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Outcomes of oral vancomycin therapy in children with atypical ulcerative colitis with or without confirmed primary sclerosing cholangitis: a real-world observational study

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ABSTRACT

Objectives Atypical ulcerative colitis (UC) presenting reverse gradient colitis, backwash ileitis, or rectal sparing and/or positive atypical antineutrophil cytoplasmic antibody serology is often associated with primary sclerosing cholangitis (PSC) and can be resistant to conventional medical therapies (CMT) for inflammatory bowel diseases. We report short-term and long-term outcomes of oral vancomycin therapy (OVT) in children with atypical UC and confirmed PSC in imaging/biopsy (PSC-UC) or treatment-resistant atypical UC without detectable PSC (aUC-non-PSC).

Methods In this retrospective real-world observational study from a tertiary paediatric centre in Brisbane, Australia, 44 children with aUC (29 PSC-UC, 15 aUC-non-PSC) received 79 OVT courses between 2014 and 2023. Pre–post-OVT characteristics were compared and relapses/repeated courses were recorded.

Results Pre-OVT, all had active colitis by Paediatric Ulcerative Colitis Activity Index (PUCAI), Feacal Calprotectin (FC) and/or colonoscopy. Post-OVT, PUCAI reduced from 15 (IQR 5–33) to 0 (IQR 0–5); 85% of children with pre-OVT PUCAI ≥10 achieved clinical remission (100% PSC-UC vs 64% aUC-non-PSC, p=0.019). FC reduced from 995 (IQR 319–1825) to 44 (IQR 16–79) µg/g; 83% of children with pre-OVT FC ≥100 µg/g achieved biochemical remission (92% PSC-UC vs 64% aUC-non-PSC, p=0.063). Colonoscopy confirmed Mayo 0 healing in 62% (67% PSC-UC vs 54% aUC-non-PSC, p=0.443) and 46% achieved pan-colonic histological remission (54% PSC-UC vs 31% aUC-non-PSC, p=0.173). All pre–post-OVT changes in these four markers were significant in both groups. After ceasing first OVT, 25/44 relapsed within 8.2 (IQR 1.9–14.5) months. Recommencing OVT regained biomarker remission in 13/25. During 3.8 (IQR 2.0–5.3) years of follow-up, 79 OVT courses in conjunction with CMT maintained deep remission in 67%. Routine stool testing (n=138) detected no vancomycin-resistant Enterococcus (VRE).

Conclusions OVT induced and reinduced remission in children with atypical UC. Relapse often followed ceasing vancomycin, half responded to reinduction. No VRE was developed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Primary sclerosing cholangitis-related ulcerative colitis (PSC-UC) often has an atypical colitis phenotype and is more resistance to conventional medical treatment (CMT).

WHAT THIS STUDY ADDS

⇒ Oral vancomycin therapy (OVT) in combination with other therapies was able to induce colitis remission and help (re)gaining response to CMT in children atypical UC with/without PSC.

⇒ Colitis relapses were common after ceasing OVT, yet reinduction of remission could be achieved by retreating with OVT.

⇒ Repeated and/or long-term OVT use in a small cohort of children with atypical UC did not lead to development of vancomycin-resistant Enterococcus.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In managing children with CMT-resistant PSC-UC type of colitis, Inflammatory Bowel Disease (IBD) clinicians can expect short- and longer-term response, when introducing well-monitored OVT to their treatment armamentarium.

INTRODUCTION

Atypical ulcerative colitis (UC) is a terminology used to describe unusual colitis characteristics, such as reverse gradient severity, backwash ileitis or rectal sparing.[1] Atypical UC is often seen in primary sclerosing cholangitis (PSC), a chronic inflammation of the biliary tract that may progress to strictures and cholestasis.[2] PSC occurring together with UC (PSC-UC) generates a colitis phenotype that is often more resistant to conventional medical therapies (CMT) for inflammatory bowel diseases,[3] showing association with positive atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) serology.[4 5]

The relationship between colitis and PSC is enigmatic as sometimes one is diagnosed long before the other. Diagnosing early stage PSC can be challenging, as not all patients with PSC-UC exhibit abnormal liver biochemistry prior to magnetic resonance cholangiopancreatography (MRCP).[6] At our unit, we have a low threshold for MRCP in any child with atypical UC, especially when the γ-glutamyl transpeptidase (GGT) is elevated. In our Inflammatody Bowel Disease (IBD) service, approximately 6% of children have a diagnosis of PSC, almost entirely with UC, representing a slightly higher prevalence than other reports.

The coexistence of PSC in children with IBD has a dramatic effect on the risk of death in early adult years and is a major risk factor for colon cancer.[7] In contrast, the more proximal inflammatory distribution of atypical UC with PSC contributes to less intrusive UC symptoms, less bloody diarrhoea than traditional left-sided UC, leading to a milder presentation and increased risk of undertreated disease.

