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Different Classes of Antibiotics, by Provoking Distinct Patterns of Dysbiosis, May Affect the Occurrence of Inflammatory Bowel Disease

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Abstract

The predominant forms of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis, which occur in approximately 0.5-1% of the World population. Alterations in the microbial flora (dysbiosis) are considered the primary precipitating factor in IBD. Because antibiotics are major disruptors of the microbiome, it was hypothesized that different antibiotic classes might induce distinct alterations in gut flora, reflected in positive or negative associations with IBD incidence at the population level. Average yearly consumption was calculated from ECDC reports (2004-2023) for the major antibiotic classes, which cover 99.87% of total antibiotic consumption across 30 European countries. Data were compared with age-stratified IBD incidence (15–39 years) estimated for 2021. Ordinal logistic regression modeled the association between antibiotic class proportions and IBD-incidence categories, entering each antibiotic class separately as a continuous predictor. Pearson correlation analyses were conducted to assess linear associations, and Kruskal-Wallis tests were applied to compare incidence categories. Statistical significance was set at $p < 0.05$. Tetracyclines (J01A), narrow-spectrum penicillin (J01CE, J01CF), and sulfonamides (J01E) showed a significant positive association with IBD incidence, indicating that higher consumption was associated with higher national incidence. In contrast, cephalosporins, macrolides, aminoglycosides, and quinolones showed significant negative associations, suggesting links to lower national incidence levels. Different antibiotic consumption patterns across 30 European countries may be associated with the IBD incidence.

Keywords: inflammatory bowel diseases (IBD); microbiome; dysbiosis; antibiotics; IBD incidence

1. Introduction

Inflammatory bowel disease (IBD) refers to diseases that cause chronic inflammation in the gastrointestinal (GI) tract. Symptoms include abdominal pain, diarrhea (often with blood), fatigue, and unintended weight loss, though they can vary depending on the disease's severity and location. Symptoms include abdominal pain, diarrhea, and weight loss, which can come and go in periods of flare-up and remission. Crohn's disease can develop anywhere along the digestive tract from the mouth to the anus, whereas ulcerative colitis is restricted to the large intestine. These diseases are non-communicable and incurable, affecting millions of people worldwide. Usually, IBD is considered a Western disease. By the 21st century, emerging industrialized nations in Asia and Latin America had experienced a rapid increase in cases, making inflammatory bowel disease a global issue (1, 2). Patients with IBD might produce a variety of symptoms that are different in UC and CD; however, frequent symptoms include persistent abdominal pain, diarrhea (with or without blood), weakness, and weight loss. IBD's clinical manifestations are characterized by recurrent episodes of gastrointestinal tract inflammation caused by an abnormal immune response to gut microflora. Ulcerative colitis (UC) generally presents itself as bloody diarrhea with or without mucus. Patients

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frequently complain of tenesmus, a sensation of incomplete evacuation, and abdominal pain. On physical exam, the patients complain of feeling predominantly left lower or left upper quadrant abdominal pain. In more severe cases, signs of an acute abdomen may develop, including guarding, rebound tenderness, or percussion tenderness, warranting investigation for toxic megacolon. The clinical manifestations of Crohn's disease (CD) vary considerably depending on the anatomical location of gastrointestinal involvement. Manifestations differ depending on the underlying inflammation, fistula formation, or the development of strictures. The symptom complex of right lower quadrant pain, weight loss, and non-bloody diarrhea is suggestive of Crohn's disease flare-up. Fistula formation can appear as fecaluria, pneumaturia, and rectovaginal fistula development. Masses in the right lower quadrant are generally related to abscess formation. Children with CD may present with growth retardation and delayed sexual maturation (3-5). The incidence of IBD has risen in the past decades, and now it is a global issue and not only a "Western" disease. Approximately 1.3 million people in Europe suffer from inflammatory bowel disease (IBD), which is about 0.2% of the population, but its rate varies by geographical regions. IBD incidence ranges from 10.5 to 46.14 per 100,000 in Europe. Crohn's disease [CD] incidence ranged from 4.1 to 22.78 per 100,000 in Europe, and ulcerative colitis [UC] estimates ranged from 3.0 to 23.36 per 100,000 in Europe. Northern European countries and the UK show the highest rates of UC, while southern and eastern European countries historically have lower rates, though these are increasing. The UK has the highest prevalence rate with 570/100000 inhabitants, followed by Denmark (530/100000) and Norway (503/100000). The lowest prevalence rates were reported from Portugal (1,6/100000) and Romania (2,42/100000). The prevalence of Crohn's disease in Europe ranges from approximately 61.6 to 178 per 100,000 people (6, 7). Genetic analyses have identified more than 200 genes associated with an increased risk of developing IBD, but most of the associations are relatively weak. Twins studies indicate a concordance rate of around 4% for dizygotic pairs. In contrast, concordance rates for monozygotic twins have been reported as 50% with higher rates among pairs with Crohn's disease than pairs with ulcerative colitis. Among pairs with Crohn's disease, the majority have disease in the exact location of the bowel (8). The single greatest known risk factor for developing IBD is having a close family member with IBD, which might raise the possibility, apart from genetics, that the "transfer" of the IBD-related microbiome also occurs (9). It is observed that about 5% and 23% of people with IBD have a first-degree relative with IBD. Among families with multiple affected family members, there appears to be a high degree of clinical similarity in disease location, disease behavior, age at diagnosis, and the presence and character of extra-intestinal manifestations (10). Reports on the environmental risk factors for IBD indicated that maternal smoking, early life antibiotic exposure, otitis media, living in urban area (for CD), adult smoking (for CD), longer NSTAID drugs taking, combined oral contraceptives, hormonal medical treatment, adult antibiotic exposure, carnivorous diet, and consuming ultra-processed foods (UBD) augment the possibility of developing CD, but not UC. Breastfeeding up to 12 months, higher consumption of vegetables and fish, exposure to farm animals, bed sharing, fruit and vegetables (UC), fiber intake (CD), appendectomy (UC), tobacco smoking (UC), presence of Helicobacter pylori, and Mediterranean diet are considered protective factors. The opposite effect of smoking for CD (aggravating the symptoms) and UC (ameliorating the disease process) is well known, but no appropriate explanation exists. Reports also indicate the role of psychological factors in the development of IBD (6, 11). Inflammatory bowel diseases arise from a convergence of genetic risk, environmental factors, and gut microbiota, where each is necessary but not sufficient alone to cause disease. However, environmental factors (diet, antibiotics, etc.) can influence the composition of gut flora by promoting or inhibiting the proliferation of different microbial taxa. The pro-colitogenic effects of intestinal dysbiosis and the amelioration of the inflammatory burden through fecal microbiota transplantation are well established.

