出國報告（出國類別：進修）

慢性鼻竇炎精準醫療研發暨內視鏡顱底手術進修

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摘要

臺大醫院耳鼻喉科臨床助理教授林怡岑醫師於 2022 年 2 月 15 日至 2023 年 2 月 14 日出國進修，造訪單位為史丹佛鼻科暨顱底手術部門(Stanford Rhinology & Endoscopic Skull Base Surgery)，同時也是史丹佛鼻竇中心(Stanford Sinus Center)，本次進修課程由 Peter Hwang 教授負責指導，研究內容包括鼻科學研究、鼻科學臨床觀摩與顱底手術觀摩，同時也積極參與各項學術活動。於期間完成一篇通訊作者論文、一篇共同作者論文與目前仍有一篇第一作者論文撰寫中。本次出國進修，對於筆者於臨床服務與教學研究都有相當大的啟發與幫助!

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一、目的

學習慢性鼻炎與鼻竇炎的最新治療方式，與臨床醫學研究方法；此外，針對顱底腫瘤與鼻竇腫瘤患者，由神經外科與耳鼻喉科醫師合作進行手術是目前世界的趨勢，希冀藉此可精進內視鏡顱底腫瘤手術。同時，希望建立與史丹佛大學的合作研究關係，未來能持續進行跨國合作之研究。

二、過程

(一) 機構介紹

本次出國進修造訪單位為史丹佛鼻科暨顱底手術部門(Stanford Rhinology & Endoscopic Skull Base Surgery)，同時也是史丹佛鼻竇中心(Stanford Sinus Center)，隸屬於史丹佛大學醫學院(Stanford School of Medicine)與史丹佛醫療中心(Stanford Health Care)，門診與手術室皆位於史丹佛醫療中心區域，附近可步行至史丹佛大學。

史丹佛鼻科暨顱底手術團隊主要有三位鼻科醫師：Peter Hwang 教授、Jayakar Nayak 教授與 Zara Patel 教授，Peter Hwang 教授為鼻科主任，領導鼻科暨顱底手術團隊進行臨床照顧與研究。Peter Hwang 教授專長為鼻竇與顱底內視鏡手術，並進行許多相關臨床研究，發表許多重要的論文，Jayakar Nayak 教授專長為空鼻症(empty nose syndrome)，並進行鼻粘膜與鼻竇炎之免疫與幹細胞研究，Zara Patel 教授專長為嗅覺疾病的治療與顱底手術，在顱底手術之團隊會議與手術訓練課程常常提供寶貴的意見與協助。團隊也包含兩位研究醫師(fellow)，協助教授們進行手術與門診，此外研究醫師也有自己的門診，並可以收治病人進行手術。史丹佛鼻竇中心經常有國外訪問學者參訪，來自各國之耳鼻喉科主治醫師會在該單位進行一年以上的參訪研究，也有許多耳鼻喉科住院醫師做短期(二至四週)的短期進修。

照片一、與史丹佛鼻科中心教授合影，由左至右為 Jayakar Nayak 教授、來自巴西的訪問學者 Bruna、筆者與 Peter Hwang 教授

照片二、與史丹佛鼻科中心教授合影，由左至右為筆者與 Zara Patel 教授

(二) 研究內容

1. 鼻科學研究

史丹佛鼻竇中心(Stanford Sinus Center)團隊進行之鼻科研究範圍包括臨床研究與基礎研究，在臨床研究方面，包含鼻竇內視鏡手術術前與術後照顧之相關治療、鼻竇癌症組織資料庫建立與分析、慢性鼻竇炎之嗅覺異常追蹤與治療、新冠肺炎患者的嗅覺異常、鼻竇顱底手術之重建與皮瓣相關研究與內視鏡下蝶顎神經節注

射用於頭痛之治療等等，基礎研究方面包括鼻黏膜表期細胞之研究、幹細胞再生研究與組織免疫表現等等。研究團隊每三個月會開一次全鼻科的鼻科討論會(rhinology research meeting)，依序討論各個研究主題與分享研究成果。

2. 鼻科學臨床觀摩

在進修第一個月觀摩 Peter Hwang 教授的門診，美國的看診時間較為充足，比較能夠與病人詳細解釋，另一個有趣的地方是，Peter Hwang 教授曾經做過相當多的臨床試驗，包含類固醇沖洗、xylitol 沖洗、口服制酸劑用於鼻竇炎與鼻部相關症狀治療等等，因此常常可以拿出過去發表的研究結果提供病人參考，這一點相當令人佩服。此外，Peter Hwang 教授擅長用各種鼻竇內視鏡手術方式進行鼻腔與鼻竇腫瘤切除手術，並善用黏膜移植與鼻中隔皮瓣做修補，給予相當大的啟發。手術過程中，Peter Hwang 教授會將不同的步驟交給不同程度的住院醫師與 fellow 來完成，並訓練 fellow 要有教導住院醫師的能力，手術教學不遺餘力，這些都是值得我們學習的地方。此外，每兩週一次的鼻科個案討論會(rhinology case conference)由 fellow 醫師負責報告並回顧相關文獻，同時由三位鼻科教授與來自各國的訪問學者共同討論，透過這樣的討論方式，我們可以了解鼻科最新進展與世界各國不同的治療方式。

3. 顱底手術觀摩

內視鏡顱底手術主要由耳鼻喉科醫師與神經外科醫師共同完成，史丹佛神經外科於 2019 年聘請了 Juan Fernandez-Miranda 教授，JFM 教授本來是在匹茲堡大學醫療中心(University of Pittsburgh Medical Center, UPMC)擔任臨床與研究工作，在顱底手術方面發表相當多重要且引用次數相當多的手術解剖構造著作，很幸運可以在史丹佛觀摩兩位鼻科與神經外科大師的手術。

