

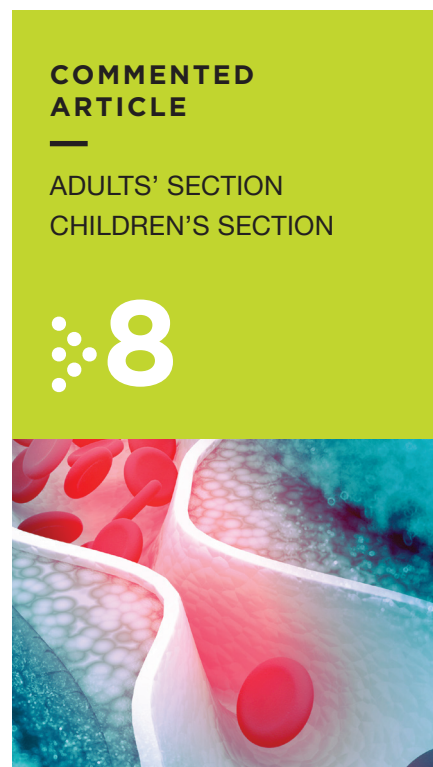
MICROBIOTA

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BIOCODEX NEWSLETTER | DECEMBER 2020



SUMMARY



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“ THE MICROBIOTA, AS A VERITABLE ENZYME-PRODUCING FACTORY, MAY EXERT A POSITIVE INFLUENCE ON DRUGS BY MODIFYING INACTIVE PRECURSORS OR, CONVERSELY, EXERT A NEGATIVE IMPACT BY DISRUPTING INTERACTIONS BETWEEN THE DRUG AND ITS RECEPTOR. ”

Dear readers, the impact of some drugs on the composition of the microbiota and, consequently, on its functions, has been reported for a number of years. The best known of such drugs are antibiotics but proton-pump inhibitors and metformin are also implicated. Conversely, what impact does the microbiota exert on drugs? The role of gut microbiota in drug metabolism, which has been observed and characterised more recently, could explain the difference in efficacy from person to person of some drugs, based on the composition of their microbiota. The microbiota, as a veritable enzyme-producing factory, may exert a positive influence by modifying inactive precursors or, conversely, exert a negative impact by disrupting interactions between the drug and its receptor. When administered orally, which is the most common route, or parenterally, where metabolites reach the gut via bile secretions, the microbiota could affect all drugs.

In this issue, Professor Balskus uses several examples to outline how the gut microbiota is involved in the metabolism of some drugs and the consequences on their efficacy. She also describes the studies underway to identify which drugs are likely to act on the metabolic activity of the microbiota vis-à-vis certain medicines. Finally, she discusses the importance of considering the metabolic role of the microbiota when developing new drugs.

Another area where the microbiota is also implicated is respiratory infections. Recent studies seem to show a decrease in certain butyrate-producing bacterial species in patients with SARS-CoV-2 (preliminary results). In addition, 7-20% of people with SARS-CoV-2 experience diarrhoea thus also having an impact on the gut.

Professor Trottein tackles the “gut-lung” axis and discusses changes to the intestinal microbiota observed during viral respiratory infections as well as the consequences of such dysbiosis. He also explains the crucial role played by the microbiota in combating respiratory infections and the potential benefit of its modulation for their prevention.

Enjoy your reading.

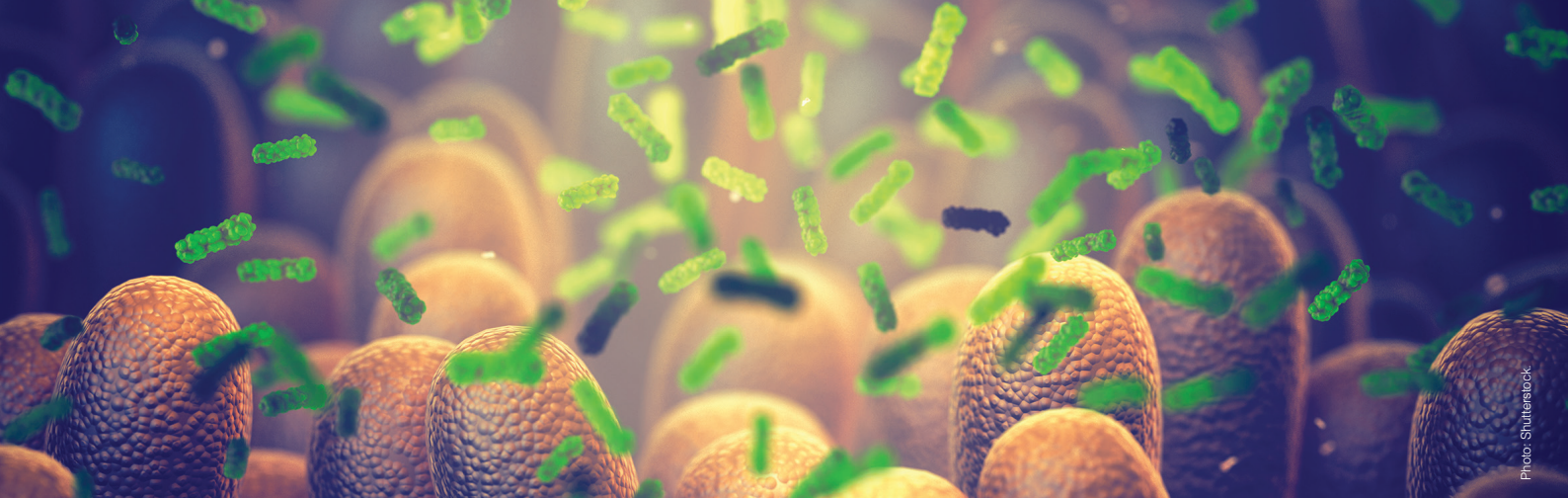


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OVERVIEW

THE GUT MICROBIOTA AND DRUG METABOLISM

The gut microbiota transforms the chemical structures of ingested compounds, including orally-administered small molecule drugs. This metabolism, which can vary substantially between patients, impacts drug efficacy in both positive and negative ways, and can also influence toxicity. Over the last 10 years, there has been a growing appreciation of the potential contribution of gut microbiota drug metabolism to inter-individual variability in patient drug response. Here, we review this topic, with a focus on recent advances and their potential future impact on patient care and drug discovery.



By Prof. Emily P. Balskus

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The trillions of microorganisms that inhabit the human gut possess a greatly expanded set of genes compared to the host genome. Many of these genes encode protein-based catalysts, or enzymes, that enable gut microbes to perform a wide range of chemical reactions, expanding the chemistry associated with the human body. A hallmark of gut microbial metabolism is its variability; just as the composition of the microbiota differs between individuals, so too can the metabolic capabilities of this community. As we continue to identify associations between the gut microbiota and health and disease outcomes, it is becoming increasingly important to characterize microbial metabolic transformations at a molecular level.

One prominent activity associated with the gut microbiota is the ability to chemically modify the structures of small molecule drugs [1]. Orally administered drugs encounter gut microbes either prior to absorption in the small intestine or in the large intestine if they are poorly orally bioavailable.

Orally administered or injected drugs, or drug metabolites, also reach the microbiota if they undergo biliary excretion into the intestine. Because a drug's pharmacological activity directly arises from its chemical structure, microbial metabolism can have a large effect on drug action.

EFFECTS OF GUT MICROBIAL DRUG METABOLISM

Gut microbial metabolism has various downstream consequences for drug action and efficacy (**Figure 1**). As the early examples of azo drugs illustrate, microbial metabolism of 'prodrugs' (inactive precursors) may be required to generate the active pharmacological agent. This knowledge has inspired the rational design of additional strategies for targeted drug release in the large intestine that rely on microbial metabolic activities.



Studies of gut microbial drug metabolism began over 80 years ago with the discovery that the early antibiotic Prontosil, an azo compound that is inactive toward bacterial isolates but displays efficacy *in vivo*, underwent reduction by the gut microbiota to give the active agent sulfanilamide. Additional examples of gut microbial drug metabolism were uncovered throughout the intervening years, often prompted by observations of varying efficacy or toxicity in patients. Importantly, despite this history, such activities still are not typically considered in drug development or administration.

Metabolism by the gut microbiota can also have negative effects on drug activity by disrupting interactions with intended host targets. One example is the natural product-based cardiac medication digoxin. In 5-10% of patients, the gut microbiota reduces the α , β -unsaturated lactone ring of digoxin to give dihydrodigoxin. This subtle modification, which is performed by the gut bacterium *Eggerthella lenta*, greatly reduces the binding affinity for digoxin's target Na⁺/K⁺ ATPase, resulting in a loss of efficacy [2]. Another prominent example is the front-line Parkinson's disease treatment L-dopa. Metabolism of L-dopa to dopamine by host enzymes in the brain is critical for alleviation of symptoms. Gut microbial metabolism of L-dopa also produces dopamine [3,4]. Because dopamine generated in the periphery cannot cross the blood brain barrier, this activity may reduce the amount of L-dopa that reaches the brain.

