The association between *Helicobacter pylori* infection and inflammatory bowel disease based on meta-analysis

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Abstract

Background: In humans there are epidemiological data suggesting a protective effect of *Helicobacter pylori* (*H. pylori*) infection against the development of autoimmune diseases and in addition, there are laboratory data illustrating *H. pylori*'s ability to induce immune tolerance and limit inflammatory responses. Thus, numerous observational studies have examined the association between *H. pylori* infection and inflammatory bowel disease (IBD) with various results.

Objective: We performed a meta-analysis of available studies to better define the association of *H. pylori* infection and IBD.

Methods: Medical literature searches for human studies were performed through September 2014, using suitable keywords. In each study the risk ratio (RR) of *H. pylori* infection in IBD patients vs controls was calculated and pooled estimates were obtained using fixed- or random-effects models as appropriate. Heterogeneity between studies was evaluated using Cochran *Q* test and *I*² statistics, whereas the likelihood of publication bias was assessed by constructing funnel plots.

Results: Thirty-three studies were eligible for meta-analysis, including 4400 IBD patients and 4763 controls. Overall 26.5% of IBD patients were positive for *H. pylori* infection, compared to 44.7% of individuals in the control group. There was significant heterogeneity in the included studies ($Q = 137.2$, $df(Q) = 32$, $I^2 = 77\%$, $p < 0.001$) and therefore the random-effects model of meta-analysis was used. The obtained pool RR estimation was 0.62 (95% confidence interval (CI) 0.55–0.71, test for overall effect $Z = -7.04$, $p < 0.001$). There was no evidence of publication bias.

Conclusion: The results of this meta-analysis showed a significant negative association between *H. pylori* infection and IBD that supports a possible protective benefit of *H. pylori* infection against the development of IBD.

Keywords

Helicobacter pylori, inflammatory bowel disease, Crohn's disease, ulcerative colitis, meta-analysis

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Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a significant, growing global health burden.^{1–3} In recent decades, many developing countries have seen a dramatic rise in the incidence of IBD.^{2–4} It is speculated that improved access to a cleaner environment and the resulting decreased incidence of common childhood infections may be contributing to this rise by altering susceptibility to certain diseases with an autoimmune component, such as IBD.^{5,6} Thus, according to this speculation, microbial infections during childhood may protect from IBD.

Helicobacter pylori is a bacterium that causes chronic gastritis and consequently mainly peptic ulcer disease and to a less extent, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer in

infected individuals.^{7,8} The inflammatory response of the gastric mucosa is mainly attributed to the stimulation of the host's immune system caused by the bacterium. This results in a T helper type 1 (Th1) response

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and elevated levels of Th1 cytokines.^{9–11} As a consequence, products of the local immune reactions may migrate to extra-gastric sites and this may explain the link between *H. pylori* infection and a variety of extra-gastric diseases, including autoimmune disorders.^{12,13} However, epidemiological data exist that suggest a protective effect of *H. pylori* infection against the development of some diseases with an autoimmune component, such as asthma, most probably by *H. pylori*'s ability to induce immune tolerance and limit inflammatory responses.^{14,15} The mechanism underlying this protective role of *H. pylori* infection is thought to be differential expression of local mucosal inflammatory response, which may elicit a systemic release of cytokines, which in turn may downregulate systemic immune responses and suppress autoimmunity.

Triggered by the above, numerous studies have examined the association between *H. pylori* infection and IBD. However, the published literature is diverse. Thus, many studies have reported that the prevalence of *H. pylori* infection is lower in patients with IBD compared to controls, whereas this has not been confirmed by other studies. This prompted us to further investigate this association by performing a meta-analysis in which we pooled the results of all existing relevant studies.

