S, et al. Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial. The Lancet. 2019;393(10181):1609-1618.
11. Yuan Y, Wang W, Xiong R, et al. Fourteen-year outcome of angle-closure prevention with laser iridotomy in the Zhongshan Angle-Closure Prevention Study: Extended follow-up of a randomized controlled trial. Ophthalmology. 2023;130(8):786-794.
12. Xu BY, Friedman DS, Foster PJ, et al. Ocular biometric risk factors for progression of primary angle closure disease Ophthalmology. 2022;129(3):267-275.
13. Bao YK, Xu B, Friedman DS, et al. Biometric risk factors for angle closure progression after laser peripheral iridotomy. JAMA Ophthalmology. 2023;141(6):516-516.
14. Bolo K, Apolo G, Pardeshi AA, et al. Automated expert-level scleral spur detection and quantitative biometric analysis on the ANTERION Anterior Segment OCT System. Br J Ophthalmol. Published online Oct. 5, 2023.
15. Steuhl K-P, Marahrens P, Frohn C, et al. Intraocular pressure and anterior chamber depth before and after extracapsular cataract extraction with posterior chamber lens implantation. Ophthalmic Surgery, Lasers & Imaging Retina. 1992;23(4):233-237.
16. Yang CH, Hung PT. Intraocular lens position and anterior chamber angle changes after cataract extraction in eyes with primary angle-closure glaucoma. Journal Cataract Refract Surg. 1997;23(7):1109-1113.
17. Hayashi K, Hayashi H, Nakao F, Hayashi F. Changes in anterior chamber angle width and depth after intraocular lens implantation in eyes with glaucoma. Ophthalmology. 2000;107(4):698-703.
18. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. The Lancet. 2016;388(10052):1389-1397.
19. Man X, Chan NCY, Baig N, et al. Anatomical effects of clear lens extraction by phacoemulsification versus trabeculectomy on anterior chamber drainage angle in primary angle-closure glaucoma (PACG) patients. Graefe's Archive for Clinical and Experimental Ophthalmology. 2015;253(5):773-778.
20. Vera V, Naqi A, Belovay GW et al. Dysphotopsia after temporal versus superior laser peripheral iridotomy: a prospective randomized paired eye trial. Am J Ophthalmol. 2014;157(5):929-935.e2.