Finally, in addition to reducing activity, the chemical modifications installed by gut microbes can produce unwanted toxicity. For example, gut microbial metabolism was implicated in the lethality of co-administering the antiviral medication sorivudine with fluoropyrimidine chemotherapeutics. This outcome was traced to gut microbial metabolism of sorivudine to bromovinyl-

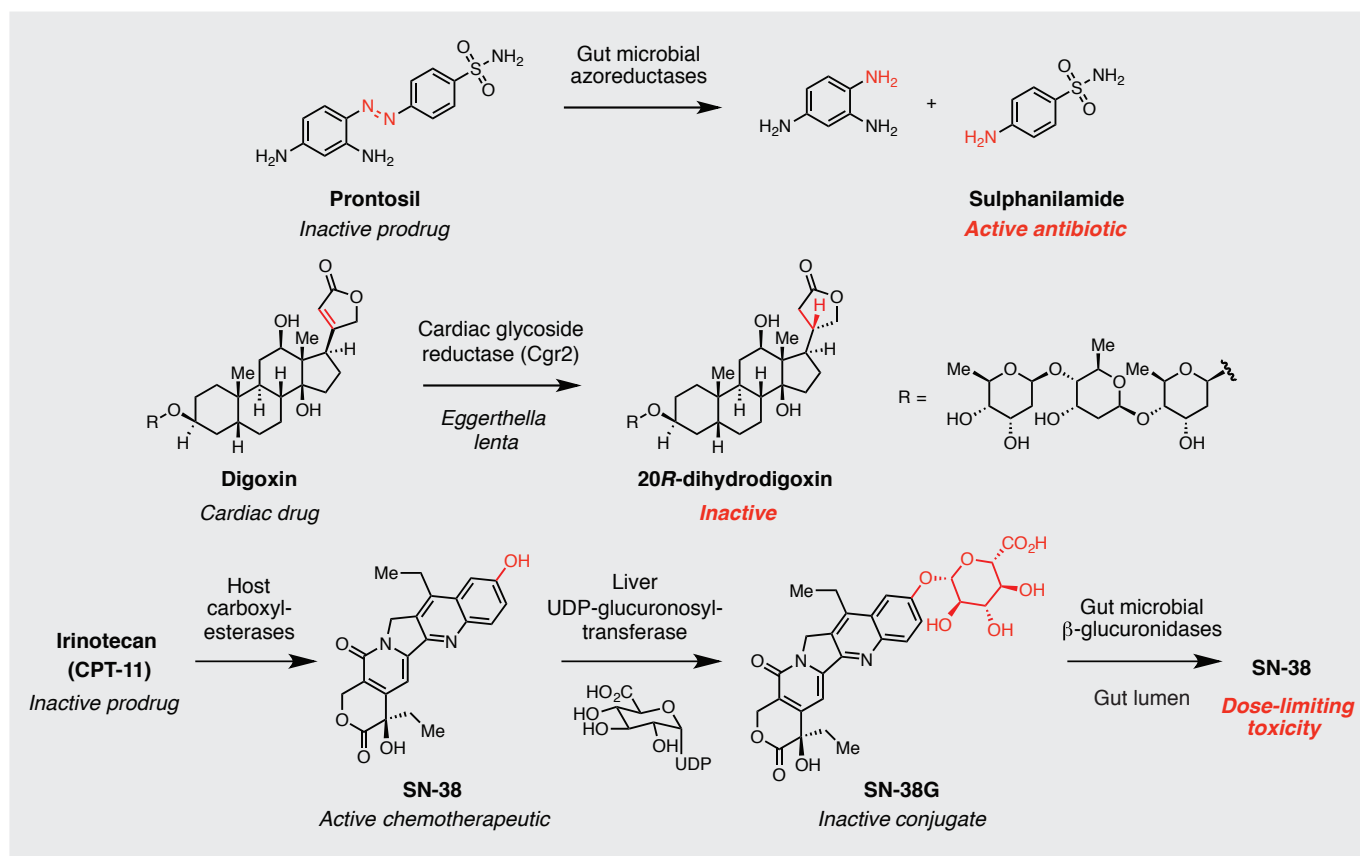
racil. This metabolite inhibits a key host enzyme involved in detoxifying 5-fluorouracil, increasing its concentration to lethal levels.



The chemistry of gut microbial drug metabolism, which tends to be reductive and hydrolytic, is often unique from that of host transformations, which involve oxidation of drugs and conjugation with more polar metabolites to facilitate excretion. Microbial metabolism often has opposing effects on drug availability, prolonging circulation in the body. However, microbial drug transformations do not have to be distinct to impact drug action; recent studies of the anti-viral drug brivudine suggest such activities can affect drug pharmacokinetics even when they are identical to host metabolism [5].

▼ FIGURE 1

Gut microbial drug metabolism has varying effects



An important characteristic of gut microbial drug metabolism is its variability across patients. This phenomenon has its origins in the variability of the gut microbiota. Though some metabolic activities are found in many organisms, others are carried out by a small, low abundant subset of the gut community. Metabolism can vary between individual strains of the same species, as even closely related bacteria can have large differences in their genomes. It is therefore perhaps unsurprising that community composition is often a poor predictor of metabolism, and metabolism of individual drugs can be extensive in some individuals and absent in others. This variation likely has important but incompletely understood consequences for patients taking a range of small molecule drugs.

UNDERSTANDING DRUG METABOLISM AT A MOLECULAR LEVEL

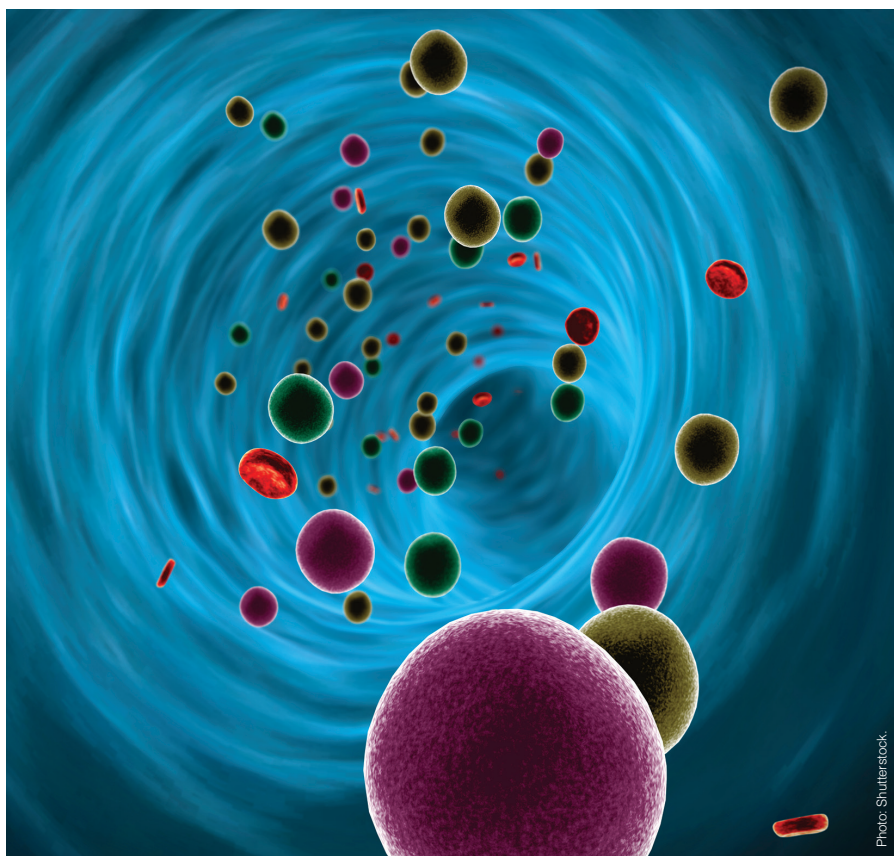
In order to fully understand gut microbial drug metabolism, it is necessary to link individual activities with microbes, genes, and enzymes. Identifying specific drug-metabolizing microbes is typically needed to enable downstream mechanistic studies. This may be accomplished through screening available gut microbial isolates or isolating metabolizing organisms directly from complex gut microbiota samples. An important next step is connecting transformations of interest to genes and enzymes. This is crucial for studying metabolism in complex gut communities, as the genes encoding metabolic enzymes allow detection and prediction of individual activities in microbial genomes and microbiome sequencing data. Linking drug metabolism to microbial genes can be accomplished in multiple ways, including rationally searching genomes for enzymes with the requisite catalytic capabilities, using RNA-Seq to identify genes that are specifically upregulated in response to a drug, and using comparative genomics to associate genes with metabolic capabilities.