Methods

Identification of studies and data extraction

We searched the PubMed, MEDLINE and Embase databases through September 2014 to identify all relevant English-language medical literature for human studies using the following key words or Medical Subject Headings (MeSH) terms: *Helicobacter pylori* AND (inflammatory bowel disease OR ulcerative colitis OR Crohn's disease). In detail, the following search items were used: ("helicobacter pylori" (MeSH Terms) OR ("helicobacter" (All Fields) AND "pylori" (All Fields)) OR ("helicobacter pylori" (All Fields) OR ("h pylori" (All Fields)) AND ("inflammatory bowel diseases" (MeSH Terms) OR ("inflammatory" (All Fields) AND "bowel" (All Fields) AND "diseases" (All Fields)) OR "inflammatory bowel diseases" (All Fields) OR ("inflammatory" (All Fields) AND "bowel" (All Fields) AND "disease" (All Fields)) OR "inflammatory bowel disease" (All Fields)) OR ("colitis, ulcerative" (MeSH Terms) OR ("colitis" (All Fields) AND "ulcerative" (All Fields)) OR "ulcerative colitis" (All Fields) OR ("ulcerative" (All Fields) AND "colitis" (All Fields)) OR ("crohn disease" (MeSH Terms) OR ("crohn" (All Fields) AND "disease" (All Fields)) OR "crohn disease" (All Fields) OR ("crohn's" (All Fields) AND

"disease" (All Fields)) OR "crohn's disease" (All Fields)). In addition we performed a full manual search of all review articles and published editorials and retrieved original studies. Data were extracted independently from each study by two of the authors (T.R. and J.P.G) by using a predefined form, and disagreements were resolved by discussion with a third investigator and consensus. The work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁶

Selection criteria

Inclusion and exclusion criteria were defined before the commencement of the literature search; thus, eligible studies were included in this meta-analysis if they met all the following criteria: (1) published as full article, (2) include data for retrieval on the association between *H. pylori* infection and IBD and (3) *H. pylori* infection was confirmed by serology and/or histology and/or urea breath test (UBT) and/or rapid urea test (RUT) and/or culture. Studies that did not meet the aforementioned criteria and duplicate publications were excluded. When two papers reported the same study, the publication that was more informative was selected.

Statistical analysis

The risk ratio (RR, 95 % confidence intervals (CIs)) was used to describe the ratio of the probability of the *H. pylori* infection occurring in IBD patients vs the controls. Thus in each study the RR of *H. pylori* infection in IBD patients vs controls was calculated and then pooled estimates were obtained using the fixed-model (Mantel and Haenszel) method,¹⁷ unless significant heterogeneity was present or if the design of the studies was considered to be different enough, in which case the random-effects model was applied (DerSimonian and Laird method¹⁸). Heterogeneity between studies was evaluated with the Cochran *Q*-test¹⁹ and it was considered to be present if the *Q*-test provided a *p* value of less than 0.10.²⁰ In addition *I*² statistic was used to measure the proportion of inconsistency in individual studies that could not be explained by chance, with *I*² > 50% representing substantial heterogeneity.²¹ We also performed a cumulative meta-analysis to examine whether the association between *H. pylori* and IBD changed over time.²² Forest plots were constructed for visual display of individual study RR. Data, in various formats, i.e. as dichotomous (number of events) or computed effect sizes, were meta-analyzed by choosing the most suitable data entry option for the meta-analysis software used

(Comprehensive Meta-Analysis, version 2; Biostat Inc, Englewood, NJ, USA).

Sensitivity analyses/publication bias

In the presence of significant statistical heterogeneity, apart from the random-effects model, we performed sensitivity analyses to evaluate the consistency of our results. Firstly, to evaluate any possible excessive influence of a single study, we examined whether the exclusion of this study substantially altered the magnitude or heterogeneity of the summary estimate. This was achieved by repeating the meta-analyses with exclusion of each individual study one at a time, to assess the overall effect of the exclusion on the pooled RRs.²² Secondly, as different study designs and populations may incorporate different biases, we performed subgroup analyses, stratifying by factors that could potentially influence the results. These factors were established a priori to the analysis. Where needed, we further explored heterogeneity by performing meta-regression analyses (method of moments).²³ The likelihood of publication bias was assessed by constructing funnel plots, which were obtained by plotting the log RRs vs SE of individual studies.²⁴ Their symmetry was estimated by Egger's regression test and the Begg and Mazumdar adjusted rank correlation test,^{25,26} whereas the adjustment for publication bias, i.e. calculation of the number of studies missing from the meta-analysis,

was estimated using Duval and Tweedie's nonparametric "trim and fill" rank-based method.²⁷

Results

Descriptive assessment and study characteristics

A flowchart describing the process of study selection is shown in Figure 1. Out of 468 titles initially generated by the literature searches, 33 studies, from various countries, remained eligible for meta-analysis.^{28–60} Some studies contained separate data on UC and CD and therefore in the 33 meta-analyzed studies there were in total 50 sets of data (22 on UC and 28 on CD) comparing *H. pylori* infection in patients and controls. The main characteristics of the papers eligible for meta-analysis are shown in Table 1. They were conducted in different parts of the world and contained a total of 4400 IBD patients and 4763 controls.

