MICROBIOTA

3 BIOCODEX NEWSLETTER | MARCH 2018

BIOCODEX Microbiota Institute

SUMMARY

EDITORIAL

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> **“TAKING ANTIBIOTICS: A MEDIUM- AND LONG-TERM IMPACT, PARTICULARLY WHEN LAST TAKEN VERY EARLY IN LIFE”**

Dear Readers, since the discovery of antibiotics in the first half of the 20th century, their efficacy in managing infectious diseases has been widely evidenced. Their actions on pathogenic bacteria have very often rendered them indispensable and sometimes vital. However, since their antibacterial efficacy is not specific to pathogenic bacteria, their use also leads to a serious imbalance in the gut microbiota, resulting in dysbiosis.
Antibiotic-associated diarrhoea, a short-term consequence of post-antibiotic dysbiosis, is well known. Here, Prof. Yvan Vandenplas (Brussels, Belgium) refers to recent work highlighting the medium- and long-term impact of antibiotic intake, especially when administered very early in life.

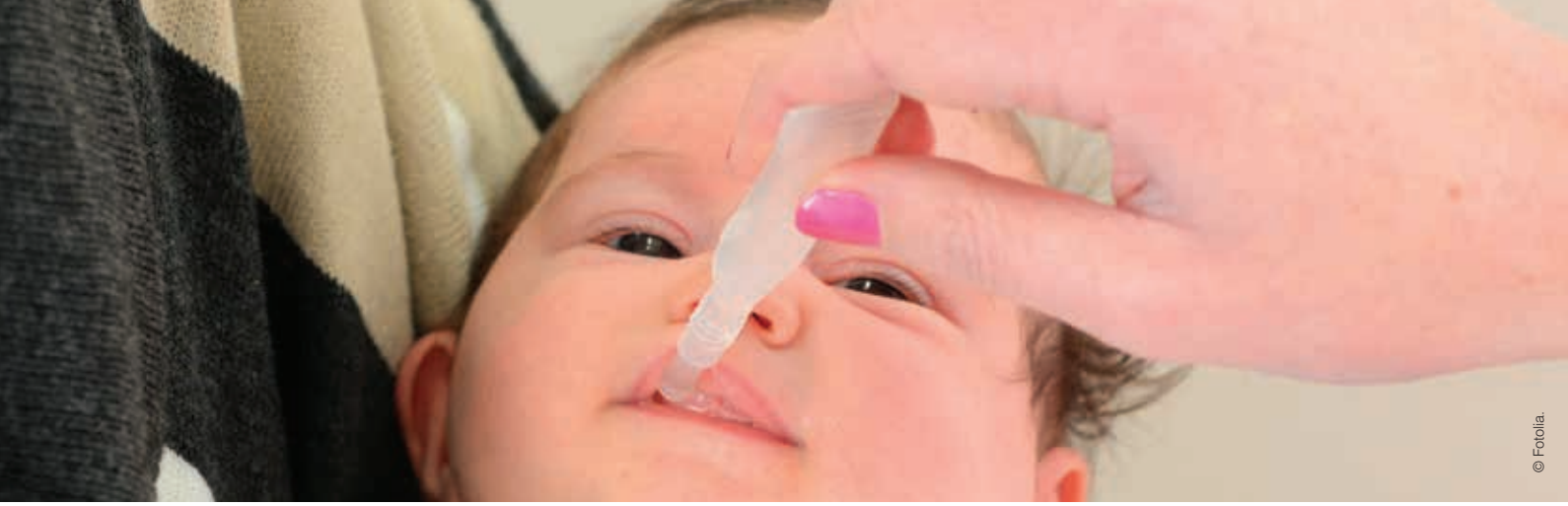
Faecal transplantation has many potential applications. Prof. Harry Sokol (Paris, France) investigates the results obtained by M. Nieuwdorp and colleagues in patients with metabolic syndrome: faecal transplantation from slim donors improves insulin sensitivity in obese patients with metabolic syndrome.

This may also prove to contribute towards advancing our knowledge in pathophysiology. Prof. Emmanuel Mas (Toulouse, France) presents his latest work showing that transferring stools from infants with colic to mice induces visceral hypersensitivity. These results point towards a painful abdominal mechanism and the direct or indirect involvement of the gut microbiota in the pathophysiology of infantile colic.

The gut microbiota was the focus of the 30th congress of the European Helicobacter & Microbiota Study Group (September 7–9, Bordeaux, France) and the Asian Pacific Digestive Week (September 23–26; Hong Kong): Profs. Francis Mégraud (Bordeaux, France) and Uday C. Ghoshal (Lucknow, India) summarise the key points.

Finally, in his press review, Prof. Ener C. Dinleyici (Eskisehir, Turkey) comments on the latest recommendations from the World Gastroenterology Organisation on the use of pre- and probiotics in paediatrics and stresses the short- and medium-term consequences of intrapartum antibioprophylaxis in infants.

Enjoy your reading.



OVERVIEW

ANTIBIOTIC TREATMENT IN INFANTS: SHORT AND LONG-TERM CONSEQUENCES OF THE MICROBIOME

The human gut microbiota refers to microorganisms living in the intestine, which have been estimated to equal the total number of human cells in the body [1]. Microbial colonization of the human gut begins in utero as bacteria have been found in the umbilical cord, placenta, amniotic fluid, and meconium [2]. After birth, the gastrointestinal tract is colonized by a rapidly diversifying microbiota, and it is in the early years of life that a stable gut microbiome is established. Microbial colonization is determined by many factors such as the maternal microbiota, delivery mode, feeding, and medication such as antibiotics and proton pump inhibitors [1]. Antibiotics will not only kill bacterial pathogens, but will also profoundly disturb the equilibrium of the gastrointestinal microbiome. The use of antibiotics has increased globally by 36% in the last decade, and they are a well-known cause of dysbiosis [3]. Although the short-term consequences of antibiotic induced-dysbiosis are fairly well known, recent data are emerging concerning the long-term consequences and this is the focus of the present review.

By Prof. Yvan Vandenplas
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ANTIBIOTIC-ASSOCIATED DIARRHOEA

The most frequent and best studied consequence of intestinal dysbiosis due to antibiotic intake is antibiotic-associated diarrhoea (AAD). AAD occurs during ±20% of all antibiotic courses and depends on the class of antibiotic, patient risk factors (host factors, hospitalization status, and nosocomial outbreaks), and the definition of AAD. AAD is defined as a change in stool frequency with at least three liquid stools/day for two consecutive days, occurring during (early onset) or two to six weeks after antibiotic treatment (late onset), when no other cause can be identified (intercurrent viral or bacterial infection, laxative use, or other cause). The class of (broad-spectrum) antibiotics, duration of administration, and age of the patient are risk factors associated with the development of AAD. The administration of some probiotic strains, such as *Lactobacillus rhamnosus* and *Saccharomyces boulardii*, reduce the incidence and severity of AAD [4].

