Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: A preliminary report

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Abstract

Background: The results of previous studies on the effectiveness of antibiotics in ulcerative colitis (UC) seem more effective when used orally. In this retrospective, multicenter study, we aimed to report our experience of using a combination of 3–4 antibiotics in children with moderate-severe refractory UC and IBD-unclassified including metronidazole, amoxicillin, doxycycline, and if during hospital admission, also vancomycin (MADoV).

Methods: All children treated during 2013 with the antibiotic cocktail for 2–3 weeks in an attempt to alleviate inflammation in refractory colitis were included. Doxycycline was substituted with oral gentamycin or ciprofloxacin in children younger than 8 years or when an allergy was known to one of the drugs. Children were assessed using the PUCAI and CRP weekly for 3 weeks.

Results: All 15 included children had moderate to severe disease with refractory disease course to multiple immunosuppressants (mean age 13.6 ± 5.1 years, median disease duration 2 (IQR 0.8–3.2) years, 11 females (73%), and 13 (87%) extensive disease; 14 (93%) were corticosteroid-dependent or resistant, and 12 (80%) refractory to anti-TNF therapy). The cocktail was definitely effective in 7 of the 15 included children (47%) who entered complete clinical remission (PUCAI < 10) without additional interventions. Questionable or partial short-term response was noted in another 3 (20%), totaling 67% of patients.

Conclusion: The use of oral wide-spectrum antibiotic cocktail in pediatric UC seems promising in half of patients, refractory to other salvage therapy. A pediatric randomized controlled trial to assess this intervention is underway.

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1. Introduction

The pathogenesis of inflammatory bowel diseases (IBDs) is multifactorial and relates to dysbiosis between an altered immune response and the enteric microbiome. The latter is a term reflecting a fascinating complex biological network that interacts with the immune system, while both are influenced by the environment and the genetic background of the host. Increased permeability of the gut may be associated with translocation of the altered micro-organisms through the mucosa thereby worsening the chronic inflammation. There are now ample of data to implicate the microbiome as a main factor in the occurrence of IBD. Our group has shown that children with ASC who respond to steroid therapy have a more diverse microbiome component than those who do not respond and requiring salvage medical therapy or colectomy.

Antibiotics have long been used in IBD with conflicting results. A recent meta-analysis has concluded that antibiotic therapy is effective in both CD and UC with OR higher in the UC studies (OR 2.17 (95%CI 1.54–3.05) as compared with 1.35 (1.16–1.58) in CD). It is noteworthy that 5 of the 6 placebo-controlled RCT’s in UC which used oral antibiotics showed treatment benefit compared with none of three other RCTs applying intravenous antibiotics (Fig. 1). Specifically, two RCTs from Japan suggested the effectiveness of oral anti- F. varium antibiotic protocol in adult UC including a 14 day triple therapy with amoxicillin 500 mg, metronidazole 250 mg and tetracycline 500 mg—all three times daily. A total of 210 mild-moderate ambulatory UC adult patients were randomized to receive the cocktail or placebo with more treated patients achieving a Mayo-score defined response at 3 months (45% vs. 23%, respectively; P = 0.001). Remission rate was similar at 3 months (19% vs 16%, respectively) but steroid-free remission was higher at 12 months (35% vs 14%, respectively; P = 0.02); notably the lost to follow-up rate was as high as 55%