H. pylori prevalence in IBD patients vs controls

In the 33 eligible for meta-analysis studies, in the IBD group, overall 1168/4400 patients were positive for *H. pylori* infection (26.5%, 95% CI (25.2–27.8)), compared to 44.7% (43.3–46.1) of individuals in the control group (2129/4763). There was significant heterogeneity in the included studies ($Q=137.2$, degree of freedom (df) (Q)=32, $I^2=77\%$, $p<0.001$) and therefore the

Figure 1. Flow diagram of the studies identified in this meta-analysis.

Table 1. The main characteristics of the included studies

First author (reference)	Publication/Year	Country	Study design	IBD pts (n) (CD/UC)	Controls (n) (group composition)	IBD diagnosis	<i>H.pylori</i> diagnostic method
el-Omar ²⁸	1994	UK	Prospective (cohort)	110 (63/47)	100 (Hospital patients for elective surgery)	Chart review	Serology
Mantzaris ²⁹	1995	Greece	Prospective (cohort)	90 (0/90)	120 (Healthy individuals)	Not reported	Serology/RUT
Halme ³⁰	1996	Finland	Prospective (cohort)	200 (100/100)	100 (Patients with acute bacterial diarrhea)	Not reported	Serology
Meining ³¹	1997	Germany	Prospective (case control)	36 (36/0)	36 (Healthy individuals)	Histology	Histology
Oberhuber ³²	1997	Germany	Prospective (cohort)	75(75/0)	200 (Crohn's disease-free controls)	Histology	Histology
Parente ³³	1997	Italy	Prospective (cross-sectional)	216 (123/93)	216 (Blood donors)	Chart review	Serology
Wagtmans ³⁴	1997	Netherlands	Retrospective (cohort)	386 (386/0)	277 (Blood donors)	Chart review	Serology
D'Inca ³⁵	1998	Italy	Prospective (cohort)	108 (67/41)	43 (Non-IBD patients)	Chart review	Histology
Duggan ³⁶	1998	UK	Prospective (case control)	323 (110/213)	337 (Hospital patients for elective surgery)	Chart review	Serology
Pearce ³⁷	2000	UK	Prospective (cohort)	93 (42/51)	40 (Patients with IBS)	Radiology and/or histology	Serology, UBT
Parente ³⁸	2000	Italy	Prospective (cohort)	220 (141/79)	141(CD- and UC-free controls)	Chart review	UBT, histology
Matsumura ³⁹	2001	Japan	Prospective (cohort)	90 (90/0)	525 (Dyspeptic patients)	Not reported	Histology
Parlak ⁴⁰	2001	Turkey	Prospective (cohort)	111 (45/66)	77 (Patients with non-organic dyspepsia)	Not reported	Histology
Vare ⁴¹	2001	Finland	Prospective (cohort)	279 (94/185)	70 (Healthy individuals)	Chart review/face to face interview	Serology
Feeney ⁴²	2002	UK	Prospective (case-control)	276 (139/137)	276 (Outpatient controls)	Conventional clinical criteria	Serology
Furusu ⁴³	2002	Japan	Prospective (cohort)	50 (25/25)	25 (patients without IBD)	Histology	Serology, histology
Guslandi ⁴⁴	2002	Italy	Not reported (cohort)	60 (60/0)	30 (Irritable bowel syndrome)	Not reported	Serology

(continued)

