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Review Article

Can Gastroesophageal Reflux Disease without Concomitant Eosinophilic Esophagitis Cause High-level Esophageal Eosinophilia?

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Abstract

There are no intraepithelial eosinophils present in the normal esophageal mucosa. It is well established that gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE) individually can result in esophageal eosinophilia and that the two disorders frequently coexist in the same patient. Nevertheless, the first step in the diagnostic algorithm for patients with esophageal symptoms associated with esophageal eosinophilia is to exclude non-EoE disorders that can cause esophageal eosinophilia, including GERD. While it is clear that GERD without EoE can cause low-level esophageal eosinophilia, it is less clear whether GERD alone can induce EoE-level esophageal eosinophilia (i.e., ≥15 eosinophils per high-power field). In this report, we have reviewed mechanisms by which reflux might induce eosinophilia in the esophagus and assessed studies suggesting that GERD alone can induce EoE-level esophageal eosinophilia. Studies on the latter issue have suffered from numerous shortcomings, including the use of outmoded or dubious methods for identifying GERD. Many of these studies were published prior to the realization that EoE can respond to proton pump inhibitor treatment. Our review of these studies suggests that GERD alone rarely, if ever, causes EoE-level eosinophilia (perhaps <1% of cases). For patients with definitive evidence of GERD associated with EoE-level esophageal eosinophilia but without endoscopic or clinical features of EoE, it is impossible to determine whether the eosinophilia is caused solely by GERD, by underlying but unrelated EoE that does not manifest typical features, or by EoE driven by GERD-induced defects, such as impaired esophageal barrier function. Until better diagnostic tests for EoE become available, this situation will remain a clinical conundrum.

Introduction

Gastroesophageal reflux disease (GERD) is a condition in which the reflux of gastric contents into the esophagus results in symptoms (typically heartburn and regurgitation) and/or complications such as peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma.[1] GERD develops through a multifactorial process that involves dysfunction or inadequacy of the mechanisms that normally prevent gastroesophageal reflux, the mechanisms that normally clear noxious material from the esophagus, and the mechanisms that normally enable the esophageal epithelium to resist acid-peptic injury.[2] GERD is especially prevalent in the Western world, where it is estimated to affect up to 20% of the population.[3] In GERD patients, biopsies of the distal, squamous-lined esophagus typically reveal thickening of the basal cell layer, papillary elongation, and dilated intercellular spaces.[4] However, neither the symptoms nor histologic features of GERD are specific to the disorder, and an objective diagnosis of GERD requires endoscopic evidence of Los Angeles grade B, C, or D reflux esophagitis, and/or Barrett's esophagus with intestinal metaplasia, and/or esophageal reflux monitoring demonstrating abnormal reflux.[5]

Eosinophilic esophagitis (EoE) is an allergy-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction (typically dysphagia and food impaction) and histologically by eosinophil-predominant esophageal inflammation.[6,7] EoE results from a type 2 inflammatory process that causes eosinophils and mast cells to infiltrate the esophagus, where they release secretory products that mediate tissue damage, tissue remodeling,

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and symptoms.[8] The first description of EoE as a unique clinicopathologic disorder was published in 1993,[9] and its frequency has increased dramatically since then. The characteristic endoscopic features of EoE include edema, rings, exudates, linear furrows, and strictures, though the esophagus can appear normal endoscopically in up to 10% of cases.[8] For patients with esophageal symptoms, the diagnosis of EoE is established when esophageal mucosal biopsies reveal ≥15 eosinophils per high-power field, and other causes of esophageal eosinophilia are excluded.[10] GERD is by far the most prevalent cause of esophageal eosinophilia other than EoE, and since EoE's first description in 1993, GERD has been the disorder causing the most confusion and controversy in defining EoE.[11]

The considerable overlap in symptoms and histologic features of EoE and GERD occasionally makes it difficult, if not impossible, to distinguish between the two disorders. Heartburn, dysphagia, and chest pain are frequent symptoms of both. Thickening of the basal cell layer, papillary elongation, and dilated intercellular spaces are characteristic histologic features common to both EoE and GERD, and there are descriptions of eosinophils in the esophagus of GERD patients dating back to at least the 1950s.[12] In fact, in 1982, Winter *et al*. proposed that the finding of intraepithelial eosinophils was a new diagnostic criterion for reflux esophagitis,[13] a notion that was quickly and widely embraced by practicing pathologists. This popular idea undoubtedly delayed the recognition of EoE as a unique clinicopathologic disorder, since many early cases were dismissed as esophageal eosinophilia due to GERD.

