

Case Report

Early Exposure of Antibiotic as A Risk Factor for Gastrointestinal Disorders: An Evidence-Based Case Report

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Abstract:

Background: Incidence rate of pediatric onset inflammatory bowel disease (IBD) has been increasing worldwide particularly in the rapidly growing countries. It has been hypothesized that environmental factors such as method of delivery, rural or urban living environment and the use of antibiotics, may play significant roles. Antibiotics are known to alter gut microbiome and henceforth may be the rational mechanism in the development of gastrointestinal autoimmune diseases.

Methods: Literature search was performed on 3 international databases (PubMed, PubMed PICO and Google Scholar) by using relevant keywords based on clinical question.

Results: Two systematic reviews were included in this study. Both studies reported strong evidence regarding the increase risk of occurrence for inflammatory bowel disease and celiac disease after exposure of antibiotics particularly in young age

Discussion: At young age, the immune system and gut microbiota is considered to be unstable and prone to disruption particularly by exposure of antibiotics. Antibiotics is known to weaken mucosal barrier of the gut which facilitates translocation of commensal bacteria. Translocation process together with the imbalance ratio of T-helper 1 and T-helper 2 may be the pathogenesis behind the development of chronic gastrointestinal diseases.

Conclusion: There is strong evidence that early life exposure to antibiotic is associated with the development of IBD and Celiac disease in childhood. Therefore, it is critical for all healthcare workers to adhere to strict guidelines regarding the rationality on when to prescribe antibiotics particularly in children of young age.

Keywords: antibiotics, Celiac disease, inflammatory bowel disease, pediatric

Introduction

Incidence rate of pediatric onset inflammatory bowel disease (IBD) has been increasing worldwide. A comprehensive review of 140 studies from 38 countries showed a steady increase in global incidence of IBD particularly in western countries; raising the suspicion of environmental factors that may contribute.¹ A systematic review of population-based studies on Crohn's disease (CD) and ulcerative colitis (UC) reported significant incidence and prevalence increments in different regions (Europe, North America, Asia, and Middle East) in the last 8 decades (1930-2010).² Furthermore, the same study also reported the increase of prevalence as much as 75% of CD and 60% of UC based on time-trend analysis.² Another systematic review analyzing the worldwide prevalence and incidence of IBD in the 21st century reported that those numbers has been rising in rapidly growing countries in Africa, Asia and South America since 1990.³

Celiac disease is an immune-mediated condition characterized by intestinal inflammation after gluten ingestion. The incidence of this disease varies geographically and appears to be increasing over time in several regions of the world. A systematic review and meta-analysis of population-based study reported the child-specific incidence of 21.3 per 100.000 person-years compared with 12.9 in adults.⁴ Furthermore, average annual percent changes showed the incidence of Celiac disease was increasing by 7.5% per year over the past several decades.⁴

Due to the recent increase of incidence of IBD and Celiac disease in newly industrialized countries, it has been hypothesized that environmental factors such as method of delivery, rural or urban living environment and the use of antibiotics, may play significant roles. Antibiotics are known to alter gut microbiome and henceforth may be the rational mechanism in the development of gastrointestinal autoimmune diseases, including IBD and Celiac disease. Animal study has shown that a disturbed microbiome due to several factors such as stress, dietary change, environmental factor or drugs, may alter the immune system dan trigger gastrointestinal.⁵

Case Illustration

A 6-year-and-9-month-old girl was admitted with the chief complaint of bloody stool for 2 consecutive days. About 2 months ago, she experienced intractable abdominal pain and bloody diarrhea which was treated at local hospital for dysentery. She was given 2 courses of antibiotic with no clinical improvement. Colonoscopy was performed and showed lumpy and brittle masses. She was then referred to Cipto Mangunkusumo Hospital (CMH).

Patient is the second child of 3 siblings. She was breastfed for less than 1 month, and continued with formula milk. In the first year of her life, she had 3 episodes of upper respiratory infection and always treated with antibiotics. In her second year, she also had several respiratory or gastrointestinal problems and always received antibiotic treatment. Similar complaint was not found in both parents as well as in her extended family. Subsequent colonoscopy and histopathological result revealed to be Crohn's disease. She was then received standard treatment for CD and responded well.