Table 1. Continued

First author (reference)	Publication/Year	Country	Study design	IBD pts (n) (CD/UC)	Controls (n) (group composition)	IBD diagnosis	<i>H. pylori</i> diagnostic method
Pascasio ⁴⁵	2003	US	Retrospective (cohort)	56 (56/0)	382 (Non-CD patients)	Histology	Histology
Piodi ⁴⁶	2003	Italy	Prospective (cohort)	72 (30/42)	72 (Non-CD patients)	Chart review	UBT
Triantafyllidis ⁴⁷	2003	Greece	Prospective (cohort)	116 (39/77)	127 (Healthy controls)	Chart review	Serology
Oliveira ⁴⁸	2004	Brazil	Prospective (cohort)	42 (0/42)	74 (Non-IBD patients)	Histology	Serology, UBT
Pronai ⁴⁹	2004	Italy	Prospective (cohort)	133 (51/82)	200 (Non-IBD patients)	Histology	UBT
Oliveira ⁵⁰	2006	Brazil	Prospective (cohort)	43 (43/0)	74 (Non-IBD patients)	Histology	UBT
Śladek ⁵¹	2007	Poland	Not reported (cohort)	94 (50/44)	194 (Non-IBD patients)	Clinical criteria/histology	RUT, histology
Ando ⁵²	2008	Japan	Prospective (cohort)	38 (38/0)	12 (Healthy individuals)	Not reported	UBT
Lidar ⁵³	2009	Israel	Prospective (cohort)	119 (80/39)	98 (Non-IBD patients)	Not reported	Serology
Song ⁵⁴	2009	Korea	Prospective (case control)	316 (147/169)	316 (Non-IBD patients)	Chart review/personal interview	UBT
Garza-González ⁵⁵	2010	Mexico	Prospective (cohort)	44 (21/23)	75 (Non-IBD patients)	Not reported	Serology
Pellicano ⁵⁶	2010	Italy	Prospective (case-control)	20 (12/8)	29 (Patients with idiopathic constipation)	Not reported	UBT, histology
Varas-Lorenzo ⁵⁷	2010	Spain	Prospective (cohort)	60 (30/30)	20 (Non-IBD patients)	Chart review	UBT
Zhang ⁵⁸	2011	China	Prospective (case-control)	208 (104/104)	416 (Healthy individuals)	Clinical presentation, endoscopic, histological, radiological findings	UBT
Jin ⁵⁹	2013	China	Prospective (cohort)	153 (0/153)	121 (Non-UC patients)	Endoscopic, histological, findings	UBT
Xiang ⁶⁰	2013	China	Prospective (cohort)	229 (229/0)	248 (Non-CD patients)	Endoscopy manifestation and biopsy, as adopted by Asia-Pacific consensus	UBT, culture, histology

IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; CD: Crohn's disease; UC: ulcerative colitis; UBT: urea breath test; RUT: rapid urea test; UK: United Kingdom; US: United States.

Figure 2. (a) Forest plot showing individual and pooled RRs (95% CIs) in studies comparing *Helicobacter pylori* prevalence in IBD patients and controls. (b) Funnel plot of all studies included in the meta-analysis. RR: risk ratio; CI: confidence interval; IBD: inflammatory bowel disease.

random-effects model of meta-analysis was used. The obtained pool RR estimation was 0.62 (95% CI (0.55–0.71), test for overall effect $Z = -7.04$, $p < 0.001$) (Figure 2(a)). There was no evidence of publication bias as judged by the construction of funnel plot and estimation of its symmetry ($p = 0.15$, by the Egger's regression test) (Figure 2(b)).

Subgroup analyses/sensitivity analyses

Due to significant heterogeneity, apart from using the random-effects model, subgroup analyses were performed. Thus, we grouped by stratifying for disease, i.e. meta-analyzing separately 28 sets of data for CD and 22 for UC (Figure 3). These subgroup analyses showed significant results for both diseases, with a trend toward a greater effect for CD (0.38 (0.31–0.47), $Z = -8.98$, $p < 0.001$) when compared to UC (0.53 (0.42–0.67), $Z = -5.39$, $p < 0.001$). However, there was significant heterogeneity in the included studies for both diseases; CD: $Q = 66.67$, $df (Q) = 27$, $I^2 = 59.5\%$, $p < 0.001$ and UC: $Q = 55.33$, $df (Q) = 21$, $I^2 = 62\%$, $p < 0.001$. In an attempt to further explore the observed heterogeneity, we stratified data based on the study design (cohort vs case control) and *H. pylori* diagnosis (serology vs UBT vs histology) (Table 2). However, none of these subgroup analyses were able to account for the observed heterogeneity. As different study designs and populations may incorporate different biases, except for grouping for the aforementioned diseases, study design and method of