Figure 1  Previously reported randomized placebo-controlled trials of antibiotic treatment in ulcerative colitis (1a orally administered antibiotics; 1b intravenously administered antibiotics). Amox, amoxicillin; Tetra, tetracycline; Metro, metronidazole; Cipro, ciprofloxacin; ASC, acute severe colitis; IVCS, intravenous corticosteroids; DC, discharge. Footnote: All p-Values in Fig. 1b were insignificant; In Gionchetti 1999 we included only the ASC arm; In Dickinson 1985 we included only the UC subgroup of the 40 included patients; Two randomized studies (Gilat T et al. 1987 and Ohkusa T et al. 2005) were not included in this chart since they did not include a placebo arm.
The treatment led to a decrease in the titer of antibodies to *F. varium*, especially in the responders, and improved endoscopic score. Similarly, a smaller RCT showed superiority of this antibiotic regimen to induce remission in 10 UC patients compared to 10 controls. The antibiotic cocktail was also used in an open label study of 27 steroid refractory and 61 steroid dependent UC patients yielding short term responses of 71% and 82%, and 3-month remission of 70% and 75%, respectively (UEGW Amsterdam 2012; oral presentation). Another open label study has shown the effectiveness of this intervention in steroid-dependent UC patients. The role of *F. varium* in UC has been suggested in an experimental model, wherein mice developed colitis after being exposed to the bacteria isolated from UC patients. In ASC, oral vancomycin led to reduced need for colectomy by hospital discharge (2 of 18 (11%) in the antibiotic arm vs. 7 of 15 (47%) in the placebo arm) (Fig. 1).

Based on the above observations, we have used a combination of oral antibiotics in patients with refractory UC or IBD-unclassified (IBD-U) with encouraging results. We aimed to retrospectively report all consecutively treated UC children with combinations of antibiotics in our institutions in the year of 2013.

### 2. Methods

This is a retrospective cohort report of children with UC and IBD-U treated with oral antibiotics during the year 2013. IBD was confirmed in all patients according to accepted pediatric criteria, including upper and lower endoscopy with biopsies and small bowel imaging. As our experience with this intervention accumulated, we have tuned the protocol as follows (all antibiotics were prescribed orally): Children over the age of 7 years were prescribed triple therapy with amoxicillin 50 mg/kg divided by 3 (up to 500 mg X 3/d), metronidazole 5 mg/kg X 3/d (up to 250 mg X 3/d), and doxycycline 2 mg/kg X 2/d (up to 100 mg X 2/d). Doxycycline was substituted to ciprofloxacin (10 mg/kg X 2/d - up to 250 mg X 2/d) in children 2–7 years and to gentamycin (2.5 mg/kg X 3/d) in infants younger than 2 years. Patients with known allergy to one of the drugs have been treated with oral gentamycin (2.5 mg/kg X 3/d) instead of the allergenic drug. If the child has been admitted to the hospital, vancomycin was added as the fourth regimen (250 mg X 4/d or 125 mg X 4/d in those younger than 8 years).

We initially prescribed the antibiotic cocktail for 2 weeks, but we revised our practice to 3 weeks as we noticed that complete response may be delayed. All children were repeatedly tested negative for fecal *Clostridium difficile* and bacterial cultures and only one was positive for CMV colitis as described below.

To avoid selection bias, this report includes all children treated with the cocktail in our institutions during the year 2013. However, children who were commenced on steroid therapy concurrently with the antibiotics were excluded.

Disease activity was assessed prospectively by the PUCAI at every ambulatory visit, and daily in hospitalized patients. The PUCAI has been validated in pediatric UC and proved to perform well also in the acute colitis setting. Other recorded data included demographics and standard laboratory variables. Predefined time points for analyses were at introduction of antibiotics (i.e. baseline), and 7, 14 and 21 days thereafter. Endoscopic evaluation, when performed, was scored using the 4-point Mayo-endoscopic subscore (0—remission, 1—mild, 2—moderate and 3—severe). We did not aim to report the long-term response as we considered this cocktail for induction of remission only; however the longest follow-up available is described in the text of each case description (Table 1 and Supplementary Table 1).

The primary analysis was based on the intention-to-treat principle, in which all patients were included, regardless of the response. A further secondary per-protocol analysis was added including only those completing the antibiotic protocol without salvage therapy. Missing laboratory data were imputed using the last observation carried forward. The last PUCAI and laboratory values recorded before treatment escalation in children not responding to the antibiotic cocktail were carried forward through the last visit, to avoid attributing the response to the failed antibiotic treatment.

