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Association Between Antibiotic Use for Non-Gastrointestinal Infections and Inflammatory Bowel Diseases Flare-Ups: A Self-Controlled Case Series Study

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Declaration of interests

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Abstract

Background

Disruption of gut microbiota by antibiotic use has been linked to the development of inflammatory bowel disease (IBD). This study aimed to evaluate the association between antibiotic use for non-gastrointestinal (GI) infections and the risk of IBD flare-ups, and to examine whether route of administration, antimicrobial spectrum, and antibiotic class modulate this risk.

Methods

We conducted a self-controlled case series (SCCS) study using territory-wide electronic medical records from Hong Kong. Adults with IBD who experienced at least one flare-up and received at least one course of antibiotics for infections outside the GI tract between 2000 and 2024 were included, to reduce indication bias related to gastrointestinal symptoms. Conditional Poisson regression models were used to estimate incidence rate ratios (IRRs) by comparing across predefined risk periods to the baseline period.

Results

Among 810 patients, IBD flare incidence was elevated during the month preceding antibiotics (IRR 2.85), increased further during treatment (IRR 3.44), and peaked within two weeks after treatment (IRR 4.79), and returned to baseline levels within six months, versus baseline. Increased incidences were observed for oral antibiotics during and two weeks after treatment (IRRs 3.91 and 3.70), but not for injectable antibiotics (interaction p-values <0.01). The IRRs for broad-spectrum antibiotics were higher than those for narrow-spectrum agents from one month before to six weeks after antibiotic use, versus baseline.

Conclusions

Antibiotic use for non-GI infections was associated with a short-term increase in IBD flare risk. Injectable or narrow-spectrum antibiotics may have a relatively smaller impact on potential IBD flare-ups.

Keywords: inflammatory bowel disease; antibiotics; flare-ups

Study highlights

WHAT IS KNOWN

- Gut microbiota disruption by antibiotics has been implicated in IBD onset.
- The impact of antibiotics on triggering flares in established IBD remains controversial.

WHAT IS NEW HERE

- Antibiotic use for non-GI infections was associated with short-term risk of IBD flare-ups.
- Flare risk peaked within 2 weeks post-antibiotics and returned to baseline within 6 months.
- Oral and broad-spectrum antibiotics were associated with increased short-term flare risk.
- Increased flare risk was observed with quinolones, penicillins, nitroimidazoles, and macrolides.

Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a group of immune-mediated conditions marked by chronic inflammation of the gastrointestinal tract. The clinical course of IBD is typically characterised by relapse and remission. Antibiotics, widely used for the treatment of infections, have attracted increasing attention in recent years for their potential role in the pathogenesis and disease activity of IBD (1). Several large-scale population-based studies have demonstrated a positive association between antibiotic use, especially broad-spectrum antibiotics, and the risk of new-onset IBD, suggesting that antibiotics may contribute to disease development by disrupting the gut microbiota (2-4). However, it remains unclear whether this potential risk also applies to individuals with established IBD, particularly in triggering disease flares (1,5,6). Mechanistically, antibiotics can significantly affect the diversity and stability of the gut microbiota, potentially leading to immune dysregulation and modulation of IBD activity (7,8). Moreover, the impact of antibiotics on the gut microbiota is influenced by several factors, such as route of administration and antimicrobial spectrum (7). Existing evidence suggest that oral antibiotics act more directly on the gut microbiota and may exert a greater disruptive effect than injectable formulations, while broad-spectrum antibiotics may cause more extensive disruption to commensal bacteria (7,9,10). Therefore, we hypothesised that antibiotic use is associated with an increased risk of IBD flares among individuals with IBD, with greater risk linked to oral and broad-spectrum antibiotics compared to injectable antibiotic and narrow-spectrum antibiotics.

Current evidence on the association between antibiotics and IBD flares in patients with established IBD remains conflicting. A case-crossover study in the US reported that antibiotic use was associated with a reduced risk of flare in CD within 60 days following exposure, with no significant effect observed in UC (11). In contrast, a recent nationwide nested case-control study from Denmark suggested that certain antibiotic classes (e.g., quinolones, nitroimidazoles, and broad-spectrum β-lactams) were associated with an increased risk of IBD flares, and were further supported by machine learning models, which identified these antibiotic classes as top predictors of flare-ups (12). These discrepancies may be attributed to differences in study design, antibiotic classification, exposure definitions, flare criteria, and population characteristics. Furthermore, prior studies have not systematically evaluated the effects of antibiotic route of administration or antimicrobial spectrum, and research in Asian populations remains limited. Moreover, these studies have defined antibiotic exposure windows using fixed 60-day periods, potentially overlooking long-term or time-varying risk patterns. Additionally, antibiotics are commonly prescribed for gastrointestinal infections, which themselves may contribute to or trigger IBD flares (13,14). Early symptoms of IBD flares (e.g., diarrhoea) may prompt antibiotic use. These scenarios introduce the possibility of confounding by indication and reverse causation, which may have influenced the observed associations. These limitations highlight the need for further research using carefully designed observational studies.

