Microb Health Dis Dis 2021; 3: e440

EDITORIAL: THE IMPAIRMENT OF THE INTESTINAL MICROBIOTA: A NEW "DISEASE" IN "NEW" PATIENTS?

T. Dionisi[1], A. Gasbarrini[2], G. Ianiro[1], G. Addolorato[1], G. Gasbarrini[1]

[1]Department of Internal Medicine and Gastroenterology, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy
[2]Department of Oncologic and Degenerative Spine Surgery, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Corresponding Author: Tommaso Dionisi, MD; e-mail address: dionisitommaso@gmail.com

The developments in medical techniques and scientific knowledge have led to the resolution of several diseases, some of which pose a serious risk to life. Some new therapies, more and more aggressive have, on one hand, allowed the survival of patients facing diseases, such as cancer, HCV, and organ failure but, on the other hand, they are not free from complications and sequelae.

Therefore, new categories of patients have now emerged: the survivors of such pathologies, suffering from all of the resulting sequelae and presenting the complications of their therapies. The increasing use of bariatric surgery for the treatment of severe obesity and treatments for anorexia also contribute to this phenomenon.

Furthermore, the importance of the intestinal microbiota in maintaining the state of health and in the pathogenesis of numerous pathologies involving numerous organs and apparatuses is now well established. The possibility to study the characteristics of the intestinal microbiota using molecular biology techniques has provided a considerable amount of information. These have enriched the knowledge acquired through the indirect study of bacteria that evaluates the qualitative and quantitative typology of the gases produced by them, and in particular H_2, CH_4 and CO_2, with breath tests (e.g., lactulose).

Certainly, the impact of the new therapies on the intestinal microbiota has been relatively little studied and how the latter contributes in determining the state of health of patients who use them has yet to be dealt with more completely.

For example, cancer therapies have a destructive effect on the intestinal microbiota. *Chemotherapies* have been associated with a reduction in richness and microbial alpha-diversity[1-3]. Although the mechanisms of interaction are not entirely clear, direct bactericidal and bacteriostatic action and immunosuppression secondary to their use alter the composition and regulation of the microbiota[4]. Several studies[5] indicate that microbial alterations are not only temporary but may accompany the patient for a long time. This may account for many of the diseases associated with cancer survivors. An emblematic example is children who have survived *acute lymphocytic leukemia*. They face serious long-term health problems, such as obesity and metabolic diseases, cardiopulmonary toxicity, secondary neoplasms and late neurotoxic effects. It has been proposed that changes in eating behavior are related to high levels of leptin and low levels of adiponectin[6] and are associated with insulin resistance[7]. Al-

though these effects may be a direct consequence of organ damage by abdominal radiotherapy or chemotherapy, it is well known that alterations in microbial composition secondary to therapies may play a role in the regulation of these hormones and the genesis of metabolic diseases and obesity[6]. Although there is little evidence[5] of the importance of the use of probiotics in the prevention and resolution of the acute effects of anticancer therapies and nothing has yet been said about the long-term effects of such therapies, the data seem to be close enough to suggest their use.

Another emblematic case is that of *radiation enteropathy*. Intestinal overgrowth, in particular of Gram-negative bacilli, and intestinal dysbiosis that seems to persist even after radiotherapy[8] induce characteristic alterations that could be involved in the acute form of this pathology but are more easily correlated to the late form. There is evidence that patients who had an appendectomy seem to be at greater risk of developing radiation enteropathy. Considering the regulatory function of the appendix on the intestinal microbiota and the reserve of Bifidobacteria[9], the impact it has on this pathology can be deduced. Although there is evidence of the beneficial effect of probiotics, synbiotics and prebiotics on this pathology[10], the evidence is not yet strong enough to affect clinical practice.

Evidence indicates a key role of the intestinal microbiota in the response to *immunotherapy for cancer*, both in terms of efficacy and toxicity. During therapy, more than 25% of patients with colitis[11] and, to date, increased levels of Bacteroidetes and Firmicutes have been associated with a reduced incidence of gastroenterological complications[12]. However, the long-term effects of this type of therapy are not clear.

Interestingly, intestinal dysbiosis may be involved in the fear of cancer recurrence and depression in cancer survivors. Treatments and altered eating habits in these patients induce neuroinflammation and reduce neurogenesis[13]. In this sense, it has been shown that dysbiosis and intestinal permeability induce a dysfunctional process of memory genesis similar to what happens in post-traumatic stress disorder, through endotoxemia, altered communication with the vagus nerve, and reduced levels of short chain fatty acids (SCFA) and neurotransmitters. Supplementation with n-3 polyunsaturated fatty acids seems to have beneficial effects on both the fear of cancer recurrence and depression in survivors of this disease[13].

