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Oral vancomycin is associated with improved inflammatory bowel disease clinical outcomes in primary sclerosing cholangitis-associated inflammatory bowel disease (PSC-IBD): A matched analysis from the Paediatric PSC Consortium

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PSC Partners Seeking a Cure

Summary

Background: Data on oral vancomycin for primary sclerosing cholangitis (PSC)-associated inflammatory bowel disease (IBD) are limited.

Aims: Using data from the Paediatric PSC Consortium, to examine the effect of vancomycin on IBD activity.

Methods: In this retrospective multi-centre cohort study, we matched vancomycin-treated and untreated patients (1:3) based on IBD duration at the time of primary outcome assessment. The primary outcome was Physician Global Assessment (PGA) of IBD clinical activity after 1 year (±6 months) of vancomycin. We used generalised estimating equations (GEE) to examine the association between vancomycin and PGA remission, adjusting for IBD type, severity and medication exposures. Secondary outcomes included serum labs and endoscopic remission (global rating of no activity) among those with available data and also analysed with GEE.

Results: 113 PSC-IBD patients received vancomycin (median age 12.7 years, 63% male). The matched cohort included 70 vancomycin-treated and 210 untreated

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patients. Vancomycin was associated with greater odds of IBD clinical remission (odds ratio [OR] 3.52, 95% CI 1.97–6.31; adjusted OR [aOR] 5.24, 95% CI 2.68–10.22). Benefit was maintained in sensitivity analyses restricted to non-transplanted patients and those with baseline moderate–severe PGA. Vancomycin was associated with increased odds of endoscopic remission (aOR 2.76, 95% CI 1.002–7.62; $N = 101$ with data), and with lower CRP ($p = 0.03$) and higher haemoglobin and albumin (both $p < 0.01$).

Conclusion: Vancomycin was associated with greater odds of IBD clinical and endoscopic remission. Additional, preferably randomised, controlled studies are needed to characterise efficacy using objective markers of mucosal inflammation, and to examine safety and define optimal dosing.

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is an immune-mediated chronic liver disease characterised by inflammation and fibrosis of the biliary tree resulting in bile duct strictures and hepatic fibrosis. PSC may progress to cirrhosis, portal hypertension and hepatic decompensation requiring liver transplant; it is associated with a markedly increased risk of hepatobiliary and colorectal cancer.[1] The aetiology of PSC remains poorly understood; however, a strong link exists between PSC and inflammatory bowel disease (IBD). Approximately three-quarters of PSC patients have concomitant IBD.[2] PSC-IBD most commonly resembles ulcerative colitis (UC) though often with distinctive features, including relative rectal sparing, more active right-sided colitis and frequent backwash ileitis.[3]

Bacterial translocation and dysbiosis may play a significant role in PSC pathogenesis. Indeed, the gut microbiome has been shown to differ in PSC patients compared to healthy controls and non-PSC-IBD.[4,5] By extension, antibiotics have been postulated to be of benefit in treating PSC and PSC-associated IBD. Oral vancomycin, a non-absorbable, bactericidal glycopeptide antibiotic active against Gram-positive bacteria,[6] has garnered particular interest. In a propensity score-matched cohort from the Paediatric PSC Consortium, a large international retrospective cohort study of paediatric PSC, gamma-glutamyltransferase (GGT), liver fibrosis and transplant listing were similar at 1 year in vancomycin-treated, ursodeoxycholic acid (UDCA)-treated and placebo cohorts.[7] However, two small randomised controlled trials (RCTs) and a few cohort studies have reported beneficial liver effects.[8,9] Acknowledging the insufficiency of the evidence, a recent Supporting Statement published by the American Association for the Study of Liver Diseases (AASLD) did not make a recommendation for or against the use of oral vancomycin for PSC.[10]

Although many PSC-IBD patients experience mild IBD symptoms, this is not the case for all, and a subset prove refractory to biologics. Moreover, even mild intestinal inflammation is clinically relevant, particularly in PSC-IBD given the heightened risk of colorectal cancer. In fact, it may be precisely this chronic low-grade colonic inflammation in PSC-IBD that drives the neoplasia risk. Only a few case reports and case series have specifically examined vancomycin for treating PSC-associated IBD. While the observations in these studies (improvement and/or normalisation of objective markers of mucosal inflammation including faecal calprotectin and endoscopic findings) are encouraging preliminary findings, they are limited by the lack of a comparator group and their small size ($N = 1$,[6,11–13] 3,[14] 7,[15] 8,[16] 17[17]). Moreover, paediatric data are sparse. While RCTs represent the gold standard design for studying a drug's efficacy and safety, RCTs are extremely challenging (and in some cases unfeasible) in rare diseases such as paediatric PSC. Given this, we aimed to examine the association between oral vancomycin exposure and clinical IBD outcomes by leveraging the large international Paediatric PSC Consortium dataset.

2 | METHODS

2.1 | Data source

The Paediatric PSC Consortium is a research database that includes 54 sites across Europe, North and South America, the Middle East and Asia.[18] Paediatric (diagnosis <18 years) PSC cases were included retrospectively based on detailed medical records review. As described, PSC diagnosis required cholestatic biochemistry and compatible radiographic and/or histopathological findings.[18] A label of PSC with autoimmune hepatitis (AIH) features was applied to patients with a 'probable' or 'definite' score on the paediatric adaptation of the Simplified AIH Criteria.[3] Patient and disease characteristics, as well as medication start and stop dates (for PSC and IBD), were extracted using standardised case report forms.