Given the widespread use of antibiotics in clinical practice for various infections, understanding the association between antibiotic characteristics and the risk of disease flares is important for optimising infection management in patients with IBD. This study employed a self-controlled case series (SCCS) design, which allows within-individual comparisons and inherently adjusts for time-invariant confounders. To minimise indication bias and reverse causation, antibiotic exposures were restricted to those prescribed for non-gastrointestinal indications. This study aimed to evaluate the temporal association between antibiotic exposure for indications other than presumed gastrointestinal infections and the risk of IBD flare, and to further investigate whether the route of administration (oral/injectable), antimicrobial spectrum (broad/narrow) and antibiotic class modify the risk.

Methods

Data Source

This study was based on data from a territory-wide electronic medical record database developed and maintained by the Hong Kong Hospital Authority (HA). The HA provides inpatient and outpatient services to over 7.4 million Hong Kong residents (15). This database contains comprehensive clinical information from all public hospitals and specialist or general outpatient clinics, including demographic characteristics, diagnostic codes, prescription records, laboratory results, and hospitalisation and discharge records. All patient records are de-identified to ensure confidentiality. The accuracy and quality of records in this database have been validated in multiple epidemiologic studies related to gastroenterology and antibiotics (16,17). This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW22-280).

Study Design

We used a self-controlled case series (SCCS) design, which is a within-individual method that includes only patients who have experienced both the exposure and the outcome (18). Each individual serves as their own control. By comparing the incidence of outcomes during predefined risk periods with baseline periods, this design effectively controls for time-invariant confounders such as sex and genetic susceptibility to obtain robust estimates. It is particularly suitable for evaluating the effects of short-term exposures, such as antibiotic use, on acute outcomes like IBD flare-ups.

Study Population

We included patients with IBD aged 18 years or older between 1 January 2000, and 31 December 2024, identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (555 for CD and 556 for UC). Eligible patients were required to have experienced at least one IBD flare and to have received at least one antibiotic prescription during the observation period. The observation period for each patient began on the IBD onset date (defined as the earliest of receiving the first IBD diagnosis code or the first prescription of 5-aminosalicylic acid (5-ASA)) and ended on 31 December 2024, or the date of death, whichever occurred earlier.

Exposure

Exposure was defined as systemic antibiotic use, including both oral and injectable formulations. To avoid reverse causality and minimise confounding by indication, the primary analysis included only antibiotic prescriptions related to infections outside the GI tract, such as respiratory, urinary tract, and skin infections. These were identified based on diagnosis codes recorded within seven days before or after the prescription, a commonly used window to infer indications, as detailed in **Supplementary Table 1** (19,20). Antibiotics prescribed for GI infections were excluded, as they may be associated with IBD flare-ups or reflect misclassified IBD flare-ups due to overlapping symptoms, such as diarrhoea.

Duration of antibiotic exposure was determined by the prescription start and end dates. Where these dates were unavailable, duration was estimated using the prescribed daily dose and total quantity. For a small proportion of prescription records where both were missing, we imputed the treatment duration using the median duration for that specific antibiotic, calculated from the study population. Prescriptions of the same antibiotic type separated by no more than seven days were considered the same treatment course.

Outcome

The primary outcome was an IBD flare-up, defined as any of the following events according to previous literature (see **Supplementary Table 2** for details) (16,21-23): (1) start date of outpatient prescription of at least a 7-day course of steroids, excluding steroid use in the 7 days before the prescription for non-IBD indications; (2) admission date of unplanned IBD-related hospitalisation with steroid use during the admission; and (3) initiation of an advanced therapy for IBD, including biologics or small molecules. As individuals with a prior flare-up are more likely to experience subsequent exacerbations, only the first IBD flare-up during the observation period was included in the analysis to fulfil the assumption of SCCS study design (21).