Clinical Question

Do children who were exposed to antibiotic at early age are more prone to gastrointestinal disorders compared to those who did not?

Methods

Literature search was performed on 3 international databases (PubMed, PubMed PICO and Google Scholar) on 15th -17th May 2021 by using keywords as following: "children, early life antibiotic, gastrointestinal disease/ disorder, risk factors". This study includes only articles that was published in the last 3-5 years in English language. Details method of the literature search can be seen in **Figure 1**.

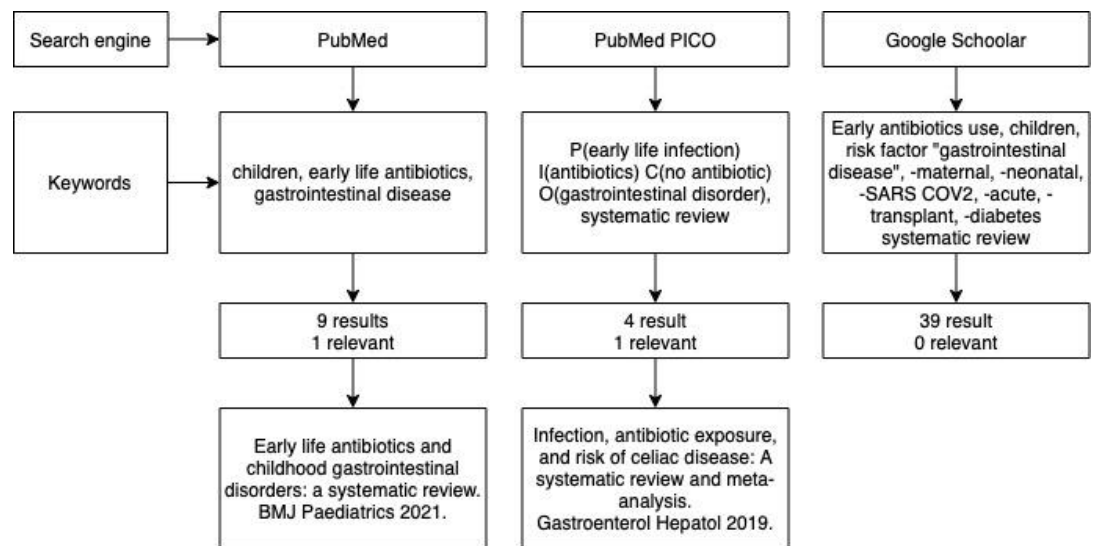


Figure 1. Flow chart of literature search

Results

The first study we analyzed was a systematic review by Kamphorst et al., which evaluated the association between exposure of antibiotics in the first 2 years of life in term born children and the development of gastrointestinal disorders in later life.⁶ This review included 22 studies with 11 cohort and 11 case-control studies that were retrieved after conducting a systematic searching on 4 international databases (MEDLINE, Embase, WHO trial register and Web of Science). Studies were included

if antibiotics were received in the first 2 years of life on full term baby, gastrointestinal disorders were evaluated during the first 18 years of life, antibiotics exposure must occur before gastrointestinal disorders and the presence of control group. The quality of each study was also assessed independently by two researchers based on The Newcastle-Ottawa Scale which evaluated 3 core areas such as the selection of subjects, comparability of groups and detection of outcome. Ten studies were of high quality, another ten were moderate and the other two were of low quality. In five out of 6 studies, inflammatory bowel disease was found to be associated with exposure of antibiotics in the first 1 year of life. Three studies also described the frequency-dependent relation, with each subsequent increased in episode of antibiotics treatment led to higher risk of the development of inflammatory bowel disease. Type-dependent relation was also described in which treatment with fluoroquinolone, metronidazole and phenoxymethylpenicillin were associated with higher risk. After stratification based on IBD type, two studies reported that only OR for Chron's disease was significant. On the other hand, 4 out of 5 studies reported that eosinophilic esophagitis was found to be associated with early exposure of antibiotics. While for Celiac disease, 4 studies in which 3 of them were of high quality, reported significant increased risk after antibiotic exposure. However, 2 studies with moderate quality proved no such association. Frequency-dependent relation as well as type-dependent relation (cephalosporins and macrolide) were also reported to be significant for Celiac disease. Infantile colic was found to be associated with early exposure of antibiotics in 2 out of 3 studies, while in 2 out of 2 studies reported no such association for functional constipation. Interestingly, the risk of recurrent abdominal pain at 12 years of age was found to be associated with exposure of antibiotics in the first 2 years of life but only in girls. Finally, regurgitation, dyschezia and functional diarrhea were reported to have no association with antibiotics exposure during early life. Based on evidence synthesis performed in this systematic review, there was strong evidence regarding the increase risk of occurrence for inflammatory bowel disease and celiac disease after exposure of antibiotics particularly in young age.