在史丹佛，每週約有三到五個腦垂體手術個案與一至兩個顱底複雜性顱底腫瘤，複雜性顱底腫瘤包括腦膜瘤(meningioma)、顱咽管瘤(craniopharyngioma)、脊索瘤(chordoma)與軟骨肉瘤(chondrosarcoma)等等。手術皆由耳鼻喉科醫師與神經外科醫師共同完成，經過觀摩學習，了解腫瘤侵犯不同解剖構造時，該如何建立好的通道(corridor)以利於進行顱底腫瘤切除手術，此外，應該選擇何種方式重建，再次手術時如何解決修補材料不足的問題，皆是顱底手術成功重要的關鍵。

4. 顱底手術課程

於 2022 年 8 月史丹佛舉辦顱底手術課程，臺大醫院神經外科楊士弘醫師也前來參加，此次課程的客座講師為匹茲堡醫學中心(University of Pittsburgh Medical Center)的 Paul Gardner 教授、Carl Snyderman 教授與 Eric Wang 教授，美國東西岸顱底手術兩大機構合併的課程真的相當精彩。課程內容包括 3D 解剖構、手術方法、疾病討論、手術觀摩與大體手術課程等等，聆聽大師們對於特殊個案的討論，讓我們能夠學習到不同的思考邏輯與手術方式設計，還有各種手術相關的病人照護細節，有很大的收穫。另外，手術操作過程與楊士弘醫師合作，我們練習了各種顱底手術的進階技巧，與較少操作的後顱窩手術，順利將 12 對顱神經均解剖展示出來，對於未來我們進行顱底手術有很大的助益！

照片三、顱底手術課程實做，由左至右為臺大醫院神經外科楊士弘醫師、筆者與賓州大學醫學中心 Carl Snyderman 教授。

(三) 與現行本院之比較

根據筆者的觀察，史丹佛大學醫院和本院有幾點不同：

1. 史丹佛大學醫院住院醫師們有較多的手術操作練習機會，且關於臨床研究的參與程度較高，主治醫師具有相當高的教學熱忱。
2. 史丹佛鼻竇中心有專門的專科護理師協助衛教病患，可以執行簡單的鼻科治療，對於鼻科看診服務有很大的幫助。
3. 定期的顱底腫瘤個案討論，每個手術個案都有經過放射科、神經外科與鼻科醫師討論，手術規劃更為詳盡明確。
4. 臨床試驗的執行能力較高，值得我們學習。

三、心得

在 Stanford 常常聽到 leadership，我過去一直不能理解的是為什麼每個人都可以有 leadership，一個群體裡面不是只需要一個或少數的領導，其他人就配合這個領導嗎？有一次在研究會議上，我聽到了一位醫學生 David 報告他的研究主題，是關於空氣污染與上呼吸道疾病的研究，在他報告完之後，Peter 讚賞他對於研究主題的分析報告，也有未來研究方向的規劃，認為他以後在這個主題就具有 leadership。這段話給了我很大的啟發，研究的進行，主要是去探索未知並透過科學的方法去驗證，其實每位學者在不同的領域，甚是同一個領域不同的研究主題，如果可以做到深入的研究，並能夠向別人分享研究成果，就是在這個學術主題成為 leader，所以每個人都可以在某個項目成為具有 leadership 的學者，一個機構之所以能夠偉大，在於每個各懷絕技的成員；同時，具有 leadership 的人，並不單純只是成就自己，並不是爭第一名就可以成為 leader，對於周遭的團隊成員具有影響力，能夠帶動整個團隊。

在美國進修的這一年，一直很佩服 Peter，他自己是一位相當優秀的醫生，在臨床領域開發了許多新的治療方式並執行了相當多的臨床試驗來驗證，發表了數量可觀的研究論文且累積了相當多的引用次數，更遑論鼻竇內視鏡與顱底手術的成就，與許多教科書的撰寫，他是一位非常成功的鼻科大師，但是他追求的不是個人的成就，而是能夠帶領整個團隊前進；對於醫學生，他透過讓學生操作內視鏡導航系統建立對於耳鼻喉科學的興趣，

對於住院醫師，他按照住院醫師的程度給予各種臨床技巧與手術方法的教學，並成立鼻科論文討論會，定期的聚會讓住院醫師們發表對於論文的看法與評論，對於 fellow 醫師，他不但要求鼻科醫師該有的手術技巧、臨床知識技能與進行鼻科研究，還會希望 fellow 醫師具有教導住院醫師的能力，對於國外學者，他鼓勵我們彼此之間多多合作，並能夠在 Stanford 學習後，更拓展自己的觀念與想法，能夠將 Stanford 的精神帶回國內。Peter 的用心，不只是追求個人的成就，而是帶動整個團隊，並不斷地教育出鼻科的心血，我想，這是最值得我們學習的 Stanford 精神！

四、建議事項

1. 建立完善的住院醫師出國進修機制

   住院醫師出國進修可以拓展國際視野，接觸不同國家的醫學環境、體系與文化，也能學習最新臨床醫學知識和技能，並能與國外學者與來自世界各地的醫師建立良好的聯繫，對於臨床工作與研究都是很大的助益。史丹佛大學醫院是一個非常好的進修環境，除了主治醫師出國進修，也非常適合住院醫師前往觀摩學習，在史丹佛進修時也常常遇到來自歐洲各國的住院醫師。然而，史丹佛大學附近的物價高昂，房租與生活費也相當驚人，按照現有出國進修之經費補助算法，生活費卻無法如同舊金山等北加州大都市計算，現實層面上是一個阻力。

2. 優化手術室的學習空間

   在史丹佛的鼻竇內視鏡手術室，影像系統相當完善，除了術者與刷手護理師有各自的螢幕之外，手術室內也有相當多的螢幕同步播放內視鏡手術畫面，這對於住院醫師、醫學生與國外訪問醫師在手術室的學習有很大的幫助。此外，若能有更為彈性的手術時間，對於住院醫師的手術操作訓練會有很大的助益。手術室團隊建立良好的溝通與技能培訓都相當重要，醫護之間的互相支持與協助也都可以提昇手術效率和安全。