In 2007, a report sponsored by the American Gastroenterological Association Institute defined EoE as a primary disorder of the esophagus characterized by upper gastrointestinal symptoms, an esophageal biopsy showing ≥15 eosinophils per high-power field (HPF), and the absence of GERD, as demonstrated by lack of response to proton pump inhibitors (PPIs).[14] That same year, Spechler *et al*. published a report arguing that the concept of establishing a clear distinction between GERD and EoE was too simplistic, suggesting at least four situations in which GERD might be associated with esophageal eosinophilia: 1) GERD-induced esophageal injury might trigger eosinophil infiltration without EoE, 2) GERD and EoE might coexist but be unrelated, 3) EoE might contribute to or cause GERD, and 4) GERD might contribute to or cause EoE.[15] Later studies established that PPIs have anti-inflammatory effects (independent of their antisecretory effects) that can heal EoE.[16,17] These developments eventually led to the rejection of the notion that GERD and EoE are mutually exclusive disorders and that a PPI trial can distinguish between the two.[18]

Despite recent advances in our understanding of the complex relationship between GERD and EoE, much confusion remains, especially regarding the level of esophageal eosinophilia that might distinguish the two disorders. There are no intraepithelial eosinophils in the normal esophagus, and the esophageal eosinophilia of GERD is typically low-grade, involving fewer than seven eosinophils per HPF.[19] However, some reports have contended that GERD can cause profound, EoE-level esophageal eosinophilia (i.e., ≥15 eosinophils per HPF).[20] We recently reviewed some of those reports and found reasons to question their conclusions. The primary purpose of this review is to explore mechanisms by which reflux might induce eosinophilia in the esophagus and to assess reports concluding that GERD alone can induce EoE-level esophageal eosinophilia.

Potential mechanisms for reflux-induced esophageal eosinophilia

Vascular cell adhesion molecule 1 is a protein that mediates the adhesion of eosinophils and other leukocytes to vascular epithelium,[21] and human esophageal vascular endothelial cells express vascular cell adhesion molecule 1 when exposed to acid.[22] Human esophageal smooth muscle cells exposed to acid produce and release the phospholipid platelet-activating factor, an eosinophil chemoattractant that mediates eosinophil adhesion to vascular endothelial cells and eosinophil degranulation.[23–27] These acid-induced effects in the esophagus could potentially lead to eosinophil infiltration in patients with GERD. In contrast, very different mechanisms appear to underlie the esophageal eosinophilia of EoE. In EoE, the Th2 cytokines IL-4 and IL-13 stimulate esophageal epithelial cells to secrete eotaxin-3, a potent eosinophil chemoattractant thought to draw eosinophils into the esophagus (Fig. 1). However, eotaxin-3 is unlikely to contribute to the esophageal eosinophilia of GERD, because acidic bile salt solutions have been shown to *decrease* the secretion of eotaxin-3 stimulated by Th2 cytokines in esophageal epithelial cells.[28] In patients who have both EoE and GERD, it is unclear how these potentially competing mechanisms influence the resulting esophageal eosinophilia.

Esophageal eosinophilia associated with gastroesophageal reflux in children

As noted above, the modern, objective diagnostic criteria for GERD include endoscopic evidence of Los Angeles grade B, C, or D reflux esophagitis, and/or Barrett's esophagus with intestinal metaplasia, and/or esophageal reflux monitoring demonstrating abnormal reflux.[5] Studies on the association of esophageal eosinophilia with GERD have used a variety of different GERD diagnostic criteria, many of which did not include the modern, objective criteria. This shortcoming is especially common in pediatric studies on this issue.