Oral vancomycin therapy (OVT) is a promising therapy to manage both colonic and biliary inflammation of children with PSC and UC.[8 9] A recent matched analysis in children with PSC comparing OVT therapy with no therapy for their associated colitis demonstrated greater symptomatic remission at 1 year and better endoscopic outcomes in the small number having a colonoscopy.[10] Our centre has used OVT for managing children with atypical UC and PSC for a decade with favourable outcomes.[11] Since MRCP is able to detect only relatively advanced PSC, with support from Infectious Diseases Service, we expanded the use of OVT to treat children with atypical UC having colitis features often associated with PSC, yet without detectable PSC on imaging.

The presence of positive perinuclear pANCA further strengthened the possibility of a PSC-like phenotype in this group and thereby a greater possibility of treatment response to OVT when conventional therapies had failed. Compared with previous failures of empiric use of OVT with more traditional left-sided typical pANCA-negative UC, OVT was successful in atypical pANCA-positive UC, prompting an increase in use. This experience is now reported here, along with the outcomes of treating atypical UC with confirmed PSC on imaging and/or biopsy.

METHODS

Data source

This is a retrospective observational study on efficacy of OVT in children under 18 years with atypical UC. Atypical UC in this study was defined as reverse gradient, right-sided or patchy colitis with/without rectal sparing and/or backwash ileitis, and expressing positive atypical ANCA serology (pANCA, myeloperoxidase or proteinase-3 ANCA). Children commencing oral vancomycin were identified using pharmaceutical dispensing log of the Queensland Children's Hospital, a tertiary paediatric centre in Brisbane, Australia, between 2014 and 2023. Those receiving OVT for *Clostridium difficile* infection or for <3 months were excluded. Data on medical history, date of starting/finishing OVT, Pediatric Ulcerative Colitis Activity Index (PUCAI), faecal calprotectin (FC), colonoscopic Mayo scores and histology of colonic biopsies were obtained from the integrated electronic medical record (ie, MR). Age, disease location and severity of atypical UC when starting OVT were noted, and all variations of atypical UC parameters were included in this study.

All children had UC confirmed by standard endoscopic and histologic findings according to ESPGHAN Revised Porto Criteria.[1] PSC-UC diagnosis was established in 29 children—23/29 by MRCP and 6/29 by liver biopsy as part of work up for autoimmune hepatitis.[12] Two young children (under 6 years) with marginally elevated GGT did not have MRCP when commencing OVT for their atypical UC, but PSC was subsequently confirmed by MRCP 3 and 11 months later and they were categorised into PSC-UC group.

MRCP was also used to screen and exclude PSC in 13/15 children labelled as atypical UC without detectable PSC (aUC-non-PSC). Two children with aUC-non-PSC were too young to undergo MRCP without general anaesthesia, but never showed abnormal liver enzymes nor liver ultrasound during routine clinical follow-up to justify risks of general anaesthesia. All 15/15 children with aUC-non-PSC had normal liver ultrasound before starting OVT, and only 2/15 had elevated baseline GGT (both had normal MRCP). During follow-up, none of the children with aUC-non-PSC and normal baseline GGT presented concerningly elevated GGT levels, and the two children with elevated baseline GGT eventually achieved normal GGT levels. Therefore, their diagnoses remained as aUC-non-PSC during the study period.

Oral vancomycin therapy

An OVT course is defined as ≥3 months of uninterrupted daily use of oral vancomycin 50 mg/kg/day (maximum 1500 mg/day) in three divided doses. OVT was used to support CMT that was failing, and never as a first-line therapy. All patients had full screening for tuberculosis and stool PCR before starting OVT. CMT including mesalazine (>40 mg/kg/day), thiopurines (6-TGN>230 pmol/8×10^8 red blood cells) and dose-optimised infliximab/adalimumab; long-term steroid dependency and had no history of vancomycin allergy. Failure to respond to CMT was defined as confirmed and continuous presence of inflammation (FC ≥100 µg/g and Mayo >0) or recurrent flares despite optimal treatment. OVT medication compliance was confirmed by the pharmacist at each prescription renewal and at each outpatient follow-ups.

