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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 [1]. 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 [2].

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) [3]. 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-*Fusobacterium varium* (*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).[4] 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%

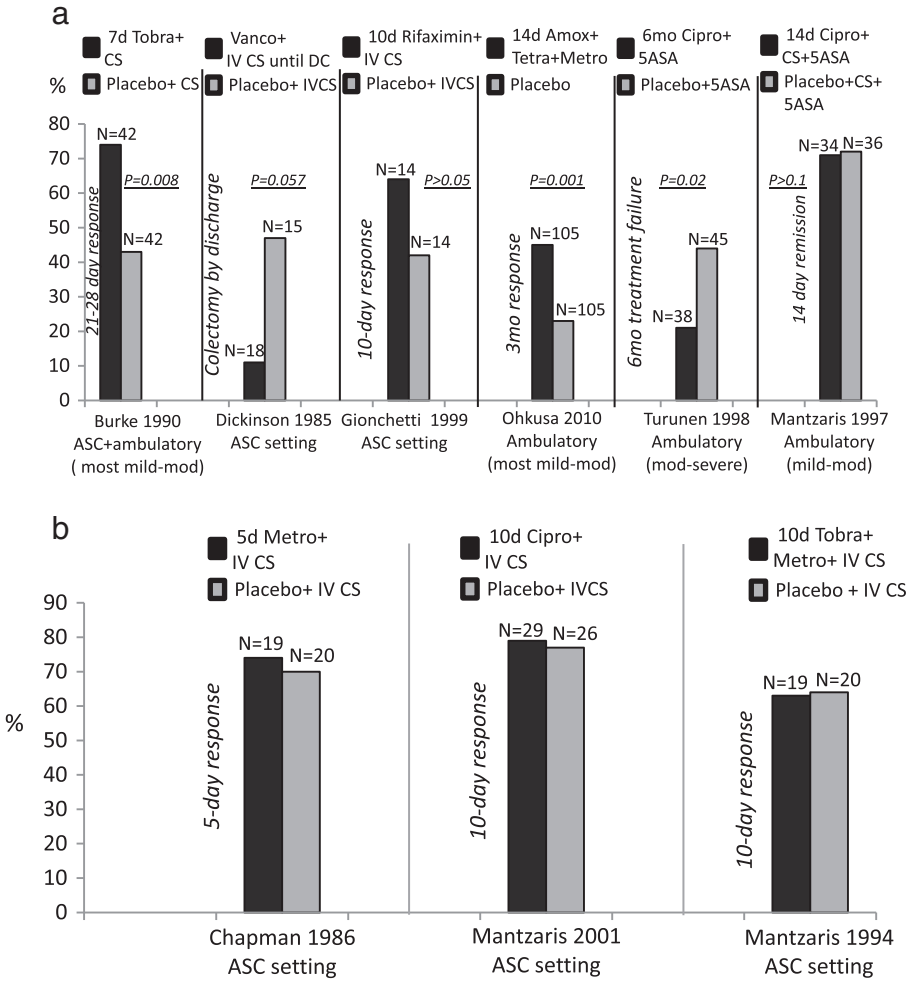

Figure 1 Previously reported randomized placebo-controlled trials of antibiotic treatment in ulcerative colitis (1a orally administered antibiotics; 1b intravenously administered antibiotics). Amox, amoxicillin; Tetra, tetracycline; Metro, metronidazole; Cipro, ciprofloxacin; ASC, acute severe colitis; 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.