An estimated 70% of gut microbial diversity is uncultivated, making it challenging to characterize their activities. Donia and co-workers used functional metagenomics, which introduces DNA isolated directly from a complex microbiota into a heterologous host, to identify a hydrocortisone-metabolizing gut bacterial enzyme [6]. Cholesterol metabolizing enzymes were also recently discovered in uncultured gut bacteria by correlating the presence of microbial genes in microbiomes with metabolomics data [7]. Both strategies may be useful for investigating drug metabolism by uncultured organisms.

IDENTIFYING NEW METABOLIC ACTIVITIES

Until 2019, approximately 60 examples of gut microbial drug metabolism were reported. Two recent studies leveraged approaches from high-throughput screening and experimentation to perform large scale surveys of gut microbial drug metabolism, greatly expanding the scope of known transformations. Goodman and co-workers screened 76 human gut bacterial isolates for their ability to metabolize 271 small molecule drugs and found that two thirds of the drugs were depleted by at least one organism [8]. The Donia group performed an analogous screen of 575 drugs using a patient gut microbiome sample ex vivo and uncovered 45 new transformations [6]. These efforts suggest the scope of drugs subject to metabolism may be larger than previously known; however, the vast majority of these newly reported activities have not yet been confirmed in vivo, so their relevance for patients is unknown.



MANIPULATING GUT MICROBIAL DRUG METABOLISM

Once the gut microbiota has been found to transform a small molecule drug, a logical next step is to ask how this activity may be controlled, both to assess the consequences of metabolism for drug action and to improve patient therapy should metabolism prove detrimental. Various methods have been employed to achieve this goal. Using gnotobiotic animal models (germ-free animals colonized in a controlled manner with a defined microbiota), one can compare communities containing either drug metabolizing gut strains or deletion mutants missing specific activities. The utility of this approach was nicely illustrated by the Goodman lab's studies of brivudine [5].

However, genetic manipulation is challenging in native, complex microbial communities, prompting evaluation of alternative approaches. One potential strategy is to leverage knowledge of gut bacterial physiology to guide manipulation of the gut environment via dietary interventions. For example, digoxin Turnbaugh and co-workers noted that the presence of L-arginine downregulates drug metabolism by *E. lenta* [2]. They then showed that administering protein-rich diets to gnotobiotic mice colonized with *E. lenta* reduced drug inactivation *in vivo*.

Another exciting strategy is to identify small molecules that inhibit the activity of gut microbial drug metabolizing enzymes, as pioneered by the Redinbo lab in their studies of irinotecan metabolism. Irinotecan is a prodrug that is metabolized by host cells to the active topoisomerase inhibitor SN-38. SN-38 is metabolized by the host via glucuronidation, which produces an inactive conjugate (SN-38G). This metabolite is excreted into the intestine, where the glucuronide is removed by gut bacterial β -gluco-

ronidase (GUS) enzymes. This reactivation causes dose-limiting gastrointestinal tract toxicity. The Redinbo group used high-throughput screening to identify selective inhibitors of gut bacterial GUS enzymes, and found they prevented the severe side effects caused by irinotecan in a mouse model [9]. Subsequent work revealed that these compounds increase the efficacy of irinotecan by limiting its toxicity [10]. Together, this work has provided exciting proof-of-concept for therapeutically targeting gut bacterial metabolism and has prompted additional inhibitor discovery efforts.

FUTURE FRONTIERS

The successful development of GUS inhibitors as therapeutic candidates highlights one way in which gaining a molecular understanding of gut microbial drug metabolism could benefit patients. Another area that could be transformed by this knowledge is precision medicine. With an understanding of how specific therapeutics are metabolized by gut microbes, physicians could one day use microbiome sequencing data or microbiota-based diagnostic assays in deciding whether and how to prescribe particular medications.

Our growing appreciation of gut microbial drug metabolism may also influence the drug discovery process itself. Due to past associations with toxicity and side effects, many functional groups known to be transformed by gut bacteria are typically avoided by medicinal chemists. One could imagine uncovering new, unanticipated transformations early in drug development by screening individual gut microbes or complex patient communities for metabolism *ex vivo*, similarly to how drug candidates are typically tested for metabolism by host enzymes. Differences in gut microbiota composition and functions between animal models and humans should be taken into account in preclinical and clinical studies.

Finally, it may be advisable to incorporate microbiome sample collection and analysis for drug metabolism into clinical trials. Correlating metabolism with differences in toxicity or efficacy might help in interpreting the results of such trials and defining target patient populations.

CONCLUSION

In summary, the last decade has witnessed great leaps in our understanding of the molecular mechanisms underlying gut microbial drug metabolism and its consequences for drug efficacy. Further efforts to explore this exciting research area are poised to advance precision medicine and drug discovery.



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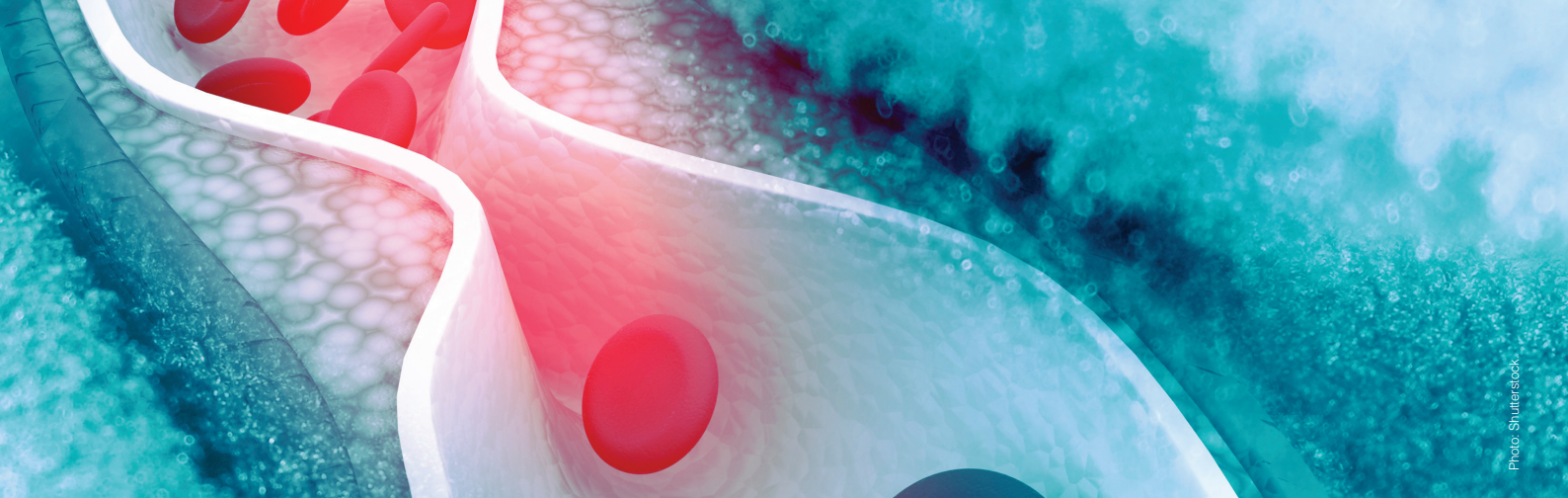


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COMMENTED ARTICLE ADULTS' SECTION



By Prof. Harry Sokol
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❖ CHOLESTEROL METABOLISM BY UNCULTURED HUMAN GUT BACTERIA INFLUENCES HOST CHOLESTEROL LEVEL

*Comments on the original article of Kenny et al.
(Cell Host & Microbe 2020 [1])*

The human microbiome possesses extensive metabolic capabilities but our understanding of the mechanisms linking gut microbes to human metabolism remains limited. In this article, the authors focused on the conversion of cholesterol to the poorly absorbed sterol coprostanol by the gut microbiota to develop a framework for the identification of functional enzymes and microbes. By integrating paired metagenomics and metabolomics data from existing cohorts with biochemical knowledge and experimentation, the authors predicted and validated a group of microbial cholesterol dehydrogenases that contribute to coprostanol formation. These enzymes are encoded by *ismA* genes in a group of uncultured microbes, which are prevalent in geographically diverse human cohorts. Individuals harbouring coprostanol-forming microbes have significantly lower faecal cholesterol levels and lower total serum cholesterol with effects comparable to those attributed to variations in lipid homeostasis genes. Thus, cholesterol metabolism by these microbes may play important roles in reducing intestinal and serum cholesterol concentrations, directly impacting human health.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Cholesterol is a key biological molecule that functions as a structural component of all animal cell membranes and is a precursor of steroid hormones, vitamin D, and bile acids. Two main sources of cholesterol are thought to influence concentrations

of this metabolite in serum: endogenous cholesterol synthesised in the liver and exogenous cholesterol derived from dietary components of animal origin (**Figure 1**). The cholesterol synthesised in hepatocytes is transported to the gallbladder and is then secreted into the small intestine along with other bile salts. In the intestine, biliary cholesterol (~1–2 g/day) mixes with

dietary cholesterol (~0.2–0.4 g/day in the average American diet), and both sources are eventually transported into enterocytes for packaging into lipoprotein particles and secretion into the plasma. Hypercholesterolaemia is a risk factor for cardiovascular disease (CVD), which is the cause of one-fourth of all deaths in industrialised countries.

