Bowel buddies: a system to save your microbiome during antibiotic treatment

Author:	Tim Arnoldus
University:	VU University
Student number:	2620073
Date:	19-01-2018
Class:	The human microbiome in health and disease

Illustration by Gemma Driessen

Abstract

Antibiotics are the single most important drug to treat bacterial infections. However their effect is extremely imprecise. Even though most infections treated with antibiotics are not gastrointestinal, antibiotic treatment takes out most of your intestinal microbiome. This loss of diversity has been associated with many different diseases, such as inflammatory bowel disease, cancer and arthritis. Furthermore, the risk of infection with opportunistic bacteria, like *C. difficile,* increases and brings with it considerable fatality rates. The goal of the bowel buddy system is to reintroduce your healthy microbiome after antibiotic treatment. This can be achieved by 1) collecting feces before treatment 2) storing the microbiome sample in a freezer 3) reintroducing your healthy microbiome after treatment via slow-release capsules. Previous developments in storage of microbiome samples and slow-release capsules should make the system feasible. Because patients receive their own microbiome the potential health risks are low. The next step is setting up the system and testing it in patients with a high risk on side-effects with antibiotic treatment, to collect data on their microbiome reinstitution and health.

Problem definition and aim

Today, antibiotics are used to treat a wide variety of bacterial infections. In the western world, on average 10-20 daily doses of antibiotics are received by the age of 18 (Sharland, 2007). The overuse of antibiotics is often criticized because the occurrence of antibiotic resistant strains is increasing. However, it is becoming clear that there is another dangerous side-effect, which may have been underrated. Besides killing the targeted pathogen many beneficial bacteria are killed during antibiotic treatment. Long-term disturbances in the microbiome (Dethlefsen & Relman, 2011) and persistence of antibiotic resistant strains (Sjlund, Wreiber, Andersson, Blaser, & Engstrand, 2003) are direct consequences. Antibiotic prescription can cause infection with *C. difficile,* for which considerable fatality rates have been described (Hota et al., 2012). This despite the fact that the targeted pathogen is usually localized in the lungs, skin, sinuses, ears, vagina or urinary tract. Furthermore, evidence linking antibiotic use in early life to other diseases like inflammatory bowel disease (IBD), asthma, allergies, arthritis, obesity, diabetes, cancer and multiple sclerosis is accumulating (Schulfer & Blaser, 2015)(Cox & Blaser, 2015). Infants and preterm babies are especially sensitive to antibiotic treatment side-effects since the formation of the microbiome at a young age is important later in life. Another risk group consists of hematopoietic stem cell transplantation patients, in whom it has been shown that a decrease in microbiome diversity caused by antibiotics increases the risk on graft versus host disease (Holler et al., 2014).

Though further study is required to fully understand these effects of antibiotics, there is sufficient evidence to warrant caution, especially at a young age. The Netherlands are leading on this, using the least antibiotics in Europe (OECD, 2017). However, because of the importance of antibiotics as treatment method, a strategy is needed to reinstate the microbiome after treatment. Developing a general probiotic could be seen as the ‘golden bullet’ of microbiome dysbiosis, and sadly such a probiotic has not yet been found. One reason for this is the extreme diversity between microbiomes (Lozupone et al., 2012) and the personal requirements of such a microbiome. The wide variance in microbiomes indicates that a one-for-all solution may not even be possible. Therefore, until the microbiome’s complexity is better understood and general probiotics are developed, personalized solutions are needed.

The aim of the bowel buddy system is to save your own microbiome before antibiotic treatment and reintroduce it after antibiotic treatment (figure 1). This could be applied during the most common antibiotic treatments of bacterial infections, since those are not gastrointestinal. The effect of such a treatment could be high and the risk relatively low. By taking your own microbiome and putting it back, the risk of infection is limited. Furthermore, because it is your microbiome from a healthy state, the composition should be right for your personal needs.