ANTIBIOTICS EARLY IN LIFE

Antibiotics may have a much broader impact, especially when given perinatally or to young infants. Intrapartum antibiotics during Caesarean and vaginal delivery are associated with infant gut microbiota dysbiosis [5]. Dysbiosis acquired perinatally or during early life will induce long-term consequences. Maternal antibiotic treatment (during pregnancy and lactation) results in profound alterations in the composition of the microbiota in mothers and infants [6]. Prenatal antibiotics are associated with a larger body mass index (BMI) at the age of two years [7].

ANTIBIOTICS AND WEIGHT

Sub-therapeutic doses of antibiotics have been used as growth promoters in animal farming since the 1950s [8]. The effect is more pronounced for broad-spectrum antibiotics, and is attenuated when animals are raised in sanitary conditions. Burgeoning empirical evidence suggests that antibiotics also affect human growth. As early as 1955, a randomized controlled trial in Navy recruits showed that a seven-week course of antibiotics led to significantly greater weight gain in the treated group compared with placebo [8].

There is a positive linear relationship between birth weight and BMI in six to seven-year-old children, which is present in both high and low-income countries [9]. The intestinal microbiota of infants is predictive of later BMI and may serve as an early indicator of obesity risk. Bifidobacteria and *Streptococci*, which are indicators of microbiota maturation in infants, are likely candidates for metabolic programming of infants, and their influence on BMI appears to depend on antibiotic use [10].

Antibiotic exposure before six months of age, or repeatedly during infancy, is associated with increased body mass in healthy children [11]. Repeated exposure to antibiotics early in life, especially β-lactam agents, is associated with increased weight and height [12]. Such effects may play a role in the worldwide childhood obesity epidemic and highlight the importance of judicious use of antibiotics during infancy, favouring narrow-spectrum antibiotics [11]. If causality of obesity can be established in future studies, this will further highlight the need for restrictive antibiotic use [12].

Administration of three or more courses of antibiotics before two years of age is associated with an increased risk of early childhood obesity [13]. In a cohort study, 6.4% children were obese at four years of age [13]. In this cohort, antibiotic exposure was associated with an increased risk of obesity at four years; the more antibiotic courses, the stronger the risk [13]. Children receiving antibiotics in the first year of life were more likely to be overweight later in childhood compared with those who were unexposed (32.4 *versus* 18.2% at 12 years of age; p=0.002) [14]. Repeated exposure to broad-spectrum antibiotics at ages 0 to 23 months is associated with early childhood obesity [15].

However, some studies have reported contradictory results. Exposure to antibiotics within the first six months of life compared with no exposure was not associated with a statistically significant difference in weight gain up to seven years of age [16].

GUT MICROBIOME - IMMUNITY & FOOD ALLERGY

Symbiotic host and microbe interactions are critical for host metabolic and immune development. Early microbiota colonization may influence the occurrence of metabolic and immune diseases [1].

A clear association was found between early-life antibiotic use (three or more courses) and milk allergy, non-milk food allergy, and other allergies in a longitudinal data analysis of 30,060 children [17]. The associations became stronger for younger age and differed according to antibiotic class [17].

Maternal use of antibiotics before and during pregnancy was shown to be associated with an increased risk of allergy to cow's milk in the offspring, and persisted after adjusting for putative confounders [17]. In children, the risk of allergy to cow's milk increased with increasing number antibiotics used from birth to diagnosis (test for trend; p<0.001) [18]. Maternal intrapartum antibiotic prophylaxis has been shown to have a significant impact on the infant faecal microbial population, particularly in breastfed infants [19]. Intrapartum

Saccharomyces boulardii CNCM I-745 © Biocodex.

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antibiotic administration was reported to result in a significant reduction in Bifidobacterium spp. strains [20]. The reduced abundance of these beneficial microorganisms, together with the increased amount of potentially pathogenic bacteria, may suggest these infants are more exposed to gastrointestinal or general health disorders later in life [20].

ANTIBIOTICS AND THE RESPIRATORY TRACT

Antibiotics given during the first week of life is a risk factor for allergic rhinitis and wheezing, while early introduction of solid foods, such as fish, and living on a farm are protective factors for the development of later allergic disease. Antibiotics taken by the infant during the first year of life is associated with an increased risk of asthma [21]. The strength of the association differs with the class of antibiotics, correlating with their effect on the gastrointestinal microbiome [21].

Antibiotic exposure has been associated with increased risk of asthma at three and six years of age [22], in the presence or absence of a lower respiratory tract infection during the first year of life [22]. The adverse effect of antibiotics was particularly strong in children with no family history of asthma (p [interaction] =0.03) [22]. Antibiotic intake was also a risk factor for a positive allergy blood or skin test. According to a systematic review published in 2011, exposure to antibiotics in the first year of life is a significant risk factor to develop asthma. Retrospective studies provided the highest pooled risk estimate for asthma compared with database and prospective studies. Respiratory infections, later asthma onset (asthma at or after two years), and exposure to antibiotics during pregnancy are all independent risk factors.

Antibiotic use in the first year of life is associated with the development of transient wheezing and persistent asthma [23]. A dose-response effect was observed; with five or more antibiotic courses, the risk to develop asthma increased significantly (p<001). There is no association between antibiotic use and late-onset asthma [23]. Antibiotic use in the first year of life is associated with an increased risk of early-onset childhood asthma, starting before three years of age. Reverse causality and protopathic bias may be confounders of this relationship [23].

ANTIBIOTICS AND IBD

Exposure to antibiotics throughout childhood is associated with IBD, and this relationship decreases with increasing age of exposure to antibiotics. Exposure before one year of age was shown to have the highest risk, decreasing at five and 15 years, although antibiotics at the age of 15 still represented a significant risk factor to develop IBD [24]. Each antibiotic course increased the IBD hazard by 6% (4%-8%) [24]. As with any observational study, causality cannot be inferred and the possibility of data confounded by indication, due to prescription of antibiotics to children with intestinal symptoms of yet undiagnosed CD, should also be considered [25]. Antibiotic use is common in childhood and its potential as an environmental risk factor for IBD warrants scrutiny [25]. Antibiotic exposure has been reported to be significantly associated with Crohn's disease, particularly in children, but not significantly associated with ulcerative colitis [26].

ANTIBIOTICS AND DIABETES

Exposure to a single antibiotic prescription was not shown to be associated with a higher adjusted risk of diabetes [27], whereas treatment with two to five antibiotic courses was associated with an increase in risk of diabetes for penicillin, cephalosporins, macrolides, and quinolones. The risk increased with the number of antibiotic courses. No association between exposure to anti-virals or anti-fungals and risk of diabetes was demonstrated [27]. Exposure to antibiotics is likely to increase the risk of type 2 diabetes [28]. However, these findings may also represent an increased demand for antibiotics due to an increased risk of infections in patients with yet-undiagnosed diabetes [28]. Antibiotic exposure in childhood is generally not associated with a risk of developing type 1 diabetes [29]. Future studies should investigate the effects of multiple exposures to broad-spectrum antibiotics during the second year of life.