Reducing cholesterol transport in the intestine is a clinically validated strategy for lowering serum cholesterol levels. A range of gut microbes metabolise and modify dietary and host-derived molecules in the small intestine. Because both sources of cholesterol pass through this environment, the gut microbiota may influence serum cholesterol levels. Indeed, microbiota transfer from human donors with elevated serum cholesterol levels can impart this hypercholesterolaemia phenotype to mice [2, 3]. Other studies have reported that administering specific bacterial species can have cholesterol-lowering effects [4]. However, the precise mechanisms underlying these observations are currently unknown. The gut microbiota may exert cholesterol-lowering effects by metaboli-

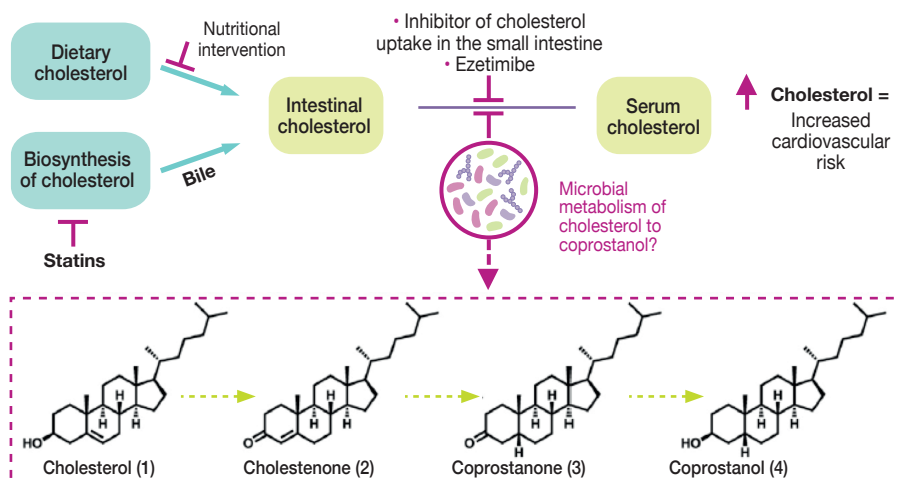


KEY POINTS

- Some bacteria found in the human intestinal microbiota possess enzymes belonging to the *ismA* family capable of breaking down cholesterol.
- The presence of *ismA*⁺ species in gut microbiota is associated with decreased faecal and serum cholesterol in humans
- The effect of *ismA*⁺ species on serum cholesterol is on par with human genetics

▼ FIGURE 1 Levels of serum cholesterol are important for human health and can be modulated by a variety of factors, including the potential metabolism of cholesterol by the gut microbiota.

Intestinal cholesterol levels are influenced by both dietary and host-derived cholesterol. Intervention by changes in diet or use of statins both affect levels of intestinal cholesterol, while the use of ezetimibe blocks uptake of intestinal cholesterol. Gut microbial metabolism of cholesterol may also serve to reduce cholesterol absorption in the intestine, resulting in lower serum cholesterol levels. The proposed pathway for microbial conversion of cholesterol (1) to coprostanol (4) in the microbiota involves the intermediates cholestenone (2) and coprostanone (3).



sing intestinal cholesterol to coprostanol (Figure 1), which would reduce the amount of cholesterol absorbed from the intestine.

This microbiota-dependent transformation has been known to occur in humans since the early 1900s. Several coprostanol-generating gut bacteria with similar physical and biochemical characteristics have been reported from a variety of different sources including rats, baboons, and humans. However, most of these strains are not currently available and were never sequenced. Early work showed that coprostanol formation by this group of gut bacteria proceeds through an indirect reduction pathway involving the initial oxidation of cholesterol (1) to cholestenone (2), followed by reduction of the D4,5 double bond to form coprostanone (3), and subsequent re-reduction of ketone to generate coprostanol (4) (Figure 1). The bacterial enzymes responsible for this metabolism were never identified. More recently, other reports have implicated additional phylogenetically diverse gut bacteria in coprostanol formation [5]. While efforts to elucidate how gut microbial metabolism of cholesterol affects human serum cholesterol levels span over 100 years, mechanistic support for this connection has remained

elusive due to a limited understanding of the gut microbes, genes, and enzymes responsible for coprostanol formation.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

The authors used a multi-disciplinary strategy to discover gut bacterial enzymes. This strategy, based on correlations between metagenomics and metabolomics data from existing human cohorts, identified and characterised an extensive family of cholesterol dehydrogenase enzymes from a clade of uncultured intestinal bacteria implicated in the metabolism of cholesterol to coprostanol. Firstly, the enzyme responsible for the first step in cholesterol transformation, called *ismA*, was identified in *Eubacterium coprostanoligenes*, a bacteria already known for this function. Analysis of sequencing data from human cohorts then identified homologous enzymes in a group of uncultured anaerobic bacteria.

The presence of these *ismA* genes in the microbiome was associated with the presence of coprostanol in stools and lower faecal cholesterol levels. Finally, to demonstrate the potential for these chole-

sterol-metabolising bacteria to influence human health, the authors showed that presence of *ismA* genes in human metagenomes is associated with a decrease in total cholesterol concentrations in serum that is on par with the effects observed from variants in human genes involved in lipid homeostasis.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

Overall, these findings confirm the role of gut-bacterial metabolism in modulating host cholesterol levels in the intestine and also, more importantly, on a systemic level. This work paves the way for the use of the gut microbiota as a predictive biomarker of high cholesterol and establishes the foundations for microbiota-targeted therapeutic interventions.

CONCLUSION

This study highlights the role of the gut microbiota in breaking down cholesterol with an effect on serum cholesterol levels. Gut microbiota could soon become the target of cholesterol-lowering therapies.

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COMMENTED ARTICLE CHILDREN'S SECTION

GUT MUCOSAL AND FAECAL MICROBIOTA PROFILING COMBINED TO INTESTINAL IMMUNE SYSTEM IN NEONATES AFFECTED BY INTESTINAL ISCHEMIC INJURIES

*Comments on the original article of Romani et al.
(Frontiers in Cellular and Infection Microbiology 2020 [1])*



By Prof. Emmanuel Mas
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Neonates can also suffer from other ischaemic and inflammatory disorders, such as small bowel volvulus and localised gastro-intestinal perforations.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

This single centre pilot study profiled the composition of the FM and MM and also the mononuclear cells of the lamina propria and the pro-inflammatory cytokines of two groups of neonates: full-term or premature. Seven infants had extensive intestinal ischaemia (EII) (5 NEC, 1 small bowel volvulus and 1 total colonic ischaemia) and 7 infants had localised intestinal ischaemia (LII) (4 isolated perforations and 3 cases of intestinal atresia). The FM of 9 full-term infants was used as control.

The MM of neonates with EII, compared with those with LII, contained: more Proteobacteria ($p = 0.049$) and fewer Bacteroidetes ($p = 0.007$) and Verrucomicrobia ($p = 0.01$) (**Figure 1**); fewer *Bacteroides*, *Lachnospiraceae*, *Ruminococcaceae* and *Akkermansia muciniphila* ($p < 0.05$).

The FM was less diverse (Shannon index) in EII than in LII ($p = 0.01$). The relative abundance for the MM was similar between EII and LII for Proteobacteria and Firmicutes

In the first weeks of life the microbiota plays a crucial role in health by acting as a barrier against the invasion of pathogens and by maintaining intestinal immune homeostasis. Changes in the ecology of the faecal microbiota (FM) have been reported in neonates with intestinal ischaemia. The aim of this study was to describe the FM, the mucosal microbiota (MM) and mucosal immunity in these patients.

Fourteen neonates underwent intestinal resection due to intestinal ischaemia. Two groups were identified on the basis of lesion severity: extensive (EII) and localised intestinal ischaemia (LII). This study showed the variations in FM and MM in the EII and LII groups.

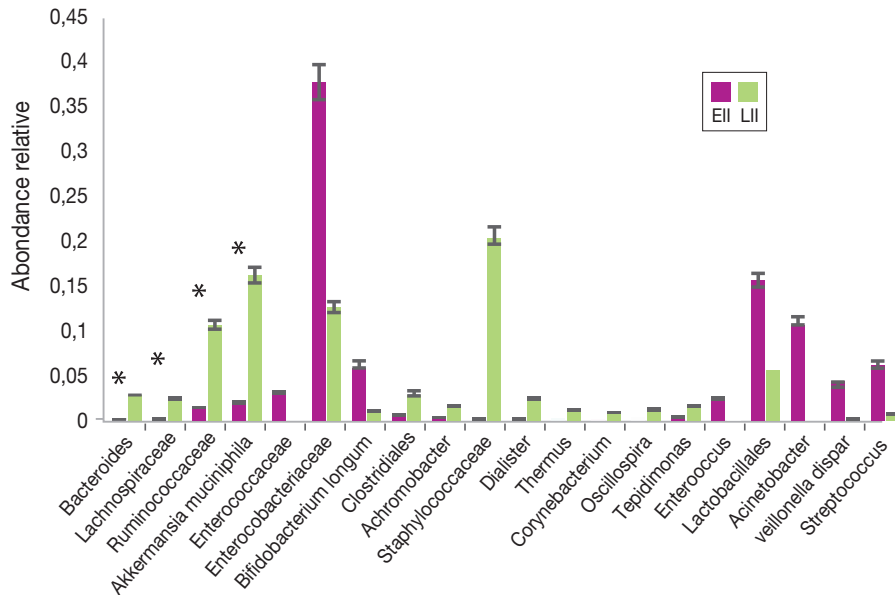
WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

The intestinal microbiota of neonates is characterised by lower bacterial diversity and a higher proportion of pathogenic bacteria. Moreover, their intestinal immune system is immature. These two factors modify the intestinal epithelial barrier and enhance the production of pro-inflammatory mediators.