Statistical Analysis

The risk period was predefined as 1 month before prescription (1-31 days pre-exposure), the duration of antibiotic use, 0-2 weeks after the end of the prescription (1-14 days post-exposure), 2-6 weeks after the end of the prescription (15-42 days post-exposure) and 6 weeks to 6 months after the end of the prescription (43-183 days post-exposure) (**Figure 1**). All other periods were considered baseline. The pre-exposure period was included to account for the possibility that IBD flare-ups might temporarily influence antibiotic prescription. The post-exposure period was included to evaluate possible delayed effects of antibiotic use on IBD flare-ups, based on prior evidence that gut microbiota undergo the most pronounced changes within the first two weeks after antibiotic exposure, with long-term alterations potentially lasting up to 2–6 months (24).

We used conditional Poisson regression models to estimate the IRRs and corresponding 95% confidence intervals (CIs), comparing the risk of IBD flare-ups during each risk period to the baseline period. Age was included as a time-varying covariate, categorized into five-year age bands. We calculated E-values to assess the robustness of our findings to unmeasured

time-varying confounding (25). An E-value quantifies the minimum strength of association an unmeasured confounder would need with both exposure and outcome to explain away the observed association. The required sample size was calculated (see **Supplementary Text 1**). All data processing and statistical analyses were conducted using R version 3.3.1 (http://www.r-project.org).

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted based on the route of antibiotic administration (oral versus injectable), antimicrobial spectrum (broad-spectrum versus narrow-spectrum), and antibiotic class. Differences in IRRs across subgroups within the same risk period were assessed using Wald tests. We also performed subgroup analyses by type of IBD (UC and CD). To evaluate the robustness of our findings, we performed several sensitivity analyses, including: (1) varying the grace period between prescriptions of the same antibiotic type from 7 to 14 days as continuous treatment; (2) varying the pre-exposure period from 31 to 14 days to assess sensitivity to the length of the pre-exposure window; (3) expanding the IBD onset definition to also include the first use of corticosteroids or biologics; (4) applying a stricter IBD case definition requiring either ≥2 IBD-related ICD-9-CM codes on separate dates or an IBD diagnosis plus an IBD medication within ±1 year (26); (5) restricting the flare definition to systemic corticosteroid prescriptions and unplanned IBD-related hospitalisations, excluding initiation of advanced therapies; and (6) removing GI infection–related antibiotic prescription periods, and any flares during those periods, from the observation period. Additionally, to assess potential detection bias, we conducted a negative control outcome analysis using acute fractures and other injuries (ICD-9-CM 800–829), which require healthcare contact but are not expected to be affected by antibiotic use.

Results

Patient Characteristics

Between 1 January 2001 and 31 December 2024, 810 adults with IBD who were prescribed at least one antibiotic for infections outside the GI tract and had at least one IBD flare-up during the observation period were included in the primary analysis (**Figure 2**). The median age at cohort entry was 47.3 years (interquartile range [IQR], 31.6–61.6); 494 (61.37%) were male, 412 (50.86%) had CD, and 398 (49.14%) had UC (**Table 1**). The mean follow-up duration per patient was 12.29 years (standard deviation [SD] 6.80). The median duration of antibiotic prescriptions was 8 days (IQR, 6–13). Oral antibiotics were prescribed to 708 patients (87.41%), and 583 (71.98%) received injectable formulations. Among the 17,565 included antibiotic prescriptions, the most common indications were pneumonia (27.18%), skin, cutaneous and mucosal infections (19.08%), septicaemia and unspecified bacterial infections (18.88%), urinary tract infections (11.52%), and tuberculosis (8.97%) (**Supplementary Table 3**).

Primary Analysis

In the primary SCCS analysis, the IRR increased during the 1–31 days pre-exposure period (IRR, 2.85; 95% CI, 1.96-4.14) (**Table 2**). It rose further during the antibiotic treatment period (IRR, 3.44; 95% CI, 2.18-5.42) and peaked in the first 14 days after treatment end (IRR, 4.79; 95% CI, 3.26-7.04). The risk then declined during days 15–42 post-exposure (IRR, 2.21; 95% CI, 1.46-3.34) and returned to baseline during days 43–183 post-exposure (IRR, 0.88; 95% CI, 0.63-1.23).