ANTIBIOTICS AND MALIGNANCIES

For gastro-intestinal malignancies, the use of penicillin has been shown to be associated with an elevated risk of oesophageal, gastric, and pancreatic cancers [30]. The association increased with the number of antibiotic courses. The risk of lung cancer increased with the use of penicillin, cephalosporins, or macrolides. The risk of prostate cancer increased modestly with the use of penicillin, quinolones, sulphonamides, and tetracyclines. The risk of breast cancer was modestly associated with exposure to sulphonamides. There was no association between the use of anti-virals or anti-fungals and risk of cancer [30].

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CONCLUSION

Antibiotics are often unavoidable and sometimes life-saving. However, they also cause intestinal dysbiosis, which, in turn, is associated with adverse outcomes, such as AAD. Prudent use of antibiotics is paramount not only to reduce the propagation of antibiotic-resistant organisms, but also to minimize the potentially detrimental long-term metabolic consequences of early antibiotic exposure. The administration of some specific probiotic strains, such as *Saccharomyces boulardii*, reduces the risk of developing AAD. Whether probiotics may also reduce the risk of developing other adverse effects of intestinal dysbiosis has not been well validated in the literature.

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Photo

COMMENTED ARTICLE
ADULTS' SECTION

By Prof. Harry Sokol
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IMPROVEMENT IN INSULIN SENSITIVITY AFTER FAECAL MICROBIOTA TRANSPLANT DEPENDS ON THE INITIAL MICROBIOTA COMPOSITION OF RECIPIENTS

Kootte RS, Levin E, Salojärvi J, et al. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. Cell Metab 2017 ; 26 : 611-619.e6.

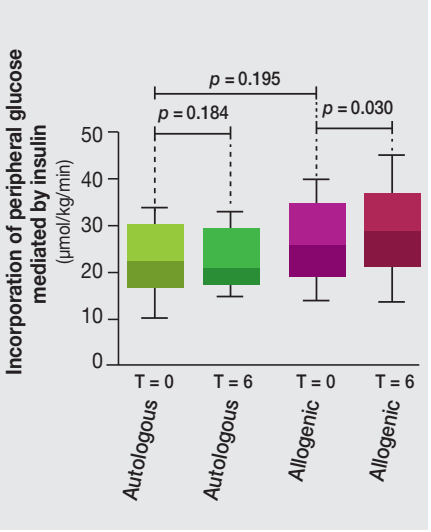
The gut microbiota is involved in insulin resistance although there is limited evidence of a causal link. We compared the effect of faecal microbiota transplant (FMT) from a thin donor (allogeneic) to that of an auto-transplantation (autologous) in male patients with metabolic syndrome. While no metabolic change was observed 18 weeks after FMT, insulin sensitivity was significantly improved at six weeks in the allogeneic FMT group and this was associated with a change in microbiota composition. We also reported changes in plasma concentrations of metabolites, such as γ-aminobutyric acid, and showed that the metabolic response after FMT (defined as the improvement in insulin sensitivity six weeks after FMT) was present in patients with a microbial diversity reduced to basal level. In conclusion, the beneficial effects of FMT from thin donors on carbohydrate metabolism are associated with changes in gut microbiota and plasma metabolites, and can be predicted by the basal microbiota composition of the recipient.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Obesity and related disorders, such as diabetes, require new therapeutic approaches because the current treatments, including lifestyle changes, and antidiabetic treatments are insufficiently effective in reducing morbidity and mortality. During the last decade, changes in gut microbiota composition have emerged as a potential new therapeutic strategy for improving insulin sensitivity [1]. Several studies have shown that gut microbiota composition is different between thin and obese animals, but also that the microbial composition may reflect impaired metabolic functions, in particular, with a disturbance of ingested food [2]. Finally, these animal studies have suggested a causal link

▼ FIGURE 1

Peripheral sensitivity to insulin before and six weeks after allogeneic or autologous faecal transplant.



KEY POINTS

- FMT from thin donors improves insulin sensitivity in obese patients with metabolic syndrome
- There is interindividual variability in the response and the latter is transient
- The improvement in insulin sensitivity is related to changes in plasma metabolites
- The response to FMT is dependent on initial microbiota composition in patients

between microbiota abnormalities and metabolic syndrome since the phenotype is transferable by FMT [2]. Although numerous observational studies have suggested correlations between an altered microbiota composition and metabolism in humans, the causality has been difficult to prove. The authors of this study have previously shown in a small pilot study that FMT from thin donors to men with metabolic syndrome induced an improvement in carbohydrate metabolism, together with changes in faecal and duodenal microbiota [3]. Based on these results, the authors have studied the short- and long-term effects of FMT from thin donors on gut microbiota composition in a larger group of men with metabolic syndrome and investigated the pathophysiology of insulin resistance by correlating changes in gut microbiota with several markers of metabolism. In addition, the authors have attempted to identify basal characteristics of the microbiota of recipients in order to explain the improvement in insulin sensitivity in some patients (referred to as metabolic responders) and not in others (non-responders).

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

Thirty-eight obese men with metabolic syndrome were included and randomized in the allogeneic (n = 26) or autologous (n = 12) FMT group. FMT was administered by nasoduodenal tube and repeated six weeks later. Eighteen weeks after FMT, no effect was observed on both the microbiota and the parameters of metabolic syndrome. However, six weeks after FMT, the microbiota of the allogeneic FMT group was changed and the metabolic parameters, in particular insulin sensitivity, were improved while no change was observed in the autologous FMT group (**Figure 1**). In contrast to their previous study, no change in faecal concentration of butyrate was observed [3]. However, allogeneic FMT was associated with an increase in faecal concentration of acetate, as well as changes in the blood level of about 30 metabolites, several of which are involved in the metabolism of tryptophan. In the subgroup of patients who favourably responded to allogeneic FMT, changes were observed in the faecal microbiota, such as, for example, an increase in *Akkermansia muciniphila* bacterium, and the favourable effects of this bacterium were demonstrated on metabolic syndrome in mice. The authors also highlighted that the basal microbiota composition, as well as a low diversity, were predictive of a good response to FMT.

WHAT ARE THE PRACTICAL CONSEQUENCES?

Interventions on the gut microbiota, and particularly FMT, are a valid therapeutic approach for metabolic syndrome. Nevertheless, there is high interindividual variability in the response, which may be related to factors from the host, but also from the donor. In addition, the effects are relatively modest with a single FMT and, at best, they are transient. More targeted strategies, such as the use of new generation probiotics (microbiota-derived bacteria) and prolonged administration, are therefore more attractive and are currently being studied.