Patients undergoing *bariatric surgery* can also be included among the "new patients". Numerous studies indicate that the slimming secondary to these procedures are at least partially due to the resulting microbiological alterations. The intestinal microbiota of obese patients has shown a reduction in microbial richness and alpha diversity, an increase in Firmicutes and a reduction in Bacteroidetes and Proteobacteria phyla. Bariatric surgery has been shown to improve these alterations in the long term, acting in particular through the increase in bile acids[14], without, however, succeeding in bringing the microbiota into a state of eubiosis. In particular, the increase in *Akkermansia* sp in these patients is related to improved glycemic control, and the increase in *Bacteroides thetaiotaomicron* and Gammaproteobacteria seems to be related to weight loss[14]. According to Debedat et al[15] this increase is identified as a "paradox effect": the increase in Proteobacteria and Enterobacteriaceae is generally deleterious in many chronic intestinal diseases, and these bacteria are known to produce lipopolysaccharides, however, these patients show a reduction in intestinal permeability and systemic inflammatory state.

The *malabsorption of nutrients*, which occurs in various ways depending on the type of intervention performed, the increase in circulating trimethylamine N-oxide (TMAO), a known cardiovascular risk factor, the reduction in blood levels of vitamins B12, K, andD, and a variety of gastrointestinal symptoms expressed in different patients, are all factors that certainly require treatment. In particular, probiotics have been shown to improve gastrointestinal symptoms, to increase vitamin B12 synthesis and to enhance weight loss[16]. Screening for vitamin K deficiency is necessary for all patients for the risk of bleeding to which they are exposed[17].

According to a preliminary analysis of our patients, *interventions for lumbosacral diseases* can also have an impact on the intestinal microbiota through alteration of intestinal motility. In particular, the analysis of lactulose Breath Tests identified a significant increase in methanogenic flora in these patients even months after surgery. This data in our opinion is even more interesting when compared to what is observed in the pseudo-obstructive intestinal syndrome (Ogilvie's disease) in which an increase in hydrogen production, with methane practically absent, is observed. Probably the different aetiology of these two pseudo-obstructive forms may explain this difference, but further studies are needed to investigate the microbiota composition of these patients.

Patients with *Anorexia Nervosa* also deserve to be mentioned. The intestinal microbiota could both contribute to the etiopathogenesis of this pathology through the gut-brain axis and mediate its clinical implications through its composition. Mack et al[18] showed that the microbiota of patients with Anorexia Nervosa, although it can improve its composition and function following therapies aimed at optimal weight recovery, does not reach a composition comparable to that of the control group, remaining altered also to the clinical resolution of the disease. As a result, the production of short-chain fatty acids and gastrointestinal symptoms in many patients do not improve significantly.

A further group to be discussed in this context is that of patients eradicated from HCV. Although some evidence in the literature is not in agreement[19], Ponziani et al[20] showed that HCV therapy with *direct-acting antivirals* in patients with cirrhosis is associated with a significantly more pronounced modification of the intestinal microbiota in patients with a lower degree of fibrosis and inflammation, although this alteration is not sufficient to improve the function of the intestinal barrier. From the study on these patients, it can be seen that the improvement in liver function has a beneficial effect on the intestinal microbiota, in particular through the action of the bile acid circulation and its action on the FXR gene, controlling the abundance of Veillonellaceae and Methanobacteriaceae and also improving intestinal function. To the contrary, the improvement of dysbiosis would contribute to the control of the liver disease[20].

One aspect that deserves particular attention is the alteration of the intestinal microbiota after *solid organ transplantation*: as an example, after liver transplantation a significant change in the intestinal microbiota has been demonstrated compared to the pre-transplantation microbiota. Both a reduction in diversity and abundance of the predominant organism and at the same time dominance of a new bacterial population, which is accompanied by an increased risk of post-transplant infections, have been observed[21]. Kato et al[22] measured the diversity of the pre- and post-liver transplant intestinal microbiota and their results show that the average diversity index decreased significantly over the 21 days following transplantation, while gradually increasing over the entire observation period (2 months post-transplantation). This alteration has been associated with increased infections and acute rejection.