3. 擴增醫學院圖書館的資源

史丹佛醫學院圖書館的資源相當完善豐富（Lane Medical Library 網站網址：https://lane.stanford.edu/index.html），透過 LibKey 可以讓我們非常方便的查詢文獻資料（使用方式可以參考 Lane Medical Library 網站之介紹 https://laneblog.stanford.edu/2023/04/01/access-articles-with-libkey-nomad/），使用者不用透過 VPN，而是經過史丹佛大學帳號的認證，就可以下載相關文獻來閱讀。此外，本次進修所使用的 Covidence 網站對於進行系統性回顧(systemic review)研究有很大的助益，倘若醫學院圖書館能夠訂閱提供醫學院與醫院同仁使用，可以增加本院臨床研究與論文撰寫的產能。最後，鼻科最主要的兩本期刊 Rhinology (2021 impact factor 5.534, 耳鼻喉科學門排名第二)與 International Forum of Allergy & Rhinology (2021 impact factor 5.426, 耳鼻喉科學門排名第四)圖書館皆沒有訂閱，造成查詢鼻科相關文獻的不變。

最後，出國進修時，如若能夠放開心胸，跳脫語言的隔閡，多多與當地醫師與研究學者談話，同時也能和來自各國的醫師交流，都會有意想不到的收穫。

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CLINICAL LETTER

Effect of dupilumab on Eustachian tube dysfunction in patients with chronic rhinosinusitis with nasal polyposis

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chronic rhinosinusitis, quality of life, therapeutics

1 | INTRODUCTION

Eustachian tube dysfunction (ETD) occurs in ~50% of patients with chronic rhinosinusitis with nasal polyposis (CRSwNP).[1] While treatment of CRSwNP with endoscopic sinus surgery (ESS) has been shown to improve comorbid ETD,[2] little is currently understood about the impact of biologics on ETD in CRSwNP. Here we study how dupilumab, a monoclonal antibody that blocks IL-4 and IL-13 signaling, affects ETD in CRSwNP.

2 | METHODS

We retrospectively reviewed adults (age >18 years) with CRSwNP treated with dupilumab (300 mg q2 weeks, subcutaneous injection) between 2018 and 2022. Included patients were prescribed dupilumab for specific treatment of CRSwNP. Patients prescribed dupilumab prior to the FDA approval date for CRSwNP (June 2019) also had a diagnosis of comorbid asthma. Patients who underwent sinus or ear surgery during the study period were excluded. The following data were extracted: demographics, comorbidities, prior sinus surgery, prior ear procedures, concurrent intranasal corticosteroid or antihistamine use, concurrent aspirin desensitization, time between most recent surgery and dupilumab initiation, Sinonasal Outcome Test-22 (SNOT-22) total, SNOT-22 ear/facial subdomain (ear fullness, ear pain, dizziness/vertigo, facial pain/pressure), Lund-Kennedy endoscopy standard scores.

The Eustachian Tube Dysfunction Questionnaire (ETDQ-7), a validated 7-item questionnaire for ETD,[3] was administered for all patient visits. ETDQ-7 scores (range 7–49) were recorded at pre-treatment baseline and longest available follow-up after dupilumab initiation. A baseline ETDQ-7 score of >14.5 was considered clinically significant ETD, or "ETD-positive," and a ΔETDQ7 value of >3.5 was considered the minimal clinically important difference (MCID).[4,5] Pre- and post-treatment ETDQ-7 were compared using *t*-tests. Multivariate logistic regression analysis controlling for age, sex, and baseline SNOT-22 was performed to identify factors associated with achieving MCID in ETDQ-7. To compare the effect of dupilumab versus ESS, we identified a CRSwNP cohort with ETDQ-7 scores of >14.5 who underwent ESS, matched for age, sex, and prior surgery status. ETDQ-7 scores pre- and post-treatment were compared using *t*-tests.

3 | RESULTS

Thirty-seven patients were included (Table 1). Four had undergone prior ear tube placement, and none had a prior

TABLE 1 Characteristics of the study cohort

	Overall ($n = 37$)	ETD-positive ($n = 16$)	ETD-negative ($n = 21$)	p-value
Age, years (mean ± SD)	52.9 ± 19.2	53.5 ± 15.4	52.4 ± 22.1	0.864
Sex, *n* (%)				
Male	16 (43.2)	6 (37.5)	10 (47.6)	0.551
Female	21 (56.8)	10 (62.5)	11 (52.4)	0.551
Race				
White	22 (59.5)	9 (56.3)	13 (61.9)	0.737
Asian	6 (16.2)	3 (18.7)	3 (14.3)	0.257
Black	1 (2.7)	0 (0.0)	1 (4.8)	0.43
Other	8 (21.6)	4 (25.0)	4 (19.0)	0.72
Ethnicity				
Hispanic	7 (18.9)	2 (12.5)	5 (23.8)	0.398
Non-Hispanic	30 (81.1)	14 (87.5)	16 (76.2)	0.398
Comorbidities				
Asthma	30 (81.1)	14 (87.5)	16 (76.2)	0.398
Allergic rhinitis	23 (62.2)	11 (68.8)	12 (57.1)	0.407
GERD	4 (10.8)	2 (12.5)	2 (9.5)	0.773
Tobacco use	4 (10.8)	2 (12.5)	2 (9.5)	0.773
Prior ear tubes	6 (16.2)	4 (25.0)	2 (9.5)	0.478
Prior sinus surgery	36 (97.3)	16 (100.0)	20 (95.2)	0.39
Baseline scores (mean ± SD)				
ETDQ-7	17.8 ± 10.9	28.6 ± 7.4	9.5 ± 2.5	<0.001
SNOT-22 total	40.6 ± 22.9	55.3 ± 20.7	30.8 ± 19.0	0.001
SNOT-22 ear/facial	3.7 ± 3.6	7.5 ± 3.8	1.3 ± 2.1	<0.001
Lund-Kennedy	1.5 ± 3.1	2.2 ± 3.6	1.0 ± 2.7	0.234

Abbreviations: ETD, Eustachian tube dysfunction; ETDQ-7, Eustachian Tube Dysfunction Questionnaire-7; GERD, gastroesophageal reflux disease; SD, standard deviation, SNOT-22, Sinonasal Outcome Test-22.
p-value is result of *t*-test comparison of ETD-positive versus ETD-negative patients.