2. Concept/working hypothesis:

Considerable scientific knowledge accumulated over the past decades suggests that the principal driving force in the development of inflammatory bowel diseases (UC, CD) is pro-

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inflammatory dysbiosis, which arises from various external factors in (probably) genetically susceptible individuals. Different diets either promote (ultra-processed food) or protect (Mediterranean diet) the development of IBD. Antibiotic exposure, particularly at early ages, is considered a risk factor for the development of IBD. Still, different antibiotic classes, depending on the susceptibility of the intestinal microbial taxa, may either promote or inhibit the growth of IBD-related dysbiosis. Antibiotic consumption reports (ECDC) from the 30 European countries included in the study indicate manifold differences in the average yearly consumption of different antibiotic classes, expressed in Defined Daily Dose/1000 inhabitants/Day (DID). The consumption of narrow-spectrum, beta-lactamase-sensitive penicillin (J01CE), calculated as an average yearly consumption, is highest in Denmark (27.733 DID) and lowest in Italy (0.009 DID). The highest average annual cephalosporin consumption was reported in Greece (23.814 DID), and the lowest in the UK (2.067). It is hypothesized that if the consumption of any antibiotic group shows a significant positive statistical association with the incidence of IBD, it might indicate that higher use of that class is linked to an increased likelihood of belonging to a higher IBD-incidence category. In contrast, a significant negative association may suggest that greater consumption of a given antibiotic class is associated with a higher probability of belonging to a lower IBD-incidence category, potentially reflecting differing impacts on gut flora. Countries with higher consumption of antibiotic classes that show positive associations might report higher IBD incidence. In contrast, increased use of classes that show negative associations may correspond to lower IBD incidence.

3. Objective

Identification of antibiotic classes that show positive or negative statistical association with the IBD incidence (ASIR 2021), which might promote or inhibit the IBD-related dysbiosis.

4. Materials and methods

An average yearly antibiotic consumption database was developed on antibiotic consumption in 30 European countries from the ECDC annual reports of 2004-2023 (twenty years) accessed in August 2025 (https://www.ecdc.europa.eu/en/publications-data/antimicrobial-consumption-eueea-esac-net-annual-epidemiological-report-2023). Total antibiotic consumption (public, hospital) was recorded for the countries included in the study for each year (2004-2023, twenty years) to calculate the yearly average consumption. The ECDC reports included 15 antibiotic categories, expressed as Defined Daily Dose/1000 Inhabitants/Day (DID), coded according to the ATC classification at level II. and III. https://qap.ecdc.europa.eu/public/extensions/AMC2_Dashboard/AMC2_Dashboard.html#eu-consumption-tab

Antibiotic categories (codes): Total systemic antibiotics: J01, tetracyclines: J01A, amphenicols: J01B, penicillin group (all): J01C, broad spectrum, beta-lactamase susceptible penicillin: J01CA, narrow spectrum, beta-lactamase susceptible penicillin: J01CE, narrow spectrum, beta-lactamase resistant, narrow spectrum penicillin: J0CF, broad spectrum, beta-lactamase resistant combination penicillin: J01CR, cephalosporin: J01D, sulfonamides: J01E, macrolides and lincomycin: J01F, aminoglycosides: J01G, quinolones: J01M, antibiotic combinations: J01R, other antibiotics: J01X, which includes glycopeptides, polymyxines, steroid antibacterials, imidazole derivates, nitrofurantoin derivates, fusidic acid etc. The average yearly total antibiotic consumption (J01, in DID) was calculated as 587. 226 DID for the 30 countries. The highest consumption was reported from the UK (41.961 DID), and the lowest from the Netherlands (9.917). Several differences in antibiotic consumption were observed across European countries. The Nordic countries preferred different narrow-spectrum penicillins, whereas in the Mediterranean countries, broad-spectrum antibiotics were predominantly used (Table 1). To develop the antibiotic database for comparison, we calculated the relative share of antibiotic consumption across different classes from the total amount (J01, DID) and expressed it as a percentage (%). Antibiotic groups of very low consumption (below 0.5 DID/year:

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amphenicols /J01B/ and combinations /J01R/) were left out of the calculation. The remaining amount covered the 99,87% of the average total yearly consumption. The database on the incidence rate of IBD in 2021 was extracted from the Global Burden of Disease (GBD) study 2021, and the age-standardized incidence rate/100,000 inhabitants (ASIR) for 2021, as reported by Chen L et al. The database included data on young people aged 15-39 years, for whom IBD occurs more frequently (12, 13). The results were featured in Table 1. The highest incidence of IBD (age-stratified incidence rate: ASIR 2021) among young people was reported in the Netherlands (28.5/100000 inhabitants), and the lowest in Romania (2.5/100000 inhabitants). The results were categorized into three ordinal groups (low, medium, and high incidence) based on tertiles of the overall distribution: Group 1 = IBD incidence < 9.867, Group 2 = IBD incidence >= 9.867 and < 17.067, and Group 3 = IBD incidence >= 17.067. Statistics: Pearson correlation coefficients were first calculated to assess the bivariate relationships between each antibiotic class and IBD incidence. Ordinal logistic regression was performed to model the association between antibiotic class proportions and IBD incidence category. Each antibiotic class was entered separately into the model as a continuous independent variable. This approach was chosen to avoid multicollinearity among antibiotic courses, as these variables represent mutually dependent components of total antibiotic consumption. A positive association indicated higher odds of belonging to a higher IBD-incidence category with increasing antibiotic consumption, whereas a negative association indicated higher odds of belonging to a lower IBD-incidence category. The regression models estimated odds ratios (OR) with corresponding 95% confidence intervals (95% CI) and p-values. Non-parametric tests were used due to violations of normality and homogeneity of variance, as assessed by the Shapiro-Wilk and Levene's tests. Therefore, differences in antibiotic consumption patterns across IBD incidence categories were examined using the Kruskal-Wallis test, followed by Dunn's test with the Dwass-Steel-Critchlow-Fligner (DSCF) correction for pairwise post-hoc comparisons. Model performance was evaluated using likelihood-ratio tests, and the proportional odds assumption was checked where applicable. Statistical significance was set at $p < 0.05$. Pearson correlation coefficients were reported alongside regression outputs and the results of the non-parametric tests for comparative interpretation. All analyses were performed using Jamovi (version 2.3.28.0) statistical software.