The aforementioned study that first proposed intraepithelial eosinophils as a diagnostic criterion for GERD included 46 children (32 under five years) who had esophageal pH monitoring and endoscopy with esophageal biopsy performed for evaluation of chronic pulmonary or upper gastrointestinal symptoms, as well as nine control children with extraesophageal disorders.[13] The pH monitoring studies were considered abnormal based on prolonged acid clearance times or increased frequencies of acid reflux—parameters that are no longer considered definitive for diagnosing GERD. Three of the nine control patients had esophageal biopsies, and no eosinophils were noted. Among the 46 study patients, 18 were found to have ≥1 intraepithelial eosinophil(s) in esophageal biopsy specimens. Maximum eosinophil counts were not described, so it is unclear whether any patient met the EoE diagnostic threshold of ≥15 eosinophils per HPF. However, eosinophilia was generally low-grade, as 12 of the 18 patients had only one eosinophil per HPF. Abnormal acid clearance was found in 35 (76%) of the 46 patients, but in 17 (94%) of the 18 with intraepithelial eosinophils. The authors concluded that intraepithelial eosinophils were a highly specific indicator for reflux esophagitis.

In a retrospective study published in 1985, esophageal biopsies from 33 infants (age < two years) with symptomatic gastroesophageal reflux (GER) were compared to post-mortem, full-thickness esophageal samples taken from a control group of 13 infants who had died of sudden accident or homicide.[29] The symptoms prompting evaluation for GER in the study patients were severe vomiting in 22 (six with failure to thrive), apneic spells in seven, and respiratory symptoms in four. GER was confirmed in 21 study patients by barium esophagram, a test no longer considered definitive for identifying pathologic reflux, and in 12 by esophageal pH monitor-

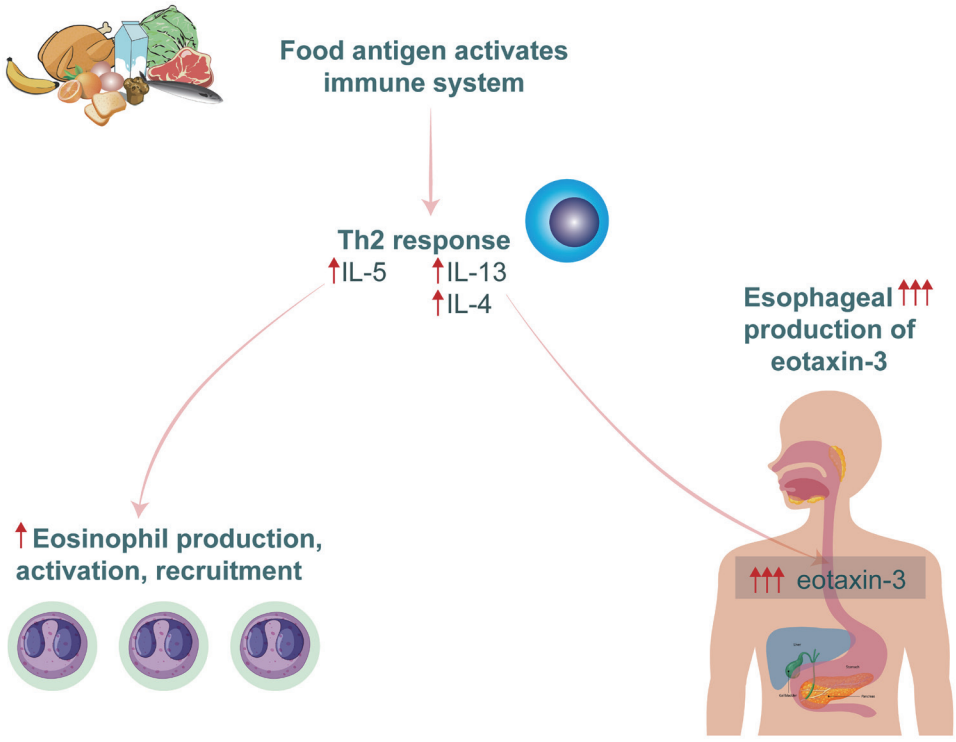

Fig. 1. Th2 and eotaxin mechanisms in EoE. A genetically susceptible individual is exposed to a food antigen, which activates the immune system and triggers differentiation into Th2 cells that release cytokines with eosinophil properties. Cytokine IL-5 promotes eosinophil production, activation, and recruitment. Additionally, cytokines IL-4 and IL-13 increase esophageal production of eotaxin-3, an eosinophil attractant. The arrow means increased. For example, IL-5 promotes increased eosinophil production, etc. (Image designed from materials by Freepik and Pixabay).