CONCLUSION

This interventional study demonstrates that the gut microbiota plays a role in metabolic syndrome and is not just a passive stakeholder. The underlying mechanisms could involve the production of metabolites by the gut microbiota, which modulate the host signalling pathways. Nevertheless, the effects are relatively modest and transient. More targeted strategies, such as the use of new generation probiotics and prolonged administration, are therefore more attractive and are currently being studied.

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COMMENTED ARTICLE
CHILDREN' SECTION

By Prof. Emmanuel Mas
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STOOL CONTENTS OF COLICKY INFANTS INDUCE VISCERAL HYPERSENSITIVITY IN MICE

Eutamène H, Garcia-Rodenas CL, Yvon S, et al. Luminal contents from the gut of colicky infants induce visceral hypersensitivity in mice. Neurogastroenterol Motil 2017 ; 29 : e12994.

The pathophysiology of infantile colic is poorly understood, though various studies report gut microbiota dysbiosis in colicky infants. Our objective was to test the hypothesis that colic-related dysbiosis is associated with visceral hypersensitivity, triggered by changes in intraluminal content.

Faecal samples from seven colicky and seven non-colicky infants were studied. Faecal supernatants (FS) were infused into the colons of C57/Bl6 mice (n=10/specimen). Visceral sensitivity was subsequently assessed in the animals by recording their abdominal muscle response to colorectal distension (CRD) by electromyography (EMG). Serine and cysteine protease activities were assessed in FS using specific substrates. Infant faecal microbiota composition was analysed by 16S rRNA gene pyrosequencing following DNA extraction.

FS from colicky infants triggered higher EMG activity than FS from non-colicky infants in response to both the largest CRD volumes and overall, as assessed by the area under the curve of the EMG across all CRD volumes. Infant crying time strongly correlated with mouse EMG activity. Microbiota richness and phylogenetic diversity were increased in the colicky group, without prominent microbial composition alterations. Only *Bacteroides vulgatus* and *Bilophila wadsworthia* were increased in the colicky group. The abundance of *Bacteroides vulgatus* positively correlated with visceral sensitivity. No differences were found regarding protease activities.

Luminal contents from colicky infants trigger visceral hypersensitivity, which may explain the excessive crying behaviour of these infants. Additional studies are required to determine the nature of the compounds involved, their mechanism of action, and the potential implications of intestinal microbiota in this age group.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Infantile colic is a functional gastrointestinal disorder, defined by the Rome criteria. The pathophysiology is still poorly known although a painful intestinal mechanism is suspected. Studies suggest that a disturbance of the gut microbiota, an increase in gut permeability, and low-grade intestinal inflammation are involved in visceral hypersensitivity. These factors are involved in the pathophysiology of irritable bowel syndrome. In this syndrome, an abnormality of the protease/antiprotease balance contributes to visceral hypersensitivity and low-grade inflammation.

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

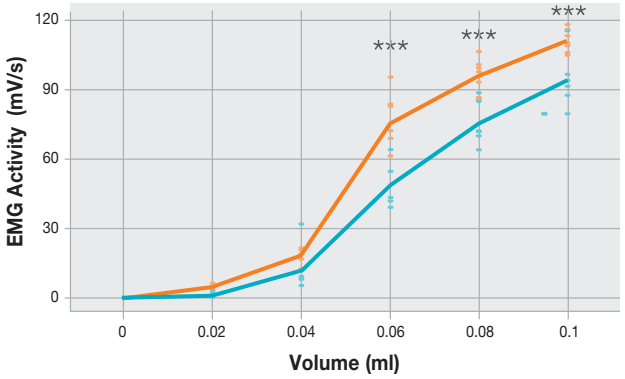
The aim of this study was to investigate whether a disturbance of the gut microbiota, associated with an increase in gut proteases, is capable of inducing visceral hypersensitivity. Breastfed infants, aged 1-4 months, were included. There was no difference in pregnancy duration, birth

KEY POINTS

- The stools of colicky infants trigger visceral hypersensitivity, as in irritable bowel syndrome.
- Further studies are needed to determine the compounds involved, their mechanism of action, and their link with a disturbance of the gut microbiota.

▼ FIGURE 1

Electromyographic (EMG) response of mice to colorectal distension after faecal transplant enema.



The dots represent the mean EMG activity of 7-10 mice having received faecal transplant enema from an infant of the colicky (red; 7 children) or control group (blue; 7 children). *** p <0.001.

weight, or family history of allergy between the colicky group (n = 7) and control group (n = 7). According to the criteria (Rome III criteria), only the mean duration of crying differed, with 240 ± 95.95 minutes (colicky) versus 24.04 ±19.65 minutes (control).

Rectal faecal transplant enemas from colicky infants induced significant visceral hypersensitivity during rectal distension with larger volumes (+55%, p <0.001 with 0.06 mL; +27%, p <0.001 with 0.08 mL, and +19%, p <0.001 with 0.1 mL) (**Figure 1**), as well as a better overall response (increase in area under the curve by +33%, p <0.001). In addition, there was a positive correlation between the duration of crying and these distension volumes (**Figure 2**).

In contrast, there was no difference in protease levels (serine, trypsin-like, and elastase-like) between both groups.

Finally, the analysis of the microbiota showed an increase in *Bacteroides vulgatus* and *Bilophila wadsworthia* diversity with an abundance in children with infantile colic. The relative abundance of *B. vulgatus* was positively associated with mouse hypersensitivity (p = 0.021), but not significantly associated with the duration of crying (p = 0.067).

WHAT ARE THE PRACTICAL CONSEQUENCES?

This study shows that a component of the stool contents of colicky infants is capable of inducing visceral hypersensitivity in mice, involving either an increase in a nociceptive compound or a decrease in an antinociceptive compound. This is not an impaired proteolytic balance, however this compound might be induced by a different gut microbiota. Further studies are needed to identify this compound and the mechanism of action.

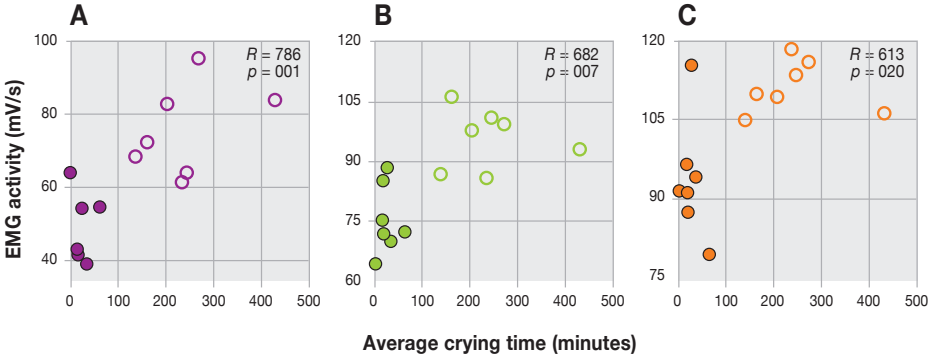
CONCLUSION

Faecal microbiota enema transplants from colicky infants to mice can induce visceral hypersensitivity. This is promoted by a painful abdominal mechanism and the direct or indirect involvement of the gut microbiota in the pathophysiology of infantile colic.
This model could be used to determine which metabolic pathways are modified by a disturbance of the gut microbiota and involved in infantile colic.