2.2 | Patients

Inclusion criteria for this analysis were concomitant IBD (any type—UC, Crohn's disease [CD] or IBD-unclassified [IBD-U]) and,

for vancomycin-treated patients, a minimum treatment duration of 3 months to treat PSC and/or IBD. Study sites were specifically instructed to not record short vancomycin courses for infectious indications (e.g. *Clostridium difficile*), but systemic stool testing was not possible as this was a retrospective study.

2.3 | Outcomes, covariates and analytic methods

We first performed a single-arm, uncontrolled analysis including all vancomycin-treated patients. We compared Physician Global Assessment (PGA) of IBD clinical activity (none, mild, moderate or severe) and serum laboratory markers (haemoglobin, albumin, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) at 6 and 12 months post-vancomycin to baseline (pre-vancomycin). We also compared global endoscopic severity (global rating of none, mild, moderate and severe) while receiving vancomycin to baseline (pre-vancomycin). These analyses were performed in patients with pre- and post-vancomycin data available.

For the adjusted analysis, the primary outcome was clinical remission (PGA none) a mean time of 1 year after vancomycin initiation ±6 months (i.e. as close to 1 year as possible, within a window of 6–18 months following vancomycin start). IBD duration at vancomycin start varied widely across treated patients, such that we could not use IBD diagnosis date as the start of the observation period in treated and untreated patients. In addition, PGA data were available at multiple timepoints for each patient. Given this and also wanting to ensure similar distributions of IBD duration at time of primary outcome assessment in both groups, we opted to generate a matched cohort, in which vancomycin-treated patients were each matched to three untreated (no vancomycin) controls, with matching based on similar IBD duration at PGA. This matched cohort was used for all subsequent analyses. Following matching which controlled only for IBD duration, we used regression to adjust for other important covariates/potential confounders. Secondary outcomes included (1) serum laboratory parameters and (2) endoscopic remission (defined as a global rating of no activity). Both were assessed within the same matched cohort, with analyses restricted to those with available data. Laboratory parameters included albumin, haemoglobin, CRP and ESR 1 year after vancomycin start ±6 months; these were compared to laboratory values in untreated controls measured at as similar an IBD duration as was available. The endoscopy sub-analysis was restricted to patients with endoscopic data available pre- and post-vancomycin to allow adjustment for baseline endoscopic severity.

The following covariates were selected a priori (based on clinical significance) for inclusion in multivariable analyses on the matched cohort: demographics including age and sex; IBD type (UC/IBD-U vs. CD); PGA at IBD diagnosis; whether biologics (tumour necrosis factor antagonists (aTNF) or vedolizumab) were ever received (as a marker of IBD severity); and medications taken at time of assessment to adjust for the confounding effects of medications taken concomitantly with vancomycin (corticosteroids, biologic and thiopurine). Given the relatively small amount of missing data for these covariates and to avoid disrupting matches due to missing data in the primary outcome analysis, only patients with complete data for the above variables were included in the matched cohort. For the primary outcome of PGA at 1 year, we performed a subgroup analysis by IBD type, and sensitivity analyses (1) restricted to patients with moderate–severe PGA at IBD diagnosis; (2) adjusting separately for endoscopic severity and extensive colitis at baseline (these two variables were not included in the multivariable model due to missing data); and (3) excluding patients with liver transplant prior to PGA determination. For the secondary laboratory outcomes, we adjusted for the same variables as in the primary outcome (PGA) model, in addition to IBD duration at time of laboratories, due to the potential for missing data in the secondary analyses to cause match disruption and imbalance of IBD duration between groups. Due to the small sample size for the endoscopy sub-analysis, we adjusted only for IBD duration at follow-up endoscopy, baseline endoscopic severity and key medication exposures.

2.4 | Statistical methods

We summarised continuous variables as medians with interquartile range (IQR) and categorical variables as frequencies with proportions. Among all vancomycin-treated patients, we used the Wilcoxon signed-rank test to compare PGA and laboratories at 6 and 12 months to baseline and the McNemar test to compare follow-up and baseline endoscopic severity. In the matched cohort, we compared continuous variables using the Mann–Whitney U test, and categorical variables using the Chi-square test, or Fisher exact test where expected cell counts were <5. We used univariate and multivariable generalised estimating equations (GEE) (to account for the matched nature of the data) to determine the unadjusted and adjusted effects of vancomycin on all outcomes, expressed as unadjusted and adjusted odds ratios (OR and aOR, respectively). CRP and ESR were log transformed given their non-normal distribution. We reported regression coefficients explaining the expected changes on the mean of laboratory parameters by treatment group. Statistical significance was defined as a two-sided $p < 0.05$. Data analysis was performed with SAS software (2015. SAS® 9.4. Cary, NC: SAS Institute Inc.) and R (version 4.2.1, R Core Team, 2021).

3 | RESULTS

3.1 | Vancomycin-treated cohort (single-arm, unadjusted analyses)

Of the 1362 children in the Paediatric PSC Consortium, 1061 (78%) had IBD. In total, 113 (11%) of these PSC-IBD patients received vancomycin for at least 3 months (Figure 1, Table 1). The median vancomycin dose and treatment duration in these 113 patients were 17 (IQR 12–33) mg/kg/day and 2.5 (IQR 1.5–4.1) years, respectively.

