Journal Summary: Do Antibiotics Predispose to the Development of Inflammatory Bowel Disease?

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Brief Overview of the Study

Imbalances in the gut microbiota, also known as dysbiosis, can be caused by external factors such as antibiotics, leading to a decrease in the diversity of gut flora. Such imbalances can predispose individuals to inflammatory bowel disease (IBD), and this association has been reported in current pediatric literature. Research has shown that the use of antibiotics during childhood, and even during the peripartum period, can lead to the development of IBD in the future.[1,2]

There is, however, a limited data available on the relation between antibiotic use and the risk of developing IBD in adults. To address this, a population-based cohort study was conducted by Faye et al. They utilized data from Danish nationwide registries and followed up on over 6 million individuals aged 10 years and above for a period of 18 years (2000–2018). The study was aimed to assess the impact of the dose–response relationship, timing, and class of antibiotics on the risk of developing IBD.[3] Since the study was done with the help of the Danish Civil Registration System, which carefully maintains patient data and prescriptions list, the risk of recall and selection bias and loss to follow-up were eliminated. The study found that antibiotic exposure was associated with an increased risk of IBD for all age groups, with the incidence risk ratio (IRR) being greatest among individuals aged 40 to 60 and $\geq$ 60 years (age 10–40 years, IRR 1.28, 95% confidence interval [CI] 1.25–1.32; age 40–60 years, IRR 1.48, 95% CI 1.43–1.54; age $\geq$ 60 years, IRR 1.47, 95% CI 1.42–1.53). For all age groups a positive dose–response was observed for both ulcerative colitis (UC) and Crohn's disease (CD). The study also found that the highest risk of developing IBD was observed 1 to 2 years after exposure to antibiotics, the risk increasing with number of courses (IRRs per antibiotic course were 1.11 [95% CI 1.10–1.12], 1.15 [95% CI 1.14–1.16], and 1.14 [95% CI 1.13–1.15] for individuals aged 10–40, 40–60, and $\geq$ 60 years). Most cases were reported after the use of antibiotic classes that are commonly prescribed to treat gastrointestinal (GI) pathogens, such as nitroimidazoles or fluoroquinolones. However, some cases were reported after the use of other non-GI-related antibiotics, such as narrow-spectrum penicillin. Interestingly, there was no association between IBD and nitrofurantoin, which is used to treat urinary tract infections and does not extensively affect the GI tract. This finding supports the hypothesis that dysbiosis in the gut can lead to IBD.

Implications of the Study

The incidence and prevalence of IBDs, which include two conditions—UC and CD, continue to increase steadily.[4] Once considered a problem of the Western countries, there has been a sharp increase in their incidence in developing nations as a result of the westernization of lifestyle and a better detection of IBD.[5] The development of IBD appears to be due to the interplay of genetic factors, environmental factors, and changes in the gut microbiota.

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The gut microbiota is mainly composed of bacteria, with the majority belonging to the phyla Bacteroides and Firmicutes. Smaller percentages are made up of Actinobacteria, Fusobacteria, Proteobacteria, and Verrucomicrobia. In cases of IBD, it has been observed that the most significant changes in the gut bacteriome of patients are an increase in Proteobacteria (especially Enterobacteria) and a decrease in Firmicutes and Bacteroidetes.[6–8] In addition, there is growing evidence of the importance of alteration in "gut mycome" and "gut virome" in the development of IBD.[6,9]

Antibiotics have often been used in the treatment of IBD in the belief that they may treat any bacterial organism responsible for flare, treat underlying causative organisms (e.g., Mycobacterium paratuberculosis in CD), or correct the underlying dysbiosis. As of today, the established indications for the use of antibiotics are only a handful—abscesses or perianal fistulas related to CD being a common indication.[10] However, it is of interest to also ascertain if exposure to antibiotics could potentially predispose to IBD. Any attempt to associate the occurrence of IBD to the use of antibiotics should, of course, ensure excluding the use of antibiotics for GI symptoms that may be related to IBD itself. To that end, the current study is a good attempt.