Further alterations in microbiota bacterial populations in liver transplant patients were detected by Matsumoto et al[23], who demonstrated a reduction in *Actinobacillus*, *Escherichia* and *Shigella* species and a significant increase in Microsporaceae, Desulfobacteriales, Eubacteriaceae and *Akkermansia* sp, while Wu et al[24] showed a significant reduction in butyrate-producing bacteria and an increase in opportunistic pathogens, such as Enterococci. This picture is similar to that of diabetic patients and could be the source of new-onset diabetes after liver transplantation[25,26]. These and other studies also contribute to demonstrating how the diversity of the intestinal microbiota can be associated with the prognosis of liver transplant patients.

Microbiota also appears to play an important role in the transplantation of other solid organs: in kidney transplantation, the microbiota has been associated with an increased risk of graft versus host disease (GvHD) and its composition has also been shown to influence the dose of immunosuppressants[27].

The intestinal microbiota is also associated with cardiac function, and its metabolites, such as TMAO can influence the outcome of cardiovascular events. It can also be assumed that due to the intestinal microbiota's key role in immune regulation, it also plays a key role in the prognosis of heart transplantation[21].

Metabolic complications after solid organ transplantation are frequent and lead to an increased risk of cardiovascular complications and reduced life expectancy and may be related to changes in the microbial intestinal composition[28]. Exposure to Sirolimus and Tacrolimus, commonly used in post-transplant immunosuppressive therapy, has been shown to mimic the changes in the intestinal microbiota present in diabetic and obese patients[29]. These modifications may contribute to the diabetic phenotype observed in a significant number of patients undergoing solid organ transplantation, with reductions in species such as *Roseburia* and *Oscillospira*, butyrate-producing bacteria strongly involved in the regulation of insulin sensitivity, and an increase in *Akkermansia*, which is characteristically overexpressed in obese and diabetic patients. Probiotics have been shown to improve diabetes and obesity in patients with transplanted organs by positively altering the microbiota[29].

Many studies[30] investigating the role of the microbiota in transplanted patients are focused on *stem cell transplantation*. During the stem cell transplantation process, the intestinal mucosa is damaged both by chemotherapy and by radiotherapy preparation regimens that may or may not accompany it. This results in damage to the gastrointestinal barrier which, together with the use of antibiotics, leads to dysbiosis with an increase in typically infrequent species, such as Enterococci, Streptococci and various species of Enterobacteriaceae[31,32]. The use of fluoroquinolones in single administration has been associated with increased intestinal dominance of Proteobacteria[32]. In patients undergoing hematopoietic stem cell transplantation, intestinal dysbiosis is associated with reduced survival, increased risk of GvHD and increased GvHD mortality[31,33]. Furthermore, high rates of bacteremia have been demonstrated in patients who have reduced intestinal microbiota diversity at the time of neutrophil engraftment[31,33]. Microbial diversity significantly influences the 3-year survival of patients undergoing this type of transplantation[31].

Finally, the *SARS-CoV-2* infection is known to have a close relationship with the gastrointestinal tract. The majority of patients with COVID-19 present with gastrointestinal symptoms, which are associated with the worse clinical picture[34]. Also, increasing evidence suggests that COVID-19 is associated with impairment of microbiota, including the bacterial gut microbiome[35], fungal microbiome[36], or lung microbiome[37].