Subgroup and Sensitivity Analyses

Subgroup analysis revealed differing IRRs of IBD flare-ups by route of antibiotic administration (**Table 3**). For oral antibiotics, the risk increased during the 1-month pre-exposure period, and remained elevated during antibiotic use (IRR, 3.91; 95% CI, 2.21–6.91) and the 1–14 days post-exposure (IRR, 3.70; 95% CI, 2.20–6.21), before gradually declining to baseline. For injectable antibiotics, although a modest increase in risk was observed in the pre-exposure period for injectable antibiotics, no evidence of an increase in risk was seen during the prescription period (IRR, 0.64; 95% CI, 0.24–1.70) and the 1–14 days post-exposure period (IRR, 1.30; 95% CI, 0.69–2.43) with wide CIs. Wald tests indicated statistically significant differences between oral and injectable formulations during treatment and the 1–14 days post-exposure period ($p < 0.05$).

Subgroup analyses by antibiotic spectrum showed that broad-spectrum antibiotics were associated with higher IRRs for IBD flares than narrow-spectrum antibiotics during both the pre-exposure and 1-42 days post-exposure periods (**Table 3**), with the highest risk observed in the 1–14 days post-exposure window (IRR 4.19; 95% CI 2.71–6.46). In contrast, no elevated risk was observed for narrow-spectrum antibiotics throughout the observation period, with consistently wide Cls. The Wald test indicated significant differences between the two groups during the pre-exposure period ($p < 0.01$) and a borderline significant difference during the 1–14 days post-exposure period ($p = 0.05$).

Subgroup analyses by antibiotic class also revealed significant difference in flare risk during the 1–14 days post-exposure period (Wald test, $p = 0.01$; **Supplementary Tables 4 and 5**). For quinolones, the highest IRR was observed during the prescription period (IRR 3.74, 95% CI 1.82–7.68). Penicillins, nitroimidazoles, and macrolides showed elevated risks primarily within the first 14 days post-exposure. The CIs for cephalosporins, tetracyclines, glycopeptides, and aminoglycosides were wide throughout the observation period, with no evidence of elevated risk observed.

In the subgroup analysis by IBD subtype, CD and UC showed similar temporal patterns of flare risk (**Supplementary Table 6**). In CD, the risk peaked during 1–14 days post-exposure (IRR 4.13, 95% CI 2.38–7.17). In UC, the risk increase was more pronounced in the same period (IRR 10.07, 95% CI 6.59–15.39), suggesting a stronger short-term effect in patients with UC.

Sensitivity analyses yielded consistent results with the main findings (**Supplementary Tables 7-13**).

Discussion

This study, based on a territory-wide electronic medical record database in Hong Kong, used a SCCS design to assess the association between antibiotic exposure and IBD flare-ups over time. We found that the risk of IBD flare-up increased during treatment and peaked within the first two weeks after the end of the prescription. This suggests a potential short-term association between antibiotic use and increased risk of IBD flare-up. Subgroup analyses further revealed differences in IRRs by route of administration, antibiotic spectrum, and drug class. Increased incidences were observed for oral antibiotics during and in two weeks after treatment, but not for injectable antibiotics. The IRRs for broad-spectrum antibiotics were higher than those for narrow-spectrum agents from one month prior to six weeks after antibiotic use. Short-term risk increases were also noted for several classes, including quinolones, penicillins, nitroimidazoles, and macrolides.

It is noteworthy that a 2.8-fold increased risk of IBD flare-up was detected before antibiotic exposure, which may partly reflect that flare-up occurrence might influence subsequent antibiotic exposure. To mitigate reverse causality from misdiagnosed prodromal IBD symptoms, we excluded prescriptions related to GI infections. This approach reduces potential indication bias, given the known association between enteric infections and IBD (13,14). Nevertheless, we still observed an increased risk of IBD flare-up before antibiotic use, a phenomenon also reported in other SCCS studies (27-29). This suggests that antibiotic prescribing may still be influenced by underlying health condition changes, such as healthcare-seeking behaviour (e.g., increased medical visits preceding symptom exacerbation), early symptoms before flare (e.g., diarrhoea or fever) prompting empirical antibiotic use, or potentially, associations between non-GI infections and IBD activity, although current evidence on this remains limited (6). Therefore, this finding should be interpreted with caution.

Importantly, we observed an approximate 3.4-fold increased risk of IBD flare-up during antibiotic use and up to 5-fold risk approximately two weeks after treatment ended, in which the IRRs far exceeded pre-exposure levels. Previous studies have demonstrated that the onset and progression of IBD are closely linked to gut microbiota dysbiosis and related metabolic disturbances in animal and in-vivo studies (8,30). While antibiotics can disrupt the intestinal microbiome, reduce microbial diversity, and impair community stability, leading to immune imbalances and inflammatory responses in susceptible individuals (7,31), it supports our findings that antibiotic use is associated with an increased risk of IBD flare. It also aligns with prior observations on the temporal dynamics of gut microbiota following antibiotic exposure, whereby dysbiosis typically peaks within days of treatment initiation and, in most individuals, the microbiota gradually returns to baseline within several weeks after antibiotic cessation (24). Consistent with this, we observed that the temporal risk of IBD flare declined toward baseline between six weeks and six months after antibiotics ended, with no sustained elevation of risk observed, suggesting a short-term effect.

Subgroup analyses further revealed significant differences in the risk of IBD flare according to the route of administration and antimicrobial spectrum. Oral antibiotics were associated with a significantly increased risk of IBD flare during treatment and within 14 days after discontinuation, whereas no such trend was observed with injectable formulations. Injectable antibiotics are typically reserved for more severe or systemic infections and may exert less direct impact on the gut microbiota, compared to oral agents, which pass through the gastrointestinal tract and more directly disrupt the luminal microbial environment (7,9). Moreover, oral antibiotics have been shown to promote the development of antibiotic resistance among healthy commensal microbes to a greater extent than intravenous antibiotics (10). In addition, broad-spectrum antibiotics had a greater impact on IBD flare risk compared to narrow-spectrum agents, potentially due to their more extensive disruption of commensal microbial communities, leading to more pronounced dysbiosis (7).

Our findings are consistent with a recent nested case-control study by Lo *et al*. using Danish national registry data (12), which reported an increased risk of IBD flare within 60 days after antibiotic exposure to various antibiotic classes, including fluoroquinolones, β-lactams, antifungals, antiprotozoals, and intestinal anti-infectives. In our subgroup analyses, similar classes such as quinolones, penicillins, and nitroimidazoles were also associated with an elevated short-term risk during treatment or within two weeks post-exposure. In contrast, a case-crossover study by Aberra *et al.* using the UK GPRD database found a decreased risk of CD flare following antibiotic use within 60 days, with no positive association observed for UC (11). These discrepancies may be partly due to differences in study design and outcome definitions. In Aberra *et al.* (11), IBD flares were defined as new prescriptions of mesalamine or corticosteroids after at least four months without either medication, which was based on treatment patterns in the 1990s and may reflect different flare thresholds compared to current standards. Moreover, the case-crossover design may be susceptible to prescribing trends between the risk and control periods. In contrast, our SCCS design is not susceptible to changing trends in antibiotic use.

Given the frequent use of antibiotics in clinical practice among patients with IBD, our findings underscore the importance of balancing antimicrobial efficacy against potential short-term risks related to IBD flare-up, particularly during and 2 weeks after treatment. Close monitoring of disease activity in the short-term is advisable following antibiotic use. Our findings also highlight the need for cautious prescribing based on the clinical context and the properties of the antibiotics used. When clinically appropriate, the use of antibiotics with less impact on the gut microbiota, such as injectable formulations or narrow-spectrum agents, may be preferable. Importantly, our results do not apply to antibiotics prescribed for gastrointestinal infections, such as *Clostridioides difficile* infections, which were not studied in our study. These findings should not discourage the appropriate use of antibiotics when clearly indicated, but rather support careful selection of route and spectrum and short-term monitoring for disease activity in patients with IBD.