The strength of the study lies in its size, reliability of the data, and its design, which also included drugs other than antibacterial drugs such as proton–pump inhibitors), antifungal, and antiviral drugs which have also been implicated in modifying the gut microbiota. The study also included a lag period of 1 to 2 years to compensate for the possibility of reverse causality, that is, the increased use of antibiotics as a result of GI symptoms of undiagnosed IBD. However, one could argue that this period may be too short as median values of diagnostic delay of IBD can range from 2 to 96 months (median delay for CD: 2–84 months and for UC 2–114 months from initial symptoms to final diagnosis), the symptoms of IBD may present intermittently, and antibiotics could result in short-lasting clinical improvements.[11] Hence, the strong association between antibiotic use and the development of IBD in the future holds significant importance in the way how antibiotics are used and calls for an increase in antibiotic stewardship and regulated monitoring and dispensing to reduce the burden of IBD in the future, which is often a lifelong, debilitating disease.

Caveats and the Way Forward

1. Studies exploring the association between antibiotic use and IBD have been done primarily in Scandinavian countries, such as Finland and Denmark, in both adult and

Table 1 Causal relation between antibiotics and the development of IBD in this study using the Bradford-Hill criteria

	Criterion for plausible causality	Association of antibiotics and IBD
1	Temporality (the cause must precede the effect)	The highest risk for developing IBD was 1–2 years after antibiotic exposure
2	Strength (strong relationship between variables)	The value of IRR is positive across all age groups for both UC and CD, thus indicating incidence is greater in the groups exposed to antibiotics vs. nonexposed group
3	Biological gradient (dose–response effect)	Any antibiotic exposure was associated with an increased risk of IBD compared with individuals with no antibiotic exposure Each subsequent course added additional risk leading to a positive dose–response relationship with highest risk among individuals receiving five or more courses of antibiotics
4	Consistency (the relationship is consistent across different studies and populations)	Both pediatric and adult population-based studies have implicated the association between antibiotics and IBD However, these studies have been limited to mostly Scandinavian countries and data from other populations is required
5	Specificity (single cause for the effect)	The study has tried to eliminate confounders to an extent by considering PPIs, antivirals, and antifungals in their study. However, additional confounders may exist
6 7	Plausibility (biological rationale for the relationship) Coherence (relationship is consistent with previous knowledge)	Antibiotics cause dysbiosis in the gut which predisposes to IBD due to the creation of a proinflammatory environment in the gut with activated immune cells
8	Analogy (the relationship is synonymous with other similar relationships)	IBD, obesity, food allergies, and diabetes all share the same mechanism of inflammation in the gut being caused by dysbiosis[17]
9	Experiment (risk is modified on intervention)	N/A

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IRR, incidence risk ratio; N/A, not available; PPI, proton–pump inhibitor; UC, ulcerative colitis.

pediatric populations. Limited data are available for developing countries such as South East Asia and Africa, where the burden of infectious disease is especially high and multiple courses of antibiotics are necessary due to resistance and reinfections.

2. Patients who emigrated frequently were not followed for the entire study period. This may be a cohort of patients prone to more frequent use of antibiotics and analyzing their natural history may lead to significant findings.
3. More studies need to be done to determine if antibiotics are the causal agents of IBD or are simply surrogate markers for other causes, such as infections. Depending upon the primary reason, use or avoidance of antibiotic use will determine the risk of IBD. Such an example has been put forward by a study involving countries in Asia and Australia, where the use of antibiotics decreased the odds of development of both UC and CD.[12]
4. The study does not include certain classes of antibiotics such as antitubercular therapy, which are used for extensive durations during treatment and are known for gut dysbiosis, and rifaximin, which has known eubiotic effects on the gut.[13,14] In addition, the effects of parenteral antibiotics such as aminoglycosides, on gut microbiome, have not been explored in the study.
5. Classes of drugs such as oral contraceptive pills, isotretinoin, mycophenolate mofetil, nonsteroidal anti-inflammatory drugs, and some biologics have shown an association with IBD development. These drugs were not considered in the study and could be potential confounders.[15]
6. Furthermore, while dysbiosis may be one mechanism for the development of IBD, the possibility of antibiotics causing direct damage to the gut epithelia and the role of drug-resistant microbes should be considered.
7. The influence of diet should be considered synergistically with the development of IBD. The type of diet can significantly affect the microbiome. It is already known that a western diet rich in animal protein, fat, sugar, polyunsaturated fatty acids, omega-6 fatty acids, and meat causes IBD while high fiber and fruit intakes are associated with decreased CD risk and high vegetable intake is associated with decreased UC risk[16] (►**Table 1**).

Ethical Statement
None.

Authors' Contributions
P.P. wrote the initial draft, performed the search, and reviewed the literature. A.C. reviewed the manuscript critically. Both approved the manuscript.

Data Availability Statements
There is no data associated with this work.

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Conflict of Interest
None declared.

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