All of these new patients represent an interesting challenge both for the clinician, who will be required to learn how to solve new problems and answer new questions and for researchers, who will have to make significant efforts to study other new diseases emerging from modern medicine, addressing particular attention to the intestinal microbiota that seems to be a pivotal factor in the development of these new diseases.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Nyhlén A, Ljungberg B, Nilsson-Ehle I, Nord CE. Impact of combinations of antineoplastic drugs on intestinal microflora in 9 patients with leukaemia. Scand J Infect Dis 2002; 34: 17-21.
2. Zwielehner J, Lassl C, Hippe B, Pointner A, Switzeny OJ, Remely M, Kitzweger E, Ruckser R, Haslberger AG. Changes in human fecal microbiota due to chemotherapy analyzed by TaqMan-PCR, 454 sequencing and PCR-DGGE fingerprinting. PLoS One 2011; 6: e28654.
3. van Vliet MJ, Tissing WJ, Dun CA, Meessen NE, Kamps WA, de Bont ES, Harmsen HJ. Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. Clin Infect Dis 2009; 49: 262-270.
4. Saghafian-Hedengren S, Söderström I, Sverremark-Ekström E, Nilsson A. Insights into defective serological memory after acute lymphoblastic leukaemia treatment: The role of the plasma cell survival niche, memory B-cells and gut microbiota in vaccine responses. Blood Rev 2018; 32: 71-80.
5. Wardill HR, Secombe KR, Bryant RV, Hazenberg MD, Costello SP. Adjunctive fecal microbiota transplantation in supportive oncology: Emerging indications and considerations in immunocompromised patients. EBioMedicine 2019; 44: 730-740.
6. Wen Y, Jin R, Chen H. Interactions Between Gut Microbiota and Acute Childhood Leukemia. Front Microbiol 2019; 10: 1300.
7. Barnea D, Raghunathan N, Friedman DN, Tonorezos ES. Obesity and Metabolic Disease After Childhood Cancer. Oncology (Williston Park) 2015; 29: 849-855.
8. Ferreira MR, Muls A, Dearnaley DP, Andreyev HJ. Microbiota and radiation-induced bowel toxicity: lessons from inflammatory bowel disease for the radiation oncologist. Lancet Oncol 2014; 15: e139-147.
9. Valdagni R, Vavassori V, Rancati T, Fellin G, Baccolini M, Bianchi C, Cagna E, Gabriele P, Mauro F, Menegotti L, Monti AF, Stasi M, Fiorino C. Increasing the risk of late rectal bleeding after high-dose radiotherapy for prostate cancer: the case of previous abdominal surgery. Results from a prospective trial. Radiother Oncol 2012; 103: 252-255.
10. Wedlake LJ, Shaw C, Whelan K, Andreyev HJ. Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy. Aliment Pharmacol Ther 2013; 37: 1046-1056.
11. Schwartz DJ, Rebeck ON, Dantas G. Complex interactions between the microbiome and cancer immune therapy. Crit Rev Clin Lab Sci 2019; 56: 567-585.
12. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, No D, Gobourne A, Littmann E, Huttenhower C, Pamer EG, Wolchok JD. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun 2016; 7: 10391.