Vancomycin-resistant Enterococcus screening

To justify long-term and repeated course of OVT, Infectious Disease Services (IDS) of our hospital mandated

detailed clinical, biomarker, and colonoscopy assessment, regular 3–6 monthly clinical follow-up, and screening for vancomycin-resistant Enterococcus (VRE) by rectal swabs and/or stool sample. Screening swabs were inoculated into VRE broth and incubated for 24 hours to observe for black colour change. If observed, the broth would be subcultured to chromID VRE agar and investigated for the growth of characteristic colonies of *Enterococcus faecium* or *Enterococcus faecalis* for up to 24–48 hours. The sensitivity of this test ranged from 86%–90% and the specificity was 100%.[13] For suspected new cases of VRE, identification would be confirmed via MALDITOF-MS, antimicrobial susceptibility would be performed and reported as new case of VRE if VItek MIC was >4.

Variables and outcomes

Before starting the first OVT, colitis activity was estimated using PUCAI, FC and colonoscopy. PUCAI was categorised as severe (>65), moderate (35–64) or mild (10–34).[14] FC ≥100 µg/g was regarded as active colitis.[15] Colitis distribution and phenotypes at colonoscopy (particularly atypical features) was noted, and degree of mucosal inflammation assessed with Mayo scoring of 0 (normal), 1 (mild), 2 (moderate) and 3 (severe). Terminal ileum, caecum, descending colon, transverse colon, ascending colon, sigmoid colon and rectum were biopsied and histology result from each site graded using 5-point inflammation scores into (0) normal, (1) quiescent, (2) mild, (3) moderate and (4) severe.[16]

PUCAI and FC were repeated after 2–4 months. Clinical remission was defined as PUCAI <10 and biomarker remission as FC <100 µg/g.[10 11] OVT was discontinued in non-responders, otherwise continued a further 3 months. Responders occasionally continued OVT for 12 months based on previous disease severity and CMT resistance. Follow-up colonoscopy was performed 3–9 months post-OVT commencement and subsequently when indicated. Mayo 0 defined mucosal healing, and 5-point inflammation score of <2 at all biopsy sites defined deep pan-colonic histologic remission. Number of clinical relapses (PUCAI ≥10 and FC ≥100 µg/g) while on/after ceasing OVT were recorded.

Statistical analyses

Demographic and clinical information were presented with frequencies and proportions (%) for categorical variables (compared with χ^2 or Fisher's exact test when the expected cell counts were <5) and with medians and IQR for continuous variables (compared with Kruskall-Wallis test). Pairwise pre–post OVT comparison was performed using Wilcoxon signed rank test for non-normally distributed continuous variables and McNemar test for categorical variables. A two-sided p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics V.29.0.0.0. Missing data are marked in the tables.

Reporting

This report is based on the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (online supplemental table 1).

Patient and public involvement

None.

RESULTS

Background

In 2014–2023, 79 OVT courses were administered to 44 children with active colitis, 29 (66%) had PSC-UC and 15 (34%) aUC-non-PSC. Of children with PSC-UC, 22/29 (76%) primarily presented to the IBD clinic with UC and PSC was diagnosed by MRCP within median 9 (IQR 2.5–15) months later. 7/29 (24%) presented to the liver clinic first with PSC, 5/7 had autoimmune hepatitis overlap. Very early onset inflammatory bowel diseases (VEO-IBD) were diagnosed before the age of 6 years in 16/44 (36%)—10/16 (63%) with PSC and 6/16 (37%) without PSC. Of them, 10/16 commenced OVT before the age of 6 years (7 PSC-UC, 3 aUC-non-PSC).

In children with PSC-UC, 10/29 had only one OVT course and 19 had repeated courses: 15 had two courses, 2 had three courses, 1 had six courses and 1 had seven OVT courses—a total of 59 courses. In children with aUC-non-PSC, 11/15 had only one OVT course, 2 had three courses and 1 had three courses—a total of 20 courses. In addition, 11/15 (73%) of children with aUC-non-PSC had magnetic resonance enterography to rule out Crohn's disease, 10 were normal and 1 had mild backwash ileitis. During follow-up intestinal ultrasound in all of them, no small bowel inflammation was seen in any of these children.

The clinical characteristics of children with atypical colitis treated with OVT are presented in table 1. Children with aUC-non-PSC had higher levels of FC at baseline and more frequent use of mesalazine, azathioprine/6-mercaptopurine, biologics and steroids than children with PSC-UC. In children with PSC-UC, OVT was initially used in children failing CMT, including biologics in 3/29 (10%) and azathioprine/6-mercaptopurine in 11/29 (40%). After demonstrating excellent efficacy of OVT in managing children with PSC-UC, more children with this UC phenotype in our centre were managed with OVT earlier in the treatment pyramid, including when primary therapy is pending completion of vaccination schedule. In children with aUC-non-PSC, all were unable to achieve remission or frequently relapsed despite maximal treatment and four were considered for colectomy. Four children were steroid dependent, 2 were steroid resistant and 11 were unresponsive to the combination of 6-mercatopurine, mesalazine and infliximab/adalimumab. Severe neutropenia contraindicated immunosuppression in one child, two were too young