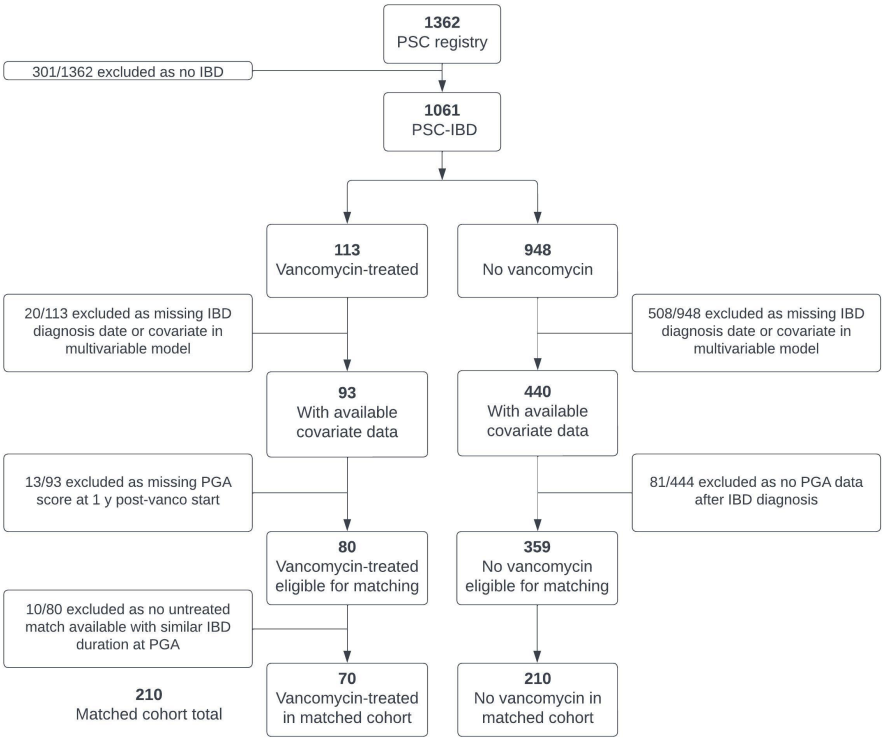

FIGURE 1 Study flow chart illustrating patient exclusions from the matched cohort.

Table S1 summarises PGA, biochemical parameters and global endoscopic severity post- versus pre-vancomycin treatment in the subset of patients with values available at both timepoints. Median PGA improved from mild at vancomycin start to none (clinical remission) at 6 and 12 months post-vancomycin ($p < 0.001$). The proportion of patients in clinical remission increased from 34% (30/88) at vancomycin start to 60% (52/86) at 6 months and 71% (55/78) at 12 months of vancomycin. Median ESR improved from the mid-20s to <10 mm/h ($p < 0.001$) over this period. Of the 113 vancomycin-treated patients, 32 had a colonoscopy pre- and post-vancomycin; the median vancomycin treatment duration at time of reassessment colonoscopy was 2.4 (IQR 2.4–7.7) years. The proportion with inactive endoscopic disease increased from 12% to 47% post-vancomycin, while the proportion with moderate–severe endoscopic disease decreased from 60% to 25% ($p = 0.004$). All of the above represent unadjusted analyses that do not consider factors such as other medication exposure.

3.2 | Matched cohort (adjusted for potential confounders)

As per Figure 1, 20/113 (18%) vancomycin-treated patients were excluded from the matched analysis for missing date of IBD diagnosis or a covariate in the multivariable analysis. Of the remaining 93, 70 could be matched to untreated controls ($N = 210$) with similar IBD duration at PGA. Therefore, the final matched cohort included 280 patients. As per Table 1, the 70 vancomycin-treated patients included in the matched analysis were fairly similar to the 113 patients from which they were drawn, with the notable exception being transplant rate; while 11% (12/113) of all vancomycin-treated patients underwent a liver transplant, all 12 were excluded from the matched cohort. All but 1 of the 12 were excluded from the matched cohort due to missing PGA data or a covariate in the primary outcome model; only 1 was excluded due to inability to match. In addition, patients included in the matched cohort started vancomycin earlier in their PSC course compared to the overall group of 113.

The median vancomycin dose and treatment duration in the 70 treated patients were 16 (IQR 12–31) mg/kg/day and 2.6 (1.8–4.6) years, respectively. Patient characteristics were generally similar in treated and untreated cohorts (Table 1), again with the exception of transplant rate (12% prior to PGA in untreated controls versus 0 in the vancomycin group; which we explored through sensitivity analysis excluding transplanted patients). In addition, untreated controls were at bit younger, more often had UC/IBD-U, and were more frequently treated with UCDA and 5ASA/sulfasalazine. As expected due to matching, IBD duration at PGA was similar between groups.

Figure 2 illustrates the primary outcome of PGA; 66% of vancomycin-treated patients were in clinical remission approximately 1-year post-vancomycin start compared to 35% of patients who did not receive vancomycin ($p < 0.001$). Table 2 presents the GEE results; these results are also graphically summarised in a Forest plot (Figure 3), along with subsequent subgroup/sensitivity and endoscopic analyses. In unadjusted analysis, vancomycin treatment was associated with significantly higher odds of IBD clinical remission compared to no treatment (OR 3.52, 95% CI 1.97–6.31). In the multivariable analysis, vancomycin remained associated with IBD remission, with an even greater magnitude of effect. Mild PGA at diagnosis was independently associated with a greater likelihood of IBD remission. A requirement for a biologic at any time in a patient's

TABLE 1 Patient characteristics—all vancomycin-treated patients and matched cohort.

