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The role of gastrointestinal pathogens in inflammatory bowel disease: a systematic review

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Introduction

- The dynamic interaction between the gut microbiome and host immune system is vital to physiologic homeostasis of intestinal tract
- Host immune system modulates immunotolerance to the host microbiome
- Dysregulation of immune system /microbiota cross talk is supposed to play an essential role in many diseases particularly in gastrointestinal tract disorders

Introduction

- The inflammatory bowel diseases (IBD), affect at least 0.4% of Europeans and North Americans
- Both genetic susceptibility and environmental factors have roles
- GI microbial dysbiosis (imbalance in the gut microbial community) and the subsequent immune response may create different phenotypes of IBD
- Enteric infections, as an environmental factor, can lead to gut microbial dysbiosis and subsequent triggering the disease.

Aim of study

Conducting a comprehensive, clinical systematic review to define the association between specific gastrointestinal infections and new onset IBD and disease relapse

Methods

Search strategy

- Literature search using databases such as PUBMED, Ovid, Scopus, ScienceDirect,……. Covering all English human and non-human studies assessing IBD and gastrointestinal infections (Jan 1990-Jan 2020)
- MeSH terms search included the broad terms inflammatory bowel disease, gastrointestinal infection, enteric infection
- searched specific pathogens including bacteria , viruses, parasites and fungi combined with "AND inflammatory bowel disease OR Crohn disease OR colitis, ulcerative OR indeterminate colitis."

Study selection

- Clinical trials, cohort studies, and cross-sectional studies were included
- Case-series, review articles, and conference abstracts were excluded
- **inclusion criteria:**

- patients diagnosed with IBD [CD, UC, or IBD-undifferentiated (IBD-U)
- Diagnosis of gastrointestinal infection as defined by positive testing on any of the following modalities: histology, culture, serology, polymerase chain reaction (PCR) and/or other molecular technique as long as defined in the study;
- Documentation of criteria for disease flare qualification (e.g., clinicalcriteria, endoscopic criteria);
- Sufficient information provided to interpret or calculate comparative effect estimates; and
- Full-text available in English.