13. Okubo R, Chen C, Sekiguchi M, Hamazaki K, Matsuoka YJ. Mechanisms underlying the effects of n-3 polyunsaturated fatty acids on fear memory processing and their hypothetical effects on fear of cancer recurrence in cancer survivors. Prostaglandins Leukot Essent Fatty Acids 2018; 131: 14-23.
14. Ulker İ, Yildiran H. The effects of bariatric surgery on gut microbiota in patients with obesity: a review of the literature. Biosci Microbiota Food Health 2019; 38: 3-9.
15. Debédat J, Clément K, Aron-Wisnewsky J. Gut Microbiota Dysbiosis in Human Obesity: Impact of Bariatric Surgery Curr Obes Rep. 2019; 8: 229-242.
16. Wagner NRF, Zaparolli MR, Cruz MRR, Schieferdecker MEM, Campos ACL. Postoperative changes in intestinal microbiota and use of probiotics in roux-en-y gastric bypass and sleeve vertical gastrectomy: an integrative review. Arq Bras Cir Dig 2018; 31: e1400.
17. Sherf-Dagan S, Goldenshluger A, Azran C, Sakran N, Sinai T, Ben-Porat T. Vitamin K-what is known regarding bariatric surgery patients: a systematic review. Surg Obes Relat Dis 2019; 15: 1402-1413.
18. Mack I, Cuntz U, Grämer C, Niedermaier S, Pohl C, Schwiertz A, Zimmermann K, Zipfel S, Enck P, Penders J. Weight gain in anorexia nervosa does not ameliorate the faecal microbiota, branched chain fatty acid profiles, and gastrointestinal complaints. Sci Rep 2016; 6: 26752.
19. Bajaj JS, Sterling RK, Betrapally NS, Nixon DE, Fuchs M, Daita K, Heuman DM, Sikaroodi M, Hylemon PB, White MB, Ganapathy D, Gillevet PM. HCV eradication does not impact gut dysbiosis or systemic inflammation in cirrhotic patients. Aliment Pharmacol Ther 2016; 44: 638-643.
20. Ponziani FR, Putignani L, Paroni Sterbini F, Petito V, Picca A, Del Chierico F, Reddel S, Calvani R, Marzetti E, Sanguinetti M, Gasbarrini A, Pompili M. Influence of hepatitis C virus eradication with direct-acting antivirals on the gut microbiota in patients with cirrhosis. Aliment Pharmacol Ther 2018; 48: 1301-1311.
21. Xiao J, Peng Z, Liao Y, Sun H, Chen W, Chen X, Wei Z, Yang C, Nüssler AK, Liu J, Yang W. Organ transplantation and gut microbiota: current reviews and future challenges. Am J Transl Res 2018; 10: 3330-3344.
22. Kato K, Nagao M, Miyamoto K, Oka K, Takahashi M, Yamamoto M, Matsumura Y, Kaido T, Uemoto S, Ichiyama S. Longitudinal Analysis of the Intestinal Microbiota in Liver Transplantation. Transplant Direct 2017; 3: e144.
23. Matsumoto M, Ooga T, Kibe R, Aiba Y, Koga Y, Benno Y. Colonic Absorption of Low-Molecular-Weight Metabolites Influenced by the Intestinal Microbiome: A Pilot Study. PLoS One 2017; 12: e0169207.
24. Wu ZW, Ling ZX, Lu HF, Zuo J, Sheng JF, Zheng SS, Li LJ. Changes of gut bacteria and immune parameters in liver transplant recipients. Hepatobiliary Pancreat Dis Int 2012; 11: 40-50.
25. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012; 490: 55-60.
26. Zhang X, Shen D, Fang Z, Jie Z, Qiu X, Zhang C, Chen Y, Ji L. Human gut microbiota changes reveal the progression of glucose intolerance. PLoS One 2013; 8: e71108.
27. Zaza G, Dalla Gassa A, Felis G, Granata S, Torriani S, Lupo A. Impact of maintenance immunosuppressive therapy on the fecal microbiome of renal transplant recipients: Comparison between an everolimus- and a standard tacrolimus-based regimen. PLoS One 2017; 12: e0178228.
28. Kesiraju S, Paritala P, Rao Ch UM, Sahariah S. New onset of diabetes after transplantation - an overview of epidemiology, mechanism of development and diagnosis. Transpl Immunol 2014; 30: 52-58.
29. Bhat M, Pasini E, Copeland J, Angeli M, Husain S, Kumar D, Renner E, Teterina A, Allard J, Guttman DS, Humar A. Impact of Immunosuppression on the Metagenomic Composition of the intestinal microbiome: a systems biology approach to post-transplant diabetes. Sci Rep 2017; 7: 10277.
30. Chong PP, Koh AY. The gut microbiota in transplant patients. Blood Rev 2020; 39: 100614.
31. Taur Y, Jenq RR, Perales MA, Littmann ER, Morjaria S, Ling L, No D, Gobourne A, Viale A, Dahi PB, Ponce DM, Barker JN, Giralt S, van den Brink M, Pamer EG. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 2014; 124: 1174-1182.
32. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A, Lee YJ, Dubin KA, Socci ND, Viale A, Perales MA, Jenq RR, van den Brink MR, Pamer EG. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2012; 55: 905-914.
33. Golob JL, Pergam SA, Srinivasan S, Fiedler TL, Liu C, Garcia K, Mielcarek M, Ko D, Aker S, Marquis S, Loeffelholz T, Plantinga A, Wu MC, Celustka K, Morrison A, Woodfield M, Fredricks DN. Stool Microbiota at Neutrophil Recovery Is Predictive for Severe Acute Graft vs Host Disease After Hematopoietic Cell Transplantation. Clin Infect Dis 2017; 65: 1984-1991.
34. Ianiro G, Porcari S, Settanni CR, Bibbò S, Ponziani FR, Zileri Dal Verme L, Franceschi F, Cammarota G, Gasbarrini A; Gemelli against COVID-19 Working Group. Letter: prevalence and patterns of gastrointestinal symptoms in a large Western cohort of patients with COVID-19. Aliment Pharmacol Ther 2020; 52: 902-903.
35. Gu S, Chen Y, Wu Z, Chen Y, Gao H, Lv L, Guo F, Zhang X, Luo R, Huang C, Lu H, Zheng B, Zhang J, Yan R, Zhang H, Jiang H, Xu Q, Guo J, Gong Y, Tang L, Li L. Alterations of the Gut Microbiota in Patients with COVID-19 or H1N1 Influenza. Clin Infect Dis 2020: ciaa709.
36. Zuo T, Zhan H, Zhang F, Liu Q, Tso EYK, Lui GCY, Chen N, Li A, Lu W, Chan FKL, Chan PKS, Ng SC. Alterations in Fecal Fungal Microbiome of Patients With COVID-19 During Time of Hospitalization until Discharge. