

Correspondence

Reply

To the Editor:

We have read both responses to our original letter published in the June issue of the *Journal* and appreciate the opportunity to address the issues raised in these communications.^{1,2} In the first response to our letter, Stevenson et al¹ provide a nice discussion of pancreatitis, with particular focus on previous attempts at categorizing drug/pancreatitis associations based on the number of reports of a given drug causing pancreatitis, with a positive rechallenge result to a given drug strengthening the association. Although reference to case reports in the literature is one of the main ways that we as physicians seek correlations between drugs and adverse effects, it can lead to missed associations because unrecognized or unpublished cases are inadvertently omitted through this process. Stevenson et al¹ cite a lack of publications regarding aspirin-induced pancreatitis as evidence that our observed association is unlikely to represent a true correlation; however, it is quite possible that the lack of published aspirin-induced pancreatitis cases stems from underrecognition of such an association. Aspirin and nonsteroidal anti-inflammatory drug (NSAID)-induced gastritis is so common that the vast majority of patients with abdominal pain after ingesting high-dose aspirin or NSAIDs would probably suspect gastritis as the cause of their symptoms and begin therapy for gastritis, as was the case for most of the patients in the 2 studies cited by Stevenson et al.^{3,4} Given the resolution of abdominal symptoms with gastritis therapy in these patients, it is probable that gastritis was indeed the cause of their abdominal discomfort, which is quite common and therefore not surprising. The patients that we would be concerned about would be the 6 of 17 patients with continued abdominal symptoms today despite gastritis therapy¹ or even more so the 3 patients who discontinued therapy because of the severity of the abdominal pain.⁴ These are the patients who would warrant pancreatic enzyme assessment to look for pancreatitis, which might be a potentially rare complication of aspirin desensitization and high-dose aspirin in the aspirin-exacerbated respiratory disease (AERD) subset of patients.

Stevenson et al¹ argue that COX-1 inhibition and subsequent leukotriene synthesis in our patients with AERD probably did not induce their pancreatitis because there are so few reports of COX-1 inhibitors causing pancreatitis. They refer to the many cases of acetaminophen-induced pancreatitis as evidence that weak inhibition of COX-1 actually leads to more cases of pancreatitis than the strong inhibition one would expect from aspirin and NSAIDs.¹ However, we believe the discrepancy in reporting this correlation is due to a difference in index of suspicion. With acetaminophen ingestion, gastritis is not a common side effect, and therefore one would be much more likely to explore all possible causes of epigastric pain, including pancreatitis, than in the case of aspirin or NSAID-induced epigastric pain, where one would generally assume gastritis and stop searching for a cause.

The intent of our original letter was not to claim causation but merely to disseminate a clinical observation that, if found to be substantiated, could lead to proper diagnosis and potentially avoid significant morbidity and even mortality in a small subset of our patients with AERD.⁵ This intent has been corroborated in the second response, a case description by Kelly and Durrani² in

this issue of the *Journal*. The patient described in their letter is complex in that she has had intermittent pancreatitis for years; however, her case addresses several of the points raised by Stevenson et al¹ as potential flaws in the association noted for our 3 patients.

One point raised by Stevenson et al¹ is the issue of microlithiasis or biliary sludge, a common cause of pancreatitis that cannot be identified by means of routine testing and therefore might have been missed in our patients.¹ This is certainly a possibility, although we would argue that it would have to be quite coincidental to have biliary sludge-induced pancreatitis occur in all 3 of these patients within hours or days of aspirin desensitization and to have this sludge resolve at the same time that aspirin therapy was discontinued, reduced in dose, or both. Although these coincidences are possible, they seem less likely than the suggestion we put forward about aspirin desensitization inducing some sort of pancreatic inflammatory response as a consequence of mediator release in a subset of patients with AERD, all of whom already have a well-described dysregulation in the leukotriene pathway.⁶ Such an aberration in the leukotriene pathway exacerbated by the aspirin desensitization procedure would be much more likely to resolve rapidly after discontinuing high-dose aspirin than would microlithiasis. In the case presented by Kelly et al,² the patient had undergone a therapeutic sphincterotomy and cholecystectomy for her biliary sludge before her aspirin desensitization, with subsequent endoscopy showing resolution of sludge. Therefore in this patient's case biliary sludge cannot be blamed for her pancreatitis episode, and an alternative explanation would need to be proposed. In addition, underlying pancreatic inflammation, which coincidentally flared during the aspirin desensitization, would also be unlikely because Kelly and Durrani² have evidence of normal pancreatic enzyme levels at the start of her symptoms, which subsequently increased as her epigastric pain progressed.

Similarly, Stevenson et al¹ comment on the fact that 2 of our 3 patients were receiving statin therapy at the time of desensitization and that there is no way of proving that the statins are not in fact the cause of their pancreatitis. Neither the patient presented by Kelly and Durrani² nor the remaining patient in our original letter was taking a statin, thereby making statin-induced pancreatitis impossible as a source for the enzyme level increase and symptomatology in these 2 patients.^{2,5}

Although Stevenson et al¹ cite the millions of patients in this country who are receiving aspirin therapy for cardioprophylaxis without published reports of pancreatitis,¹ we would argue that these millions of patients are a completely different cohort than our patients with AERD, both because they are generally taking aspirin at much lower doses than our patients with AERD undergoing desensitization and because they do not have the same immune system dysregulation that accounts for the airway inflammation we see in patients with AERD, much of which is thought to relate to the leukotriene pathway. To compare our patients with millions of Americans without the specific immune dysregulation previously described in the population with AERD and with normal levels of leukotrienes and leukotriene receptors is akin to comparing 2 unrelated populations.

Given how infrequent this observation has been in our cohort of patients, we propose that a large-scale study with a nested case-control design would be necessary to determine whether this

clinical observation is representative of a true association. Unfortunately, such a study would be expensive and difficult to carry out, especially because AERD itself is so rare and patients with AERD having gastrointestinal complaints during desensitization are thought to represent less than a quarter of the total number of patients.³ Therefore, for events with a low frequency of occurrence, such as this, awareness of possible adverse drug reactions in a given cohort of patients and the increase in clinical suspicion that generally follows become even more powerful not only to further validate the underlying association that might have been missed but also to avoid unnecessary morbidity.

*Flavia C. L. Hoyte, MD
Rohit K. Katial, MD*

From the Division of Allergy and Immunology, National Jewish Health, Denver, Colo.
E-mail: katialr@njhealth.org.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Stevenson DD, White AA, Simon RA. Aspirin as a cause of pancreatitis in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2012;129:1687-8.
2. Kelly JT, Durrani SR. Pancreatitis as a complication of aspirin desensitization for aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* ■■■;■■■:■■■.
3. Williams AN, Simon RA, Woessner KM, Stevenson DD. The relationship between historical aspirin-induced asthma and severity of asthma induced during oral aspirin challenges. *J Allergy Clin Immunol* 2007;120:273-7.
4. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin exacerbated respiratory disease. *Ann Allergy Asthma Clin Immunol* 2010;105:30-5.
5. Hoyte FC, Weber RW, Katial RK. Pancreatitis as a novel complication of aspirin therapy in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2012;129:1684-6.
6. Daffern PD, Muilenberg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E₄ excretion during oral aspirin challenges with severity of respiratory responses. *J Allergy Clin Immunol* 1999;104:559-64.

<http://dx.doi.org/10.1016/j.jaci.2012.09.035>