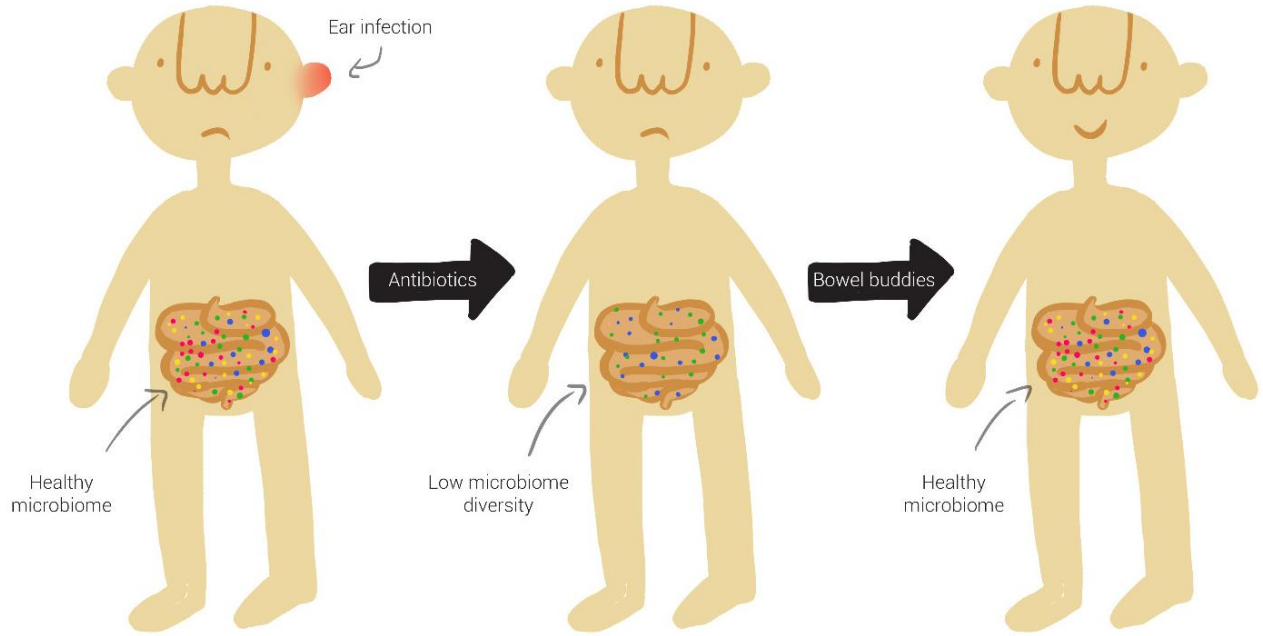

Figure 1. The goal of the bowel buddy system. *Antibiotics used for a non-gastrointestinal infection destroy the microbiome diversity. Afterward, the bowel buddies system reintroduces your own healthy microbiome to induce the state before the antibiotics treatment.(Illustration by Gemma Driessen)*

Approach

The goal, reintroducing your own microbiome, can be achieved in different ways. For example, by identifying the bacterial strains present before transplantation, afterwards missing strains could be reintroduced. However a simpler and cheaper the method is more feasible. Therefore taking samples before antibiotic treatment and reintroducing those is a better approach. In this approach three different steps are needed. A sufficiently large sample without contamination needs to be taken from your microbiome. This sample needs to be stored for the duration of the treatment. Finally the sample needs to be safely reintroduced to the gut. For each of these steps different possibilities will be discussed.

Collection

The easiest way to collect a sample of the microbiome is taking feces. The amount of bacteria in feces is high and comes from the whole intestine, whereas a swab sample would represent less of your microbiome and yield fewer bacteria. It is important to prevent infection of the feces sample, because seeding the gut after antibiotic use with bacteria from outside the body brings significant risk. Another important step is homogenizing the sample, so that the diversity can be preserved during the storage and delivery steps.

Store using proven bio-banking methods

Viable storage of the mixed bacterial sample without a high loss is required. Several bio-banking methods are available, each with its up and down sides. The simplest would be to store the sample in a glycerol solution at -20 °C or -80 °C, depending on the length of storage. This has already been optimized for fecal transplantation and storage of your microbiome is already possible at openbiome (Openbiome, 2018). At home storage in a normal freezer might even be possible for short periods, though contamination risk and bacterial viability after treatment are challenges that first need to be assessed.

Delivery

Currently, fecal transplants are delivered via colonoscopy or endoscopy. Because of the preventative nature of this system such an invasive and expensive procedure is not suitable. Therefore less invasive slow-release capsules are the proposed delivery system (figure 2). These protect the intestinal bacteria against stomach acids while at the same time preventing the patient from tasting or seeing the feces sample. A suppository could also be used, but might not allow for seeding the complete intestine. Though many different slow release capsules are available, unassembled halves are needed for this purpose. Possibly a simple click and close method would need to be developed, though likely, such halve pills are already being produced to supply biopharmaceutical companies. One example of slow-release capsules that may be suitable are DRCAPS Capsules, which are specifically designed for carrying probiotics to the intestine and have been tested in clinical trials (Capsugel, 2018).