▼ FIGURE 2

Pearson correlations between the electromyographic (EMG) response to colorectal distension and duration of crying.

The distension volumes were 0.06 mL (**A**), 0.08 mL (**B**), and 0.1 mL (**C**).



CONGRESS REVIEW

European Helicobacter & Microbiota Study Group

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EHMSG CONGRESS IN BORDEAUX

REPORT OF THE 30TH CONGRESS OF THE EUROPEAN HELICOBACTER AND MICROBIOTA STUDY GROUP

SEPTEMBER 2017

BORDEAUX, FRANCE

The 30th Congress of the European Helicobacter and Microbiota Study Group was held on September 7-9, 2017, in Bordeaux, France, where the first gathering of this group was held in 1988. An important new addition was the inclusion of the topic of gut microbiota, including a post-graduate course on "Antibiotherapy and the gut – New concepts"; a master class on microbiota and several symposia and workshops on the topic.

THE KEY CONTRIBUTION OF CULTUROMICS

The first presentation of the post-graduate course was provided by D. Raoult from Marseille, France, who revisited the concept of gut microbiota using culturomics. Studies using 16S rDNA sequencing and metagenomics have opened the field, but these techniques have limitations due to discrepancies that may arise at the level of DNA extraction, sequencing, and bioinformatic analysis, moreover, these techniques are missing minority partners. However, the emergence of the concept of culturomics has enabled the discovery of an important number of new bacterial species, *Archae*, as well as large viruses, which could not be detected by metagenomic analyses. This approach employed by D. Raoult was initially extremely cumbersome (using 200 different media), but is now more

straightforward, using only 17 media, and new bugs continue to be discovered every week.

GUT MICROBIOTA AND ANTIBIOTICS

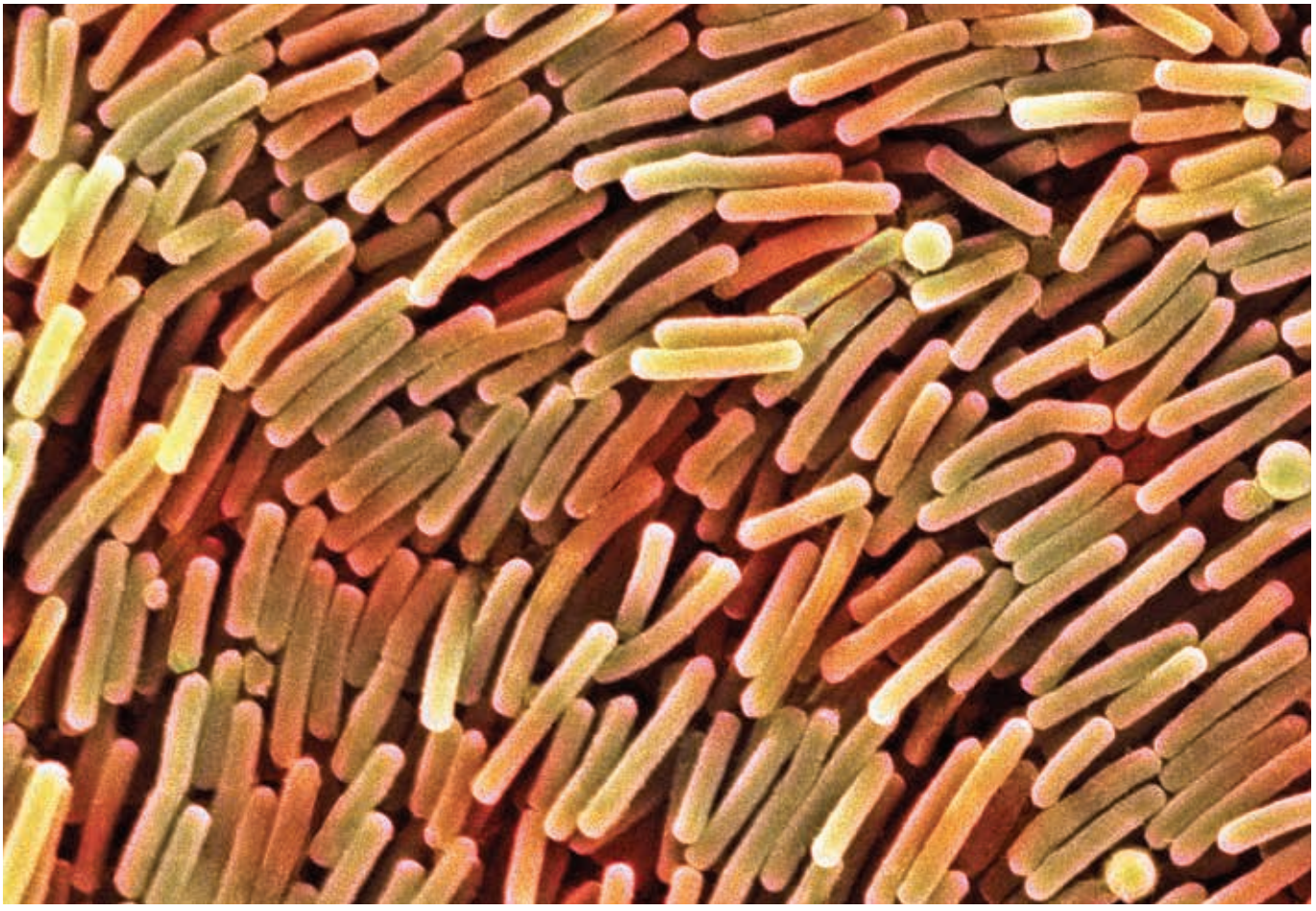
The second talk was also fascinating. M. Blaser (New York, NY, USA) presented the suspected link between gut microbiota disturbances and several chronic diseases for which the aetiology is still doubtful, such as asthma, obesity, diabetes, inflammatory bowel disease, *etc*. The prevalence of these diseases is increasing worldwide and parallels the increased use of antibiotics. There are now data showing that bacteria that have co-evolved with humans are crucial to their good health. There is an age window when the microbiota is established (0-3 years), and consumption of antibiotics at this age may lead to the disappearance of part of the microbiota and therefore the bacterial diversity which is an important criterium for health. Experiments in mice have shown that antibiotics can modify the composition of gut microbiota leading to increased adiposity and modification of the immune response, favouring several diseases.