Our study employed a within-individual comparison design based on data from the territory-wide public healthcare system in HK, effectively controlling for time-invariant confounders. Multiple predefined risk periods enabled exploration of temporal associations between antibiotic exposure and IBD flare-up. Furthermore, we conducted in-depth analyses of antibiotics across multiple dimensions, including route of administration and antimicrobial spectrum. However, there are several limitations. First, our database does not include data from the private healthcare sector; therefore, some patients who sought care in private settings may not have been captured. Nonetheless, as the Hospital Authority is the predominant healthcare provider in Hong Kong and IBD is a chronic condition requiring ongoing management, the potential for loss to follow-up is likely limited. Second, our identification of IBD patients was based on ICD-9 codes, which may have missed a small subset of patients with unclassified IBD. Additionally, although antibiotic indications were inferred from diagnosis codes near the prescription date, this is a commonly used method in antibiotic pharmacoepidemiologic research and provides a reasonable approximation for our study to distinguish non-gastrointestinal infections. Moreover, our definition of IBD flare may not capture mild relapses managed without corticosteroids. However, it was based on definitions commonly used in prior studies, including outpatient corticosteroids and hospitalisations involving corticosteroids. We further incorporated advanced therapies for IBD in our definition of flare-up to maximise the accuracy and clinical relevance of flare identification. Additionally, the effects of infections and antibiotics cannot be completely disentangled in routine clinical data. However, we restricted our analysis to antibiotics for non-GI infections, and the observed gradients by route and spectrum suggest an additional effect of antibiotics beyond infections alone. Furthermore, because our data were derived from the Hong Kong healthcare system, evidence from other regions, such as the United States, would be helpful in further evaluating the generalizability of these findings across different infection epidemiology and prescribing patterns. Given the SCCS design, we focused on the first IBD flare during follow-up; recurrent flares could be investigated in future studies. Lastly, some antibiotic classes had limited sample sizes, which may reduce the precision of risk estimates; however, the class-specific findings were broadly consistent with previous literature, supporting the overall robustness of our results.

Conclusion

Our study showed a 3-5-fold increased risk of IBD flare-up during antibiotic use and within two weeks after discontinuation. The risk then gradually declined and returned to baseline approximately six weeks post-exposure. This temporal pattern suggests that antibiotics may act as short-term triggers for IBD flare-up. We further demonstrated that oral formulations and broad-spectrum antibiotics were associated with a higher short-term incidence of IBD flare-up, whereas no such association was observed for injectable or narrow-spectrum antibiotics. Considering short-term risks of flare associated with antibiotics, our findings highlight the need for more judicious antibiotic use in patients with IBD, particularly the choice of route and type of antibiotic.

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Data sharing statement

Data from Hong Kong is not available as the data custodians (the Hospital Authority and the Department of Health of Hong Kong SAR) have not given permission for sharing due to patient confidentiality and privacy concerns. Local academic institutions, government departments, or non-governmental organisations may apply for access to data through the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data).

Supplementary materials_clean----http://links.lww.com/AJG/D860

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Figure legends

Figure 1. Illustration of observation timeline for the self-control case series design
This figure shows the study design and timeline for a single IBD participant, including baseline (unexposed) time, the month before antibiotic initiation, the prescription period, and the post-antibiotic risk periods. The IBD flare-up can occur at any time during the observation period.