Table 1 Clinical characteristics of children with atypical ulcerative colitis and PSC (PSC-UC) or without PSC (aUC-non-PSC) before starting oral vancomycin therapy (OVT)

Baseline characteristics	Type of colitis		P value	Total (N=44)
	PSC-UC (n=29)	aUC-non-PSC (n=15)		
Sex, n (%)			0.894*	
Boys	18 (62)	9 (60)		27 (61)
Girls	11 (38)	6 (40)		17 (39)
Age of UC diagnosis (years), median (IQR)	10.3 (4.5–13.6)	8.10 (3.9–11.6)	0.260†	9.6 (4.2–13.1)
Number of very-early onset IBD, n (%)	10 (34)	6 (40)	0.718*	16 (36)
Atypical colitis feature, yes n (%)				
Worse right-side involvement	12 (41)	4 (27)	0.336*	16 (36)
Backwash ileitis	5 (17)	6 (40)	0.098*	11 (25)
Rectal sparing	10 (35)	4 (27)	0.598*	14 (32)
Serology, n (%)				
Positive atypical pANCA	18 (59)	9 (60)	0.894*	27 (59)
Positive MPO-ANCA	7 (24)	2 (13)	0.341*	9 (20)
Positive PR3-ANCA	17 (59)	7 (47)	0.341*	24 (55)
Negative for any serology	3 (10)	5 (33)	0.104*	8 (18)
Not tested	1 (3)	0		
Baseline PUCAI, n (%)			0.495*	
< 10 (remission)	11 (38)	4 (27)		15 (34)
10–34 (mild)	11 (38)	6 (40)		17 (39)
35–65 (moderate)	5 (17)	4 (27)		9 (20)
> 65 (severe)	0	1 (6)		1 (2)
Missing	2 (7)	0		2 (5)
Baseline faecal calprotectin (FC), median (IQR) µg/g	725 (190–1500)	1300 (770–2800)	**0.048**†	990 (339–1800)
Baseline Mayo scores			0.098*	
0 (normal)	2 (7)	0		2 (4)
1 (mild colitis)	17 (58)	4 (27)		21 (48)
2 (moderate colitis)	8 (28)	9 (60)		17 (39)
3 (severe colitis)	2 (7)	2 (13)		4 (9)
Baseline 5-point inflammation score, n (%)			0.467*	
< 2 at all sites of biopsy	1 (3)	0		1 (2)
≥ 2 at any site of biopsy	28 (97)	15 (100)		43 (98)
Duration of colitis (months) when starting OVT, median (IQR)	6.6 (1.6–14.4)	16 (2.5–54.5)	0.085†	7.3 (2.0–24.7)
Used medications when starting OVT (vs not used), n (%)				
Mesalazine	14 (48)	15 (100)	**0.003***	28 (64)
Azathioprine or 6-mercaptopurine	11 (38)	11 (73)	**0.026***	22 (50)
Infliximab or adalimumab	3 (10)	11 (73)	**<0.001***	14 (32)
Steroids	1 (3)	7 (47)	**<0.001***	8 (18)
UDCA	5 (17)	0	0.149	5 (11)
Age at starting OVT, median (IQR)	11.7 (5.8–14.2)	11.0 (6.6–14.5)	0.892†	11.3 (6.2–14.2)
Commenced OVT<6 years old, n (%)	7 (24)	3 (20)	0.756*	10 (22)
Duration of the first OVT (months), median (IQR)	8.0 (6.2–12.1)	6.0 (4.1–8.0)	**0.035**†	7.6 (5.6–11.9)
Total number of OVT courses, n (%)			0.092*	
One	10 (34)	11 (73)		20 (45)
Two	15 (52)	3 (20)		19 (43)
Three	2 (7)	1 (7)		3 (7)
More than five	2 (7)	0		2 (5)
Follow-up time (years), median (IQR)	3.7 (2.1–5.4)	3.8 (1.5–4.9)	0.544*	3.8 (2.0–5.3)

Continued

Table 1 Continued

Baseline characteristics	Type of colitis PSC-UC (n=29)	aUC-non-PSC (n=15)	P value	Total (N=44)
Reason for ending follow-up, n(%)			0.123*	
End of study in March 2024	16 (55)	8 (53)		24 (55)
Transition to adult care	13 (45)	5 (33)		18 (41)
Colectomy	0	2 (13)		2 (4)

Significant P values are written in bold.
P values were obtained using:
*Pearson's χ^2 with Fisher's exact test when required.
†Kruskall-Wallis test.
IBD, Inflammatory Bowel Disease; MPO, myeloperoxidase; (p)ANCA, (perinuclear) anti-neutrophil cytoplasmic antibodies; PSC, primary sclerosing cholangitis; PUCAI, Paediatric Ulcerative Colitis Activity Index; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

for Pharmaceutical Benefit Scheme approved Infliximab but started biologics later, one trialled OVT after not responding to 6-mercaptopurine/mesalazine combination and eventually no longer required biologics.

