and compared them with a Hungarian cohort of 1225 patients with acute pancreatitis of any cause. Because case reports and case series are composed in retrospect, we were wondering why the authors did not consider data from published prospective cohort studies for their analysis, particularly because this was not explicitly excluded by the study design.

A recent study[2] comparing identifiable causes of acute pancreatitis in a prospective and in a retrospective cohort concluded that patients who were prospectively characterized (a) undergo a more thorough investigation more often using ultrasonography and/or magnetic resonance imaging and (b) report a more detailed history of taking drugs possibly related to acute pancreatitis than patients who were retrospectively recruited. In the prospective group, more than one-half of the patients had $\geq$2 possible causes of pancreatitis, being mostly a combination of gallstones and drugs.[2] We, therefore, believe that a prospective study following a prespecified investigational protocol would allow a more precise patient characterization than retrospective data extracted from medical records.

As recognized by the authors of the actual review in *Gastroenterology*,[1] the use of case reports and case series may be prone to publication bias. It seems indeed very likely that more often severe than mild disease courses of putative DIAP will be prepared for publication. To reinforce this argument, our previously published prospective multicenter cohort study on patients with inflammatory bowel disease treated with azathioprine[3] identified only mild courses of DIAP without any deaths,[3] as compared with only 69% mild courses and >8% DIAP-related deaths in the overall cohort by Meczker et al.[1] Although the analysis of data from adverse event reporting systems[4,5] may partially compensate for some of the limitations of collected case series, they are still susceptible to underreporting, selective reporting, lack of information about total drug consumption, and many other inaccuracies.

We, therefore, support the claim of others[2] that prospective studies should have an important role in furthering our knowledge of the role drugs play in the etiology of acute pancreatitis.

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References

1. Meczker Á, et al. Gastroenterology 2020;159:1958–1962.
2. Rashidi M, et al. World J Gastroenterol 2016;22:2104–2110.
3. Teich N, et al. J Crohns Colitis 2016;10:61–68.
4. Nango D, et al. J Pharm Health Care Sci 2019;5:5.
5. Niinomi I, et al. Int J Toxicol 2019;38:487–492.

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Most current article

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Reply. We are very grateful for the thoughts and comments on our study of 1060 cases of drug-induced acute pancreatitis (DIAP)[1] by Teich et al. We found their concept so interesting and potentially useful that we decided to do a complementary study to identify all prospective studies on DIAP, reporting its severity and mortality, because our analysis included only case reports and case series. We aimed to determine the severity and mortality of DIAP in published data from prospective cohort studies on DIAP.

Therefore we performed a systematic search on January 23, 2020, in Embase, Medline via Pubmed, and Cochrane Central with the following search key: (acute pancreatitis) AND (prospective OR cohort) AND (drug induced). We included prospective cohort studies with at least a subgroup of DIAP with data on severity or mortality during screening and selection. We excluded non-English reports, non-human studies, conference abstracts, case reports, case series, retrospective cohort studies, reviews, and meta-analyses. Data on the study, author, year, implicated drugs, number of patients, severity, and mortality rate were extracted. We planned proportion meta-analyses on severity and mortality rates if there were enough data or a systematic analysis if the meta-analytical calculations were impossible.

We identified 368, 231, and 40 potentially eligible records in Pubmed, Embase, and Cochrane Central, respectively. After the removal of duplicate records, 553 titles were screened. We identified 135 titles, of which 23 abstracts seemed eligible. Only 2 studies were identified during the full-text screening fulfilling all the eligibility criteria.[2,3]

The study of Teich et al reported 37 cases of azathioprine (AZA)-induced acute pancreatitis in consecutively enrolled inflammatory bowel disease adult patients. All patients were naive to AZA. No patient died from the DIAP, and all cases were mild.[3]

Abu-El-Haija et al[2] reported a cohort of 165 pediatric patients with acute pancreatitis, of whom 40 had DIAP. There were 18 culprit drugs with mercaptopurine or AZ in 4 cases. There were 24 (60%) mild, 9 (22.5%) moderate, and 7 (17.5%) severe cases, and no deaths were reported. In particular, the study did not report on the outcomes of AZA-induced acute pancreatitis.