Eustachian tube balloon dilation. A total of 97.3% of the patients had undergone prior sinus surgery. Dupilumab was started at a mean of 41.4 months (median 14, range 1–178) since the most recent surgery. The mean follow-up length was 12.1 ± 8.2 months. Sixteen patients (43.2%) were ETD-positive at baseline and demonstrated significant improvement in ETDQ-7 (28.6 ± 7.4 to 20.5 ± 8.6, $p = 0.022$). Twelve of 16 (75%) patients achieved MCID in ETDQ-7. Six (37.5%) patients had ETD resolution with a follow-up ETDQ-7 score of <14.5. Baseline ETD-negative patients did not have significant changes in ETDQ-7 (9.5 ± 2.5 to 11.0 ± 4.2, $p = 0.328$).

In regression analysis, higher baseline ETDQ-7 (odds ratio [OR] = 1.97, 95% confidence interval [CI], 1.93–2.06) and prior history of ear tubes (OR = 1.47, 95% CI, 1.08–1.87) were associated with achieving MCID in ETDQ-7, while history of asthma, allergic rhinitis, gastroesophageal reflux disease, smoking history, baseline SNOT-22, SNOT-22 ear/facial subdomain, and Lund-Kennedy score had no significant association. No medications (steroids, antihistamines, or aspirin) were significantly associated with ETDQ-7 change.

When comparing ETD-positive cohorts treated with dupilumab ($n = 16$) versus ESS ($n = 16$), both cohorts had similar age, sex, baseline SNOT-22, baseline ETDQ-7, and follow-up length (Table 2). ETDQ-7 improved significantly following treatment with dupilumab (28.6 to 20.5, $p = 0.022$) and ESS (25.9 to 16.3, $p = 0.0004$). The magnitude of improvement in the ETDQ-7 score was similar for dupilumab versus ESS (8.1 vs. 9.6, $p = 0.629$).

4 | DISCUSSION

This study suggests that in patients with CRSwNP and ETD, dupilumab can alleviate ETD at a similar rate and magnitude as ESS.[1] Patients with a higher burden of ETD—as inferred from higher baseline ETDQ-7 and

TABLE 2 Comparison of Eustachian tube dysfunction outcomes in dupilumab versus endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyposis and with a baseline ETDQ-7 score of >14.5

	Dupilumab ($n = 16$)	Surgery ($n = 16$)	p-value
Age (years)	53.5	52.9	0.630
Male sex (%)	62.5	62.5	1.000
Follow-up time (months)	12.6	12.8	0.867
SNOT-22 Baseline	55.3	49.8	0.574
Lund-Kennedy Baseline	6.0	5.8	0.920
ETDQ-7 Baseline	28.6	25.9	0.219
ETDQ-7 Post-Treatment	20.5	16.3	0.065
ETDQ-7 Change	−8.1	−9.6	0.629

Abbreviations: ETDQ-7, Eustachian Tube Dysfunction Questionnaire-7; SNOT-22, Sinonasal Outcome Test-22.

history of ear tubes—are more likely to improve. While the clinical association between CRSwNP and ETD is well-established,[1,2] the mechanism of this relationship is poorly understood. This study suggests that Th2 cytokines driving sinonasal inflammation may also be involved in Eustachian tube pathology.

Eustachian tube balloon dilation is widely employed in ETD management, though the added value of balloon dilation in the setting of CRSwNP is unknown. A small study found that balloon dilation alone had a 75% rate of ETD improvement in CRSwNP, defined as >20% reduction in the ETDQ-7 score.[6] In our study, though many patients achieved MCID, the mean post-treatment ETDQ-7 of 21.7 was still well above the clinically significant threshold of 14.5. The role of Eustachian tube balloon dilation in CRSwNP certainly warrants further study.

This study has several limitations. This study was retrospective and had a relatively small sample size; thus comparisons may be underpowered to detect differences. There was significant variation in follow-up intervals and reasons for follow-up visits. Furthermore, this study lacked objective measures of ETD such as audiograms and tympanograms. Additionally, the clinical employment of dupilumab varied significantly—from upfront medical therapy to post-ESS maintenance therapy to salvage therapy for recurrent polyposis—thus causing potential heterogeneity of the data.

5 | CONCLUSION

Patients with CRSwNP and comorbid ETD are likely to experience improvement in ETD symptoms on dupilumab, at a similar magnitude as sinus surgery.

CONFLICT OF INTEREST

Peter H. Hwang: Speaker Bureau for Sanofi, Speakers Bureau and clinical trial funding for GlaxoSmithKline. All other authors declare no conflicts of interest.

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The link between allergic rhinitis and chronic rhinosinusitis

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Purpose of review
Allergic rhinitis and chronic rhinosinusitis (CRS) are common disorders affecting millions of people worldwide. Although allergic rhinitis and CRS are distinct clinical entities, certain CRS endotypes share similar pathological mechanisms as those seen in patients with allergic rhinitis. This review assesses the literature behind the similarities and differences seen in patients with CRS and allergic rhinitis, and the role atopy might play in the pathophysiology of CRS.

Recent findings
In examining the associations between allergic rhinitis and CRS, most studies have focused primarily on CRS with nasal polyps and type 2 inflammation in CRS. Recent studies have demonstrated the similarities and differences in pathologic mechanisms behind allergic rhinitis and CRS, with an emphasis on patient endotypes, genetics, and the nasoepithelial immunologic barrier. Related immunopathology shared by allergic rhinitis and type 2 inflammation in CRS has allowed for therapeutic overlap with biologic treatments.

Summary
Allergic rhinitis and CRS often present as comorbid conditions, and understanding the relationship between allergic rhinitis and CRS is important when considering treatment options. Advances in understanding the genetics and immunology, as well as biologic and immunotherapeutic treatments have improved outcomes in patients with CRS, especially in the setting of atopy.

Keywords
allergic rhinitis, biologics, chronic rhinosinusitis, mucosal immunity

INTRODUCTION

The pathophysiologic relationship between allergic rhinitis and chronic rhinosinusitis (CRS) is complex. In this review article, we aim to address the prevalence of allergic rhinitis in CRS patients, as well as genetic and pathophysiologic mechanisms common to both allergic rhinitis and CRS. We also summarize related studies of the treatment for allergic rhinitis and CRS, and current strategies in immunotherapy and biologics.