Necrotising enterocolitis (NEC) is an ischaemic and inflammatory disorder of the gastro-intestinal tract which affects premature neonates. The physiopathology of NEC remains poorly understood but intestinal dysbiosis is present, and also an inflammatory process. The use of antibiotics and antacids promote dysbiosis and also increases the risk of onset of NEC.

▼ FIGURE 1

Phyla of the microbiota associated with the gastro-intestinal mucosa in groups EII and LII.



($p < 0.05$). Similarly, a bacterial distribution with more Enterobacteriaceae in EII and more Ruminococcaceae, Bacteroides, Lachnospiraceae and Staphylococcaceae in cases of LII.

The EII group exhibited increased numbers of lymphocytes B, T and NK (Natural Killer), in particular T CD3+ lymphocytes, TH17 (Figure 2A) and reduced numbers of T lymphocyte regulators (Tregs), with increased numbers of cells expressing TNF α (Figure 2B) and INF γ (Figure 2C).

WHAT ARE THE CONSEQUENCES IN PRACTICE?

This pilot study confirms that lack of bacterial diversity and the predominance of Enterobacteriaceae are risk factors for NEC, as is a reduction in numbers of Akkermansia muciniphila.

Correction of this dysbiosis could modify the TH17/Tregs imbalance and reduce the production of mediators of inflammation (TNF α and INF γ).



KEY POINTS

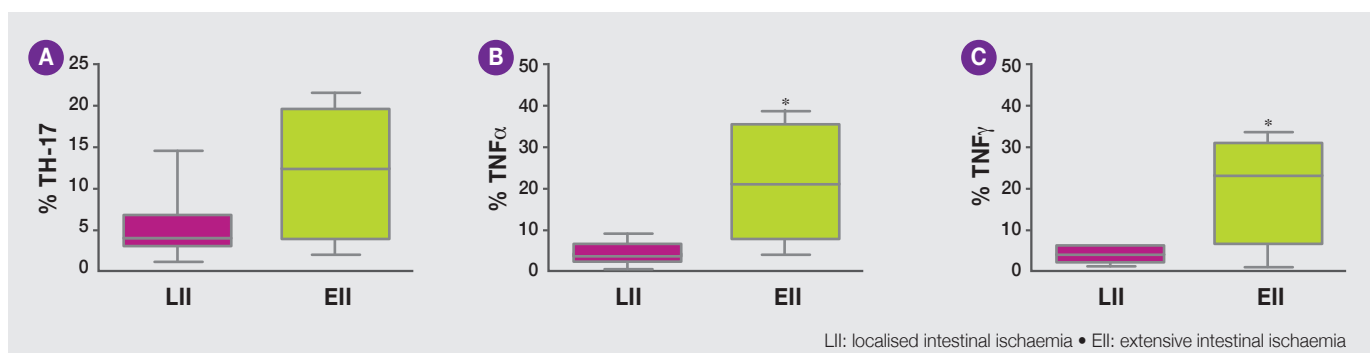
- Necrotising enterocolitis is a severe gastro-intestinal pathology which affects premature neonates
- Anomalies of the faecal microbiota and the gastro-intestinal-associated microbiota may be involved in the inflammatory and ischaemic processes NEC

CONCLUSION

The faecal microbiota and the gastro-intestinal mucosal microbiota have specific characteristics in premature neonates with ischemic lesions. Additional studies are needed to determine the role of these bacteria in the inflammatory and ischaemic process of NEC.

▼ FIGURE 2

Immunological profile of the intestinal mucosa in groups EII and LII: mononuclear cells of the lamina propria expressing IL-17 (A), TNF α (B) and INF α (C).



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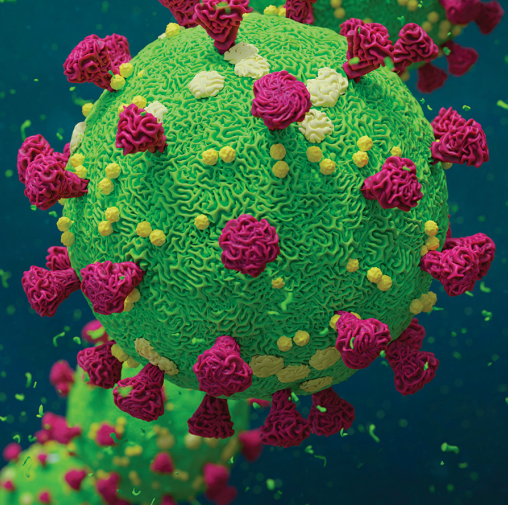


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MICROBIOTA & COVID-19

THE GUT-LUNG AXIS DURING VIRAL RESPIRATORY INFECTIONS

The novel coronavirus (SARS-CoV-2) disease 19 (COVID-19) reminds us that interactions between the gut microbiota and the immune system are essential during viral respiratory tract infections. Respiratory viruses can trigger gastrointestinal symptoms emphasizing the role of the lung-gut axis in disease. Clinical studies and experimental models indicate that acute viral respiratory infections alter the composition and functions of the gut microbiota, an essential component of human health. Here, we review these major changes and discuss the potential causes of intestinal dysbiosis. We also present the consequences of gut dysbiosis that develops during infection on secondary disease outcomes. Lastly, we suggest interventional strategies that might be used to target the gut microbiota in order to reduce the viral respiratory disease severity.

THE ONGOING THREAT OF RESPIRATORY VIRAL INFECTIONS

Viral respiratory tract infections are still a major concern worldwide as they lead to considerable socio-economic and health issues. Despite vaccine campaigns and antiviral medications, influenza - the commonly called "flu" - remains the most impacting in terms of infected individuals (5-10% of the global population) and deaths (> 600,000 per year). Along with annual epidemics, influenza is also responsible for pandemics every 10-20 years, the most famous being the 1918-1919 Spanish flu (50 million deaths) and the most recent, the 2009 H1N1 influenza pandemic (400,000 excess deaths) [1]. Pandemics are not restricted to influenza, as exemplified by the COVID-19 [2]. Of great concern

is the increasing frequency of pandemics occurring over the last few decades, a phenomenon explained in part by climate changes and human practises, in general.

THE GUT MICROBIOTA IN HEALTH AND DISEASES

The gut microbiota has a crucial role in the maintenance of human health and is critical in the control of (respiratory) infections [3, 4]. Many factors can alter the diversity and composition of the gut microbiota, leading to dysbiosis. Among them, disease situations, such as infections and chronic inflammatory or metabolic disorders, can trigger profound alteration of the gut microbiota's composition and function. Changes in intestinal bacterial communities can influence disease outcomes even in distant organs (including the lungs) [3, 4], as



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demonstrated by transfer experiments with dysbiotic microbiota. Below, we summarize the effects of acute viral respiratory infections on the gut microbiota.