We found that most studies focused on the adverse reactions of certain drugs or acute pancreatitis. In these studies, DIAP represented only a small subgroup of all cases

with very few data, lacking data on severity and mortality. Besides, most studies used retrospective data extracted from various databases (hospital records, disease- or drug-specific registries).

AZA is a well-known drug with documented strong evidence for causing DIAP.[4] We believe that in a prospective study run by gastroenterologists proactively detecting early signs of pancreatitis, the severity rates of AZA-induced AP will be favorable owing to early diagnosis of DIAP and prompt discontinuation. This may partly explain the favorable outcomes of all AZA-induced cases in the study of Teich et al.[3]

In our cohort of 1060 patients with DIAP, a subgroup analysis of the 19 AZA-induced cases showed predominantly mild disease course (16 [88.9%] mild; 0 moderate; 2 [11.1%] severe), and no deaths occurred. The indications for the AZA treatment were Crohn's disease in 13 and hepatitis, autoimmune pancreatitis, severe eczema, ulcerative colitis, vasculitis, unknown in 1 each. The limited data do not allow statistical analysis. Still, these severity rates do not seem to be significantly different from the Teich et al[3] study results.

In the prospective pediatric cohort, DIAP cases were prospectively enrolled, but there were many culprit drugs, and the published results did not determine which drugs were associated with poorer outcomes.[2] However, the higher severity rates reported in this small cohort are similar to our extensive analysis' results, although the statistical comparison was not possible between the two studies.

We note that none of the above studies used the Naranjo criteria to ascertain disease.[5] Therefore, the lack of unequivocal confirmation that the episodes of AP were drug induced leaves some doubt.

In summary, we agree that data from high-quality studies should have been included in our previous analysis; however, they would not have changed the results. The result of the systematic search for prospective data showed that these studies on DIAP are lacking; hence, they would be warranted to understand the natural history of this important form of acute pancreatitis. Future studies should use the Naranjo criteria and the Badalov classification.[4,5] This could ensure that unequivocal DIAP cases are analyzed.

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References

1. Meczker Á, et al. Gastroenterology 2020;5:1958–1961.
2. Abu-El-Haija M, et al. Pancreatology 2020;6:1103–1108.
3. Teich N, et al. J Crohn's Colitis 2016;1:61–68.
4. Badalov N, et al. Clin Gastroenterol Hepatol 2007;6:648–661.
5. Naranjo CA, et al. Clin Pharmacol Ther 1981;2:239–245.

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IL-33 in Gastric Metaplasia—Implications for Therapeutic Targets

Dear Editors:

We read with interest the article by De Salvo et al,[1] which suggested a potential role for eosinophils during the process of metaplasia triggered by IL-33 in a chronic model of gastritis-prone mice. The mechanisms responsible for the progression of metaplastic mucosa to dysplasia and cancer have always been the central problem in tumor research field. Through the use of mouse model and neutralization antibodies, the authors clearly demonstrated the importance of IL-33/ST2 axis in the development of chronic inflammation and metaplasia in the stomach. In addition, the current study also implicated eosinophils as an early, IL-33–responsive innate immune cell population that participated in the complex orchestration leading to spasmolytic polypeptide-expressing metaplasia (SPEM)/intestinalized SPEM. However, combining previous results and current results by the same group,[1–3] we still would like to raise the following concerns.

First, if the SPEM process is induced by an early eosinophil-dependent response, the neutralization of eosinophils should result in a dramatical decrease in the following events, including gastric inflammation and M2 macrophage infiltration. Anti–IL-5 treatment efficiently decreased the numbers of eosinophils, both in the peripheral and local environments, as expected. However, anti–IL-5 treatment only partially decreased gastric inflammation and M2 macrophage infiltration, which was more profound in anti-CCR3 treatment, especially for the control of M2