	Matched cohort			
Median (IQR) or *N* (%)	**All vancomycin-treated (*N* = 113)**	**Vancomycin-treated (*N* = 70)**	**Controls (*N* = 210)**	***p*-value[a]**
Demographics				
Male	71/113 (63%)	47/70 (67%)	131/210 (62%)	0.47
Age at IBD diagnosis (years)	12.5 (8.8–15.1)	12.9 (9.7–15.1)	11.3 (7.1–14.6)	0.054
Age at PSC diagnosis (years)	12.7 (9.8–15.1)	13.1 (10.6–15.4)	11.3 (8.1–15.1)	0.046
IBD characteristics				
IBD type				
UC/IBD-U	76/105 (72%)	48/70 (69%)	183/210 (87%)	<0.001
CD	29/105 (28%)	22/70 (31%)	27/210 (13%)	
IBD duration at vancomycin start (years)	1.4 (0.3–3.4)	1.1 (0.3–2.5)	—	—
IBD duration at PGA assessment (years)	—	2.1 (1.3–3.0)	2.0 (1.0–3.0)	0.53
PGA at IBD diagnosis				
None	6/99 (6%)	3/70 (4%)	11/210 (5%)	0.51
Mild	22/99 (22%)	15/70 (21%)	63/210 (30%)	
Moderate	54/99 (55%)	42/70 (60%)	107/210 (51%)	
Severe	17/99 (17%)	10/70 (14%)	29/210 (14%)	
Endoscopic severity at IBD diagnosis				
None (microscopic changes only)	5/65 (8%)	3/47 (6%)	6/132 (5%)	0.41
Mild	21/65 (32%)	11/47 (23%)	36/132 (27%)	
Moderate	31/65 (48%)	28/47 (60%)	64/132 (48%)	
Severe	8/65 (12%)	5/47 (11%)	26/132 (20%)	
Colitis proximal to hepatic flexure (E4)	80/92 (87%)	55/62 (89%)	159/192 (83%)	0.27
PSC characteristics				
PSC with AIH features	40/113 (35%)	24/70 (34%)	64/210 (30%)	0.55
Duct type				
Large duct	103/113 (91%)	63/70 (90%)	190/210 (90%)	0.91
Small duct	10/113 (9%)	7/70 (10%)	20/210 (10%)	
GGT at PSC diagnosis (U/L)	254 (114–430)	254 (110–425)	230 (110–384)	0.36
ALP at PSC diagnosis (U/L)	374 (252–489)	358 (252–470)	350 (214–543)	0.99
ALT at PSC diagnosis (U/L)	98 (45–221)	100 (45–232)	105 (48–200)	0.71
AST at PSC diagnosis (U/L)	76 (44–194)	66 (42–194)	83 (42–167)	0.59
Albumin at PSC diagnosis (g/L)	40 (37–42)	40 (37–43)	39 (36–43)	0.12
Platelets at PSC diagnosis ($\times 10^9$)	335 (247–426)	343 (265–446)	364 (283–433)	0.99
CRP at PSC diagnosis (mg/L)	0.6 (0.1–1.8)	0.7 (0.1–1.9)	0.7 (0.3–1.5)	0.64
ESR at PSC diagnosis (mm/h)	29 (14–57)	29 (15–57)	40 (17–70)	0.45
PSC duration at vancomycin start (years)	1.0 (0.1–3.0)	0.4 (0.04–1.7)	—	—
PSC duration at PGA assessment (years)	—	1.6 (1.0–2.8)	1.8 (0.9–3.3)	0.73
Liver transplant	12 (11%)	0	36 (17%)	<0.001
Liver transplant prior to PGA assessment	—	0	26 (12%)	0.002
Medication exposure (ever)				
Ever treated with UCDA	72/113 (64%)	37/70 (53%)	172/209 (82%)	<0.001

(Continues)

TABLE 1 (Continued)

Median (IQR) or *N* (%)	Matched cohort			
	All vancomycin-treated (*N* = 113)	Vancomycin-treated (*N* = 70)	Controls (*N* = 210)	*p*-value[a]
Ever treated with corticosteroids	46/113 (41%)	23/70 (33%)	82/210 (39%)	0.35
Ever treated with 5ASA/sulfasalazine	60/113 (53%)	42/70 (60%)	156/210 (74%)	0.023
Ever treated with thiopurine	55/113 (49%)	38/70 (54%)	103/210 (49%)	0.45
Ever treated with aTNF	36/113 (32%)	25/70 (36%)	56/210 (27%)	0.15
Ever treated with vedolizumab	9/113 (8%)	9/70 (13%)	15/210 (7%)	0.14
Medication exposure (at PGA)				
On corticosteroids at PGA	—	9/70 (13%)	30/210 (14%)	0.76
On 5ASA/sulfasalazine at PGA	—	27/70 (39%)	135/210 (64%)	<0.001
On thiopurine PGA	—	27/70 (39%)	59/210 (28%)	0.10
On aTNF at PGA	—	12/70 (17%)	20/210 (10%)	0.083
On vedolizumab at PGA	—	4/70 (6%)	2/210 (1%)	0.036

Abbreviations: AIH, autoimmune hepatitis; ASA, aminosalicylates; aTNF, anti-tumour necrosis factor-alpha; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IBD-U, IBD-unclassified; PGA, Physician Global Assessment; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

[a]*p*-values refer to comparison of vancomycin-treated and untreated patients in the matched cohort.