With the description of the association between gut dysbiosis and several diseases at present, an interesting approach to consider is how to limit the impact of antibiotics on gut microbiota. A first step is to add probiotics to antibiotic treatments, however, all probiotics are not equal. *Saccharomyces boulardii* appears to be the leader in this area. All studies have shown a beneficial effect of this yeast on antibiotic-related diarrhoea. Among *Lactobacilli*, there is one emerging species in this respect; *Lactobacillus rhamnosus* GG, as revealed by H. Sokol.

NON-PROBIOTIC APPROACHES

There are currently non-probiotic approaches to prevent gut dysbiosis which were presented by A. Andremont (Paris, France). Indeed, antibiotics are absorbed in the small intestine and their negative effects on gut microbiota occur essentially in the colon. Thus, first attempts were made to deliver β-lactamase to the colon to avoid the effect of β-lactam antibiotics, and subsequently other alternatives using specifically coated absorbent-like activated charcoal. Experiments in mice and dogs have been successful, especially for fluoroquinolone antibiotics.

Once dysbiosis is established, restoration is possible by faecal microbiota transplantation (FMT). It is possible to successfully treat *Clostridium difficile* infection using allogenic FMT. Autologous transplantation could be an option in the case of planned antibiotic treatment and would be more acceptable given that the risk of unknown pathogens would be avoided. For FMT, there is a need for common legislation in Europe as well as standardization of the process.



Clostridium difficile © Getty images.

CONGRESS REVIEW

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FOCUS ON THE ASIAN PACIFIC DIGESTIVE DISEASE WEEK

THE FUTURE IN DIGESTIVE DISEASES

SEPTEMBER 2017

HONG KONG

INTRODUCTION

Recently, understanding the gastrointestinal (GI) health and its disorders have improved with knowledge on gut microbiome (GM) and dysbiosis [1]. At the Asian Pacific Digestive Disease Week 2017, several aspects of GM were presented, e.g. introduction to GM to physicians, its role in colorectal cancer (CRC), obesity, non-alcoholic fatty liver disease (NAFLD), relationship with Helicobacter pylori (*H. pylori*)-related diseases, its modulation to treat GI diseases, particularly inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS), misuse of antibiotics in Asia, role of probiotics in *H. pylori* eradication, and *C. difficile* treatment.

INTRODUCTION TO THE GM

Gut microbiota, the largest human organ, has 10 times more cells (10^{14}) than the human cells in the body (10^{13}) [2]. The functions of the GM include, digestion of food, metabolism of the drugs and toxins and their detoxification, vitamin synthesis, prevention of attachment of pathogenic bacteria to the gut wall, modulation of immune, neuro-hormonal, central nervous system functions [2]. Considering the diverse functions of the GM, its alteration is expected to be associated with several diseases and its modulation to be beneficial.

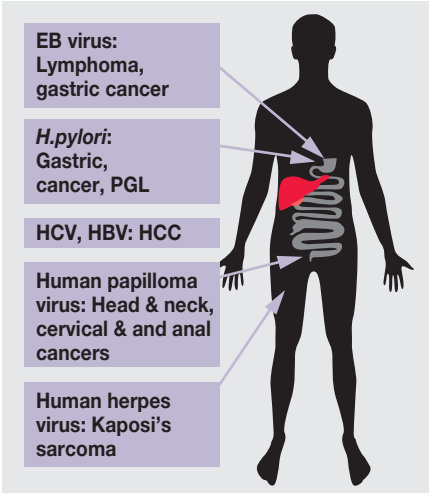
ROLE OF GM IN CRC

Microbes are well-known to cause several cancers **(Figure 1)** [3]. Recently, emerging data suggest the role of dysbiosis in CRC. Fecal microbiota of patients with colonic polyposis resembles that of CRC. Whereas Clostridium spp., Bacteroides

▼ **FIGURE 1**

Relationship between microbes and cancers

(abbreviations used: *H. pylori: Helicobacter pylori*; PGL: primary gastric lymphoma; HCV: hepatitis C virus; HBV: hepatitis B virus; HCC: hepatocellular cancer.



and Bifidobacterium spp. are associated with CRC, lactic acid-producing bacteria (e.g. Lactobacillus spp. and Eubacterium aerofaciens) are negatively associated. GM associated production of methane, H2S, and presence of Streptococcus bovis may play role in CRC development. Obesity, recently thought to be related to GM, is a predisposing factor for CRC.

GM & OBESITY

Calorie extraction from foods not only depends on digestive function of the small bowel, but also on the extraction of malaborbed calorie by the colonic microbiota. Whereas presence of Firmicutes is associated with greater calorie extraction, Bacteroidetes have opposite effect [4]. Examples from the Nature include development of obesity in elephants in spite of their low-calorie diet. In animal husbandry, use of low-dose antibiotic from the childhood increases the amount of meat. The difference in the fecal microbiota among obese and non-obese individuals have been shown. In a retrospective cohort study from the UK, of 21,714 infants, 1306 (6%) became obese at 4-y of age. On logistic regression analyses adjusting for mothers' and sibs' obesity, maternal diabetes, mode of delivery, socioeconomic status, year and country of birth, and urban dwelling, antibiotic exposure before 2-y age was associated with development of obesity and the number of exposure correlated with it [5].

OTHER METABOLIC SYNDROMES INCLUDING NAFLD, CORONARY ARTERY DISEASE, & DIABETES MELLITUS

NAFLD, associated with metabolic syndrome may have dysbiosis including a quantitative increase in upper gut bacteria (SIBO ≥10^5 colony forming unit, CFU/mL, and low-grade ≥10^3 CFU/mL) [6].An uncontrolled and three case-control studies showed SIBO to be associated with NAFLD [6]. Two studies showed lower relative abundance of Bacteroidetes, and higher abundance of *C. coccoides*, and Prevotella in NAFLD patients. Higher extraction of calorie from unabsorbed complex carbohydrates, insulin resistance and endogenous production of alcohol may contribute to the pathogenesis of NAFLD due to dysbiosis.

GM plays important role in glucose metabolism, insulin resistance, diabetes, and has implication in its treatment. Patients with diabetes have different fecal microbiota than the control population [4]. GM was shown to be an important factor regulating glucose levels after intake of different foods independent of physical exercise, lifestyle, and anthropometric measures [7]. Metformin, an oral hypoglycemic, may partly work by altering the GM. Though studies on the role of GM on coronary artery disease are scanty and results mixed, data suggesting its role in this condition is emerging.

ANTIBIOTIC MISUSE IN ASIA

Antibiotic use is high in Asia and the implementation of policies for appropriate use is poor, with risk of emergence of antibiotic-resistant "super-bug".Reasons for misuse of antibiotics include, unrestricted availability, and use in inappropriate indications e.g. common cold, acute gastroenteritis due to non-invasive pathogens. Use of probiotics, when indicated, may help to contain misuse of antibiotics.

