Use your antibiotics wisely. Consequences to the intestinal microbiome

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One sentence summary: Consequences of antibiotic usage go beyond *Clostridium difficile*-associated diarrhea, and have a role in the severity of inflammatory bowel disease.

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ABSTRACT

Antibiotic therapy has long term consequences in the intestinal microbiome. *Clostridium difficile* has a well-known role in antibiotic-associated diarrhea, but in addition, persistent infection with this organism may increase the risk for developing inflammatory bowel disease. Here, recent literature on how the intestinal microbiome is altered by antibiotic therapy is presented.

Keywords: microbiome; antibiotic; inflammatory bowel disease; *Clostridium difficile*

INTRODUCTION

Advances in next generation sequencing have allowed us to investigate not only the role of the microbiome in health and disease (Cox, Cookson and Moffatt 2013), but also how it can become affected by drugs like antibiotics or chemotherapy.

The term microbiota refers to the types of organisms that are present in an environmental niche. The collection of their genes and surrounding environmental conditions is called the microbiome (Marchesi and Ravel 2015). Commensal organisms have an important role regulating the physiology of their hosts (Kamada and Nunez 2014), participating in human metabolism, nutrition, physiology and immune function (Bull and Plummer 2014). One of the major functions of the microbiota is to protect the intestine against colonization by exogenous microorganisms and overgrowth of indigenous ‘pathobionts’ (Kamada et al. 2013a) (Fig. 1A), not only by competition of nutrients, but also by modulation of the immune response of the host (Kamada et al. 2013b). There are clinical consequences when perturbing the microbiota (Blaser 2014; Lei, Nair and Alegre 2015), a term known as ‘dysbiosis’ (Marchesi et al. 2016). A recent review has nicely compiled the current knowledge of the gut microbiome and GI-related disorders such as metabolic syndrome, liver disease, inflammatory bowel disease (IBD), and colorectal cancer (Marchesi et al. 2016).

ANTIBIOTIC-ASSOCIATED DIARRHEA

*Clostridium difficile* diarrhea constitutes the best example of overgrowth of a pathobiont after disruption of the normal microbial community in the gut. Treatment with broad spectrum antibiotics eliminates competition, *C. difficile* spores then germinate (Fig. 1B), and toxin-producing forms increase in abundance. Toxin-mediated disruption of the intestinal barrier leads to a severe pathological condition termed pseudomembranous colitis, and potentially septic shock (Kamada et al. 2013a). Cessation of antibiotics is crucial in this setting, and although metronidazole and vancomycin are used in severe cases, it would potentially open the door to a second threat of sepsis in immunocompromised patients with the emergence of a second antibiotic-related infection by vancomycin-resistant Enterococcus (Arias and Murray 2012) (Fig. 1C). Commensal microbiota
Figure 1. Consequences to the intestinal microbiome after antibiotic therapy. In health, the microbiome protects the intestine against colonization by exogenous microorganisms and overgrowth of indigenous ‘pathobionts’ like *C. difficile* (A). Antibiotic-associated diarrhea and pseudomembranous colitis constitute the best example of overgrowth of a pathobiont after disruption of the normal microbial community in the intestine after antibiotic treatment (B). Utilization of vancomycin for severe cases poses the risk of emergence of vancomycin-resistant *Enterococcus* (C). Fecal transplantation appears as a promising therapy for *C. difficile* infection (D). Recovery of the intestinal microbial community diversity starts to occur after long periods of time, and not in a complete way (E). Antibiotic treatment is also associated with more severe IBD (F), possibly due to loss of *H. pylori* which could exert an immunomodulatory effect in IBD (G).

**MICROBIAL COMMUNITY RECOVERY AFTER ANTIBIOTIC TREATMENT**

The impact of antibiotics in the human microbiome seems to remain for extended periods of time. A group from the Swedish Institute for Infectious Disease Control has studied changes in the gut microbiota after antibiotic treatment used to treat *Helicobacter pylori* infections (Jakobsson et al. 2010; Jernberg et al. 2010), and found that some members of the gut microbiota are affected for up to four years post-treatment. These changes start to revert after long periods of time, and not in a complete way. Recovery of the diversity in the composition of species from the phylum Bacteroidetes after a seven-day course of clindamycin starts taking place after a period of two years (Jernberg et al. 2007) (Fig. 1D). This is of great importance as colonization by some microbiota components, like *Bacteroides fragilis*, enhances mucosal tolerance and can suppress pathogen-mediated colitis (Buffie and Pamer 2013).

**RISK OF IBD AND ANTIBIOTIC TREATMENT**

Besides the known short- and long-term changes in the composition of normal human microbiota caused by antibiotics, a relationship between antibiotic use and clinical behavior in IBD has been reported. So far, it is unclear whether dysbiosis is a cause or a consequence of IBD (Stecher 2015). Antibiotics do appear to have a beneficial role in Crohn’s disease, after meta-analysis of randomized clinical trials, but the evidence does not seem to be enough to warrant any recommendation (Bejaoui, Sokol and Marteau 2015). A recent prospective longitudinal study has shown that not only the majority of patients with IBD receive antibiotic treatment, but that those individuals have more severe disease (Hashash et al. 2015) (Fig. 1F). A possible correlation between IBD and the number of courses of antibiotics taken was pointed out by Martin Blaser in 2011 (Blaser 2011). In that same article, he also discussed that *H. pylori* was a dominant microbe in the pre-antibiotic era, and that it must have carried some benefit to the human host (Blaser 2011). It turns out that this concept was correct, at least in the context of IBD development. A recent study by Castano-Rodriguez shows a negative association between *H. pylori* and IBD (Castano-Rodriguez et al. 2015). These results infer that *H. pylori* might exert an immunomodulatory effect in IBD, and in a way explain the increasing trend in the rate of IBD (Zhai et al. 2016) (Fig. 1G).

Recently, there has been significant interest in the association between IBD and *C. difficile* infection (Monaghan, Cockayne and Mahida 2015). Studies have reported a higher carriage rate of *C. difficile* in patients with IBD. Colonization with toxigenic *C. difficile* may be associated with a wide spectrum of clinical presentation ranging from asymptomatic carriage to mild diarrhea to life-threatening colitis. Over the last 15 years, there has been a marked increase in the incidence of *C. difficile* infection, which predominantly affects elderly patients on antibiotics. Transplant patients are also at a higher risk of *C. difficile* infection due to the...
extensive use of antibiotics, their immunosuppressed states and other clinical factors (Paudel et al. 2015). Dysbiosis and inflammation not only lead to IBD but colitis-associated cancer as well (Asquith and Powrie 2010).

CONCLUSIONS

Consequences of antibiotic therapy in the intestinal microbiome go beyond C. difficile antibiotic-associated diarrhea, as persistent infection with this organism may increase the risk for developing IBD. Elucidation of the actual role of antibiotics in the development of IBD is necessary, as it will have important implications in the ictus for promising therapeutic prospects like fecal transplantation for this condition. Research on the recovery of microbial communities, and how probiotic treatment can positively or negatively affect it is needed. Stimulation and regulation of the immune system constitutes an important avenue that must be considered (Ashraf and Shah 2014), especially in cases of dysbiosis present in immunocompromised patients (Paudel et al. 2015).

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