The children were followed up for median 3.8 (IQR 2.0–5.3) years. The reasons for ending the follow-up were the end of study period in March 2024 (n=24), transition to the care of adult gastroenterologists (n=18) or colectomy in two children who did not respond to OVT as their last treatment option.

Pediatric Ulcerative Colitis Index

Baseline PUCAI was recorded in 42 children, 27/42 (64%) had active colitis symptoms (PUCAI ≥10)—16/27 (59%) in PSC-UC and 11/15 (73%) in aUC-non-PSC. Before and on-treatment pairwise comparison within median 3.7 (IQR 3.0–5.2) months after starting the first course of OVT was available for 41 children (26 PSC-UC and 15 aUC-non-PSC). Overall PUCAI reduced from median 15 (IQR 5–33) to 0 (IQR 0–5) (p<0.001) (figure 1)—from median 10 (IQR 5–27) to 0 (p<0.001) in PSC-UC and from median 25 (IQR 5–40) to 5 (IQR 0–10) (p=0.002) in aUC-non-PSC. 37/41 (90%) children were in clinical remission (PUCAI<10)—26/26 (100%) in PSC-UC versus 11/15 (73%) in aUC-non-PSC. Of the 27 children with baseline PUCAI≥10, 23/27 (85%) achieved clinical remission (16/16 (100%) in PSC-UC versus 7/11 (64%) in aUC-non-PSC, p=0.019), 3/27 (11%) had reduced and 1/27 (4%) increased PUCAI. Clinical remission was achieved in 7/9 (78%) of children commencing OVT before the age of 6 years versus 16/18 (89%) in children commencing OVT after the age of 6 years (p=0.444).

Faecal calprotectin

At baseline, 43 children had available FC and 39/43 (91%) were elevated (FC ≥100 µg/g). Paired before-treatment and on-treatment FC within median 3.7 (IQR 2.7–4.8) months after starting OVT was available for 38 children (27 PSC-UC and 11 aUC-non-PSC), of which 35/38 (92%) were elevated at baseline. While on OVT, FC reduced from 995 (IQR 319–1825) µg/g to 44

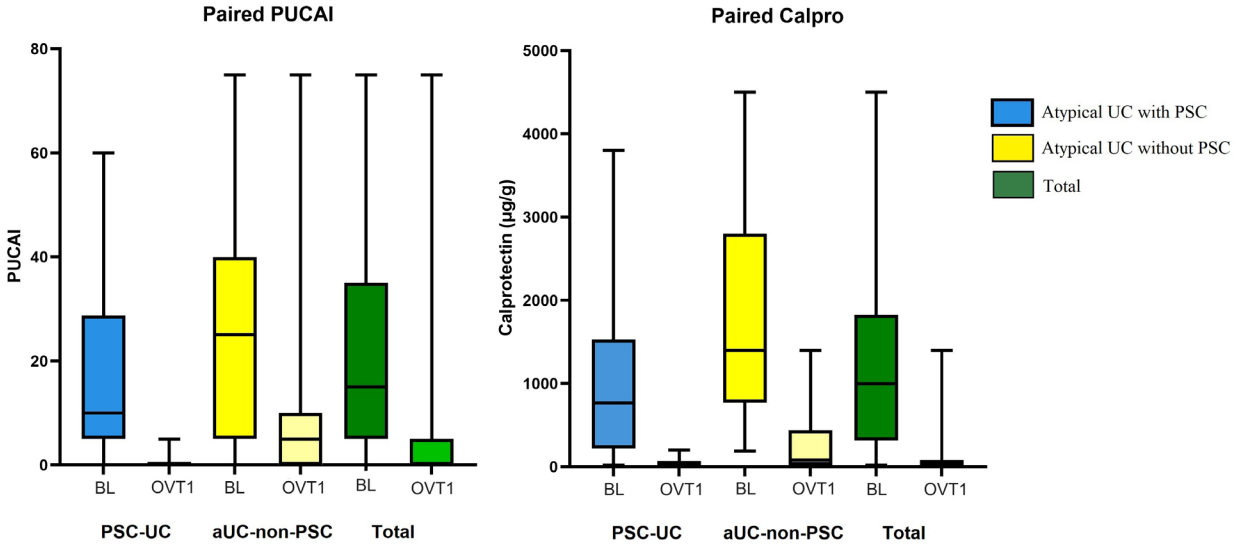

Figure 1 Paired Paediatric Ulcerative Colitis Activity Index (PUCAI, n=41) and faecal calprotectin (FC, n=38) in 44 children with atypical ulcerative colitis with/without primary sclerosing cholangitis (PSC-UC/aUC-non-PSC) at baseline (BL) and while on first oral vancomycin therapy (OVT1), with median (black line), interquartile range (box) and range (whiskers). aUC-non-PSC, atypical UC without detectable PSC; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

(IQR 16–79) µg/g (p<0.001). In PSC-UC FC reduced from median 725 (IQR 190–1500) µg/g to 37 (IQR 16–74) µg/g (p<0.001), while in aUC-non-PSC, FC reduced from median 1300 (IQR 770–2800) µg/g to 84 (IQR 22–440) µg/g (p=0.002) (figure 1). Of the 35 children with elevated baseline FC, 29/35 (83%) achieved biochemical remission (22/24 (92%) in PSC-UC vs 7/11 (64%) in aUC-non-PSC, p=0.041), 5/25 (14%) had reduced and 1/35 (3%) had increased FC. The one child with increased both PUCAI and FC while on OVT ended up with colectomy. Biochemical remission was achieved in 7/10 (70%) of children commencing OVT before the age of 6 years vs in 22/25 (88%) in children commencing OVT after the age of 6 years (p=0.202).

Colonoscopy

In total, 141 colonoscopies were performed. All children (n=44) had baseline colonoscopy within median 1.0 (IQR 0.4–3.6) months before starting the first OVT. All had atypical phenotype based on macroscopic findings before starting OVT (either at baseline and/or at diagnosis), 36/44 (82%) had positive atypical ANCA serology. Mucosal inflammation (Mayo >0) was seen in 42/44 (95%) and 43/44 (98%) had histologically confirmed active colitis. One child with PSC-UC had normal histology in pre-OVT colonoscopy but flared shortly after by presenting increased PUCAI and FC prior to commencing OVT. Paired followed-up colonoscopy data were available for 37 children within median 6.4 (IQR 5.0–10.4) months, 23 in children with PSC-UC and 14 in aUC-non-PSC. Of the follow-up colonoscopies, 27/37 (73%) were while on OVT (18 in PSC-UC and 9 in aUC-non-PSC) and 10/37 (27%) were within median 4.2 (IQR 2.5–14.4) months after ceasing OVT.

In 37 paired colonoscopy findings (24 PSC-UC, 13 aUC-non-PSC), all had mucosal inflammation (17 mild (Mayo 1), 16 moderate (Mayo 2) and 4 severe (Mayo 3)) at baseline or at the time of diagnosis, all had confirmed histological inflammation. Post-OVT, Mayo score reduced in 29/37 (78%) from median 2 (range 1–3) to median 0 (range 0–3) (p<0.001). Pre–post-OVT Mayo improvement were significant in both PSC-UC (from median 1 (range 1–3) to 0 (range 0–1), p<0.001) and aUC-non-PSC (from median 2 (range 1–3) to 0.5 (range 0–3), p=0.010. **23**/37 (62%) achieved complete mucosal healing (Mayo 0) (16/24 (67%) PSC-UC vs 7/13 (54%) aUC-non-PSC, p=0.443), **6**/37 (16%) had reduced Mayo, **6**/37 (16%) were unchanged and **2**/37 (5%) had increased Mayo score. These two children with aUC-non-PSC not responding to OVT proceeded to colectomy. Mucosal remission was achieved in 4/7 (57%) of children commencing OVT before the age of 6 years vs 19/30 (63%) in children commencing OVT after the age of 6 years (p=0.761). Deep pan-colonic histological remission (five points inflammation scores <2 at all 7 sites of biopsy) was achieved in 17/37 (46%)—13/24 (54%) in PSC-UC versus 4/13 (31%) in aUC-non-PSC (p=0.173). It was 3/7 (43%) in children commencing OVT before the age of 6 years versus 14/30 (47%) in children commencing OVT after the age of 6 years (p=0.855).