Conservative estimates place the prevalence of allergic rhinitis between 15 and 30%, with symptomatology peaking in the second to fourth decade of life [1]. In contrast, CRS prevalence is estimated at around 5–12% based on patient-reported nasal symptomatology, but less prevalent at 3–6.4% when confirmed with radiologic evidence [2]. Peak prevalence for CRS is later in life around the 5th or 6th decade [2–4]. Globally, trends indicate an increasing prevalence of allergic rhinitis and a stable prevalence of CRS [5,6]. de Marco *et al.* [5] observed an increasing prevalence of allergic rhinitis from 16.8% to 25.8% over a 20-year period. In contrast, Xu *et al.* [6] utilized a retrospective healthcare administrative claims database to identify that the prevalence of CRS appeared to be stable around 2–2.5% over a nearly 10-year period.

EPIDEMIOLOGIC ASSOCIATIONS

Differentiating between overlapping symptoms in allergic rhinitis and CRS is challenging. Between 25 and 70% of patients with CRS are codiagnosed with

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KEY POINTS

- The reported rate of concomitant allergic rhinitis in patients with CRS varies between studies, and certain subtypes of CRS, such as central compartment atopic disease, allergic fungal rhinosinusitis, and aspirin-exacerbated respiratory disease, are demonstrated to be more related to aeroallergen sensitization.
- Allergic rhinitis and type 2 CRS share relevant immunopathophysiologic pathways, but the dominant innate or adaptive immune cells and the extent of the inflammation-related tissue remodeling may be different between them.
- Emerging biologics targeting type 2 inflammatory mediators have been shown to provide favorable treatment results in patients with CRS and allergic rhinitis, while the role of immunotherapy in CRS may require more evidence to select appropriate patient subgroups.

allergic rhinitis [7–9]. The coexistence of allergic rhinitis with CRS varies widely depending on the CRS subtype [10]. The relationships among CRS subtypes, allergic rhinitis, and asthma were illustrated in Fig. 1. Some studies have identified a higher prevalence of allergic rhinitis in chronic rhinosinusitis with nasal polyps (CRSwNP) compared with chronic rhinosinusitis without nasal polyps (CRSsNP), whereas others have shown no difference between the two groups [11–15]. Certain subtypes of CRS have reported a closer association with allergic rhinitis [12,16▪]. Central compartment atopic disease, for example, has been closely correlated with allergic rhinitis from inhalant allergen sensitization. Other CRS subtypes, such as allergic fungal rhinosinusitis and aspirin-exacerbated respiratory disease, have also been demonstrated to have relevant links to atopy [17–19]. As for the prognostic impact of comorbid allergic rhinitis on the severity of CRS, allergy does not appear to affect symptom scores, modify the clinical manifestations of CRS, nor influence the recurrence of polyps [15,20,21].

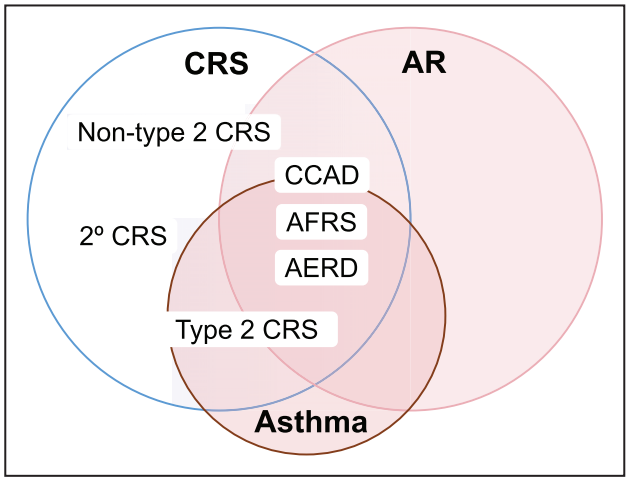

FIGURE 1. The relationship between chronic rhinosinusitis and allergic rhinitis. Chronic rhinosinusitis is a heterogeneous disease that constitutes several subtypes. Patients with non-type 2 chronic rhinosinusitis and secondary chronic rhinosinusitis are less likely to experience comorbid allergic rhinitis, while those of type-2 chronic rhinosinusitis are usually overlapping with coexisting asthma and allergic rhinitis. Patients of aspirin-exacerbated respiratory disease, allergic fungal rhinosinusitis, and central compartment atopic disease are reported to have a higher ratio of coexisting allergic rhinitis.

Both allergic rhinitis and CRS often present with comorbid asthma. The prevalence of asthma in allergic rhinitis is around 40%, and nearly 60% in CRSwNP [22–25]. CRS patients may be differentially affected by asthma based on their CRS endotype. In CRSwNP type 2 disease mediated predominantly by eosinophils, coexisting asthma has been reported in as much as 60% of patients, whereas in CRSwNP type 1 disease mediated by neutrophils, lower rates of comorbid asthma have been reported, ranging from 4.5 to 22% [22–25]. Additional studies report the prevalence of asthma in patients with CRSsNP between 21 and 47% [12,26]. Given the high incidence of asthma in patients with atopy, rhinologists involved with allergy management should consider screening for comorbid asthma in CRS patients with allergic rhinitis.

GENETIC STUDIES OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

The genetics underlying patients' predisposition toward allergic rhinitis is complex. Concordance in monozygotic vs. dizygotic twin studies suggests a heritability as high as 70–80% [27]. Recent genome-wide association (GWAS) and human leukocyte antigen fine-mapping studies have attributed 39% of allergic rhinitis to 41 associated loci [28]. Additional GWAS studies have identified loci associated with mechanistic modification of IgE pathways that are associated with allergic rhinitis [29]. Polymorphisms associated with cytokine dysfunction, receptor dysregulation, and IL-4, IL-13, IL-18, and IL-33 are also associated with allergic rhinitis [30–32].