ing assessed using either an obsolete gastroesophageal reflux score or a now-defunct Tuttle test, in which 0.1N HCl is instilled in the stomach and acid reflux is monitored for up to one hour thereafter. In the control group, histologic evaluation revealed a mean of only 0.08 ± 0.28 intraepithelial eosinophils. Therefore, the investigators defined histologic reflux esophagitis as ≥1 intraepithelial eosinophil in the most extensively involved HPF. By that criterion, 20 of the 33 patients had histologic reflux esophagitis; nine had <8 eosinophils per HPF, while 11 had ≥25 eosinophils per HPF. This report was published eight years before EoE was first described as a unique clinicopathologic entity,[9] and the authors attributed the esophageal eosinophilia to GER. However, vomiting and failure to thrive are now recognized as typical EoE symptoms in infants, and it seems likely that many of the patients with EoE-level esophageal eosinophilia in this study actually had EoE.

Researchers at the University of Pennsylvania, early leaders in recognizing and studying EoE, reported their experience in 381 children with EoE in a paper published in 2005.[30] At that time, they had been identifying EoE in patients with "chronic symptoms of reflux or dysphagia that persisted despite a two-month trial of a PPI." Patients were categorized into a GER subgroup of 312 patients who presented with "reflux symptoms" (including one or a combination of complaints of vomiting, regurgitation, epigastric pain, heartburn, and water brash) and a subgroup of 69 patients who presented with dysphagia. Both subgroups had significantly more eosinophils in biopsies from the distal esophagus (mean eosinophils per HPF 34.9 ± 10.2 in the GER subgroup, 56.2 ± 18.7 in the dysphagia subgroup) than from the mid-esophagus (mean eosinophils per HPF 19.7 ± 10.5 in the GER subgroup, 39.7 ± 10.0 in the dysphagia subgroup), and the dysphagia subgroup had significantly greater eosinophil numbers than the GER subgroup at both esophageal levels. It should be noted that this study was performed at a time when EoE and GERD were considered mutually exclusive disorders. While all patients in this study were ultimately diagnosed with EoE and not GERD, formal GERD testing was not described for any patient. It is now clear that EoE patients often have GERD, and that failure to respond to PPIs does not exclude a diagnosis of GERD, nor does it establish a diagnosis of EoE. Thus, it is unclear how many EoE patients in this study had concomitant GERD. Furthermore, none of the pediatric studies reviewed in this report provide convincing evidence to support the notion that GERD alone can result in EoE-level esophageal eosinophilia.

Esophageal eosinophilia and gastroesophageal reflux in adults

Although the 1993 report that first described the clinicopathologic syndrome we now recognize as EoE included only adult patients,[9] reports of EoE published prior to 2007 emerged almost exclusively from pediatric centers. One of the first large studies of predominantly adult patients, published in 2008, is widely cited as evidence that GERD alone can sometimes cause EoE-level eosinophilia.[20] That study was from a surgical unit specializing in the treatment of esophageal disease, particularly GERD refractory to medical therapy. The researchers reviewed pathology records of 3,648 patients who had undergone esophageal biopsies (obtained from the squamocolumnar junction [Z-line] and distal esophagus within a few centimeters above the Z-line), and they identified 40 (1.1%) who had >20 eosinophils per HPF in ≥1 biopsy specimen

(range 20–204 eosinophils per HPF). Those 40 patients were classified by whether the predominant presenting symptom was reflux (i.e., heartburn and/or regurgitation) or dysphagia, and further categorized based on esophageal pH monitoring studies into subgroups: 12 patients with normal acid reflux (pH < 4 for <4.5% of the 24-h period), nine with moderately abnormal acid reflux (pH < 4 for 4.6–11% of the 24-h period), 11 with severe acid reflux (pH < 4 for >11% of the 24-h period), and eight patients who did not have pH monitoring. Based on these findings, as well as other clinical and endoscopic features, the investigators assigned a probable diagnosis to each of the 40 patients as follows: six (15%) with EoE, 28 (70%) with GERD, two (5%) with EoE and coincident GERD, two (5%) with esophageal diverticulum, and two (5%) with achalasia. There was no significant difference in the maximum eosinophil numbers among the groups, and the authors concluded that all histologic features attributed to EoE can occur in GERD. Nevertheless, the authors acknowledged that the possibility of coexisting EoE should be considered in patients with a clinical diagnosis of GERD whose esophageal biopsies show >20 eosinophils per HPF. This study clearly shows that patients with abnormal acid reflux and clinical features typical of GERD can occasionally have EoE-level esophageal eosinophilia. However, it does not exclude the possibility that those patients may have both GERD and EoE. Indeed, no clinical feature or endoscopic finding alone can unequivocally establish or refute a diagnosis of EoE. Rather, an EoE diagnosis is made in patients with esophageal symptoms and esophageal eosinophilia only when non-EoE disorders that can cause esophageal eosinophilia have been excluded.