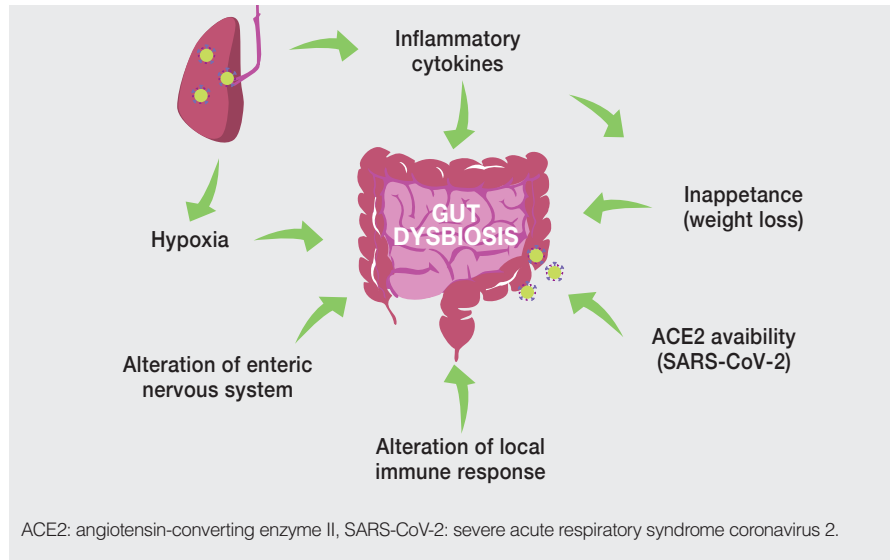
VIRAL RESPIRATORY TRACT INFECTIONS LEAD TO GUT DYSBIOSIS

Clinical evidences suggest a gut microbiota dysbiosis during influenza infection. The relative abundance of *Actinobacteria*, *Erysipelotricha*, *Clostridia* and beneficial butyrate producers (*Lachnospiraceae* and *Ruminococcaceae* families) is decreased in patients H1N1. On the other hand, opportunistic pathogens such as *Escherichia-Shigella* and *Prevotella* develop [5]. In experimental (mouse) models, transient gut dysbiosis also occurs with a peak at 5-7 days post-infection [6-9]. Changes occurred at taxonomic levels with no change in alpha diversity. Infection blunts the growth of health-promoting bacteria such as *Lactobacilli*, *Bifidobacteria*, and segmented filamentous bacteria. Many species capable of fermenting dietary fibres into short-chain fatty acids (SCFAs) are affected. In line, the production of SCFAs dramatically drops during influenza infection [9]. The reduced levels of beneficial commensals associate with the overgrowth of deleterious bacteria including *Gammaproteobacteria* (*Escherichia coli*) and mucus-degrading bacteria such as *Verrucomicrobia* (*Akkermansia*

▼ FIGURE 1

Potential causes of gut dysbiosis during a respiratory viral infection.

The impact (and the causes leading to) of respiratory viral infection on the lung microbiota is beyond the scope of this review.



genus) and *Ruminococcus*. SARS-CoV-2 infection also triggers gut microbiota alterations in patients, including lower abundance of butyrate producers such as several genera from the *Ruminococcaceae* and *Lachnospiraceae* (*Roseburia*) families [5, 10]. On the other hand, a significantly higher relative abundance of opportunistic bacterial pathogens including *Streptococcus* (class Bacilli), *Rothia* and *Actinomyces* was observed. Of note, overgrowth of opportunistic fungal pathogens (*Aspergillus* and *Candida* spp) was also described in COVID-19 patients [11]. Collectively, viral respiratory infections lead to depletion of beneficial commensals and enrichment of opportunistic harmful pathogens. Putative changes in the gut microbiota's structure, composition and functional activity might be biomarkers of disease severity.

MECHANISMS LEADING TO GUT DYSBIOSIS

There are probably several causes of gut dysbiosis during viral respiratory infections; these may include the release of inflammatory cytokines and the reduced food intake (Figure 1). Infection induces substantial weight loss due to a loss of appetite. Pair-feeding experiments in mice clearly indicate that a rapid fall in food intake mimics the changes in the gut microbiota observed during influenza infection [8]. Recent evidence suggests a role for $\text{TNF}\alpha$ in inappetence-associated dysbiosis during viral respiratory infection [12]. Type I and II interferons, which are essential for the host

antiviral response, also play a part in gut dysbiosis [5,6]. Hypoxia (a feature of acute viral respiratory infection), alterations of the enteric nervous system and dysregulated local immune response are also likely to participate in gut dysbiosis [13] (Figure 1). In the case of COVID-19, along with these mechanisms, local viral replication is likely to play a role in gut dysbiosis. Angiotensin-converting enzyme II (ACE2), the receptor of SARS-CoV-2, is instrumental to

maintain the gut's microbial ecology. Considering the lack of available ACE2 during SARS-CoV-2 infection, one expects that this might influence the composition and functions of the gut microbiota [13].

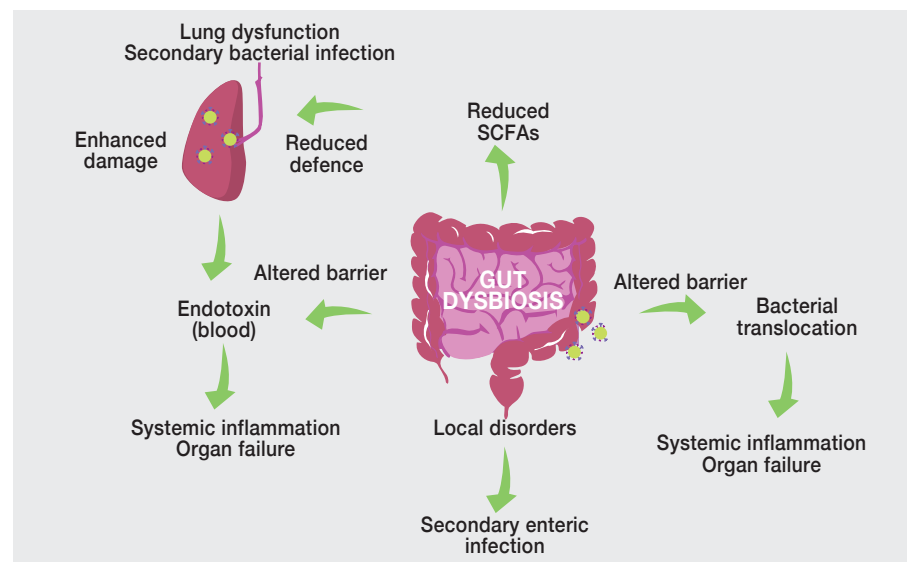
CONSEQUENCES OF GUT DYSBIOSIS ON SECONDARY OUTCOMES

Gut dysbiosis during viral respiratory infection has local and distal consequences and might be an important contributor of disease severity and fatal outcomes (Figure 2). Patients experiencing viral respiratory infection can develop gastroenteritis-like symptoms such as abdominal pain, nausea, vomiting and diarrhoea. Alterations of the gut microbiota may explain these disorders. It is also likely that altered gut microbiota including the emergence of pathobionts and mucus degrading bacteria play a role in intestinal inflammation and disruption of the gut barrier integrity [6]. In turn, intestinal barrier leakage might increase endotoxin concentrations in the blood, ultimately triggering inflammation, cytokine overproduction and lung dysfunctions [14]. Acute viral respiratory infections can lead to secondary enteric infections and sepsis. Gut dysbiosis (and drop of SCFAs) might be important in this setting. Indeed, SCFAs play a key role in intestinal homeostasis, barrier integrity and control of enteric pathogens [15]. Along with local disorders, our recent data show that gut dysbiosis can remotely hamper host defense in the lungs [9] (Figure 2).

▼ FIGURE 2

Potential consequences of gut dysbiosis during a respiratory viral infection.

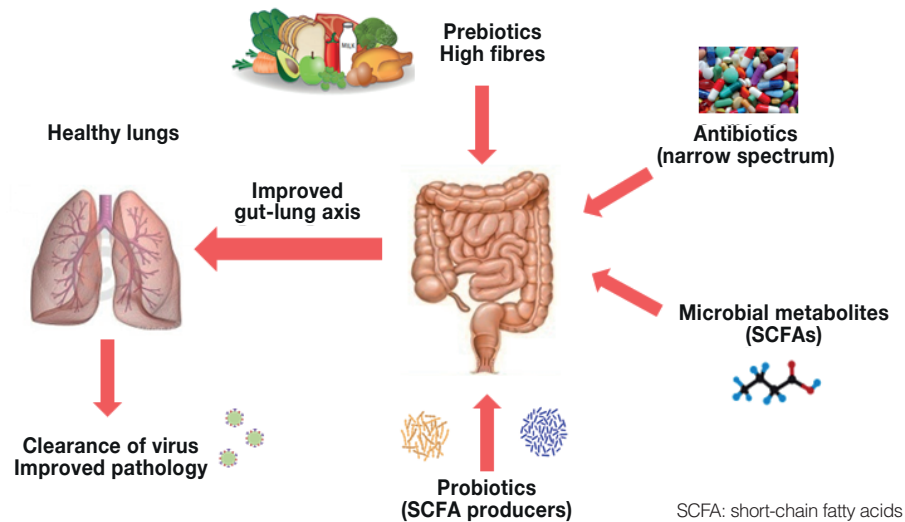
Alteration of the gut microbiota during a viral respiratory infection is likely to initiate or maintain intestinal disorders, favour systemic disorders, aggravate lung damage and participate in bacterial superinfection (through reduced innate defence).



▼ FIGURE 3

Strategies targeting the gut microbiota to control respiratory viral infections and to lower disease outcomes.