Although allergic rhinitis and CRS share common symptomatology, the quest to identify overlapping genes regulating shared pathways is limited by the small sample sizes of genetic studies in CRS. Small sample size GWAS studies have tried to provide insight into some of the genetics associated

with CRS, but extensive large sample size genetic analysis of the multiple phenotypes and endotypes comprising CRS is lacking [33,34]. Smaller scale studies have identified nearly 70 candidate genes associated with CRS requiring further investigation [35]. Some of these include mutations in the cystic fibrosis transmembrane conductance regulator gene, while others include epithelial barrier dysfunction, genetic variations in taste receptors, and immune dysregulation [36–38]. Specific to the known genes affecting CRS and allergic rhinitis, we do not see a definitive genetic overlap. Given the small sample sizes of existing CRS studies, broader studies focused on connections between acute rhinosinusitis and CRS will be necessary for the future to demonstrate any direct associations.

IMMUNOLOGIC PATHOPHYSIOLOGY OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

The role of allergy and aeroallergens in the pathophysiology of CRS is controversial [39,40]. CRS is a heterogeneous and multifactorial inflammatory disease, with distinct and mixed endotypes. Here, we address several proposed pathophysiologic mechanisms of allergic rhinitis and CRS, and the related immune pathways summarized in Fig. 2.

Barrier dysfunction of airway epithelium

Loss of epithelial integrity has been hypothesized to be a significant mechanism of disease in both allergic rhinitis and CRS. Aeroallergens and other environmental irritants, including tobacco smoke, particulate matter, and air pollution, are thought to contribute to epithelial barrier dysfunction. Dysregulation of tight junction proteins including E-cadherins (E-cad), zonula occludens 1 (ZO-1), and occludins may be an inciting event that disrupts the integrity of the epithelial barrier, leading to the development of allergic rhinitis [41▪▪,42–44]. Patients with dust mite allergy and allergic rhinitis exhibited decreased expression of ZO-1 and occludins [45], while expression of E-cad and ZO-1 were downregulated after exposure to IL-4, IL-5, and TNF-α in patients with allergic rhinitis vs. controls [46].

Similar to studies supporting the barrier dysfunction hypothesis in allergic rhinitis, studies in CRS have shown that mucosal tissue of patients with CRSwNP expressed decreased ZO-1 and occludins and increased tissue permeability [47]. Disruption of epithelial integrity is thought to lead to translocation of microbes across the epithelial barrier, microbial dysbiosis, colonization of opportunistic pathogens, as well as the microinflammation of the subepithelial areas [41▪▪]. Decreased integrity of the nasoepithelial barrier may specifically allow bacteria such as *Staphylococcus aureus* and *Pseudomonas* to invade, which have been shown to disproportionally affect patients with CRS [48,49].

Barrier dysfunction is also exacerbated by the inability to maintain mucociliary clearance. Mucociliary clearance contributes to the maintenance of this barrier by clearing out surface irritants, pollutants, and bacteria to reduce local inflammation in the microenvironment [50,51]. Patients with underlying genetic ciliary dysfunction such as cystic fibrosis show an increased risk for CRSwNP; likely, in part, to this inability to clear irritants producing inflammation [52]. Additionally, bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Pseudomonas aeruginosa* have been shown to generate inflammatory microenvironments impeding mucociliary clearance and increasing the risk for CRS [53]. Similar to CRS, patients with allergic rhinitis have also been noted to have increased mucociliary clearance times vs. controls [54]. Impaired epithelial barriers facilitate continued immune responses, allergen uptake, and allergen exposure mediating type 2 inflammation in CRS and allergic rhinitis.

In addition to epithelial integrity and impaired mucociliary clearance, the composition and distribution of various cell types in the airway epithelium may differ between normal and diseased epitheliums [55]. High throughput transcriptomic studies at the level of the individual cell have characterized different cell types and states that have not been documented when using microscopy [56,57]. In a study of allergic diseases and type 2 inflammation, basal cell differentiation was impaired through the activation of IL-4/IL-13 and Wnt pathways [58]. Changes in the differentiation of epithelial basal cells may alter subepithelial immune responses and contribute to the persistence of inflammatory disease [58]. This study indicates that airway epithelium may play a role in inflammatory/allergy memory, further directing immune responses in type 2 inflammation. Additional studies are required to verify these proposed mechanisms.

Mucosal immune responses

In addition to shared commonalities in barrier dysfunction in both allergic rhinitis and CRS, the subsequent immune responses also share intriguing commonalities.

Allergic rhinitis follows a classic type 1 hypersensitivity reaction, and type 2 inflammation later on [59,60▪]. The initiating factor for the development of allergic rhinitis is exposure and sensitization to