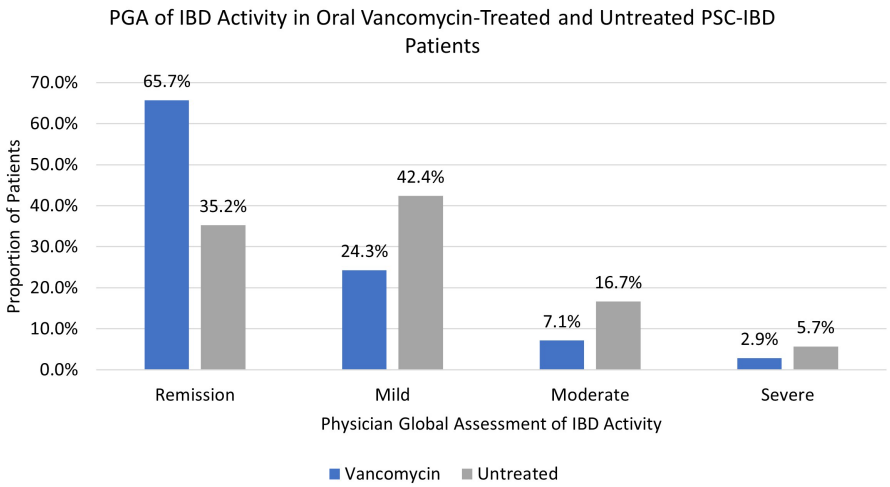

FIGURE 2 Bar graph illustrating IBD clinical activity (by Physician Global Assessment) in vancomycin-treated and untreated cohorts. Patients are matched on IBD duration at time of PGA assessment, and PGA is measured approximately 1-year post-vancomycin start in the vancomycin-treated group.

disease course (denoting more severe IBD) was independently associated with lower odds of clinical remission.

3.3 | Matched cohort (sensitivity and subgroup analyses)

In sensitivity analyses adjusting separately for baseline endoscopic severity (aOR 3.36, 95% CI 1.64–6.89) and baseline colitis extent (aOR 3.47, 95% CI 1.87–6.44), vancomycin remained associated with increased odds of IBD clinical remission (Tables S2 and S3). In the 52 vancomycin-treated patients with moderate–severe PGA at IBD diagnosis and their 136 matched untreated controls, vancomycin remained associated with greater odds of PGA remission (OR 6.18, 95% CI 3.02–12.67; aOR 8.53, 95% CI 3.75–19.41, adjusting for the same covariates as in the original multivariable model minus diagnostic PGA).

Median IBD duration at vancomycin start in the matched cohort approximated 1 year (1.1, IQR 0.3–2.5) years, with 34/70 starting vancomycin within 1 year of IBD diagnosis and 36/70 starting beyond 1 year. Both were superior to no vancomycin for the primary outcome in unadjusted analysis, but early initiation had a greater magnitude of benefit than later initiation (Table S4).

A multivariable analysis by IBD type was possible only for UC/IBD-U (Table S5; not possible for CD due to insufficient clinical remission events). Adjusting for the same covariates as the primary multivariable analysis, vancomycin was an independent predictor of clinical remission in the UC/IBD-U cohort (aOR 5.04, 95% CI 2.45–10.35). In a univariate analysis restricted to CD patients, vancomycin remained associated with greater odds of remission (OR 3.58, 95% CI 1.16–11.03).

TABLE 2 Unadjusted and adjusted generalised estimating equation examining likelihood of clinical remission with vancomycin in the matched cohort.

	Unadjusted OR (95%CI)	*p*-value	Adjusted OR (95%CI)[a]	*p*-value
Vancomycin treatment	3.52 (1.97–6.31)	<0.001	5.24 (2.68–10.22)	<0.001
Male	0.86 (0.50–1.49)	0.60	0.72 (0.40–1.30)	0.28
Age at IBD diagnosis (years)	1.02 (0.97–1.08)	0.36	1.00 (0.95–1.06)	0.91
Age at PSC diagnosis (years)	1.03 (0.98–1.10)	0.25		
IBD type				
UC/IBD-U	0.81 (0.37–1.76)	0.59	1.19 (0.49–2.88)	0.69
CD	Ref		Ref	
PGA at IBD diagnosis				
No more than mild	2.10 (1.28–3.50)	0.004	2.40 (1.32–4.36)	0.004
Moderate to severe	Ref		Ref	
Endoscopic severity at IBD diagnosis				
None (microscopic changes only)	Ref			
Mild	0.67 (0.13–3.43)	0.63		
Moderate	0.42 (0.10–1.86)	0.25		
Severe	0.33 (0.07–1.67)	0.18		
Missing 101				
Colitis proximal to hepatic flexure (E4)	1.74 (0.90–3.36)	0.099		
Missing 26				
PSC with AIH features	0.90 (0.52–1.57)	0.72		
Duct type				
Large duct	0.93 (0.44–1.96)	0.86		
Small duct	Ref			
PSC duration at PGA assessment (years)	0.92 (0.85–1.01)	0.078		
Ever treated with UCDA	0.98 (0.60–1.62)	0.94		
Ever treated with corticosteroids	0.65 (0.38–1.11)	0.12		
Ever treated with 5ASA/sulfasalazine	1.00 (0.61–1.63)	0.996		
Ever treated with thiopurines	0.68 (0.43–1.09)	0.11		
Ever treated with a biologic	0.37 (0.21–0.66)	<0.001	0.30 (0.14–0.67)	0.003
On corticosteroids at PGA	0.45 (0.22–0.92)	0.028	0.46 (0.18–1.17)	0.10
On 5ASA/sulfasalazine at PGA	1.43 (0.92–2.21)	0.11		
On thiopurine at PGA	0.97 (0.59–1.59)	0.89	0.93 (0.51–1.72)	0.82
On biologic at PGA	0.60 (0.31–1.14)	0.12	1.16 (0.43–3.11)	0.77