5. Results

In the 30 European countries analyzed, average annual antibiotic consumption varied considerably by class. Pearson correlation analyses identified positive associations between the proportional use of tetracyclines (J01A, r = 0.519, p = 0.003), narrow spectrum, beta-lactamase–sensitive penicillin (J01CE, r = 0.465, p = 0.010), narrow spectrum, beta-lactamase–resistant penicillin (J01CF, r = 0.503, p = 0.005), and sulfonamides (J01E, r = 0.424, p = 0.020) with IBD incidence. In contrast, cephalosporins (J01D, r = –0.478, p = 0.008), macrolides (J01F, r = –0.337, p = 0.068), aminoglycosides (J01G, r = –0.524, p = 0.003), and quinolones (J01M, r = –0.452, p = 0.012) demonstrated inverse correlations. Other antibiotic classes did not show significant associations (Table 1).

The results of univariate ordinal logistic regression analyses paralleled these patterns. Higher consumptions of tetracycline: J01A (OR = 1.215, 95% CI [1.074-1.412]), narrow-spectrum, beta-lactamase-sensitive penicillin: J01CE (OR = 1.223, 95% CI [1.065-1.513]), narrow-spectrum, beta-lactamase resistant penicillin: J01CF (OR = 1.715, 95% CI [1.234-2.779]) and sulfonamides: J01E (OR = 1.555, 95% CI [1.062-2.399]) were associated with increased odds of belonging to higher IBD-incidence categories, respectively. On the other hand, higher consumptions of cephalosporin: J01D (OR = 0.843, 95% CI [0.742-0.943]), macrolides: J01F (OR = 0.795, 95% CI [0.652-0.936]), aminoglycosides: J01G (OR = 0.041, 95% CI [0.002-0.314]), and quinolones: J01M (OR = 0.772, 95% CI [0.609-0.944]) were associated with lower odds of higher IBD incidence. (Table 1.) These trends were visualized in a forest plot summarizing odds ratios and 95% confidence intervals across all antibiotic classes (Figure 1) and in diagrams (Figure 2-3).

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Non-parametric Kruskal–Wallis tests confirmed significant differences in antibiotic consumption across IBD incidence categories for multiple classes, including J01A, J01C, J01CE, J01CF, J01CR, J01D, J01E, and J01 G. Post-hoc pairwise comparisons using the DSCF method revealed that the most significant differences were between low- vs high-incidence groups (G1 vs G3) and medium- vs high-incidence groups (G2 vs G3) (Table 1). For example, J01A consumption differed significantly between G1 and G3 ($p = 0.018$) and G2 vs G3 ($p = 0.006$), while J01CF showed differences between G1 vs G2 ($p = 0.034$) and G2 vs G3 ($p = 0.003$).

Overall, results demonstrate a consistent pattern: certain antibiotic classes, particularly those targeting Gram-positive bacteria, were positively associated with higher IBD incidence, whereas classes with broader Gram-negative activity were inversely associated, with some overlap.

Table 1. The average total yearly systemic antibiotic consumption (J01, 2004-2023, 20 years) expressed in defined daily dose/1000 inhabitants/day (DID) in 30 European countries, and the consumption of antibiotic classes is described as a relative share in percentage (%) of the total systemic consumption (J01) with the IBD age-standardized incidence rates (ASIR). The table also shows the results of the statistical analyses.