Longer term outcomes

After first course of OVT, the 44 children took different treatment journeys: 7 (16%) children (5 PSC-UC, 2 aUC-non-PSC) finished a single OVT course and maintained remission by continuing their pre-existing CMT; 3 (7%) children (2 PSC-UC, 1 aUC-non-PSC) continued using OVT and remained in remission for at least 9 months; 25 (57%) children (20 PSC-UC, 5 aUC-non-PSC) having achieved remission with first OVT course, relapsed after ceasing OVT but regained remission following personalised pathways of repeated OVT courses in combination with CMT; 5 (11%) children (2 PSC-UC, 3 aUC-non-PSC) had partial response to OVT (ie, reduced PUCAI from median 25 (IQR 1–56) to 0 (IQR 0–15) and reduced FC from median 1100 (IQR 515–2350) µg/g to 440 (IQR 190–770) µg/g) and continued with non-OVT based CMT. 4 (9%) children with aUC-non-PSC did not respond to OVT, including two children with difficult treatment-resistant colitis who proceeded to colectomy, two achieved remission with CMT later after ceasing OVT. An annual snapshot of patient progress based on the presence of remission with/without OVT as part of ongoing maintenance therapy is presented in figure 2. By end of follow-up (median 3.8 (IQR 2.0–5.3) years), 67% achieved deep remission confirmed by all four remission categories (PUCAI <10, FC <100 µg/g, Mayo 0 and 5-point inflammation scores at all seven biopsy sites were <2).

Relapses and repeated OVT courses

After ceasing the first OVT course, 25/44 (57%) children (20/29 (69%) PSC-UC vs 5/15 (33%) aUC-non-PSC, p=0.524) had clinical and biomarker relapse within median 8.2 (IQR 1.9–14.5) months after ceasing the first OVT. Remission was regained in 13/25 (52%) with recommencing OVT (12 PSC-UC, 1 aUC-non-PSC) and in 5/25 (20%) with CMT (3 PSC-UC, 2 aUC-non-PSC). Relapses occurred 47 times by the end of the follow-up—38/47 (81%) after ceasing an OVT course, 6/47 (13%) while on OVT and 3/47 (6%) after remissions achieved with CMT but not OVT. Of the 44 children, 24 (55%) had a second OVT course (19/29 (66%) PSC-UC vs 5/15 (33%) aUC-non-PSC, p=0.252) and 5 (11%) had multiple (3–7) courses. The duration of these repeated OVT was compatible to the first OVTs (median 7.3, IQR 5.6–11.3 months). One child had a temporary loss of response to OVT but regained response by achieving remission after recommencing a second course of OVT 2.5 years later.

VRE testing

Since OVT was commenced at our institution in 2014, not one case of VRE has been detected. A total of 138 VRE testing results on 44 children were found using our hospital's patient records (ie, MR), all negative. VRE screening performed by private laboratories outside our

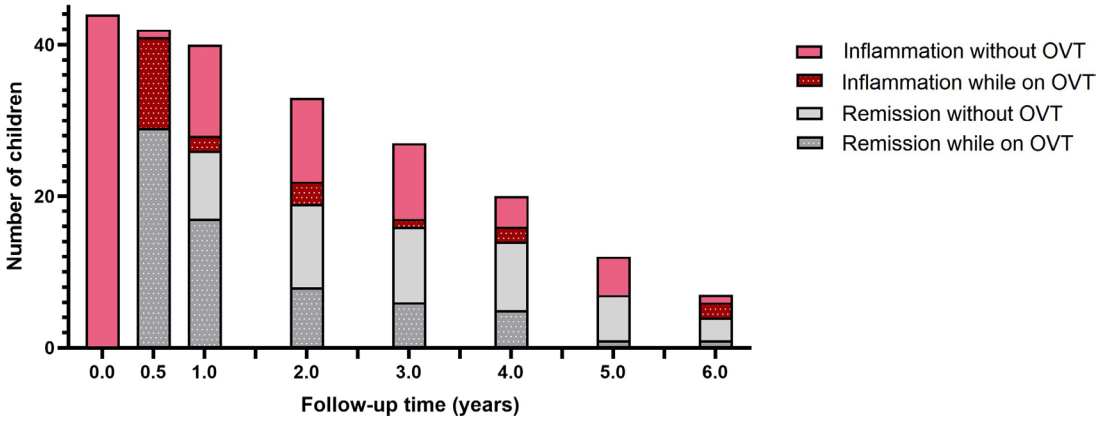

Figure 2 Annual snapshots of patient progress based on the presence of remission with/without oral vancomycin therapy (OVT).

hospital could not be referenced, but our IDS received no notifications on positive findings from these laboratories.

DISCUSSION

Our study reports the remarkable efficacy of OVT in inducing and maintaining clinical, biomarker, mucosal and deep pan-colonic histological remission in children with atypical colitis with/without PSC. Although PSC-UC may achieve better clinical and biomarker remission with OVT than aUC-non-PSC, mucosal and histological outcomes were similar. Clinical, biomarker, mucosal and histological outcomes were similar whether OVT was commenced before or after the age of 6 years. Alongside CMT, OVT had been part of our long-term strategy for managing atypical UC. Relapse was common after ceasing OVT, but every other responded to repeated OVT. Importantly, VRE was not observed in any screening samples after prolonged or repeated OVT use.