Statistical analyses included description summary presentation of mean ± SD, medians (interquartile range) and rates (95% confidence intervals). Values before and after the intervention were compared by paired Student’s-t-test or the sign test, as appropriate for the data distribution. All analyses were performed using IBM SPSS V21, taking a P < 0.05 as the threshold for significance.

### 3. Results

Twenty patients were treated in the four centers with the oral antibiotic cocktail for refractory colitis, five of whom were excluded since concomitant steroid therapy was initiated with the antibiotics, serving as a possible confounding factor.

All 15 children (11 females (73%)) had moderate to severe disease at antibiotic initiation with frequently active disease course, refractory to multiple immunosuppressants (Table 1 and Supplementary Table 1). Fourteen (93%) of the children were corticosteroid dependent or resistant, 12 (80%) were refractory to anti-TNF therapy (4 of whom to both infliximab and adalimumab), 11 (73%) failed extended trials of thiopurines with adequate levels, and 1 (7%) showed only partial transient response to tacrolimus. Ten patients were treated as in-patients for ASC. Further reflecting the severity of this cohort, 13 (87%) had extensive or pancolitis and only 2 (13%) had left sided colitis; the mean PUCAI score at antibiotic initiation was 65 ± 13 points. Five patients underwent colonoscopic assessment prior to starting the antibiotic cocktail, four demonstrating a Mayo endoscopic score of 3/3 and one with a score of 2/3. Mean age was 13.6 ± 5.1 years, median disease duration 2 (IQR 0.8–3.2) years, 11 (73%) were diagnosed with UC and the others with IBD-U.

Of the 15 included children, 9 (60%) children entered complete remission (PUCAI <10 points, 2 after one week, 6 after two weeks and one after 3 weeks) and one (7%) showed a response (PUCAI decrease from 80 to 45 points within 2 weeks of treatment) but is considered in the failure group since she relapsed shortly thereafter (Fig. 2).

Of the 9 children entering remission we excluded two questionable cases, totaling seven children (47%) who had definite complete short term remission to the antibiotic cocktails.
The first questionable case (Case 5) had ASC and failed intravenous steroids and infliximab (imminent colectomy). Significant response followed 5 days of antibiotic treatment (PUCAI decreased from 85 to 40 points), but then ganciclovir was added due to finding of CMV in a previous rectal biopsy. He was discharged in complete remission (PUCAI = 0) after two weeks. All other children did not have any additional treatments commenced besides the antibiotic cocktail. The second questionable case (Case 6) entered complete remission within 2 weeks (PUCAI decreased from 50 to 0 points) for the first time in 3 years (despite multiple immunosuppressants and biologics; the family refused colectomy). However, the disease relapsed 1 week after stopping the antibiotics.

One of the five children who we defined as non-responder, Case 15, was admitted for ASC and failed intravenous steroids and infliximab. She showed a significant improvement to the antibiotic cocktail within 5 days (PUCAI decreased from 85 to 20) but she then elected to have fecal microbiome transplantation with subsequent prompt worsening of diarrhea and severe abdominal pain; colectomy followed within 2 days.

In an intention to treat analysis of the total cohort (responders and non-responders), the mean PUCAI score dropped from 65 ± 13 points pretreatment to 23 ± 28 points thereafter (P < 0.0001) (Fig. 2). CRP dropped from 2.9 ± 2.6 to 2.3 ± 2.9 mg/dL (P = 0.09). There was no change in hemoglobin (P = 0.32) and albumin (P = 0.41) possibly given the fact that these tests are less responsive to change in the short term.