MANIPULATION OF GM USING AGENTS OTHER THAN ANTIBIOTICS

Though GM manipulation using rifaximin is well-known, probiotics and fecal transplantation have potential to treat dysbiosis associated disorders, e.g. antibiotic-associated diarrhea (AAD), IBD, IBS, *Clostridium difficile*-associated diarrhea (CDD), and as a co-prescription during anti-*H. pylori* treatment. ACG made a weak recommendation (from 23 randomized controlled trials, RCTs) that probiotics improve global symptoms, bloating, and flatulence in IBS [8]. A Cochrane review showed probiotics to be useful for preventing CDD [9]. A meta-analysis showed multi-species probiotics to induce and maintain remission in UC, though data on Crohn's are scanty [10]. Shorter anti-*H. pylori* treatment duration is well-known to reduce frequency of its eradication; meta-analyses showed that probiotic co-administration increase the eradication rates due to lower adverse effects and better compliance [9]. *H. pylori* eradication treatment may lead to fecal dysbiosis and co-administration of probiotics may restore eubiosis.

FUTURE DIRECTIONS

In an attempt to form an Asia-Pacific Consortium on GM similar to European and North American groups, and to review the current evidence supporting manipulation of GM using probiotics in gastrointestinal disorders in the Asia-Pacific region, a consensus has been developed and published recently [9]. The major conclusions of this consensus were: there is growing evidence to support the therapeutic potential of probiotics in modulating gastrointestinal functions and relieving symptoms of these disorders, but more research is needed both in Asia-Pacific regions and internationally [9].

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LITERATURE SELECTION

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WORLD GASTROENTEROLOGY ORGANISATION 2017

GUIDELINES ON PROBIOTICS AND PREBIOTICS

IN FEBRUARY 2017, THE WORLD GASTROENTEROLOGY ORGANISATION (WGO) UPDATED ITS GUIDELINES FOR PROBIOTICS AND PREBIOTICS

Consistent with previous WGO guidelines, scientific experts evaluated recent publications to prepare their guidelines. These guidelines include information about the definitions, quality, nomenclature, and spectrum of probiotic-containing products, as well as the safety and mechanism of action of probiotics and prebiotics.

The WGO 2017 guidelines relate to the use of probiotics and prebiotics in adults and children, which have undergone at least one well-designed clinical trial. They do not provide grades of recommendation, but only levels of evidence, in accordance with the Oxford Centre for Evidence-Based Medicine criteria (2011), designed to address the question "does this intervention help". The Oxford Centre for Evidence-Based Medicine criteria are classified as (1) to (5): systematic review of randomized trials or initial trial (1); randomized trial or observational study with an incontestable effect (2); non-randomized controlled cohort / follow-up study (3); case study, case-control studies or historically controlled studies (4); and reasoning based on mechanism-of-action (5). This report only addresses the probiotics which have been assessed in certain child pathologies and which correspond to evidence level (1) or (2).

In the treatment of acute infectious diarrhoea, *Saccharomyces boulardii* CNCM I-745 and *Lactobacillus GG* correspond to evidence level (1) and *Lactobacillus reuteri* DSM 17938 to level (2). The evidence level for three other studied groups *(Lactobacillus acidophilus rhamnosus* 573L/1, 573L/2, 573L/3; *Lactobacillus helveticus* R0052 and *L. rhamnosus* R0011; and *Lactobacillus delbrueckii* var. *bulgaricus*, *L. acidophilus, Streptococcus thermophilus,* and *Bifidobacterium bifidum* [strains LMG-P17550, LMG-P 17549, LMG- P

17503, and LMG-P 17500]) is level (2), however, these have undergone only one randomized controlled clinical trial.

In the prevention of antibiotic-associated diarrhoea, *Saccharomyces boulardii* CNCM I-745 and *Lactobacillus GG* correspond to evidence level (1), and in the prevention of nosocomial diarrhoea, *Lactobacillus GG* corresponds to level (1) and *Bifidobacterium bifidum* and *Streptococcus thermophilus* level (2). Regarding the prevention of infections in children attending day-care centres, *Lactobacillus GG* or *Lactobacillus reuteri* DSM 17938 corresponds to evidence level (1) and *Lactobacillus casei* DN-114 001 or *Lactobacillus casei Shirota* in fermented milk correspond to level (2).

In the prevention of infantile colic, *Lactobacillus GG* and *Lactobacillus reuteri* DSM 17938 correspond to evidence level (1).

In the prevention of necrotizing enterocolitis in premature new-borns, *Lactobacillus reuteri* DSM 17938 corresponds to evidence level (2). Finally, in the remission of ulcerative-haemorrhagic rectocolitis among children, *E.coli Nissle* 1917 and VSL#3 correspond to evidence level (2).

There are numerous probiotic/symbiotic products within the global market and an evidence-based approach is key for current use. The WGO guidelines, as well as those of the ESPGHAN/ESPID, the Yale Workshop Group, and Latin America on probiotics, should be routinely re-evaluated regarding recent randomised and controlled clinical trials.

Reference:
worldgastroenterology.org/guidelines/global-guidelines/probiotics-and-prebiotics/probiotics-and-prebiotics-english