Abbreviations: AIH, autoimmune hepatitis; ASA, aminosalicylates; aTNF, anti-tumour necrosis factor-alpha; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IBD-U, IBD-unclassified; OR, odds ratio; PGA, Physician Global Assessment; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

[a]280 observations, 120 clinical remission events.

We then explored the effect of liver transplant on our primary outcome. Liver transplant prior to PGA was not associated with PGA remission (OR 0.65, 95% CI 0.28–1.52); similarly, the addition of transplant prior to PGA to the primary outcome multivariable model did not alter the association between vancomycin and IBD clinical remission (aOR 5.14, 95% CI 2.59–10.20). Moreover, in a sensitivity analysis excluding the 26 controls with liver transplant prior to PGA and adjusting for the same covariates as in the primary outcome model, the effect of vancomycin remained similar (aOR 4.82, 95% CI 2.51–9.24).

3.4 | Matched cohort (secondary outcomes—Biochemistry and endoscopy)

The results of the adjusted GEE models examining the secondary biochemical outcomes are shown in Table S6. In the matched cohort, vancomycin treatment was associated with significantly lower CRP and significantly higher haemoglobin and albumin at 1 year of vancomycin exposure compared to untreated patients.

Within the matched cohort, 28 vancomycin-treated patients had a baseline (diagnostic) and follow-up (on vancomycin) colonoscopy

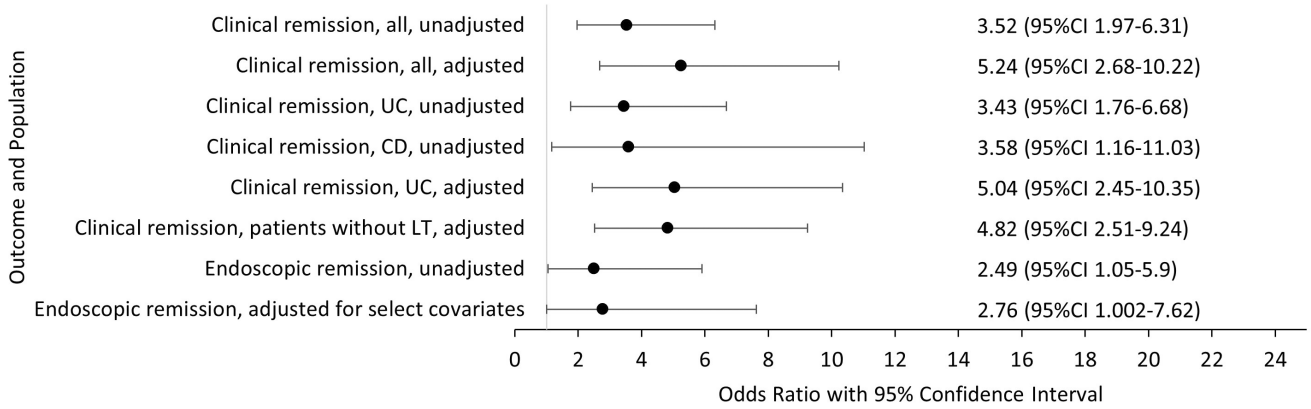

FIGURE 3 Summary of odds ratios and 95% confidence intervals for the effect of vancomycin on clinical remission and endoscopic remission across several populations/analyses.

available, and 73 untreated controls had both diagnostic and follow-up colonoscopies. IBD duration at reassessment scope was median 3.2 (IQR 1.8–5.8) years in the vancomycin group and 2.3 (IQR 1.2–5.0) years in the untreated group. Median vancomycin duration at reassessment endoscopy was 2.4 (IQR 1.0–3.4) years. In unadjusted analysis, 46% (13/28) of vancomycin-treated patients displayed endoscopic remission at reassessment compared to 26% (19/73) of untreated controls ($p=0.048$, GEE OR 2.49, 95% CI 1.05–5.90). In a multivariable GEE model adjusting for IBD duration at colonoscopy, baseline endoscopic severity, requirement for biologic at any time and corticosteroid exposure at the time of reassessment endoscopy, vancomycin remained significantly associated with increased odds of endoscopic remission (aOR 2.76, 95% CI 1.002–7.62; Table S7). Of note, biologic exposure at reassessment endoscopy was infrequent in both groups so was not included in the model.

4 | DISCUSSION

In this large, retrospective, matched cohort of patients from the Paediatric PSC Consortium, vancomycin treatment was associated with more than triple the odds of IBD clinical remission based on PGA. The association was maintained in multivariable analysis, adjusting for markers of IBD severity and medication exposure as well as multiple subgroup and sensitivity analyses. Interestingly, the benefit was greater in patients who initiated vancomycin within the first year of IBD diagnosis. These findings were supported by improvements in certain laboratory parameters, as well as a higher rate of endoscopic remission in the smaller subset of patients with such data available.