H. pylori diagnosis, further sensitivity analyses were performed. Thus, exclusion of any study did not considerably alter the magnitude of the summary estimate (Figure 4(a)). In addition, the results of the cumulative meta-analysis of studies, ordered by the year of publication (Figure 4(b)), were consistent over the years. Finally, the meta-regression analysis evaluating the regression of publication year on log risk ratio, showed no significant results ($z = -0.48$, $p = 0.63$) (Figure 4(c)).

Discussion

H. pylori infection is acquired early in childhood and if not treated is carried throughout life. Epidemiological data show that IBD is more prevalent in areas with lower rates of *H. pylori* infection and suggest a possible protective effect of *H. pylori* infection against IBD and some diseases with an autoimmune component such as asthma.^{14,15,61} In parallel, there is a steady rise in the incidence of IBD in *H. pylori* endemic regions that may correspond to the beginning of anti-*H. pylori* therapy for peptic ulcer disease.²

All the above piqued research interest and triggered numerous observational studies examining the relationship between *H. pylori* infection and IBD. This meta-analysis pooled all data from eligible relevant studies and showed a statistically significant inverse relationship between *H. pylori* infection and IBD (both CD and UC), which may suggest a possible protective effect of *H. pylori* against the development of IBD. These results

Figure 3. Forest plot showing individual and pooled RRs (95% CIs) in studies (grouped by disease, i.e. CD and UC) comparing the *Helicobacter pylori* prevalence in patients and controls. RR: risk ratio; CI: confidence interval; CD: Crohn's disease; UC: ulcerative colitis.

confirmed an earlier study that pooled the data of studies published up to March 2009.⁶² In addition our results are also in agreement with those of a recent large study⁶³ that examined whether the prevalence of *H. pylori* is lower among IBD patients compared with non-IBD individuals based on material from surgical pathology and concluded that these findings may open new avenues to study the pathogenesis of IBD.

In attempting to explain the negative association between *H. pylori* infection and IBD, the possibility that the treatment previously given against IBD is responsible for the lower prevalence of *H. pylori* infection in IBD patients remains a controversial subject.

Thus, the aspect that treatment with drugs, such as sulfasalazine, could be responsible for *H. pylori* eradication and lower *H. pylori* prevalence in IBD patients has been raised by some authors.²⁸ However, others did not support this notion as treatment with sulfasalazine or any other medical therapy (i.e. 5-aminosalicylic acid (5-ASA), steroids, thiopurines, antibiotics) had no influence on *H. pylori* prevalence.^{30,36,44,54} Furthermore, it seems that even newer therapeutic modalities, such as anti-tumor necrosis factor (TNF) treatment, have no influence on *H. pylori* status in IBD patients.⁶⁴

Nonetheless, the notion that the immunomodulatory properties of *H. pylori* may confer protection against

Table 2. Sub-group analyses by stratifying the data according to study design and method of *Helicobacter pylori* diagnosis

	RR (95% CI)	Z value	p value	Heterogeneity			
				Q value	df(Q)	I ² %	p value
Study design							
Case control	0.59 (0.43–0.82)	−3.12	0.002	29.15	5	82.85	<0.001
Cohort	0.62 (0.53–0.72)	−6.04	<0.001	100.41	25	75.10	<0.001
H. pylori diagnosis							
Histology	0.61 (0.45–0.83)	−3.15	0.002	29.48	6	79.65	<0.001
Serology	0.62 (0.51–0.76)	−4.72	<0.001	58.99	14	76.27	<0.001
Urea breath test	0.63 (0.50–0.79)	−3.93	<0.001	42.85	10	76.66	<0.001

RR: risk ratio; CI: confidence interval.