Average, yearly antibiotic consumption (2004-2023, 20 years) expressed in defined daily dose/1000 inhabitants/day (did) in 30 European countries.														**IBD incidence**
Countries	**J01**	**J1A %**	**J01C%**	**J01CA %**	**J01CE %**	**J01CF %**	**J01CR %**	**J01D%**	**J01E%**	**J01F%**	**J01G%**	**J01M%**	**J01X%**	**ASIR 2021**
Austria	**10.193**	3.726	47.435	8.219	4.060	0.704	34.880	15.933	2.519	18.670	0.245	7.291	4.209	**13.600**
Belgium	**22.537**	8.829	45.889	19.787	0.442	1.599	24.086	8.575	1.169	14.330	0.208	10.307	11.520	**12.300**
Bulgaria	**20.213**	10.362	29.583	17.131	1.446	0.002	10.877	21.720	4.276	19.338	1.500	14.033	0.548	**9.000**
Croatia	**19.808**	6.391	41.336	11.226	5.069	0.558	24.391	17.831	4.338	15.972	0.517	8.289	5.700	**9.400**
Cyprus	**26.500**	11.637	35.256	10.078	0.339	0.154	25.226	21.249	1.060	11.368	0.367	17.340	2.358	**11.900**
Czech Rep.	**15.627**	11.237	35.439	4.541	8.542	0.828	21.537	14.952	5.414	20.147	0.433	3.742	7.362	**24.000**
Denmark	**16.540**	9.734	61.570	20.188	27.733	9.239	4.432	1.877	4.916	12.079	0.316	3.534	4.794	**19.900**
Estonia	**11.716**	15.600	32.813	16.051	2.062	1.489	13.699	12.355	4.429	19.962	0.684	8.246	5.605	**4.600**
Finland	**17.484**	21.589	28.447	15.068	7.685	0.850	4.848	16.004	7.263	7.443	0.095	5.646	12.290	**18.400**
France	**24.836**	13.069	49.806	28.256	0.678	1.251	19.963	9.563	1.964	14.346	0.376	7.697	2.935	**13.900**
Germany	**12.928**	16.406	34.990	18.489	5.271	0.427	10.796	17.491	4.932	15.880	0.204	5.966	4.118	**25.000**
Greece	**32.505**	7.737	28.884	12.497	1.335	0.038	15.007	23.814	1.198	25.229	1.716	8.448	2.946	**4.800**
Hungary	**14.754**	8.964	33.696	8.003	2.890	0.004	24.380	14.905	4.175	21.737	0.406	14.421	1.978	**18.000**
Iceland	**19.202**	25.577	47.629	18.816	10.831	6.115	11.867	4.022	4.591	7.617	0.371	4.035	5.796	**21.000**
Ireland	**20.689**	15.021	45.876	15.274	4.588	6.562	19.369	7.118	4.979	18.766	0.398	4.016	3.094	**17.000**
Italy	**22.860**	2.550	43.891	11.437	0.009	0.086	31.530	11.536	3.014	20.022	0.474	13.645	3.943	**8.300**
Latvia	**13.162**	18.965	36.168	22.988	0.808	0.449	12.083	9.310	5.799	T12.710	1.426	8.972	6.434	**4.800**
Lithuania	**16.412**	9.961	46.183	29.731	5.427	0.478	11.259	10.986	2.348	11.881	1.255	6.555	10.531	**5.900**
Luxembourg	**22.502**	8.312	38.870	13.111	0.305	0.884	24.022	17.585	1.659	16.466	0.277	11.190	6.398	**15.900**
Malta	**19.815**	8.114	36.043	3.125	0.627	0.884	31.406	20.561	1.674	19.062	1.272	11.324	4.117	**10.100**
Netherlands	**9.917**	20.846	32.962	13.176	2.572	5.652	11.919	2.394	4.988	14.822	0.635	7.894	14.764	**28.500**
Norway	**16.195**	17.996	40.831	13.521	22.184	4.662	0.493	2.307	4.909	9.318	0.469	2.940	21.368	**21.000**
Poland	**22.225**	10.058	29.536	15.044	1.361	0.150	12.981	14.387	2.441	18.011	0.304	6.548	15.427	**3.200**
Portugal	**19.290**	4.563	45.254	10.305	0.558	2.824	30.814	12.061	2.625	15.865	0.353	10.093	6.421	**10.300**
Romania	**25.095**	3.963	45.695	15.954	2.534	2.172	25.031	18.764	3.176	13.387	1.088	12.848	0.823	**2.500**
Slovakia	**20.805**	8.237	32.417	6.135	7.974	0.029	18.451	21.932	2.685	25.282	0.402	9.481	0.998	**8.900**
Slovenia	**13.354**	3.610	54.967	16.239	13.072	2.023	23.632	5.836	6.903	16.126	0.486	9.484	2.935	**12.600**
Spain	**24.050**	6.311	54.587	22.790	0.445	1.005	30.343	11.100	1.925	11.966	0.314	10.477	2.937	**11.700**

Sweden	**14.052**	20.911	48.537	8.712	25.907	12.013	1.941	2.790	3.679	5.000	0.163	6.356	12.449	**21.100**
UK	**41.961**	25.900	38.492	18.626	4.601	9.435	5.828	2.067	7.099	13.570	0.586	2.822	6.401	**17.200**
Pearson's r		**0.519**	0.112	-0.144	**0.465**	**0.503**	-0.334	**-0.478**	**0.424**	**-0.337**	**-0.524**	**-0.452**	0.310	
Pearson's p-value		**0.003**	0.554	0.447	**0.010**	**0.005**	0.071	**0.008**	**0.020**	**0.068**	**0.003**	**0.012**	0.095	
Odds ratio		**1.215**	1.041	0.966	**1.223**	**1.715**	0.934	**0.843**	**1.555**	**0.795**	**0.041**	**0.772**	1.165	
95%CI		**1.074-1.412**	0.961-1.131	0.869-1.071	**1.065-1.513**	**1.234-2.779**	0.864-1.003	**0.742-0.943**	**1.062-2.399**	**0.652-0.936**	**0.002-0.314**	**0.609-0.944**	0.998-1.407	
p value		**0.005**	0.331	0.510	**0.023**	**0.007**	0.068	**0.005**	**0.031**	**0.011**	**0.008**	**0.019**	0.072	
Kruskal-Wallis p		**0.003**	**0.048**	0.924	**0.002**	**0.014**	**0.001**	**0.030**	**0.004**	0.114	**0.010**	**0.006**	0.096	
	G1 vs G2	0.893	**0.041**	0.893	0.322	**0.034**	0.050	0.285	0.251	0.404	**0.022**	0.893	0.997	
Post-Hoc test	G1 vs G3	**0.018**	0.636	0.972	**0.011**	**0.041**	**0.041**	0.060	**0.018**	0.165	**0.027**	**0.011**	0.220	
	G2 vs G3	**0.006**	0.285	0.988	**0.009**	0.636	**0.003**	0.165	**0.018**	0.404	0.988	**0.027**	0.103	

Glossary: Antibiotic categories (ACT codes): Total systemic antibiotics: J01, tetracyclines: J01A, penicillin group (all): J01C, broad spectrum, penicillinase susceptible penicillin: J01CA, narrow spectrum, penicillinase susceptible penicillin: J01CE, narrow spectrum, penicillinase resistant, narrow spectrum penicillin: J0CF, broad spectrum, penicillinase resistant penicillin: J01CR, cephalosporines: J01D, sulfonamides: J01E, macrolides and lincomycin: J01F, aminoglycosides: J01G, quinolones: J01M, other antibiotics: J01X, which includes glycopeptides, polymyxine, steroid antibacterial, imidazole derivates, nitrofurantoin derivates, etc.