Barrett's esophagus with intestinal metaplasia is regarded as definitive evidence for GERD.[5] In a study designed to determine the prevalence of EoE-level eosinophilia in patients with Barrett's esophagus, investigators reviewed pathology findings from 200 patients with biopsy-confirmed Barrett's esophagus (96 long-segment, 104 short-segment) who also had biopsies of esophageal squamous mucosa just proximal to the squamocolumnar junction.[31] Fourteen patients (7%) with an average Barrett's segment length of 3 cm were found to have eosinophil counts ≥ 15 per HPF in squamous mucosa. While this study further establishes that patients with GERD can have EoE-level eosinophilia, it does not establish that GERD was the cause of the esophageal eosinophilia. In other words, it cannot exclude the possibility that patients had both GERD and EoE, and it cannot determine which of those disorders caused the esophageal eosinophilia.

Identifying high-level esophageal eosinophilia due to gastroesophageal reflux

The following question arises from this review of the studies discussed above: In patients who have esophageal symptoms and esophageal biopsies showing ≥15 eosinophils per HPF, and who also have definitive evidence of GERD (LA grade B, C, or D esophagitis, Barrett's esophagus, or abnormal reflux monitoring studies), is there any way to establish conclusively whether GERD or EoE is the etiology of the esophageal eosinophilia? As discussed, response to PPIs is not useful in this regard since PPIs have both antisecretory and anti-inflammatory effects that might resolve eosinophilia caused by GERD, EoE, or both disorders. The finding of esophageal eosinophilia responding to antireflux surgery might be more supportive of GERD rather than EoE as the etiology, but very few data on this issue are available. One study described 16 children with EoE and abnormal reflux documented by impedance-pH monitoring.[32] Eleven of those 16 children responded to PPI therapy, and four of those 11 subsequently underwent Nissen fundoplication. The report states that the patients were able to discontinue PPIs after the surgery, and no relapse of EoE was observed during follow-up of unspecified duration.

A recent study described the outcome of fundoplication in 10 patients who had a GERD/EoE overlap syndrome defined as EoE diagnosed by consensus guidelines and GERD diagnosed by typical GERD symptoms, along with evidence of erosive esophagitis on endoscopy or abnormal pH testing.[33] All 10 patients had heartburn and regurgitation, and eight also had dysphagia. All had been treated with double-dose PPIs without symptomatic or histologic response. After fundoplication (eight Nissen, one Toupet, one Nissen followed by Roux-en-Y gastric bypass), follow-up endoscopy was available in nine patients. Average peak eosinophil counts fell from 47.1 ± 35.9 per HPF to 7.7 ± 12.3 after surgery, and seven of the nine patients achieved eosinophil counts < 15 per HPF. These findings document that esophageal eosinophilia can respond to fundoplication in some highly selected patients. However, the authors specifically stated that they believed their patients had both EoE and GERD, not a GERD variant with esophageal eosinophilia. They cited reports suggesting that GERD can render the esophageal epithelium permeable to antigens that might trigger type 2 inflammation and concluded that GERD might drive EoE in a subset of patients for whom GERD therapy might improve or resolve EoE. Thus, response to fundoplication cannot be construed as proof that GERD alone can cause EoE-level esophageal eosinophilia.

