Antibiotics, microbiota and health: are there dangers hiding in plain sight?

A. Clinton White Jr[a] *and Gagandeep Kang*[b]

Antibiotics are among the most commonly used medications. Not only have they revolutionized treatment of infections, but they also play a critical role in the prevention of infections and thus allow a wide range of life-saving medical procedures (from surgical implants to organ transplantation) that would otherwise be fraught with infectious complications. Their obvious benefits and limited recognition of adverse consequences have led to expanded use for empiric and directed therapy and for prophylaxis. Up to half of all antibiotic use is thought to be inappropriate [1].

The infectious disease community has recognized the dangers of antibiotic misuse for decades. Most of the focus has been on selection pressure and the emergence of resistant pathogens, which is an evolving global health catastrophe [2]. The effects on the host microbial flora were, however, until recently not considered to have significant physiologic effects. For example, the World Health Organization's 2014 Global Report on Antimicrobial Surveillance highlights the widespread and the clinical and economic impact of antimicrobial resistance, but did not account for the consequences of antibiotic use on human health through microbiome modifications [2].

For most of the antibiotic era, the host microbiome was regarded as a group of commensal organisms, which colonized the human host, with limited or no significant interaction with the host. This view began to change with the recognition that normal flora provided a significant barrier to the development of *Clostridium difficile* colitis. More recently, data from microbiome projects have revealed a more complex role for the microbiome in human health. Tuddenham and Sears in this issue discuss the important role of the microbiome in development of host immune and regulatory responses [3]. There are also key roles in human metabolism and prevention of carcinogenesis.

Antibiotics have potent effects on the intestinal microbiome [4]. Even after a relatively short course of antibiotics, it can take months to a year for the microbiome to recover. This profound effect of antibiotics raises concerns that the current pattern of antibiotic overuse may lead to eradication of critical symbiotic species before their role is even recognized [5].

Data on adverse consequences on human health are increasingly recognized. Studies of children born by Caesarian section, after maternal antibiotics, or with frequent antibiotics as children differ from otherwise normal children in the establishment of intestinal flora [5,6]. This alteration, which some have termed dysbiosis, is increasingly associated with profound effects on human health. For example, dysbiosis has been linked to altered metabolism and rates of obesity. For example, obesity can be transferred to germ-free mice with fecal microbiota from obese subjects, but not from lean twins [7]. In fact, altered flora may lead to increased energy uptake from the diet. A similar transplant of the microbiota from Malawian children with kwashiorkor with a Malawian diet, however, produces weight loss in mice, accompanied by alterations in amino acid, carbohydrate and intermediate metabolism [8].

There has also been increased recognition of the effects of dysbiosis on the development and function of the host immune response [6,9]. Intestinal microbiota play a key role in the development of proper immune function. Antibiotics have also been linked to failure to develop appropriate immunoregulation. Furthermore, dysbiosis has been linked to emerging epidemics of asthma and atopic dermatitis. At the same time, altered intestinal microbiota has been linked to poor vaccine responses in resource-poor countries. In India, antibiotic use in early childhood has been linked to an increased incidence of subsequent diarrhea [10].

[a]Infectious Disease Division, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, USA and [b]The Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu, India

Correspondence to A. Clinton White Jr or Gagandeep Kang, Vellore, Tamil Nadu, India. E-mail: acwhite@utmb.edu or gkang@cmcvellore.ac.in

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Given this context, how should Infections Disease practitioners respond? First, there needs to be a major shift in the way physicians think of and are taught to use antibiotics. Most physicians are trained to use antibiotics frequently with little focus on adverse consequences. 'Just in case' is a common mantra. The result is massive overuse of antibiotics in situations in which they provide no benefit such as upper respiratory infections, acute bronchitis and asymptomatic bactiuria. The second issue relates to the sense that more is better. Generally, physicians err on the side of overtreatment. When duration of therapy has been studied, optimal response is often achieved with narrower spectrum antibiotic and/or shorter duration of therapy. Third, the importance of diagnosis of specific pathogens and narrower therapy rather than empiric therapy should be an important priority. Finally, researchers need to consider treatments that are less likely to disrupt the microbiota and focus on targets that are less mutable than the enzymes targeted by antibiotics as has been done in cancer therapy.

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Conflicts of interest

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