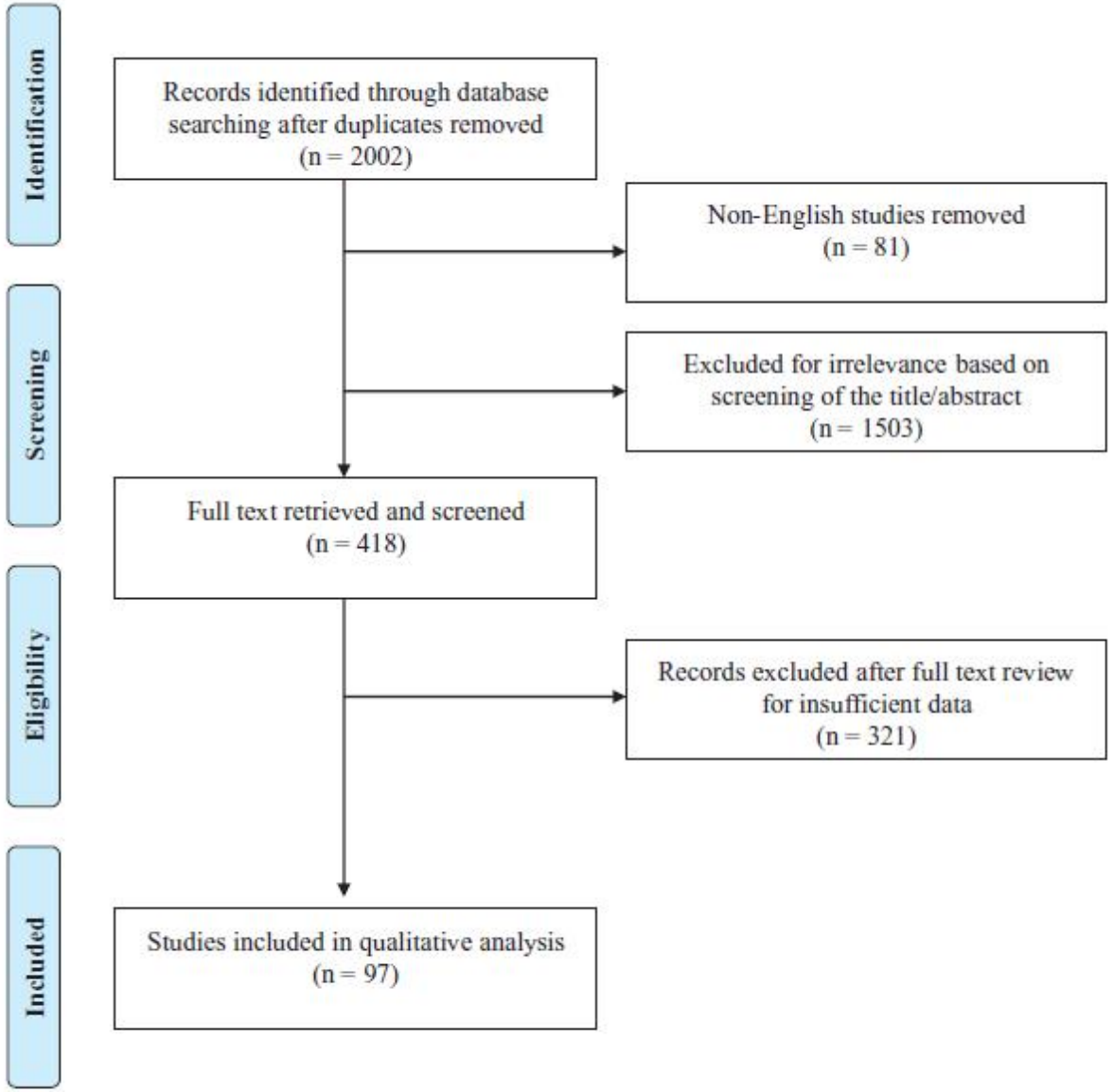

Figure 1. Flowchart of study selection.

Results

Gastrointestinal pathogens and increased risk of IBD

Results

- Campylobacter species:
  - Denmark cohort study: UC & CD more common after an episode of campylobacter induced gastritis
  - Sweden case control study: Campylobacter was associated with higher odds of UC & CD
  - other studies:

C. concisus Ab s and DNA detected with significantly higher frequency in patients with CD and UC compared with patients without IBD. (pediatric and adults)

C. concisus ,C. showae,C. hominis,C. ureolyticus associated with increased odds of IBD

C. jejuni , C. rectus, and C. gracilis were not associated with odds of IBD,CD or UC.

Results

- Salmonella species:
  - Denmark cohort study: increased risk of new onset UC & CD after an episode of S/C + gastroentiritis for salmonella
  - Sweden case control study: positive association between a diagnosis of salmonella and likelihood of IBD
- Enterohepatic helicobacter species:
  - non-HPL EHS detected significantly more often in the intestinal biopsies of patients with CD compared with non-IBD controls. However, statistically non-significant positive association between EHS and IBD has been demonstrated in the same study.

Results

- Mycobacterium avium paratuberculosis:
  - conflicting conclusions in different studies suggest that MAP may play a role in the pathogenesis or disease course of CD in a subset of individuals.
- Clostridioides difficile:
  - Sweden case control study : diagnosis of C. *difficile* was associated with higher odds of UC and CD
  - IgG Abs to C. difficile toxins A and B were detected on culture of large and small intestinal mucosal samples only in subjects with IBD.

Results

- Listeria monocytogenes:
  - No significant relationship has been detected yet
- Yersinia species:
  - Sweden case control study : diagnosis of Yersinia enterocolitica was associated with higher odds of CD but not UC
  - Other studies support the aforementioned result
- Viruses:
  - CMV, HHV-6 have had association with IBD
  - EBV's association with IBD is age dependent
  - Norovirus is associated with CD but not UC
  - However, it is unclear that whether these viruses are really associated with IBD disease or are simply innocent bystanders of active disease or immunosuppression

Gastrointestinal pathogens and attenuated risk of IBD

- ***H. pylori***

The most recent and most comprehensive meta-analysis by Castano-Rodriguez (40 case-control studies with 6130 IBD cases and 74,659 non- IBD controls) has shown that *H. pylori* exposure was associated with lower odds of IBD