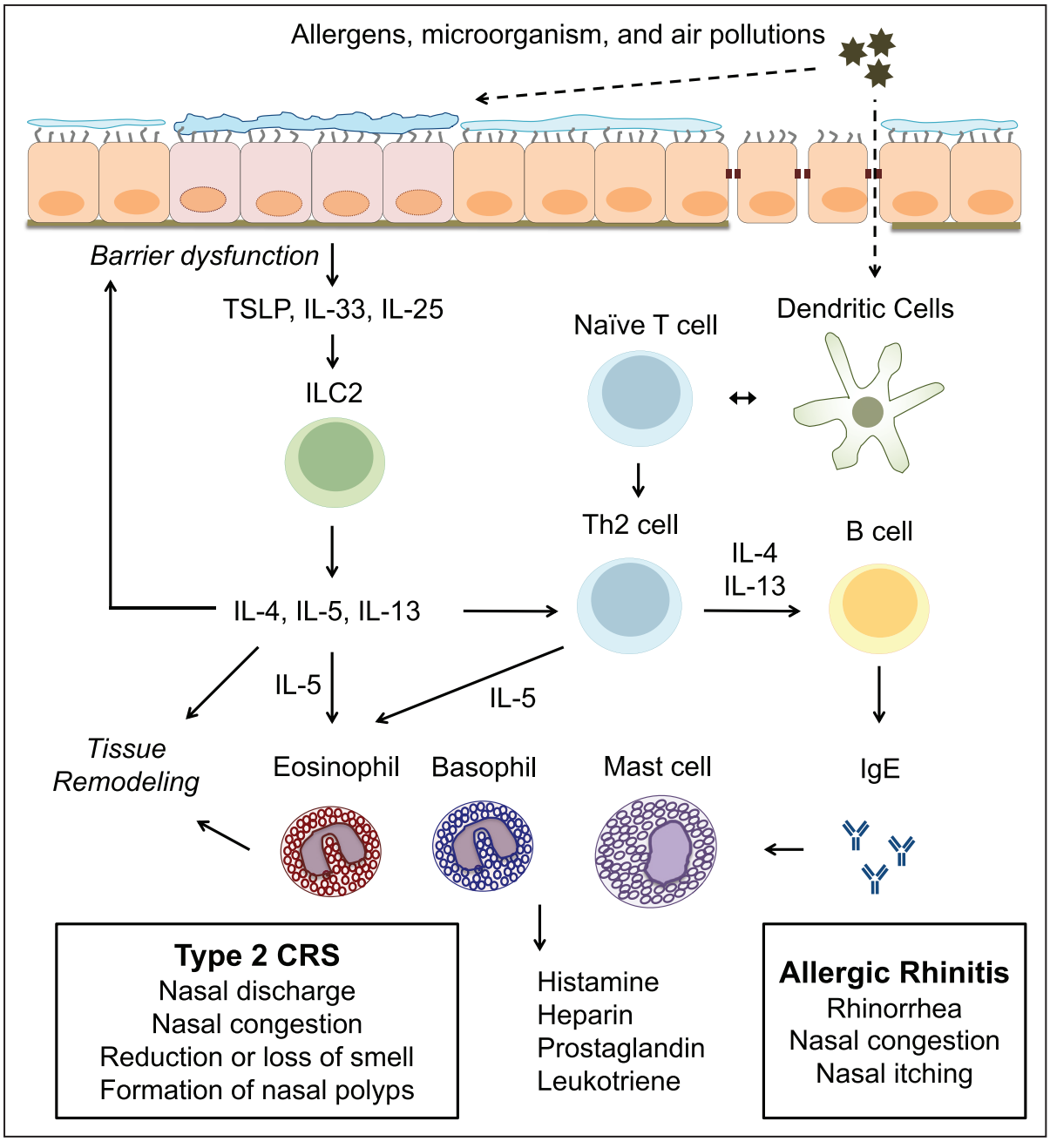

FIGURE 2. Overview of the immune responses in type 2 chronic rhinosinusitis and allergic rhinitis. In the diseased mucosa, the epithelial barrier is dysregulated by decreased expressions of tight junction molecules, impaired mucociliary clearance, and altered composition and distribution of various cell types, allowing allergen and other environmental stimulants to provoke further innate and adaptive immune responses. Allergens are presented to naïve T cells by dendritic cells, with subsequent Th2 cell differentiation promoted through IL-4. Th2 cells encourage B-cell activation and IgE class switching to produce specific IgE, which bind effector cell IgE receptors (FcεRI) on mast cells and basophils. Meanwhile, dysregulated epithelial barrier produces alarmins, such as IL-25, IL-33, thymic stromal lymphopoietin, and activates innate lymphoid cells group 2. As a result, type 2 inflammatory cytokines are generated robustly, and both innate and adaptive immune responses are intensified leading to tissue remodeling and symptoms of both chronic rhinosinusitis and allergic rhinitis.

local allergens. These allergens are taken up by dendritic cells within the nasal mucosa, processed, and presented to naïve CD4+ helper T cells residing within local lymph nodes [61]. Naïve CD4+ helper T cells differentiate into Th1/Th2 lineages, with Th2 cell differentiation promoted by IL-4 activation of tyrosine phosphorylation of STAT6 leading to upregulation of GATA3 expression [62,63]. GATA3

functions to upregulate the expression of IL-4, IL-5, and IL-13 which all serve to mediate type 1 hypersensitivity reactions and further type 2 inflammation in patients with allergic rhinitis [64,65]. Other signaling pathways such as T-cell receptor (TCR)-mediated signaling, STAT5 activation, and notch signaling lead to the upregulation of the Th2 cell lineage [66–68]. Allergen-specific Th2 cells encourage IgE class switching and B-cell activation into plasma cells producing allergen-specific IgE [69]. Allergen-specific IgE binds effector cell IgE receptors (FcεRI) on mast cells, and basophils. When previously sensitized allergens are encountered, allergen-specific IgE can crosslink IgE and FcεRI leading to effector cell activation. Crosslinked mast cells release a range of mediators including histamine, heparin, leukotrienes, and prostaglandins while allergen-specific Th2 continues to release IL-4, IL-5, and IL-13 [70]. Effector cell degranulation and Th2 cytokine release contribute to increased vascular permeability, mucus production, and eosinophilic infiltration seen in the clinical symptomatology of patients with allergic rhinitis.

The pathophysiology of type 2 CRS is similar to the late phase of allergic reactions where Th2 cells activate Il-4, IL-5, and IL-13 signaling pathways with the production of local IgE and eosinophilia [71]. In CRS Type 2 inflammation appears to mediate much of the shared symptomatology between allergic rhinitis and CRS through similar effector cell activation. Recent studies have also identified innate lymphoid cells (ILCs), which are tissue-resident immunocytes that can rapidly respond to alarmin signals from the epithelium and direct multiple immune responses. Some of these ILC2 cells have been found in sinonasal mucosa and nasal polyps [72,73]. Epithelial alarmin, such as IL-25, IL-33, and thymic stromal lymphopoietin, can activate ILC2, leading to the secretion of IL-5 and IL-13 from Th2 cells [72,73]. Accumulation of these type 2 cytokines ultimately results in tissue remodeling from the recruitment of eosinophils and other associating immune cells [74].

Emerging characteristics of IgE in allergy and type 2 inflammation

IgE may play an integral role in mediating many of the shared inflammatory reactions seen in nonatopic allergic rhinitis patients, and CRS patients with IgE specific to *S. aureus* enterotoxins.