Table 3 summarises recent studies examining the effects of vancomycin on IBD activity in PSC-IBD cohorts. They describe marked improvement or normalisation of objective markers of mucosal inflammation, including faecal calprotectin and endoscopic activity, often in patients refractory to multiple biologic treatments. These studies, however, are limited by their small size, the lack of an untreated comparator group and their uncontrolled nature (with no adjustment for concomitant medications or other confounders). A bias against publication of negative case series may also exist. Sufficiently powered RCTs are extremely challenging for rare diseases like paediatric PSC. Real-world observational data can help to address this gap, and our study, a large, comparative and adjusted analysis, helps to do this. Moreover, in the context of a rare paediatric disease like PSC where limited financial incentive hinders novel drug development by pharma, repurposing existing drugs is an attractive alternative.

While our findings are observational, previous work has investigated possible mechanisms underlying antibiotics' effects in PSC/PSC-IBD. PSC/PSC-IBD pathogenesis centres around a few main themes, including an inflamed, leaky and dysbiotic gut; immune activation in the liver potentially due to aberrant trafficking of gut lymphocytes and/or translocation of microbial products; and biliary epithelial cell response to immune activation, which perpetuates inflammation and senescence.[19] Several of these themes implicate microbial perturbations; compositional changes in the faecal microbiome, as well as altered gut microbial metabolism of essential nutrients, have been described in PSC, including differences between PSC-IBD and non-PSC-IBD.[4,20] The mechanism by which vancomycin might be efficacious for treating PSC-associated IBD is unclear. It may relate directly to its anti-microbial properties and consequent alteration of the gut microbial profile or microbial products, including bile acids. Bile acids have emerged as a key class of microbiota-associated metabolites that are perturbed in non-PSC-IBD, with metabolomic studies revealing an increase in primary bile acids and a decrease in secondary bile acids.[21,22] In a small pilot study, vancomycin for up to 11 weeks was a potent inhibitor of secondary bile acid production in participants with IBD and PSC, particularly deoxycholic acid.[23] While secondary bile acids have been shown to exert anti-inflammatory effects on the intestinal mucosa, certain primary bile acids or combinations of primary bile acids may impart protective effects too.[22] Vancomycin has also been postulated to improve PSC-associated IBD via immunomodulatory properties, including an increase in T regulatory cells.[24] With the exception of suspected

TABLE 3 Recent studies reporting on IBD outcomes in PSC-IBD with oral vancomycin.

Study	Population	Vancomycin dose	Comparator	Outcomes	Follow-up
Paediatric					
Buness 2021[12,29]	*N* = 1 13 year old F, PSC-UC	500 mg TID	None	Endoscopy/histology: quiescent to mild chronic colitis	8 years
Tan 2019[17]	*N* = 17 Paediatric, PSC-UC	?	None	PUCAI: mean 26 (range 0–60) to 1.8 (0–20); 0 in 12/17 FCAL: mean 1055 to 55 μg/g; <200 μg/g in 15/15 Endoscopy/histology: Mayo endoscopic score 0 in 15/15; histological remission in 9/15	Mean 8 months (min 3 months)
Adult					
Ahmed 2023[6]	*N* = 1 Adult, PSC-UC, post-LT	125 mg QID	None	FCAL: 43 μg/g at 6 weeks Endoscopy/histology: Mayo endoscopic score 0, inactive chronic colitis	3 months
Almomen 2023[13]	*N* = 1 Adult, PSC-UC, post-LT	500 mg BID × 6 months, then 250 mg BID	None	FCAL: 277 μg/g at 6 months Endoscopy/histology: Mayo endoscopic score 0, quiescent colitis without activity at 6 months	
Shah 2022[15]	*N* = 7 Adult, PSC-UC, 4 post-LT, 1 with J-pouch	250–1500 mg/day × min 6 months	None	Mayo score: mean reduction of 9.3 (93%) CRP: mean reduction of 21.9 mg/L (74%) FCAL: mean reduction of 634 μg/g (87%) VRE: no cases	Mean 32 months
Rahman 2021[11]	*N* = 1 Adult, PSC-UC, post-LT	125 mg BID	None	Endoscopy: resolution of colitis (after 3 months, with decreasing dose/frequency of infliximab)	10 months
Dao 2019[16]	*N* = 8 Adult, PSC-UC, 5 post-LT	125 mg QID × 6–8 weeks, then 125 mg BID or TID for maintenance	None	At 6–12 months: Mayo score: 0–2; average reduction of 7 points Mayo endoscopic score: 0–1	9–36 months
De Chambrun 2018[14]	*N* = 3 Adult, PSC-UC	500 mg BID	None	At 5 months-3 years: PGA: 0 Mayo endoscopic score: 0	15–49 months

Abbreviations: CRP, C-reactive protein; F, female; FCAL, faecal calprotectin; LT, liver transplant; min, minimum; PGA, Physician Global Assessment; PSC, primary sclerosing cholangitis; PUCAI, Paediatric Ulcerative Colitis Activity Index; QID, four times per day; TID, three times per day; UC, ulcerative colitis; VRE, vancomycin-resistant enterococcus.; yo, year old.

monogenic disease (which was not included in our study), there is no compelling evidence that the underlying pathophysiology of PSC/PSC-IBD differs between children and adults. We therefore hypothesise that our findings are extrapolatable to adult PSC-IBD cohorts.