- **Parasites**:

studies have suggested that the absence of intestinal helminths is associated with an increased likelihood of new onset IBD

Trichuris helmianth exposure *versus* non-exposure was associated with lower odds of IBD

The protective effect of intestinal helminths in IBD has been shown in several studies

Gastrointestinal pathogens in relapse of IBD

- **Clostridioides difficile**
- Current clinical guidelines recommend testing for **C. difficile** in all patients with IBD who have worsening or new onset diarrhea
- However different reports indicate inconsistent results, which prevents to reach any major conclusions regarding the contribution of CDI to IBD relapse
- ***Non-Clostridioides difficile enteric infections***
- In a study covering 214 IBD patients and using multiplex stool PCR technique during a flare, after *C. difficile*, the most commonly detected microbes were *E. coli* subtypes (8%) and viruses (5%).83
- In other studies ,Culture data have demonstrated higher rates of complications by *Campylobacter* and *Salmonella*

- **CMV** in patients with severe active IBD, particularly if there is concomitant steroid use and disease refractory to medical therapy.

Table 1. Specific pathogens associated incident IBD.

	Increased risk	Decreased risk
Bacteria	*Salmonella species*	*Helicobacter pylori*
	Escherichia coli	
	Yersinia enterocolitica	
	Campylobacter species	
	Enterohepatic Helicobacter species	
	Mycobacterium avium paratuberculosis	
	Clostridioides difficile	
	Listeria monocytogenes	
	Proteus mirabilis	
	Klebsiella pneumoniae	
	Citrobacter species	
Viruses	Norovirus	
	Cytomegalovirus	
	Epstein–Barr virus	
	Human herpes virus 3	
	Human herpes virus 6	
	Human herpes virus 8	
	Measles virus	
	Mumps virus	
	Rubella virus	
	Rotavirus	
	Adenovirus	
Fungi	*Candida species*	
	Aspergillus species	
	Cryptococcus neoformans	
Parasites	Amoeba/*Entamoeba histolytica*	*Trichuris suis*
	Toxoplasma gondii	*Hymenolepis diminuta*
		Schistosoma species
		Nector americanus

IBD, inflammatory bowel disease.

Table 2. Specific pathogens associated flare of prevalent IBD.

	CD	UC
Bacteria	+ *Campylobacter* species	+ *Campylobacter* species
	+ *Clostridioides difficile*	+ *Plesiomonas shigelloides*
		+ Enteroaggregative *Escherichia coli*
		+ Enteropathogenic *Escherichia coli*
		+ *Clostridioides difficile*
Viruses	+ Norovirus	– Norovirus
		+ Cytomegalovirus
Parasites	– *Giardia lambia*	– *Giardia lambia*
	– *Cryptosporidium*	– *Cryptosporidium*
	– *Cyclospora cayetanensis*	– *Cyclospora cayetanensis*
	– *Entamoeba histolytica*	– *Entamoeba histolytica*

+, Increased cross-sectional prevalence during flare compared to symptomatic patients without IBD.
–, Decreased cross-sectional prevalence during flare compared to symptomatic patients without IBD.
CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Discussion

- Specific gastrointestinal infections may modify the risk of developing IBD and trigger or complicate flares in patients with established IBD
- The limitations of published studies does not allow to establish a direct causal relationship between gastrointestinal infection or colonization and new onset or flare of IBD.
- The possibility of reverse causality is present which means IBD may increase the risk of infection or colonization acquisition, and that these species are merely "innocent bystanders"
- Clinical data described in this meta-analysis demonstrated a lower overall pathogen detection rate in patients with an exacerbation of existing IBD compared with non-IBD controls, the reasons for which are unclear
- *C. difficile* carriage occurs in antibiotic consumption, disrupting microbiota
- Pathogens such as *Helicobacter* and certain helminths, and their downstream products, might reduce dysbiosis and/or counteract inflammatory pathways, preventing IBD
- Overall, the underlying genetic susceptibility, and change in the gut microbiome, rather than a singular pathogen, may be most relevant, particularly when considering the complexity of IBD pathogenesis
- the role of gastrointestinal pathogens in IBD flares is also challenging, since testing for enteric infections is generally limited to those with an exacerbation in symptoms and is not routine for asymptomatic patients, thus limiting a true "control" population


THANK
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