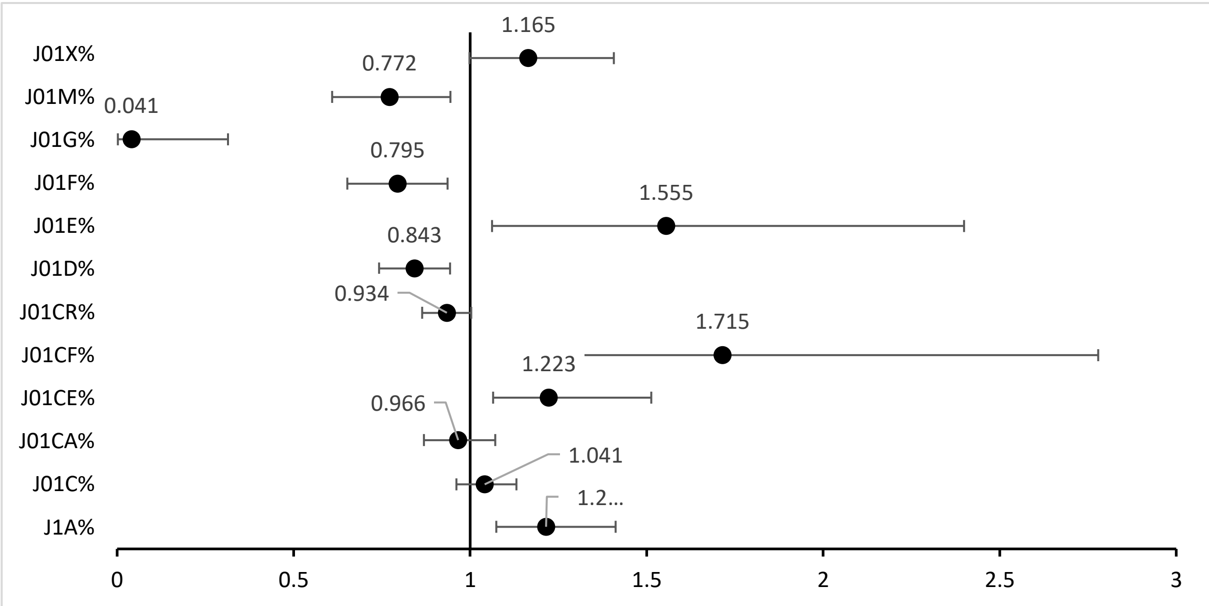

Figure 1. Forest plot showing the results (OR) of the ordinal regression model with the corresponding 95% CI.

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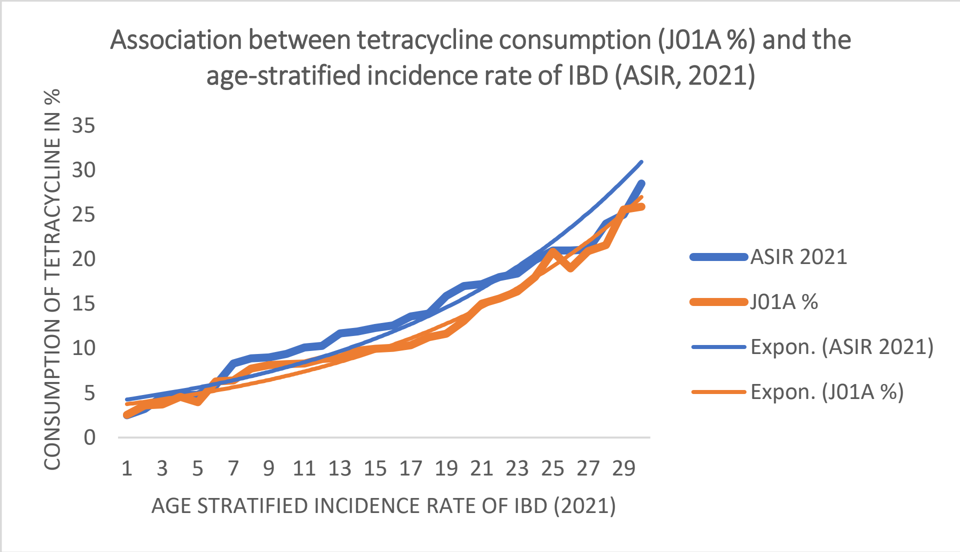

Figure 2. Positive association between tetracycline consumption and the prevalence of IBD (ASIR, 2021).

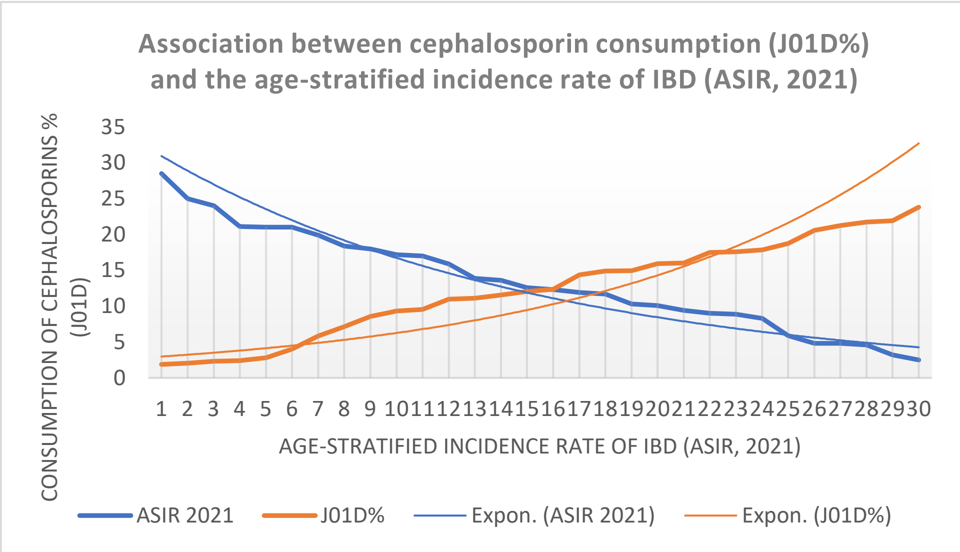

Figure 3. Inverse association between cephalosporin consumption and the incidence of IBD (ASIR, 2021).

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Table 2. Rank order of the incidence of IBD (ASIR 2021) and the rank order distribution of the countries with higher consumption of antibiotic classes with positive (J01A, J01CE, J01E) and the low consumption of antibiotic groups with negative statistical association (J01D, J01F, J01M). The first 10 countries in the IBD rank order appear (**bold, bigger font**) in the top 10 for positive consumption and the bottom 10 for negative association with antibiotic classes. Seven countries are identical in the antibiotic groups with a positive statistical association, and 5-8 in the low-consumption groups with a negative association and higher IBD incidence.