In a subgroup analysis, the beneficial effect of vancomycin was observed in both the UC and CD cohorts, although the CD subgroup was much smaller, precluding an adjusted analysis. Vancomycin has been used and studied for non-PSC colitis for generations,[25] though admittedly with conflicting results and a lack of large RCTs. In 2019, a pilot RCT found an oral antibiotic cocktail including vancomycin to improve colitis symptoms in children with acute severe colitis treated with intravenous corticosteroids, compared to placebo.[26] Whether vancomycin exerts its effects in PSC-associated colitis and non-PSC-IBD by the same mechanism(s) is unknown, but clinical and molecular data suggest that the diseases are two distinct entities, at least raising the possibility of distinct mechanisms being at play.

Our study has several strengths, including its size, a control group and adjustment for important potential confounders, including IBD severity, medication exposure and IBD duration. We acknowledge, however, the limitations of PGA as a primary outcome, the limited endoscopic data and the study's retrospective nature. Moreover, we examined outcomes at 1 year only and not longer-term. An additional limitation is the lack of data on vancomycin-resistant enterococci (VRE), as this was not collected as an outcome. This is an important limitation of the vast majority of the studies on this subject to date. Although a substantial fraction of vancomycin-treated patients had only mild clinical activity at time of vancomycin start, with median PGA decreasing from 1 to 0 in the unmatched analysis, resolution of any degree of colonic inflammation is clinically relevant in PSC-IBD given the risk of colorectal cancer. Moreover, in a sensitivity analysis restricted to vancomycin-treated patients with more active IBD, the effect of vancomycin remained significant with even greater magnitude of effect. Lastly, not all vancomycin-treated patients could be included in the matched cohort due to missing data. That said, those included were generally similar to the overall group with the exception of transplant rate, which caused an imbalance in transplant rates between untreated and treated groups in the matched cohort. However, a sensitivity analysis restricted to patients without liver transplant showed similar results. The absence of transplanted patients in our vancomycin group, however, does mean that our findings cannot be generalised to the post-transplant setting. This should be examined in future work. We did not comment on the effect of vancomycin on the liver in this analysis as this was the subject of a previous publication utilising the Paediatric PSC Consortium dataset.[7] However, as highlighted by the authors of a recent systematic review supporting the effectiveness of biologics for PSC-associated colitis,[27] any treatment selected to treat IBD in a patient with PSC must also cautiously consider the drug's effects on the liver.

In summary, vancomycin was independently associated with increased odds of IBD clinical remission in this large matched paediatric PSC-IBD cohort and increased odds of endoscopic remission in a smaller subset. Additional large prospective studies or ideally RCTs with objective IBD endpoints (e.g. faecal calprotectin, endoscopy) are needed to conclusively ascertain the efficacy (short- and long-term) of vancomycin in this population, as well as to delineate the optimal dosing regimen and exclude safety concerns. Such studies should carefully document treatment adherence and include efforts to elucidate pathogenic disease pathways and drug mechanisms of action. More recently, target trial emulation using causal inference technique[28] is gaining attention as a method to estimate the effect of a treatment using observational data and this represents a potential alternate strategy to study vancomycin in PSC patients, given the difficulties inherent to performing RCTs in PSC. At present, however, decisions around vancomycin use for PSC-IBD should be made on a case-by-case basis with transparency about the lack of high-quality evidence. In the setting of a progressive and difficult to manage condition, consideration may be given to a trial of oral vancomycin in the PSC-IBD patient who has proven unresponsive to other, conventional therapies. In our opinion, it is not unreasonable for future PSC guidelines to include a recommendation to this effect. Moreover, for those who respond favourably, an argument can be made for health insurers to cover the cost of oral vancomycin.

AUTHOR CONTRIBUTIONS

Amanda Ricciuto: Conceptualization; data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Kuan Liu:** Conceptualization; formal analysis; methodology; writing – review and editing. **Wael El-Matary:** Conceptualization; data curation; writing – review and editing. **Mansi Amin:** Data curation; writing – review and editing. **Achiya Z. Amir:** Data curation; writing – review and editing. **Madeleine Aumar:** Data curation; writing – review and editing. **Marcus Auth:** Data curation; writing – review and editing. **Matthew D. Di Guglielmo:** Data curation; writing – review and editing. **Eleonora Druve Tavares Fagundes:** Data curation; writing – review and editing. **Alexandre Rodrigues Ferreira:** Data curation; writing – review and editing. **Katryn N. Furuya:** Data curation; writing – review and editing. **Nitika Gupta:** Data curation; writing – review and editing. **Stephen Guthery:** Data curation; writing – review and editing. **Simon P. Horslen:** Data curation; writing – review and editing. **Kyle Jensen:** Data curation; writing – review and editing. **Binita M. Kamath:** Data curation; writing – review and editing. **Nanda Kerkar:** Data curation; writing – review and editing. **B. G. P. Koot:** Data curation; writing – review and editing. **Trevor J. Laborda:** Data curation; writing – review and editing. **Christine K. Lee:** Data curation; writing – review and editing. **Kathleen M. Loomes:** Data curation; writing – review and editing. **Cara Mack:** Data curation; writing – review and editing. **Mercedes Martinez:** Data curation; writing – review and editing. **Aldo Montano-Loza:** Data curation; writing – review and editing. **Nadia Ovchinsky:** Data curation; writing – review and editing. **Alexandra Papadopoulou:** Data curation; writing – review and editing. **Emily R. Perito:** Data curation; writing – review and

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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