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Title: Antibiotic Use and Subsequent Development of Functional Gastrointestinal Disorders:
Effect of Symptom-reporting and Consultation Behavior.

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Abbreviations: FGID functional gastrointestinal disorder

GI gastrointestinal

Word count: 336

Sirs;

We read the nested case-control study by Paula et al. with interest. (1) The authors identified new-onset cases of functional gastrointestinal disorders (FGIDs) in the community, and demonstrated a statistically significant relationship between treatment with antibiotics for a non-gastrointestinal (GI) infection and the subsequent development of FGIDs (odds ratio 1.90; 95% confidence interval 1.21-2.98). They concluded that the use of antibiotics to treat non-GI infections was a risk factor for developing an FGID.

The development of FGIDs, attributable to dysbiosis, following acute enteric infection is well-described. (2, 3) Despite this, there have been few studies that have examined the association between antibiotic use and subsequent development of FGIDs in humans, (4-6) so the authors are to be commended. Strengths include a relatively large population, as well as an impressive 78% response to the initial survey. In addition, the authors' method of identifying new onset cases allowed for targeted chart review to identify events that might reasonably be related to the onset of symptoms.

However, data collection concerning the event of interest relied on all episodes of infective symptoms being reported by patients and documented by physicians. This is further complicated by increased symptom reporting among patients with FGIDs, (7) which may then drive consultation rates with GI symptoms, (8, 9) and with symptoms referable to other organ systems. These are all therefore potential confounding factors for the prescription of antibiotics. For these reasons, it would have been interesting to know overall consultation rates with GI, and extra-GI, symptoms among the study population.

It would also have been useful in a study of this type to have identified a drug with no theoretical link to the development of FGIDs, and included this in a separate analysis. If the use of this drug was not shown to be associated with the subsequent development of an FGID

it may have reduced the likelihood that any association between antibiotic use and development of FGIDs was driven by consultation behavior, and resultant prescribing of medications as an exit strategy for the physician.

The influence of antibiotics on gut flora is one of the explanations given for the observed association with subsequent FGID development. Although the authors included a breakdown of the antibiotics used into their pharmacological subgroups, these were not used in logistic regression analysis, presumably due to the low numbers in some of these classifications. A useful alternative would have been to conduct an analysis of broad vs. narrow spectrum antibiotics, in order to elucidate whether antibiotics with a greater potential impact on gut flora had a stronger relationship with the development of FGIDs.

Despite these criticisms, this is a valuable study that provides important evidence of an association between antibiotic use and the subsequent development of FGIDs, which has biological plausibility, and serves as yet another reason for judicious use of these drugs.

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