In a per-protocol analysis of the 9 responders who completed antibiotic treatment, there was a clinical (PUCAI decrease from 64 ± 19 to 5 ± 13; P < 0.0001) and biochemical (CRP dropped from 1.73 ± 1.5 to 0.82 ± 1.1 mg/dL; P = 0.007) improvement within three weeks of treatment (Fig. 2). Hemoglobin and albumin increased from 10 ± 1.9 to 11.2 ± 1.4 (P = 0.035) and 3.6 ± 0.6 to 4 ± 0.4 (P = 0.063), respectively. Since some of these patients received blood transfusions and total parenteral nutrition (TPN) the results of the hemoglobin and albumin must be interpreted with caution.

Three of the five patients who had baseline endoscopic evaluation repeated sigmoidoscopy within the treatment period. The period is too short to judge mucosal healing, but nonetheless, one had an endoscopic improvement from Mayo score of 3 to 2 points after 10 days (Case 10), a second (Case 6) from 3 to 2 and the third (Case 9) from 2 to 1, both after 21 days. Serial fecal calprotectin levels were measured on Case 9 with initial measure of 155 μg/g and normalization after treatment (26 μg/g upon treatment completion and 38 μg/g 6 weeks thereafter).

The mean follow-up period of the 9 children who entered remission was 5.1 ± 2.8 months (Table 1, Supplementary Table 1).
response to a greater extent than in patients with an intact translocating bacteria to stimulate the adaptive immune further impairs the epithelial barrier which might enable group 4). Secondly, the mucosal inflammation in severe UC bacteria (C. difficile, F. Varium, for instance, as suggested by the Japanese studies of amoxicillin, metronidazole and tetracycline4, 6 and the oral vancomycin trial8 described in the introduction, three other placebo-controlled trials showed a significant benefit to oral antibiotics, including tobramycin21, long term ciprofloxacin22 and rifaximin23, although the latter was underpowered to show statistical significance. One study of oral ciprofloxacin was negative24.

Endoscopic evaluation was available in three of our patients, showing improvement within a short period (severe to moderate in two patients and moderate to mild in one patient within 21 days). Although we did not have endoscopic evaluation for all patients, a strong PUCAI-endoscopy concordance has been well verified in several cohorts in children10,25,26. In previous oral antibiotic trials, endoscopic improvement followed the clinical benefit when included as an outcome. In Burke et al., oral tobramycin led to complete histological remission in 17% of patients within 21 days. Although we did not have endoscopic evaluation for all patients, a strong PUCAI-endoscopy concordance has been well verified in several cohorts in children10,25,26. In previous oral antibiotic trials, endoscopic improvement followed the clinical benefit when included as an outcome. In Burke et al., oral tobramycin led to complete histological remission in 17% of patients within 21–28 days of treatment as compared with 0% in those receiving placebo.
Six months of oral ciprofloxacin led to improved endoscopic findings at 6 months but not at 3 months, and the Japanese 2-week cocktail was associated with better endoscopic scores both at 3 and 12 months follow-up visits. In contrast, the negative oral ciprofloxacin trial showed no apparent endoscopic benefit.

We have considered our antibiotic intervention as an induction of remission regimen which mandates a strategy for long-term maintenance of remission. Indeed, most studies that followed the patients receiving oral antibiotic treatment did not show a sustained benefit over 6–12 months, except for the Japanese cocktail that showed superior remission rate at 12 months compared with placebo.

Our findings are intriguing and give some short-term hope to half of children otherwise refractory to standard and salvage therapy. Our cohort was enrolled consecutively from several centers which increases our confidence in the results and lessens the likelihood for selection bias. However, our study is merely an uncontrolled, retrospective report. Moreover, our longer term follow-up has been anecdotal, since we focused on induction-of-remission effect. Therefore, this preliminary report should not be used to change clinical practice and guidelines of treating children with UC. However, it formed the basis for further research and a pediatric RCT in ASC is underway, evaluating the 3-week MAoDV protocol described here.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcSTRUCT.2014.05.010.

Conflict of interest

The authors declare no conflict of interest in relation to the content of this manuscript.

References