Countries	ASIR 2021	Countries	J01A %	Countries	J01CE %	Countries	J01E %	Countries	J01D %	Countries	J01F %	Countries	J01M %
Netherlands	28,5	**UK**	**25,900**	**Denmark**	**27,733**	**Finland**	**7,263**	Greece	23,814	Slovakia	25,282	Cyprus	17,340
Germany	25	**Iceland**	**25,577**	**Sweden**	**25,907**	**UK**	**7,099**	Slovakia	21,932	Greece	25,229	**Hungary**	**14,421**
Czechia	24	**Finland**	**21,589**	**Norway**	**22,184**	Slovenia	6,903	Bulgaria	21,720	**Hungary**	**21,737**	Bulgaria	14,033
Sweden	21,1	**Sweden**	**20,911**	Slovenia	13,072	Latvia	5,799	Cyprus	21,249	**Czechia**	**20,147**	Italy	13,645
Iceland	21	**Netherlands**	**20,846**	**Iceland**	**10,831**	**Czechia**	**5,414**	Malta	20,561	Italy	20,022	Romania	12,848
Norway	21	Latvia	18,965	**Czechia**	**8,542**	**Netherlands**	**4,988**	Romania	18,764	Estonia	19,962	Malta	11,324
Denmark	19,9	**Norway**	**17,996**	Slovakia	7,974	Ireland	4,979	Croatia	17,831	Bulgaria	19,338	Luxembourg	11,190
Finland	18,4	**Germany**	**16,406**	**Finland**	**7,685**	**Germany**	**4,932**	Luxembourg	17,585	Malta	19,062	Spain	10,477
Hungary	18	Estonia	15,600	Lithuania	5,427	**Denmark**	**4,916**	**Germany**	**17,491**	Ireland	18,766	Belgium	10,307
UK	17,2	Ireland	15,021	**Germany**	**5,271**	**Norway**	**4,909**	**Finland**	**16,004**	Austria	18,670	Portugal	10,093
Ireland	17	France	13,069	Croatia	5,069	**Iceland**	**4,591**	Austria	15,933	Poland	18,011	Slovenia	9,484
Luxembourg	15,9	Cyprus	11,637	**UK**	**4,601**	Estonia	4,429	**Czechia**	**14,952**	Luxembourg	16,466	Slovakia	9,481
France	13,9	**Czechia**	**11,237**	Ireland	4,588	Croatia	4,338	**Hungary**	**14,905**	Slovenia	16,126	Latvia	8,972
Austria	13,6	Bulgaria	10,362	Austria	4,060	Bulgaria	4,276	Poland	14,387	Croatia	15,972	Greece	8,448
Slovenia	12,6	Poland	10,058	**Hungary**	**2,890**	**Hungary**	**4,175**	Estonia	12,355	**Germany**	**15,880**	Croatia	8,289
Belgium	12,3	Lithuania	9,961	**Netherlands**	**2,572**	**Sweden**	**3,679**	Portugal	12,061	Portugal	15,865	Estonia	8,246
Cyprus	11,9	**Denmark**	**9,734**	Romania	2,534	Romania	3,176	Italy	11,536	**Netherlands**	**14,822**	**Netherlands**	**7,894**
Spain	11,7	**Hungary**	**8,964**	Estonia	2,062	Italy	3,014	Spain	11,100	France	14,346	France	7,697
Portugal	10,3	Belgium	8,829	Bulgaria	1,446	Slovakia	2,685	Lithuania	10,986	Belgium	14,330	Austria	7,291
Malta	10,1	Luxembourg	8,312	Poland	1,361	Portugal	2,625	France	9,563	**UK**	**13,570**	Lithuania	6,555
Croatia	9,4	Slovakia	8,237	Greece	1,335	Austria	2,519	Latvia	9,310	Romania	13,387	Poland	6,548
Bulgaria	9	Malta	8,114	Latvia	0,808	Poland	2,441	Belgium	8,575	Latvia	12,710	**Sweden**	**6,356**
Slovakia	8,9	Greece	7,737	France	0,678	Lithuania	2,348	Ireland	7,118	**Denmark**	**12,079**	**Germany**	**5,966**
Italy	8,3	Croatia	6,391	Malta	0,627	France	1,964	Slovenia	5,836	Spain	11,966	**Finland**	**5,646**

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Lithuania	**5,9**	**Spain**	6,311	Portugal	0,558	Spain	1,925	**Iceland**	**4,022**	Lithuania	11,881	**Iceland**	**4,035**
Greece	**4,8**	**Portugal**	4,563	Spain	0,445	Malta	1,674	**Sweden**	**2,790**	Cyprus	11,368	Ireland	4,016
Latvia	**4,8**	**Romania**	3,963	Belgium	0,442	Luxemburg	1,659	**Netherlands**	**2,394**	**Norway**	**9,318**	**Czechia**	**3,742**
Estonia	**4,6**	**Austria**	3,726	Cyprus	0,339	Greece	1,198	**Norway**	**2,307**	**Iceland**	**7,617**	**Denmark**	**3,534**
Poland	**3,2**	**Slovenia**	3,610	Luxemburg	0,305	Belgium	1,169	**UK**	**2,067**	**Finland**	**7,443**	**Norway**	**2,940**
Romania	**2,5**	**Italy**	2,550	Italy	0,009	Cyprus	1,060	**Denmark**	**1,877**	**Sweden**	**5,000**	**UK**	**2,822**