In this cohort of children, OVT was not used as a first-line therapy. The benefit of OVT in managing colitis of children with PSC is supported by a recent study, showing better remission at 12 months follow-up in children treated with OVT compared with propensity matched controls.[10] Our study complements and extends this finding by presenting detailed clinical outcomes both short-term and long-term using PUCAI, FC, Mayo scores and histological results. All significantly improved within the first 6–7 months of treatment.

Our report showed excellent responses to OVT in children with atypical UC both with and without PSC. In PSC-UC, OVT would likely be used earlier in the treatment pyramid because of historical success, while in aUC-non-PSC, OVT was used where all other, then available, treatments had been employed. Nevertheless, of the four children at risk for colectomy after failing all available treatments, two had temporary relief with OVT before escalating to colectomy, while the other two achieved complete mucosal healing. Due to rapid PUCAI and FC response, OVT may serve as a bridge to more advanced treatments for CMT-resistant atypical UC or used to help manage atypical UC.

In our study, small-duct PSC was not ruled out by liver biopsy in children with aUC-non-PSC. An interesting concept is the proposal that the striking response of aUC-non-PSC to OVT could be explained by undetected or yet to develop PSC, given the difficulty of early diagnosis of PSC prior to detectable sclerosing changes on MRCP.[17] We repeated MRCP in three children with aUC-non-PSC and intermittent GGT after 2–3 years. Thus far, no new PSC diagnosis was established after starting OVT. However, some of the children with aUC-non-PSC might still have small-duct PSC, and some might eventually advance to confirmed PSC. Long-term follow-up study comparing prevalence of PSC in OVT-treated versus untreated aUC-non-PSC to determine whether OVT may prevent PSC progression is warranted.

Confirmed UC relapse was frequent within 6–12 months after discontinuing OVT in 70% of children, but most had remission successfully reinduced after repeating OVT. After starting OVT, many children in our cohort maintained remission with conventional treatment. A few were able to cease biologics and were stable on mesalazine for a few years before relapsing. Studies to investigate potential predictors of remission after starting and relapse after ceasing OVT are warranted to better select patients for OVT and for prolonged therapy.

Our retrospective study is the first to report VRE screening results in long-term or repeated use of OVT. Only hospital VRE screenings were reliably referenced, 138 screening results in 44 children (approximately three screening per children) were all negative. Furthermore, no alerts from private screening results from outside our hospital were received. As the chromID VRE screening used in our clinic has 86.3% sensitivity (85.4% to *E. faecium* and 90% to *E. faecalis*) and 100% specificity,[13] we are quite confident that our long-term OVT usage has not contributed to the development of VRE to date.

A strength of our report is the well-characterised, detailed and comprehensive longitudinal data on FC, colonoscopy, and histology of our cohort, as required to comply with good antibiotic governance. OVT was only used in this cohort, and long-term and/or repeated

courses were only given to those with unequivocal success. Most children were reviewed every 3 months, covering several years of treatment. Another strength is the outcome of OVT in children with atypical UC without PSC, which has not been reported before. This supports the concept that like PSC-UC, atypical UC may demonstrate significant differences in treatment responses and pathophysiology from more typical left-sided colitis. Finally, more than 80% of children in our study have paired before and after therapy data on all important phenotypic outcomes from PUCAI to histology. Using these paired samples, we were able to study the impact of OVT in several distinct levels of remission: clinical (using PUCAI and FC), mucosal (using Mayo scores) and histological (using pathological report on seven different biopsy sites). We performed also 141 colonoscopies during the study period, which meant that our long-term follow-up also included remission at histological level.

Despite detailed long-term follow-up, our cohort is small as the proportion of children with PSC-UC in our clinic is approximately only 7% of all IBD patients with approximately 2–3 new patients diagnosed each year (online supplemental table 2). In addition, our data are retrospective and collected outside of a formal schedule. Moreover, patients had great variations in age, treatment journeys and outcomes, further limiting more detailed long-term outcomes. We were also not able to collect data beyond adult transition to multiple centres, as these data were outside the scope of our ethics approval. Our study did not search for explanations for the efficacy of OVT. As non-absorbed antibiotic, it may treat unrecognised opportunistic pathogen, modify gut microbiota[18] or act as anti-inflammatory agent.[19]

In conclusion, OVT was effective for inducing and reinducing deep remission in children with atypical UC with/without PSC, including many children who previously were unresponsive to CMT. OVT was also helpful in regaining remission in children who then continued to maintain remission on CMT, after ceasing OVT. Despite long-term use of OVT, all VRE screenings in this cohort were negative. OVT should be considered for induction and reinduction of remission in children with PSC-UC and in children with aUC-non-PSC not responding to CMT. The role of OVT for long-term maintenance of remission in this setting still needs to be determined.

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