Experimental evidence demonstrate that a healthy microbiota plays a role of the management of viral respiratory infection. Different approaches, including prebiotics and probiotics, to optimize the gut-lung axis are presented. Upon dysbiosis due to a viral respiratory infection, approaches like antibiotic treatment targeting pathobionts (preferably with a narrow-spectrum drug) and microbiota-derived metabolites, such as SCFAs, might be relevant.



in individuals with a general imbalance of the gut microbiota such as the elderly and individuals with co-morbidities, well known to be more susceptible to infections. Approaches like (i) dietary ingredients intended to nourish our beneficial microorganisms (like prebiotic fibres) and (ii) indigenous bacteria (known as probiotics) to replenish our gut with missing beneficial microorganisms and to optimize their metabolic functions, might be relevant. These strategies, especially personalized (i.e. based on the analysis of the gut microbiota in the “at risk” population) might improve clinical outcomes and accelerate the recovery of patients that experience acute viral respiratory tract infections. Probiotics, including some *Bifidobacteria* and *Lactobacillus* spp, can decrease the severity of influenza infection, through still undetermined mechanisms [17]. Of highly topical concern, a recent study showed that oral bacteriotherapy in addition to the standard drug therapy showed promising clues in the management of COVID-19 patients [18].

In healthy conditions, the gut microbiota remotely arms the lungs against bacterial infection, in part by reinforcing the bactericidal activity of pulmonary macrophages [16]. During influenza, this axis is altered and opportunistic bacteria invade the lungs leading to bacterial superinfection, a major cause of death during influenza epidemics and pandemics [1]. We have shown that the reduced production of acetate (the major SCFAs) by the gut microbiota is partly responsible for this effect [9]. Collectively, dysbiosis might influence the gastrointestinal and pulmonary signs and symptoms (and overall mortality) of viral respiratory in-

fections. Can we use the gut-lung pathway as a basis to better control the severity and mortality rate of viral respiratory infections?

INTERVENTIONAL PERSPECTIVES

The gut microbiota is vital in the lung's defences against respiratory infection and interventional strategies that target intestinal commensals to preventively arm the lungs against viral pathogens and to protect the microbiota against the perturbations associated with viral infections are of major interest (Figure 3). This is particularly true

CONCLUSION AND PERSPECTIVES

The gut-lung axis is important during viral respiratory tract infections. Alterations of the gut microbiota plays a part in secondary outcomes. The gut microbiota therefore represents a target to limit disease severity. Solutions for disease management include dietary ingredients (like prebiotic fibres) and probiotics.

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CONGRESS REVIEW



By Dr. Dragos Ciocan
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EJFHOD 2020

Despite the Covid-19 pandemic, this year we were able to benefit from an on-line version of the *Journées francophones d'hépto-gastroenterologie* (French-speaking hepato-gastroenterology congress) with the advantage of being able to access presentations recorded between 3 and 20 July 2020. These eJFHOD reached a total of 7,924 users, and 172,937 pages were viewed. As each year, original studies on the intestinal microbiota (IM) were presented at this congress.

MICROBIOTA AND COLORECTAL CANCER

Third most frequent cancer in humans, sporadic colorectal cancer (CRC) develops following interactions between the host and its environment, and the IM is thought to be implicated [1]. Professor Sobhani presented the results of a study which investigated the links between epigenetic mechanisms promoted by bacteria of the IM and the onset of CRC [2]. Mice transplanted with faecal samples from patients with CRC developed pre-cancerous colonic lesions, associated with an increase in hypermethylated genes. Donors with CRC exhibited methylation anomalies of several gene promoters associated with intestinal dysbiosis. Using the identified microbial and epigenetic signatures, a pilot study (n = 266) was conducted in humans in order to develop a blood test for the diagnosis of CRC. A cumulative methylation index (CMI, measuring the hypermethylation level of 3 genes) was identified as a predictive factor in the onset of CRC. These results were validated in a prospective cohort of 1,000 patients. Intestinal dysbiosis in patients with a positive CMI was characterised by an increase in pro-methylating bacterial species. This work indicates that intestinal

dysbiosis associated with CRC could promote colon carcinogenesis via deregulation of the methylation of certain genes. The cumulative hypermethylation index (CMI) and/or pro-methylating bacteria are thus potential biomarkers for CRC diagnosis, or be used in the evaluation of the effects of treatments modulating the IM in patients with CRC.

A NEW DYSBIOSIS MARKER IN CROHN'S DISEASE

In a study coordinated by Professor Seksik, the authors studied the role of MAM (microbial anti-inflammatory molecule, produced by *Faecalibacterium prausnitzii* and reduced in patients with Crohn's disease, CD [3]) as a biomarker of intestinal dysbiosis and diagnostic aid in CD. The authors showed that loss of MAM is associated with the diagnosis of CD. This preliminary study in a small number of patients (24 patients in relapse, 24 in remission and 12 healthy controls) paves the way to the diagnosis of CD based on the IM, but these preliminary results require validation in independent cohorts.

A NEW THERAPEUTIC PERSPECTIVE IN IBD

It is known that bacteria detect and respond to environmental signals (an ability called Quorum Sensing). Of the molecules which are part of this system, 3-oxo-C12:2 is low in patients with chronic inflammatory bowel disease (IBD), this reduction appears to be correlated with



JULY 2020

the observed intestinal dysbiosis [4]. In a study presented by D. Aguanno, the authors studied the impact of this molecule on the epithelial cells of the intestine and showed that this did not modify paracellular permeability but attenuated the deleterious effects on the tight junctions induced by pro-inflammatory cytokines. In a second study, Coquant et al. showed that 3-oxo-C12:2 exerted an anti-inflammatory effect on immunoreactive cells, partly mediated by the T2R138 receptor. This molecule may therefore have protective effects on the intestinal barrier, modulate the inflammatory response and thus represent a novel therapeutic perspective in IBD.

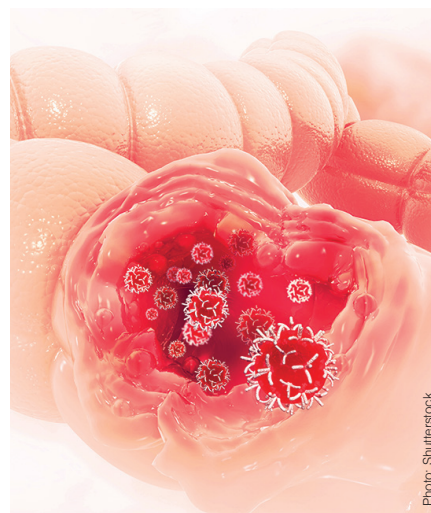


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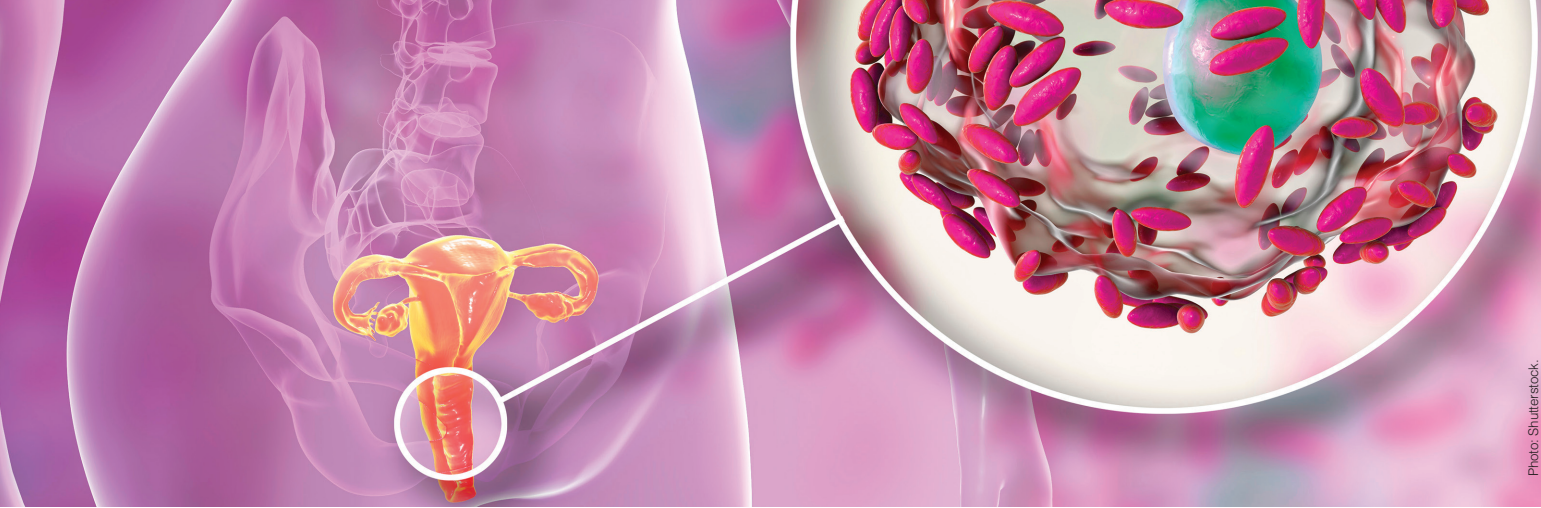


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LITERATURE SELECTION

VAGINAL MICROBIOTA

❖ VAGINAL DYSBIOSIS AND RECURRENT IMPLANTATION FAILURE

Fu M, Zhang X, Liang Y, *et al.* Alterations in vaginal microbiota and associated metabolome in women with recurrent implantation failure. *mBio* 2020 ; 11 : e03242-19.