6. Discussion

The possible role of the gut microbiome in the development of inflammatory bowel diseases (IBD) was first raised over 20 years ago through the process of dysbiosis, an imbalance of gut bacteria that leads to reduced diversity and an increase in pro-inflammatory microbes (14). Early efforts to correct microbiome composition through fecal microbiota transplantation and achieve clinical remission had also been reported (15). The role of the gut microbiota in the establishment and maintenance of health, and in the pathogenesis of different diseases, including IBD, has also been identified over the past two decades. The gut microbiota interacts with the host through metabolites, small molecules produced as intermediates or end products of microbial metabolism. These metabolites can arise from bacterial metabolism of dietary substrates, modification of host molecules, such as bile acids, or directly from bacteria (16). In healthy adults, Firmicutes and Bacteroidetes are the predominant phyla in the intestines, with Proteobacteria and Actinobacteria accounting for the majority of the remaining bacteria (17). The possible roles of viruses and plant metabolites have also been considered (18). The most crucial change observed in IBD-related dysbiosis is the significant reduction of the diversity of microbiome, with the decrease in taxa with anti-inflammatory or protective properties like Lachnospiraceae, Bifidobacterium, *Faecalibacterium prausnitzii*, Roseburia species, Bacteroides, and the proliferation of the pro-inflammatory Proteobacteria, Fusobacterium species, and *Ruminococcus gnavus* species has also been observed. Biopsy specimens from the ileum and the rectum showed similar dysbiosis, but the biopsy and fecal isolates were not identical (19). Firmicutes and Bacteroides, together, constitute approximately 90% of gut microbiota and are key producers of short-chain fatty acids (SCFAs). Bacterial 'dysbiosis' in IBD has been typically characterized by an increased ratio of potentially pathogenic to beneficial bacteria and lower overall diversity. Recently, the focus of microbiome research has shifted from microbial composition to the functional properties of specific bacterial species and strains. Comprehensive multi-omics investigations have elucidated the composition of bacterial species and their metabolic profiles in patients with IBD, enabling more accurate detection of alterations in bacterial ecology that coincide with disease initiation and progression. An extensive, detailed review summarizes the roles of different microbial metabolites and their interactions with the immune system (20). A multi-omics study of UC patients indicated that *B. vulgatus* proteases are associated with UC disease activity, and this observation has also been confirmed in animal experiments (21). The mechanisms by which the microbiota damages the intestinal epithelial barrier are complex and remain a subject of study (22). Several risk factors are considered for the development of IBD. However, the decisive role in the development of IBD is the modification of the microbiome, because external factors can induce dysbiosis, which may act as a "risk factor" for IBD or have a "protective" effect against its development (23). The crucial role of the microbiome in the development of IBD or in the amelioration of symptoms is further supported by fecal microbiota transfer (FMT) experiments (24). Fecal microbiota transplantation from healthy donors induced clinical remission and endoscopic improvement in active ulcerative colitis (UC) and is associated with distinct microbial changes that relate to outcome

(25). The clinical symptoms of Crohn's disease had also been ameliorated after using FMT (26). By restoring microbial diversity and correcting dysbiosis, FMT offers a novel, microbiota-targeted alternative to conventional therapies. While data support its efficacy in improving disease remission, variability in outcomes underscores the need for standardized protocols and additional large-scale, controlled studies (27). The role of antibiotics in the development of IBD and their use as therapeutic agents are controversial. A combination of amoxicillin, metronidazole, and tetracycline was reported to be beneficial in a limited number of steroid-resistant UC patients without a control group (28, 29). An extensive study from Denmark reported that antibiotic use is a risk factor, with practically all antibiotic classes identified as risk factors, except nitrofurantoin. A meta-analysis of publications reporting on the association of antibiotic use and the development of IBD confirmed that antibiotic exposure could be considered a risk factor for IBD. This study was based on prescription analyses and questionnaires. They concluded that almost all antibiotic classes were associated with increased IBD risk, and the extent of the risk varied across classes (30). Recent reports indicate a significant shift in healthy gut flora even before IBD diagnosis (31). These changes include a general decrease in microbial diversity, a reduction in beneficial bacteria like Faecalibacterium and Ruminococcaceae, and an increase in potentially harmful bacteria such as Enterobacteriaceae and Fusobacterium (32).

1. Conclusion

The role of the altered microbiome (dysbiosis) in the development of various diseases, including IBD, is well known and has been reported in several publications, as included in the references. The most significant microbiome-disrupting agents that cause dysbiosis are antibiotics, which enter the human body either as therapeutic agents or as environmental pollutants through drinking water or the food chain. Our research focused on identifying potential antibiotic classes associated with higher or lower IBD incidence and on estimating their possible role in IBD development across 30 European countries. The results of our statistical analysis were further strengthened by the observation that the list of the countries with the highest top 10 of IBD prevalence showed similar rank order (7 out of 10), with the rank order of the antibiotic classes showing positive associations, and the lowest 10 consumption group of the antibiotic classes showing negative associations (5-8 out of 10) (Table 2.). Our findings highlight the possibility that antibiotic consumption patterns from 30 European countries might influence the incidence of IBD.

Limitations of our study: Our comparative analysis of antibiotic consumption and IBD prevalence cannot be interpreted at the individual level because we lacked individual-level data on antibiotic use.

Strength of the study: The comparison of large databases and the extensive statistical analysis of the results clearly indicate that antibiotic consumption patterns may drive IBD development by altering the microbiome.

Author contribution:

Gábor Ternák: Conceptualization, Data curation, Formal Methodology, Writing original draft

Gergely Márovics: Statistics, Conceptualization, Data curation, Writing – review & editing

István Kiss: Conceptualization, Writing – review & editing

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References

1. Ng SC, Shi HY, Hamidi N, Underwood FE, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017 Dec 23;390(10114):2769-2778. doi: 10.1016/S0140-6736(17)32448-0. 2.

