Microbes and man - expanding our understanding of the dynamics and biology of microbiota

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Prudent use of antibiotics is important to prevent spread of resistant strains but also to protect human normal microbiota, 1,5 kg of bacteria that normally colonize our gut, mucous membranes and skin.

Physicians - and we all love antibiotics

Curing deadly and disabling infections with a few antibiotic pills is something that we, people of the modern era, have not fully comprehended. Regrettably, for many physicians these magic bullets are no more than a few lines on a prescription form to satisfy the patients' needs and show that they are real healers. This translates into excessive antibiotic use especially for acute respiratory tract infections on most parts of the world.

The microbes' perspective

Microbes of many different species live and compete in almost all thinkable niches of the earth – from the ices of the Antarctic to the hot springs of Iceland. Many of them have important roles in nature, such as degrading and assisting recycling of organic material, nitrogen fixation etc.

Man and animals are also hosts to many, many species of bacteria. The normal flora of a person weighs about 1.5 kg and is composed of more cells than the human body itself. It has important functions, such as assisting our digestion in various ways, and occupying space and thereby helping us to withstand pathogens.

In evolutionary terms, exposure to antibiotics exerts a selective pressure on bacterial populations, giving bacteria with advantageous traits (i.e. resistance) a competitive advantage ("survival of the fit"). This means that when we use antibiotics, susceptible bacteria will be killed or inhibited and resistant bacteria will continue to multiply and become more common. The more antibiotics we use, the more we loose their effect.

It is important to realise that at each treatment, not only the disease-causing bacterium but also the entire normal flora is exposed to antibiotics. Resistance may be selected also in the normal flora, or even in environmental bacteria. These will act as a reservoir of resistance, sometimes referred to as 'the pool of resistance genes'. Unless specifically looked for, this reservoir will go unnoticed until the resistance genes pass into clinically relevant bacteria.

Over the last 50 years, a powerful selective pressure has been applied on the microbial communities of the world. A large pool of resistant bacteria has been created, favouring more extensive spread of resistance genes within and between different ecological niches.

Antibiotic resistance and use of antibiotics

How to get bacterial resistance visible? To understand bacterial resistance is a difficult matter. If we could see the resistant bacteria as red spots on our skin or in our throat, there would be no difficulty in managing the resistance problem! But our destiny is to be blind and trust on bacteriologists. They give us surveillance reports on bacterial resistance that are, although very important, only a small chink in the wall through which to look into the bacterial world.

To decrease selection of resistant bacteria, the first task is to reduce use of antimicrobial agents. About 85-90% of antibacterial drugs are used in the community, and up to 80% of these are used to

treat respiratory tract infections. Thus, major efforts have to be targeted on proper diagnosis and treatment of respiratory tract infections in the community.

In hospitals, effective prevention of cross infection and the development of strict antibiotic policies should be in the hands of experts. One urgent practical question is how to raise the standard of hand hygiene in hospitals: at best hand disinfection is achieved on fewer than half the occasions it is required.

Effect of antibiotics on normal microbiota

In addition to emergence bacterial resistance, antibiotic treatment kills bacteria belonging to our normal microbiota. This microbiota may have greater impact on human health than we believe.

First, microbiota protects us. Every antibiotic treatment causes imbalance in gut, mucosal membranes and skin. Antibiotic diarrhoea caused by *Clostridium difficile*, difficult *Clostridium*, is one of the most striking examples. This bacterium survives when majority of other bacteria have died due to antibiotic treatment in the gut. It invades the gut and produces toxins that cause watery and often bloody diarrhoea. Most difficult form of the disease is pseudomembranous colitis, often a lethal disease. This disease may be treated with other antibiotics, but the best way is to transfer faeces, e.g. from spouse, directly to gut. This is called bacteriotherapy.

Also many other bacterial diseases are linked to disturbed normal microbiota. These include e.g. recurrent otitis media and urinary tract infections.

Secondly, our microbiota produces health-promoting and regulating substances. One of most studied is enterolactone, a weakly active hormonal compound that improves cardiovascular health. Enterolactone inhibits also proliferation of cancer cells. Antibiotic treatment greatly decreases enterolactone production for 12-16 months. More than 500 days of antibiotics increases women's breast cancer risk by two-fold and risk for fatal breast cancer by four-fold.

In addition, microbiota processes food by various different ways. Gut bacteria nourish human gut cells by glycosylation of short-chain fatty acids from glucose in vegetables. ***"To avoid colon cancer, eat vegetables and avoid antibiotics", say researchers.***

In mice, gut microbiota regulates fat synthesis. Inoculation of faecal content to germ-free mice, leads to dramatic weight increase in their fat tissue. Gut microbiota may also be behind obesity, one of the leading health problems in the western world.

There is also preliminary evidence that deficient microbiota is linked not only to development of allergy but also to inflammatory bowel diseases and celiac sprue. It is interesting that allergy can be prevented by giving bacteria. In mice, antibiotic treatment predisposes to major increase in allergic reaction against environmental fungi. Crohn's disease, an inflammatory process of gut, can be treated by giving eggs of pig's worm, *Trichuris suis*; inflammation and symptoms are greatly decreased within some months. Gluten, protein of wheat and some other grain plants, is very resistant molecule. The only enzyme that breaks gluten is bacterial prolylendopeptidase, a product of lactobacilli and some other bacteria. It is reasonable to ask, is celiac sprue caused by a lack of bacteria in the gut?

Autism, liver cirrhosis, kidney and gallstones are also suggested to be linked to gut microbiota.

Understanding companionship

Better knowledge of human normal microbiota is necessary to understand human welfare. But already know we can say: protect your normal microbiota, it will protect you! So, let us stop improper use of antibiotics!

In future, we may commonly use alternative therapeutic options to antibiotics. These may include bacteriotherapy and bacteriophagetherapy. Or other unexpected and surprising solutions? Like antibiotics were for 60 years ago.