In 2006, Blanchard *et al*. reported that whole-genome-wide transcript expression profile analysis of esophageal biopsy samples from EoE patients revealed a unique transcriptome involving 1% of the human genome, distinguishing EoE patients from those with other forms of chronic esophagitis.[34] This EoE transcriptome became the foundation for the subsequent development of an EoE diagnostic panel (EDP), a quantitative polymerase chain reaction array of 96 genes that has been shown to identify EoE patients with excellent sensitivity and specificity.[35] Although studies have shown that the EDP can distinguish EoE from GERD with low levels of esophageal eosinophilia, it is unclear whether the EDP can differentiate GERD with high-level eosinophilia from GERD with comorbid EoE.[36] A more recent study has identified additional markers that might differentiate GERD from EoE, but the clinical applicability of these findings remains to be established.[37]

EoE and GERD are no longer considered mutually exclusive disorders. To the contrary, it is now widely accepted that EoE and GERD frequently coexist. However, the first step in the diagnostic algorithm for patients who have esophageal symptoms associated with esophageal eosinophilia is to exclude non-EoE disorders that can cause esophageal eosinophilia, including GERD. It is not uncommon for GERD (without EoE) to be associated with low-level esophageal eosinophilia that would not be confused with EoE. When GERD and EoE coexist in patients with EoE-level esophageal eosinophilia, there are often endoscopic and clinical features strongly suggesting that EoE is driving the eosinophilia (e.g., patients have endoscopic rings and furrows, dysphagia as a predominant symptom, atopic history, response to topical steroids, etc.). However, in the uncommon circumstance when patients with documented GERD have high-level esophageal eosinophilia without typical endoscopic or clinical features of EoE, it is not possible to determine whether the eosinophilia is caused by GERD alone, by underlying but unrelated EoE that does not manifest typical EoE features, or by EoE that is being driven by GERD-induced defects such as impaired esophageal barrier function. PPI treatment is certainly warranted

for such patients, but a response would not distinguish among the three scenarios just described. Far more problematic is the situation in which such patients do not respond to PPIs, as it then becomes unclear whether subsequent treatment should focus on EoE (e.g., topical steroids, diet, dupilumab) or more aggressive treatment of GERD (e.g., vonoprazan, antireflux surgery).

Conclusions

In this report, we have attempted to determine whether GERD alone can induce EoE-level esophageal eosinophilia. We have concluded that this question cannot be answered definitively, but it appears that GERD alone rarely (in perhaps <1% of all GERD patients) causes EoE-level eosinophilia. Nevertheless, the inability to determine unequivocally whether GERD alone can induce EoE-level esophageal eosinophilia creates a conundrum in the management of patients with esophageal eosinophilia.

Despite these limitations, some clinical practices may help clarify whether the etiology of EoE-level esophageal eosinophilia (i.e., ≥15 esophageal eosinophils per HPF) is due to EoE or GERD. First, ensure that sufficient mapping biopsies of the esophagus are obtained (i.e., at least three to four from the distal and three to four from the proximal esophagus) after PPIs have been stopped for at least two weeks. Since EoE is a patchy disease, while GERD predominantly affects the distal esophagus, the finding of eosinophilia at multiple esophageal locations would favor a diagnosis of EoE. Next, if GERD is suspected as the etiology of the esophageal eosinophilia, ensure there is objective evidence of GERD—either by endoscopic findings of LA grade B, C, or D esophagitis, or by ambulatory pH monitoring demonstrating abnormal acid reflux. This would establish that GERD is indeed present, although it still would not definitively exclude the presence of coexisting EoE. Until better diagnostic tests for EoE become available, this situation will remain a clinical conundrum.

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Conflict of interest

CAR has been an Editorial Board Member of the *Journal of Translational Gastroenterology* since 2023, RFS is a consultant for Ironwood Pharmaceuticals, Castle Biosciences, Phathom Pharmaceuticals, IsoThrive, CDx, AstraZeneca, Capsulomics, and Sanofi, SJS is a consultant for Takeda Pharmaceuticals, Phathom Pharmaceuticals, Lucid Diagnostics, and Castle Biosciences. The other authors have no conflict of interests related to this publication.

Author contributions

Conception, design (CAR, SJS), critical revision of manuscript (RFS, SJS), analysis and interpretation of the data (CAR, JPS), drafting of the manuscript (CAR, JPS), important intellectual content (CAR), and important intellectual content (SJS). All authors have approved the final version and publication of the manuscript.

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