A subset of nonatopic allergic rhinitis patients exhibits a local, organ-specific IgE inflammatory response without additional atopic features. Patients with local allergic rhinitis demonstrate similar symptoms to their atopic counterparts including increased lymphocytes, basophils, eosinophils, and mast cells [75,76]. A study conducted by López *et al.* [77] identified patients with IgE-positive local inflammatory reactions in dust mite allergen nasal challenges, but lacked systemic and allergen-specific IgE. A notable local response to dust mite allergen and symptomatic allergic rhinitis without a provable systemic sensitization suggests a population of allergic rhinitis patients with organ or site-specific hypersensitivity to allergens.

Meanwhile, antigen-specific IgE towards *S. aureus* enterotoxins has been identified in some CRS populations [78,79]. This finding appears to be an IgE-mediated process localized to the nasal mucosa in patients with CRSwNP, similar to the localized response seen in nonatopic patients with allergic rhinitis [80]. *S. aureus* produces potent superantigen capable of indiscriminately activating T-cells via bind of the TCR β-chain [81]. *S. aureus* enterotoxins have also been shown to activate additional inflammatory cells within the nasal mucosa, including B-cells and eosinophils, followed by subsequent type 2 inflammation [82]. Expansion of local polyclonal IgE against *S. aureus* superantigens has been noted specifically in CRSwNP, with higher rates in patients with comorbid asthma [83▪]. The role of IgE in allergic rhinitis and CRS, and oligoclonal vs. polyclonal immune responses, reflects the complexity of underlying pathophysiology, while common to both, is not necessarily causally related [80,84]. Hence, while allergic rhinitis and CRS share common immunologic characteristics, the factors leading to their divergent clinical manifestations constitute an important knowledge gap.

TREATMENT

With the introduction of biologic therapies for the treatment of type 2 CRSwNP (omalizumab, mepolizumab, dupilumab), endotype-directed treatment can be determined based on the immunologic profile of patients. Recent studies of cytokine expression profiles of CRSwNP in Asian populations have revealed a higher incidence of neutrophilic inflammatory type 1 response vs. type 2 in western populations [85,86]. Certain biomarkers have been proposed to predict the endotypes of CRS, including blood eosinophilia, concomitant asthma, and the ethmoid predominant pattern on computed tomography scans [87–89]. Because serum IgE and ImmunoCAP testing has not shown significant associations with eosinophilic CRS, allergy may not be an applicable indicator for type 2 or eosinophilic CRS given the lack of observable atopy [74,76].

Biotherapeutic agents focused on cytokines have shown efficacy in treating both allergic rhinitis and CRS, possibly secondary to targeting shared

pathologic mechanisms [90–92,93▪▪]. Omalizumab, a recombinant anti-IgE mAb, has been demonstrated as safe and effective in treating both seasonal and perennial allergic rhinitis [92,94–96]. Adding omalizumab to allergen immunotherapy for the treatment of allergic rhinitis may provide superior treatment outcomes with reduced adverse events per recent evidence [97–100]. In patients with CRSwNP treated with omalizumab, phase 3 clinical trials noted improvements in sinonasal scores and objective clinical outcomes as well [93▪▪]. Similarly dupilumab, a mAb targeting IL-4 receptor α subunit, significantly improved allergic rhinitis-related symptoms according to post-hoc analyses from phase 2 and phase 3 studies of patients with uncontrolled asthma and comorbid perennial allergic rhinitis [91,101▪▪]. In a phase 2a, multicenter, randomized, placebo-controlled study in adults with seasonal allergic rhinitis, dupilumab improved tolerability toward subcutaneous immunotherapy (SCIT) but did not affect post-allergen challenge nasal symptom scores compared with SCIT alone [102]. However, these biotherapeutic agents are not yet widely used in treating allergic rhinitis. Similar treatment efficacy has been shown with the biologic treatment of CRSwNP. In Liberty NP Sinus-24 and Liberty NP Sinus-52 phase 3 trials, the effects of dupilumab improved patient-reported sinonasal symptoms [90]. Objective outcome measures, including sinus opacification and polyp size, were also improved with dupilumab [90]. In SYNAPSE phase 3 trials, mepolizumab, a mAb targeting IL-5 was likewise shown to be effective in reducing nasal obstruction and nasal polyp size in patients with CRSwNP [103▪▪]. Extensive studies and trials on the effects of mepolizumab on patients with allergic rhinitis are still currently lacking. In addition, head-to-head randomized controlled clinical trials of biologics indicated for CRSwNP have yet to be performed. Even with evidence of favorable treatment outcomes in both allergic rhinitis and CRS with these novel treatments, the cost of biologic agents should be considered.

In addition to biologics, allergen desensitization immunotherapy has been evaluated as an adjunctive treatment for CRS patients. There has been demonstrated efficacy in the reduction of symptoms and recurrence of allergic fungal sinusitis, and in a prospective study, postoperative SCIT has shown improved nasal symptoms scores of CRS patients with concomitant allergic rhinitis [104–107]. Whether specific immunotherapy desensitizing against common allergens, such as pollen or house dust mites, will modify clinical presentations of CRS is unknown. This is likely due to the success of current medical and surgical treatments in reducing nasal symptoms in patients with CRS, decreasing the need for these cost-prohibitive methods of desensitization. Currently, the impact of immunotherapy on the development of CRS and disease severity in allergic rhinitis patients is undetermined, and whether immunotherapy can provide an extra advantage in the treatment of type 2 CRS with comorbid asthma requires further study.

CONCLUSION

Allergic rhinitis and CRS are common pathologies affecting millions of patients every year. Efforts in the literature have primarily focused on the correlation and shared disease mechanisms of allergic rhinitis and CRSwNP, especially in the setting of type 2 inflammation, with the connection between allergic rhinitis and non-type 2 CRS requiring further study. Advancements in our understanding of genetics, immune pathophysiology, and recent developments in biologics, may afford physicians the ability to treat these differing pathologies. In the future, large population-based studies identifying the genetics underlying specific subtypes of CRS as well as studies focused on how immunotherapy may affect CRS and allergic rhinitis will contribute greatly.

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Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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