Recurrent implantation failure (RIF) is defined as a failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a woman under the age of 40 years. Embryonal and uterine factors or maternal systemic diseases may cause RIF, but some women do not have recognizable etiology. The authors focused on the vaginal microbiota and metabolome of women with RIF. They found that RIF patients suffered vaginal dysbiosis, having a more diverse and abundant bacteria with an increase of many anaerobic and aerobic bacteria which could be linked to bacterial vaginosis and aerobic vaginitis or urinary tract infection, respectively. Conversely, at genus level their vaginal microbiota was decreased in *Lactobacillus* (LB); at species level *L. iners* was reduced and *L. crispatus* was the most abundant species in the RIF group. Increased vaginal bacterial diversity, LB depletion and related metabolic changes could serve as biomarkers capable of predicting the risk of RIF.



By Prof. Markku Voutilainen
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 of Gastroenterology, Turku, Finland*

❖ THE ROLE OF VAGINAL MICROBIOTA IN URINARY TRACT INFECTIONS

Lewis A, Gilbert NM. Roles of the vagina and the vaginal microbiota in urinary tract infection: evidence from clinical correlations and experimental models. *GMS Infect Dis* 2020 ; 8 : Doc02.

This review summarizes the role played by vaginal microbiota in urinary tract infections (UTI) as mounting evidence indicates that vagina may serve as a reservoir for uropathogens and increase susceptibility to UTI. *Escherichia coli* is the commonest cause of UTI and can colonize the vagina, which can be increased if the vaginal *Lactobacillus* (LB) colonization is reduced. Some vaginal bacteria are frequently detected in the urine but are underappreciated as uropathogens, because they are difficult to detect in routine clinical practice. For example, bacterial vaginosis (BV) is characterized by Gram-negative anaerobes, species belonging to Actinobacteria and Firmicutes phyla while LB is reduced and BV patients have a higher UTI risk. *Gardnerella vaginalis* is detected in BV and can cause acute or recurrent UTI. Group B *Streptococcus* may cause both aerobic vaginitis and UTI. Finally, some vaginal bacteria may enter the urinary tract and can transit briefly, cause immunomodulation or injury and unbalanced the host-pathogen interactions to influence the outcomes of uropathogenesis.



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SKIN MICROBIOTA

❖ THE ROLE OF SKIN MICROBIOTA IN ITCH

Kim HS, Yosipovitch G. The Skin Microbiota and Itch: Is There a Link? *J Clin Med* 2020 ; 9 : 1190.

The authors discuss the role of skin microbiota in the pathogenesis of itch. Itch sensation is mediated via epidermal nerve fibres (pruriceptors) driving by chemical mediators that originate from a complex interaction between keratinocytes (KC), inflammatory cells, nerve endings and the skin microbiota, relaying itch signals to the brain. Skin dysbiosis is characterized by production of proteases, pathogen-associated molecular patterns, and toxins, leading to skin barrier damage. Mast cell degranulation induced by delta-toxin

prompt inflammation and itching. Skin microbiota and brain communicate via neurochemicals (acetylcholine, histamine, catecholamines, corticotropin) originate from skin microbiota. Stress intensifies itch via the skin-brain axis, where the amygdala seems to modulate itching sensation via microbial signals. Chronic stress increases cortisol production, directly activates skin bacteria by increasing the virulence of skin pathogens, leading to a weakening of the skin barrier and to an aggravation of the itch sensation. The authors conclude that cosmetics/transdermal drugs that modulate skin microbiota might have the potential to ameliorate itch.



❖ SKIN MICROBIOTA IN PSORIASIS

Quan C, Chen X-Y, Li X, *et al.* Psoriatic lesions are characterized by higher bacterial load and imbalance between *Cutibacterium* and *Corynebacterium*. *J Am Acad Dermatol* 2020 ; 82 : 955-61.

The authors examined the microbiota in psoriatic lesions and unaffected skin in psoriasis vulgaris (PS) patients and healthy controls by quantitative PCR and 16S rRNA sequencing. Higher bacterial load and lower diversity was observed in PS lesions than patients unaffected and controls' skin. *Cutibacterium* (Cu) was reduced in lesions, whereas *Corynebacterium* (Cr) was increased. Compared with patients' unaffected skin, Cr/Cu + Cr ratio was higher in the lesions. These findings indicate that PS was the major cause for the imbalance between Cu and Cr between lesions and unaffected skin or controls. Cr load correlated with the severity of PS lesions, whereas Cu load showed correlation with the abnormality of skin capacitance.

The present study suggests that skin microbiota might play a significant role in the pathogenesis of PS.



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GUT MICROBIOTA



❖ TUBERCULOSIS AND GUT MICROBIOTA

Eribo OA, du Plessis N, Ozturk M, *et al.* The gut microbiome in tuberculosis susceptibility and treatment response: guilty or not guilty? *Cell Mol Life Sci* 2020 ; 77 : 1497-509.

5-10% of persons infected worldwide with *Mycobacterium tuberculosis* (MT) will progress to active TB. Recent research highlighted that gut dysbiosis induced by treatment could be involved in the disease development by compromising immune protection against MT. This review summarizes how the gut microbiota, lung immunity could be linked during the disease; and how the gut microbiota dysbiosis induced by the protracted anti-TB antibiotics treatment is involved to an increased susceptibility to MT re-infection or TB recrudescence after successful treatment cure. The authors also indicate that the gut microbiota biosignature might help recognizing healthy from active TB patients.

❖ KETOGENIC DIET, GUT MICROBIOTA AND IMMUNE RESPONSES

Ang QY, Alexander M, Newman JC, *et al.* Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. *Cell* 2020 ; 181 : 1263-75.

Very low-carbohydrate, high-fat ketogenic diet (KD) is used in refractory pediatric epilepsy, and some evidence supports KD use in diabetes and obesity but their metabolic and immune consequences remain unclear. The authors examined the impact of KD on human and mice gut microbiota via metagenomics and metabolomics and compared with high-fat diets impact: several bifidobacterial species were reduced, and an increase of Firmicutes/Bacteroidetes ratio induced by high-fat diet reversed. Increased plasma β -hydroxybutyrate levels inhibit bifidobacterial growth. KD reduced proinflammatory Th17 cell accumulation in mice adipose tissue and inhibited induction of intestinal Th17 cells.



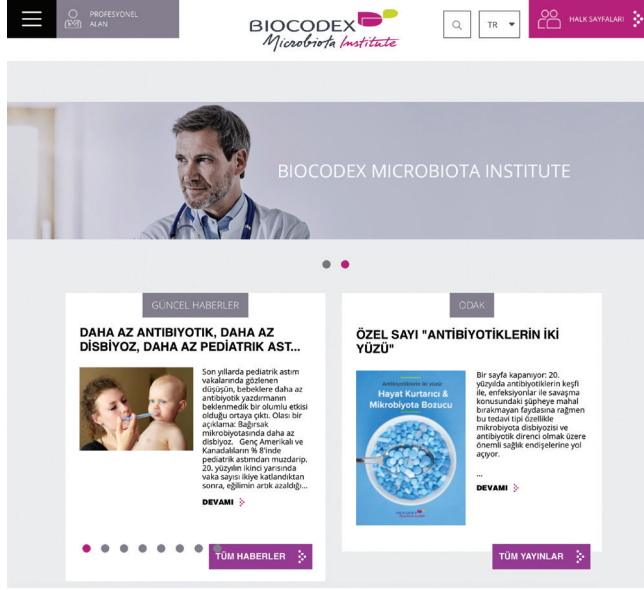
NEWS

BIOCODEX MICROBIOTA INSTITUTE

NEW BORN

Welcome to our new Turkish website. Biocodex Microbiota Institute is now available in 7 languages.

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THANK YOU!

You were more than 1.5 million visitors to Biocodex Microbiota Institute website in 2020. It shows the growing interest on microbiota and its consequences on health.

GROWING UP

Biocodex Microbiota Institute is today the largest international platform dedicated to educate both Health Care Professional and General Public on microbiota.

DON'T MISS!

From 18 to 24th of November 2020, the World Health Organization (WHO) has hold the World Antimicrobial Awareness Week (WAAW) to increase attentiveness among the general public on antimicrobial resistance. In that perspective, Biocodex Microbiota Institute has developed a special edition folder "A Janus face of Antibiotics: Live savers and Microbiota Disrupters". The objective of this folder is to explain antibiotic consequences on microbiota to reinforce WHO's message:

- be cautious when using **antibiotics**,
- demonstrate the importance of **microbiota on health**

You can visualize this folder or download it here: <https://www.biocodexmicrobiotainstitute.com/pro/services/publications/dossiers-thematiques/les-2-visages-des-antibiotiques-sauveurs-de-vie-et-perturbateurs-de-microbiote-0>.

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