The second study was a systematic review and meta-analysis by Jiang et al., with the objective was to identify the relationship of infections as well as the associated antibiotics exposure with the likelihood of occurrence of Celiac disease.⁷ Literature search was performed on 2 international databases (Pubmed and Embase). This study included 19 studies in which 15 of those evaluated the risk of this disease after episode of infection, while 6 studies assessed the same risk after antibiotic exposure. Three of the studies which evaluated antibiotic exposure were cohort studies while the other 3 were case-control studies. Similar to previous review, this review also utilized the Newcastle-Ottawa Scale to assess the quality of each study. Five out of 6 studies that evaluated the role of early antibiotic exposure were deemed to be of high quality. All of those reported the significant increase risk of Celiac disease after antibiotic

exposure with combined OR of 1.2 (95% CI: 1.04-1.39; $p < 0.001$) with significant heterogeneity across all studies reviewed ($I^2 = 92.5\%$, $p < 0.001$).

Discussion

Based on two systematic reviews, early exposure of antibiotics particularly in the first 2 years of life was associated with higher risk of inflammatory bowel diseases and celiac disease.^{6,7} However, whether this association was exclusively attributed to antibiotic exposure or by other factor such as infection remains elusive. One meta-analysis reported that infection was associated with 37% of increase in the odds of Celiac disease regardless the timing and site of infection as well as the type of infectious agents.⁷ However, the role of infections and antibiotics was difficult to be differentiated as antibiotics were prescribed in the event of an infection episode.⁶

Irrational use of antibiotics is often observed particularly among children with viral acute respiratory infections. At such young age, the immune system and gut microbiota is considered to be unstable and prone to disruption by environmental factors such as exposure of antibiotics.⁸ Furthermore, antibiotics exposure is known to weaken mucosal barrier of the gut which facilitates translocation of commensal bacteria.⁸ This translocation process together with the imbalance ratio of T-helper 1 and T-helper 2 may be the pathogenesis behind the development of chronic gastrointestinal diseases such as inflammatory bowel diseases and celiac disease.^{9,10} Disruption of gut microbiota (dysbiosis) was also associated with increased number of *Candida albicans* within the gut, which may further direct immune response towards T-helper 2 by secreting prostaglandin-like molecules.¹¹

Given the myriad evidence of association between chronic gastrointestinal disorders and early antibiotics exposure, it is critical for all healthcare workers to adhere to strict guidelines regarding the prescription of antibiotics. When antibiotics are indicated, the use of narrow-spectrum antibiotics as well as minimal duration of treatment are preferred to minimize preserve the healthy commensal bacteria.⁶ Prescription of pre/probiotics should also be considered to restore any dysbiosis after antibiotics exposure whenever possible.⁶

Conclusion

Both IBD and Celiac disease are chronic autoimmune disorders that affect the gastrointestinal tract. Signs, symptoms, and endoscopically mucosal image could be alike, though the pathogenesis is completely different. Familial predisposition, environmental factors, and gut microbiome dysbiosis are long known as risk factors in both diseases. There is strong evidence that early life exposure to antibiotic is associated with the development of IBD and Celiac disease in childhood. Therefore,

it is critical for all healthcare workers to adhere to strict guidelines regarding the rationality on when to prescribe antibiotics particularly in children of young age.

Conflict of Interest

None declared.

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