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2. Rosen MJ, Dhawan A, Saeed SA et al. Inflammatory Bowel Disease in Children and Adolescents. JAMA Pediatr. 2015 Nov;169(11):1053-60. doi: 10.1001/jamapediatrics.2015.1982.
3. Rubin DT, Ananthakrishnan AN, Siegel CA, et al Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413. doi: 10.14309/ajg.0000000000000152.
4. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517. doi: 10.1038/ajg.2018.27.
5. McDowell C, Farooq U, Haseeb M. Inflammatory Bowel Disease. [Updated 2023 Aug 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470312/
6. Caron B, Honap S, Peyrin-Biroulet L. Epidemiology of Inflammatory Bowel Disease across the Ages in the Era of Advanced Therapies. J Crohns Colitis. 2024 Oct 30;18(Supplement_2):ii3-ii15. doi: 10.1093/ecco-jcc/jjae082.
7. Bruner LP, White AM, Proksell S. Inflammatory Bowel Disease. Prim Care. 2023 Sep;50(3):411-427. doi: 10.1016/j.pop.2023.03.009. Epub 2023 May 10.
8. Borowitz SM. The epidemiology of inflammatory bowel disease: Clues to pathogenesis? Front Pediatr. 2023 Jan 17;10:1103713. doi: 10.3389/fped.2022.1103713.
9. Halfvarson J, Ludvigsson JF, Bresso F, et al. Age determines the risk of familiar inflammatory bowel disease – a nationwide study. Alim Pharmacol Ther. (2022) 56:491–500. doi: 10.1111/apt.16938
10. Halfvarson J. Genetic epidemiology of inflammatory bowel disease, early twin and family studies. In: C Hedin, JD Rioux, M D'Amato, editors. Molecular genetics of inflammatory bowel disease. 2nd ed. Cham: Springer Nature Switzerland (2019). p. 25–46.
11. Agrawal M, Sabino J, Frias-Gomes C, et al. Early life exposures and the risk of inflammatory bowel disease: Systematic review and meta-analyses. EClinicalMedicine. 2021 May 15;36:100884. doi: 10.1016/j.eclinm.2021.100884.
12. Lin D, Jin Y, Shao X, et al. Global, regional, and national burden of inflammatory bowel disease, 1990-2021: Insights from the global burden of disease 2021. Int J Colorectal Dis. 2024 Sep 7;39(1):139. doi: 10.1007/s00384-024-04711-x.
13. Chen L, Xu Y, Ai F, et al. Dissecting the rising tide of inflammatory bowel disease among youth in a changing world: insights from GBD 2021. Int J Colorectal Dis. 2025 Feb 18;40(1):44. doi: 10.1007/s00384-025-04821-0.
14. Swidsinski A, Ladhoff A, Pernthaler A, et al. Mucosal flora in inflammatory bowel disease. Gastroenterology. 2002 Jan;122(1):44-54. doi: 10.1053/gast.2002.30294.
15. West CE, Renz H, Jenmalm MC, et al in-FLAME Microbiome Interest Group. The gut microbiota and inflammatory noncommunicable diseases: associations and potentials for gut microbiota therapies. J Allergy Clin Immunol. 2015 Jan;135(1):3-13; quiz 14. doi: 10.1016/j.jaci.2014.11.012.
16. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020 Apr;17(4):223-237. doi: 10.1038/s41575-019-0258-z.
17. Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota. World J Gastroenterol 2015; 21(29): 8787-8803
18. Rahaman MM, Wangchuk P, Sarker S. A systematic review on the role of gut microbiome in inflammatory bowel disease: Spotlight on virome and plant metabolites. Microb Pathog. 2025 Aug;205:107608. doi: 10.1016/j.micpath.2025.107608.
19. Dalal SR. The Microbiome and Inflammatory Bowel Diseases. Surg Clin North Am. 2025 Oct;105(5):941-951. doi: 10.1016/j.suc.2025.06.007.
20. Iliev ID, Ananthakrishnan AN, Guo CJ. Microbiota in inflammatory bowel disease: mechanisms of disease and therapeutic opportunities. Nat Rev Microbiol. 2025 Aug;23(8):509-524. doi: 10.1038/s41579-025-01163-0.
21. Mills RH, Dulai PS, Vázquez-Baeza Y, et al Multi-omics analyses of the ulcerative colitis gut microbiome link Bacteroides vulgatus proteases with disease severity. Nat Microbiol. 2022 Feb;7(2):262-276. doi: 10.1038/s41564-021-01050-3.

22. Foppa C, Rizkala T, Repici A, et al. Microbiota and IBD: Current knowledge and future perspectives. Dig Liver Dis. 2024 Jun;56(6):911-922. doi: 10.1016/j.dld.2023.11.015.
23. Agrawal M, Allin KH, Petralia F, et al. Multiomics to elucidate inflammatory bowel disease risk factors and pathways. Nat Rev Gastroenterol Hepatol. 2022 Jun;19(6):399-409. doi: 10.1038/s41575-022-00593-y.
24. Yadegar A, Bar-Yoseph H, Monaghan TM, et al. Fecal microbiota transplantation: current challenges and future landscapes. Clin Microbiol Rev. 2024 Jun 13;37(2):e0006022. doi: 10.1128/cmr.00060-22. Epub 2024 May 8. PMID: 38717124; PMCID: PMC11325845.
25. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet 2017;389:1218–28. doi:10.1016/S0140-6736(17)30182-4.
26. Fehily SR, Wright EK, Basnayake C, et al. Faecal microbiota transplantation in Crohn's disease: an Australian randomised placebo-controlled trial protocol. BMJ Open. 2025 Apr 19;15(4):e094714. doi: 10.1136/bmjopen-2024-094714.
27. Lahoud C, Habib T, Kalta D, et al. Intestinal Microbiota and Fecal Transplantation in Patients with Inflammatory Bowel Disease and Clostridioides difficile: An Updated Literature Review. J Clin Med. 2025 Jul 25;14(15):5260. doi: 10.3390/jcm14155260.
28. Koido S, Ohkusa T, Kajiura T, et al. Long-term alteration of intestinal microbiota in patients with ulcerative colitis by antibiotic combination therapy. PLoS One 2014; 9: e86702 [PMID: 24489770 DOI: 10.1371/journal.pone.0086702])
29. Faye AS, Allin KH, Iversen AT, et al. Antibiotic use as a risk factor for inflammatory bowel disease across the ages: a population-based cohort study. Gut. 2023 Apr;72(4):663-670. doi: 10.1136/gutjnl-2022-327845.
30. Duan R, Zhang C, Li G, et al. Antibiotic Exposure and Risk of New-Onset Inflammatory Bowel Disease: A Systematic Review and Dose-Response Meta-Analysis. Clin Gastroenterol Hepatol. 2025 Jan;23(1):45-58.e15. doi: 10.1016/j.cgh.2024.02.010. Epub 2024 Feb 28.
31. Boppana K, Almansouri NE, Bakkannavar S, et al. Alterations in Gut Microbiota as Early Biomarkers for Predicting Inflammatory Bowel Disease Onset and Progression: A Systematic Review. Cureus. 2024 Apr 11;16(4):e58080. doi: 10.7759/cureus.58080.
32. San-Martin MI, Chamizo-Ampudia A, Sanchiz Á, et al. Microbiome Markers in Gastrointestinal Disorders: Inflammatory Bowel Disease, Colorectal Cancer, and Celiac Disease. Int J Mol Sci. 2025 May 17;26(10):4818. doi: 10.3390/ijms26104818.