INTRAPARTUM ANTIBIOTIC PROPHYLAXIS FOR GBS INFECTION

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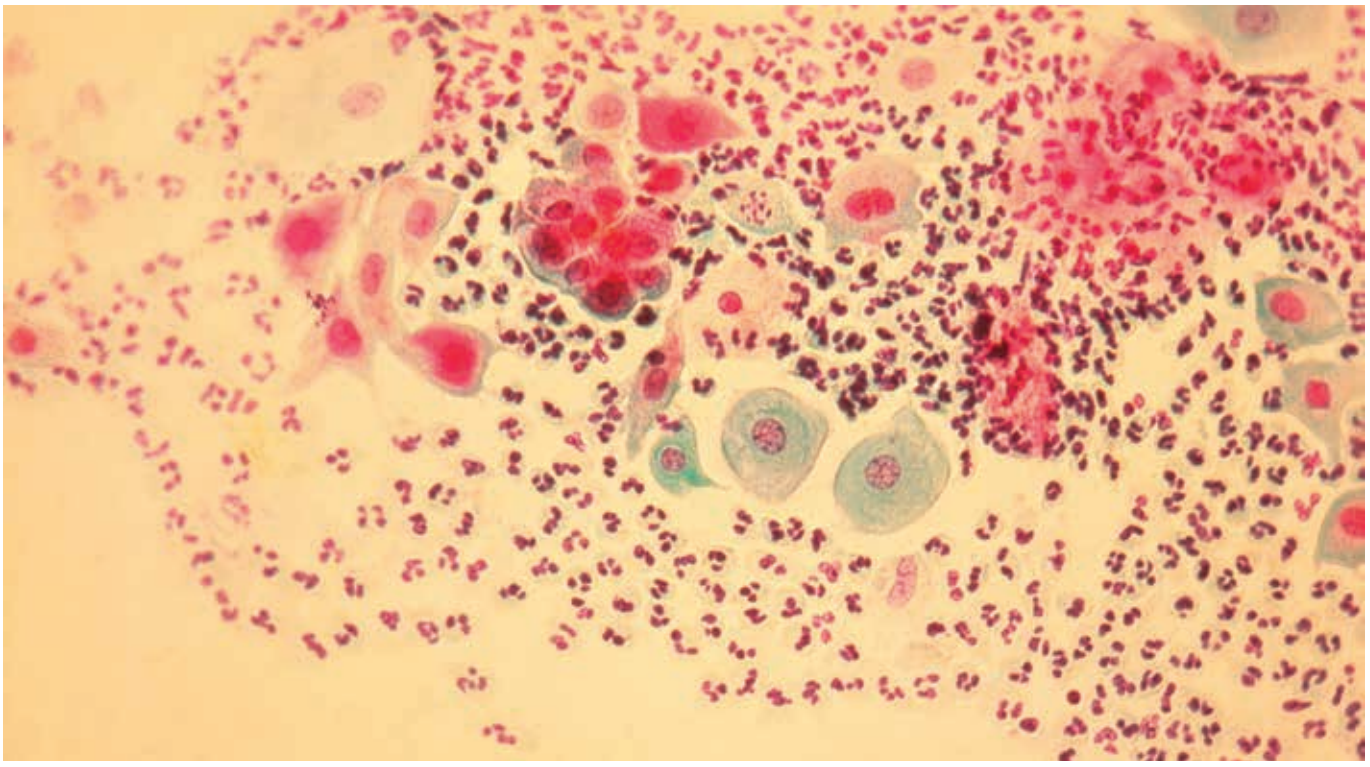
ANOTHER IMPORTANT EARLY-LIFE RISK FACTOR ASSOCIATED WITH INFANT INTESTINAL MICROBIOTA COMPOSITION

Microbiota composition during early infancy has an important influence on early immunological and metabolic programming that may predispose children to disease risk later in life. The first 1,000 days of life is a critical period for whole-life and early-life events (delivery mode, preterm birth, feeding practices, and antibiotic consumption) which may affect the intestinal and nasopharyngeal microbiota.

Recent and planned studies are focused on the evaluation of other potential risk factors during pregnancy and after early infancy. Intrapartum antibiotics are extensively used worldwide for the prevention of maternal infection associated with C/S birth and prevention/management of Group B streptococcal (GBS) infections.

Stearns *et al.'s* recent study, which was published in *Scientific Reports* (2017) [1], entitled "Intrapartum antibiotics for GBS prophylaxis alter colonization patterns in the early infant gut microbiome of low risk infants", is an important example of the effects of antibiotics on intestinal microbiota composition in healthy, term, breastfed infants. In this study, the authors investigated the microbiota composition in 53 infants born vaginally, with no exposure to antibiotics; of these, 14 infants were exposed to intrapartum antibiotic prophylaxis for Group B Streptococcus, and seven infants were born by C-section (in Canada). Overall, the intestinal microbiota of infants born vaginally without exposure to intrapartum antibiotic prophylaxis differed significantly from that of infants born vaginally but exposed to intrapartum antibiotic prophylaxis for GBS or infants born by C-section (also exposed to IAP).

Regarding the results of this study, the faecal microbiota of intrapartum antibiotic prophylaxis-exposed infants exhibited significantly lower alpha diversity, and intrapartum antibiotic prophylaxis for GBS exposure during vaginal birth might therefore affect the *Bifidobacterium* levels/predominance (delay in expansion) over the first 12 weeks of life. This study also



Vaginal flora. Colored micrograph of PAP smear showing normal stellate cells.

showed that colonization of the infant gut microbiota differs in the distribution of bacteria, similar to the majority of published studies on the effect of delivery mode on infant intestinal microbiota composition.

This study found that intrapartum antibiotic prophylaxis for GBS affected all aspects of gut microbial ecology including species richness, diversity, community structure, and the abundance of colonizing bacterial genera. These study results also showed that antibiotic prophylaxis for any purpose may affect infant intestinal microbiota composition and this highlights the importance of appropriate antibiotic use.

In 2016, Cassidy-Bushrow and colleagues published a report on an association between maternal Group B streptococcus and infant gut microbiota [2]. In this study, as part of a population-based, general-risk birth cohort, stool specimens were collected from infants' diapers at one and six months of age. The authors showed that maternal GBS status was statistically significantly associated with gut bacterial composition in the sixth month, and infants of GBS positive mothers were significantly enriched for *Clostridiaceae, Ruminococcoceae*, and *Enterococcaceae* also in the sixth month. In addition, Mazzola *et al*. demonstrated the short-term consequences of maternal intrapartum antibiotic prophylaxis, to prevent GBS infection, on the faecal microbial population in infants, particularly in breastfed infants [3]. The long-term effects on intestinal microbiota composition have not been addressed in previous studies.

Altered microbiota composition has been associated with obesity, allergy, inflammatory bowel disease, and colon cancer, and further studies are needed to define causal effects. These results also highlight the unmet medical need for maternal immunization using potential GBS vaccines.

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CALLS FOR RESEARCH PROPOSALS

BIOCODEX MICROBIOTA FOUNDATION

The first international call for proposals launched by Biocodex Microbiota Foundation closed on November 30, 2017. This focused on the topic "Liver diseases and gut microbiota" and generated 33 applications from 13 different countries. The international scientific committee will meet in March to choose the winner. The topic of the 2019 call for proposals will also be decided during this meeting.

National calls for proposals are also underway in Belgium, Canada, France, Mexico, Morocco, the Russian Federation, Finland, Ukraine and the USA.

• **For further information, visit the website www.biocodexmicrobiotafoundation.com.**

SCIENTIFIC INFORMATION ON MICROBIOTA

BIOCODEX MICROBIOTA INSTITUTE

The Biocodex Microbiota Institute continues to expand its new website with news, interviews, summaries of the latest publications and, very shortly, thematic sections. A calendar of upcoming conferences on microbiota and previous editions of the Microbiota newsletter can also be downloaded.

• **Visit the website at www.bmi-pro.com**

MEETINGS

MEET BIOCODEX AT THE FOLLOWING CONGRESSES:

GUT SUMMIT
MARCH 9-11 2018
ROME, ITALY

GFHGNP
MARCH 29-31 2018
DIJON, FRANCE

JFHOD
MARCH 22-25 2018
PARIS, FRANCE

ESPGHAN
MAY 9-12 2018
GENÈVE, SWISS

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www.jle.com

Graphic design:
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Realisation:
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Photo credits:
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I - 18.01 (03/18) - Code SAP 99033 - Achevé d'imprimer par Corlet, Imprimeur, S.A. en février 2018