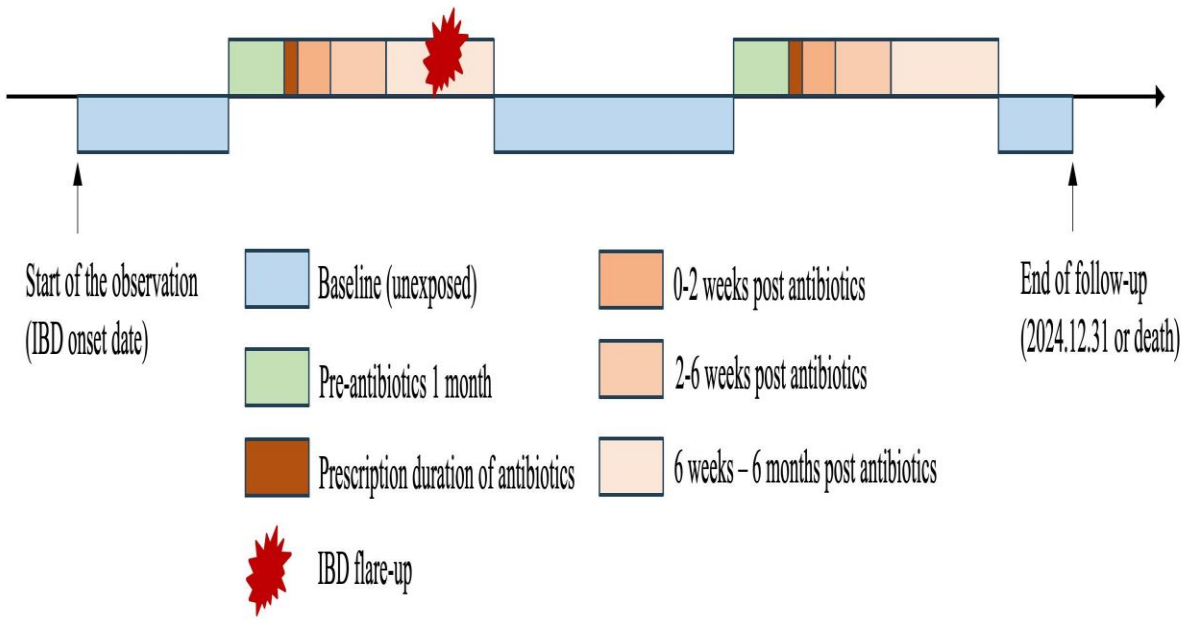


Figure 2. Flowchart for patient inclusion

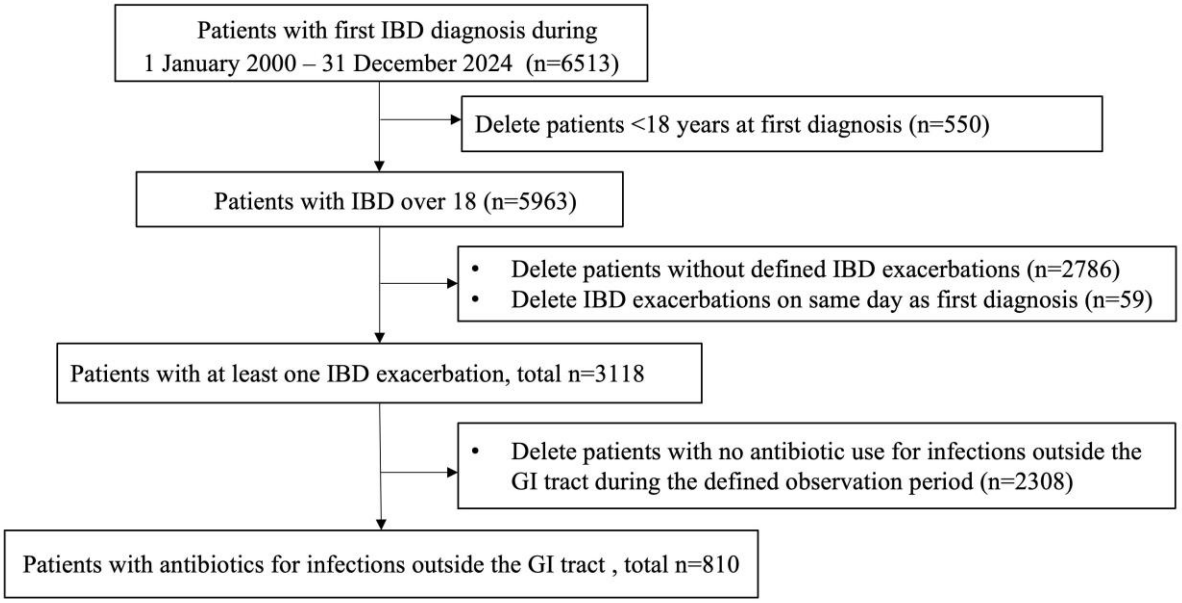


Table 1. Baseline Characteristics of the Study Population

Characteristic	**Study population (n = 810)**
Demographics	
Age at cohort entry, median (IQR), years	47.3 (31.6–61.6)
Male, n (%)	494 (61.37%)
Type of IBD	
Crohn's Disease, n (%)	412 (50.86%)
Ulcerative Colitis, n (%)	398 (49.14%)
Antibiotic exposure characteristics	
Number of antibiotic prescriptions, median (IQR)	12 (5–25)
Duration per antibiotic prescription, median (IQR)	8 (6–13)
Patients with broad-spectrum antibiotic use, n (%)	788 (97.28%)
Patients with narrow-spectrum antibiotic use, n (%)	265 (32.72%)
Patients with oral antibiotic use, n (%)	708 (87.41%)
Patients with injection antibiotic use, n (%)	583 (71.98%)
Follow-up characteristics	
Duration of follow-up, mean (SD), years	12.29 (6.80)
Total duration of antibiotic-related risk periods, person-years	940.68
Total follow-up time, person-years	9956.46

IQR: interquartile range; SD: standard deviation.