Figure 4. (a) Exclusion sensitivity plot showing the effect of exclusion of any study on the magnitude of the summary estimate. (b) Cumulative meta-analysis of studies ordered by year of publication. (c) Meta-regression analysis showing regression of publication year on log risk ratio. Circles represent each study in the meta-analysis, and the size of the circle is proportional to study weighting.

allergic and chronic inflammatory disorders has been addressed and recently reviewed.^{65,66} Toward this notion there is laboratory evidence illustrating *H. pylori*'s role in the regulation of the immune system. Thus, a proposed model of *H. pylori*'s effect on host immune regulation is that *H. pylori*, through its interaction with dendritic cells (DCs), is able to upregulate regulatory T-cells leading to decreased production of proinflammatory cytokines. In more detail, *H. pylori* has been associated with increased gastric mucosal expression of Foxp3 (a T-regulatory cell marker) altering the host immunologic response away from the inflammatory Th1/Th17 pathway.^{67–71} Furthermore, in mice evidence has emerged proving protective effects of *H. pylori* infection against *Salmonella typhimurium*-induced colitis.⁷² Thus in co-infection with both bacteria, *H. pylori* suppressed *Salmonella*-specific Th17 responses in the cecum, reducing cecal inflammation. These protective effects were attributed to increased levels of interleukin (IL)-10 in the mesenteric lymph nodes of co-infected mice as opposed to *Salmonella*-only-infected mice, suggesting that this regulatory cytokine modulates the differentiation and/or activity of Th17 cells. In addition it is speculated that the protective effect of *H. pylori* on colitis may be associated with *H. pylori*'s chromosomal DNA, which in mice, through a high ratio of immunoregulatory to immunostimulatory sequences, is capable of preventing sodium dextran sulfate-induced experimental colitis.⁷³ Nonetheless it must be stressed that whether *H. pylori* DNA is indeed a relevant factor in the protection against IBD remains to be elucidated in more detail, since data showing protection by live bacterial infection in IBD models, other than acute *Salmonella*-induced colitis, are currently not available.

The consistency of the results over the years, as shown in the cumulative meta-analysis of studies ordered by the year of publication and the lack of publication bias, strengthens the results of this meta-analysis. However, despite the random-effects model used and the sensitivity analyses performed, the persisting significant heterogeneity found among the studies may call the results into question. An additional drawback is that the possible role of confounders, which could influence the results, was not adequately addressed in the studies involved. For example, low socioeconomic status could be a strong common confounder and perhaps the real cause for both the higher *H. pylori* prevalence and the lower IBD prevalence observed. In fact the prevalence of both may not be truly associated, and it should be stressed that epidemiological studies and meta-analyses based on epidemiological studies can only suggest associations, but not establish cause-effect relationships.

In the future, in order to overcome problems that may contribute to significant heterogeneity, relevant

prospective studies should address all the related confounders, stratifying by factors that could potentially influence the results, such as the method of *H. pylori* diagnosis, method of IBD diagnosis, study origin and study population age. Ideally, controls who are age- and sex-matched to the IBD group should be selected from the same area as the IBD group, tested for *H. pylori* by the same method and in addition in both IBD and control groups previous *H. pylori* treatment should be taken into account. Most important, *H. pylori* testing should be conducted at the time of IBD diagnosis, i.e. in patients naïve for IBD treatment, which potentially could influence *H. pylori* status. Furthermore, in *H. pylori*-positive patients the presence of *cagA* should be considered, as it is claimed that the possible protective effects of *H. pylori* against other autoimmune diseases come from *cagA*-positive strains.^{74,75} The mechanism underlying the inverse association between *cagA*-positive *H. pylori* strains and the lower incidence of autoimmune disease has yet to be defined. However, it has been suggested that the intense host immune responses to *cagA*-positive *H. pylori* strains may further alter Th1- and Th2-type immune responses with subsequent induction of immunoregulatory lymphocytes.⁷⁴

In conclusion, the results of this meta-analysis support a protective effect of *H. pylori* infection against the development of IBD. However, the heterogeneity among studies may limit the value of these results. Therefore, further prospective studies examining the precise role of *H. pylori* and its eradication in the development of IBD may be necessary, taking into account the role of confounders such as environmental factors.

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Conflict of interest

None declared.

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