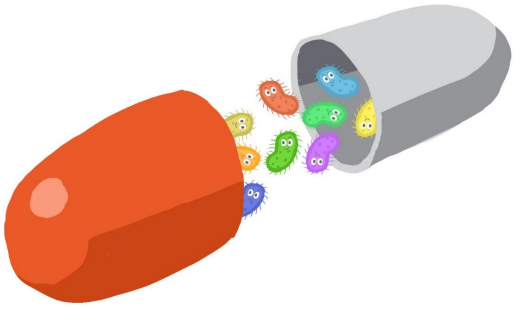

Figure 2. A slow-release capsule containing your own microbiome. *(Illustration by Gemma Driessen)*

Application

To get to the application of this product a collaboration is needed. Slow-release capsules and a facility to store the feces samples are needed. Before actually treating patients animal tests could be considered. However, because of the non-invasive nature, low-risk and similarities to fecal transplantation of this method animal tests might not be needed. There are different groups of patients that could benefit from the bowel buddies system. First of all high risk groups using antibiotics should be targeted, since they can benefit the most from this treatment. However, because the cost of the procedure is low, it could be used widely once its effectiveness is shown. This requires extensive testing of the system and a clinical trial to assess its effect. The second step would be to introduce it to many patients taking antibiotics that do not have a gastrointestinal disease. If the storage of the samples is developed for at home use this wouldn't require much infrastructure, otherwise extra freezers are needed at the medical facility. Finally a back-up of people's healthy microbiome could be a possibility. Then reintroducing this healthy microbiome after antibiotic treatment of gastrointestinal diseases would be possible using the bowel buddies system. Overall, application of this system may significantly reduce the side-effects of antibiotic treatment at a low cost, and safe many lives along the way.

References

Capsugel. (2018, January 19). *Digestive Health*. Retreived on January 19, 2018, from capsugel.com: https://www.capsugel.com/product-suites/digestive-health

Cox, L. M., & Blaser, M. J. (2015). Antibiotics in early life and obesity. *Nature Reviews. Endocrinology*, *11*(3), 182–90. https://doi.org/10.1038/nrendo.2014.210

Dethlefsen, L., & Relman, D. A. (2011). Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences of the United States of America*, *108 Suppl 1*(Supplement 1), 4554–61. https://doi.org/10.1073/pnas.1000087107

Holler, E., Butzhammer, P., Schmid, K., Hundsrucker, C., Koestler, J., Peter, K., … Oefner, P. J. (2014). Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*, *20*(5), 640–5. https://doi.org/10.1016/j.bbmt.2014.01.030

Hota, S. S., Achonu, C., Crowcroft, N. S., Harvey, B. J., Lauwers, A., & Gardam, M. A. (2012). Determining mortality rates attributable to Clostridium difficile infection. *Emerging Infectious Diseases*, *18*(2), 305–7. https://doi.org/10.3201/eid1802.101611

Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, *489*(7415), 220–30. https://doi.org/10.1038/nature11550

Openbiome. (2018, January 19). *PERSONALBIOME*. Retrieved on January 19, 2018, from openbiome.org: https://www.openbiome.org/personalbiome/

Organisation for Economic Co-operation and Development. (2017). *Health at a Glance 2017 : OECD Indicators.* OECD Publishing.

Schulfer, A., & Blaser, M. J. (2015). Risks of Antibiotic Exposures Early in Life on the Developing Microbiome. *PLoS Pathogens*, *11*(7), e1004903. https://doi.org/10.1371/journal.ppat.1004903

Sharland, M. (2007). The use of antibacterials in children: a report of the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) Paediatric Subgroup. *Journal of Antimicrobial Chemotherapy*, *60*(suppl_1), i15–i26. https://doi.org/10.1093/jac/dkm153

Sjlund, M., Wreiber, K., Andersson, D. I., Blaser, M. J., & Engstrand, L. (2003). Long-Term Persistence of Resistant *Enterococcus* Species after Antibiotics To Eradicate *Helicobacter pylori*. *Annals of Internal Medicine*, *139*(6), 483. https://doi.org/10.7326/0003-4819-139-6-200309160-00011