Table 2. Results of SCCS analysis

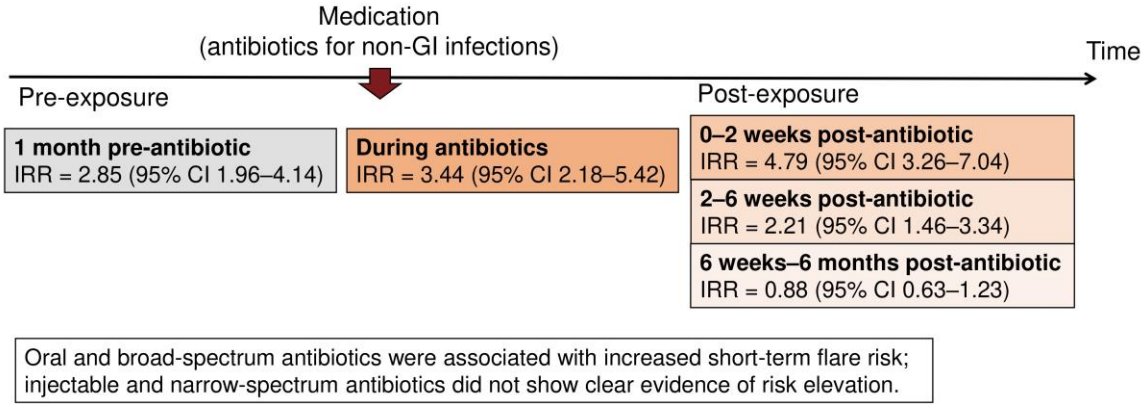
Periods	Events	Person-years	Incidence rate per 100 person-years	IRR (95% CI)	E-value
Baseline	658	9164.05	7.18	Ref	
1-31 days pre-exposure	33	103.40	31.92	2.85（1.96–4.14）	5.15
Prescription duration of antibiotics	22	58.24	37.78	3.44（2.18–5.42）	6.34
1-14 days post-exposure	31	59.02	52.51	4.79（3.26–7.04）	9.05
15-42 days post-exposure	26	108.09	24.05	2.21（1.46–3.34）	3.84
43-183 days post-exposure	40	463.65	8.63	0.88（0.63–1.23）	1.53

Table 3. Results of self-controlled case series analysis subgrouped by antibiotic route of administration and antibiotic spectrum

Periods	Events	Person years	IRR (95% CI)	E-value	Events	Person years	IRR (95% CI)	E-value	Wald Test p-value (Subgroup comparison)
Subgroup by route of administration	**Oral**				**Injection**				
1-31 days pre-exposure	23	88.01	1.74 (1.00–3.03)	2.85	26	68.97	1.88 (1.09–3.23)	3.10	0.88
Prescription duration of antibiotics	19	44.81	3.91 (2.21–6.91)	6.84	5	21.70	0.64 (0.24–1.70)	2.23	0.01
1-14 days post-exposure	24	50.90	3.70 (2.20–6.21)	6.47	17	37.51	1.30 (0.69–2.43)	1.95	0.04
15-42 days post-exposure	19	93.47	1.61 (0.92–2.80)	2.70	21	68.41	1.42 (0.8–2.51)	2.36	0.81
43-183 days post-exposure	33	407.16	0.78 (0.50–1.21)	1.93	31	291.46	1.07 (0.67–1.72)	1.43	0.44
Subgroup by antibiotic spectrum	**Broad**				**Narrow**				
1-31 days pre-exposure	33	100.22	3.13 (2.11–4.64)	5.79	5	26.00	0.57 (0.22–1.50)	2.66	<0.01
Prescription duration of antibiotics	21	53.97	3.19 (1.93–5.28)	5.92	<5	10.09	1.32 (0.44–3.95)	2.01	0.20
1-14 days post-exposure	28	57.02	4.19 (2.71–6.46)	7.89	7	12.94	1.43 (0.61–3.33)	2.38	0.05
15-42 days post-exposure	24	104.30	2.16 (1.38–3.38)	3.83	<5	24.27	0.65 (0.22–1.86)	2.46	0.06
43-183 days post-exposure	38	447.32	0.83 (0.57–1.20)	1.69	13	110.93	1.11 (0.59–2.10)	1.49	0.50

Note: Wald test p-values assess the statistical significance of the difference in IRRs between the two groups within each subgroup (e.g., oral vs. broad-spectrum; broad-spectrum vs. narrow-spectrum) for the same exposure period.

Association Between Antibiotic Use for Non-Gastrointestinal Infections and Inflammatory Bowel Disease Flare-Ups: A Self-Controlled Case Series Study



Oral and broad-spectrum antibiotics were associated with increased short-term flare risk; injectable and narrow-spectrum antibiotics did not show clear evidence of risk elevation.

Zhang Y, et al. *Am J Gastroenterol.* [Year]. [doi]

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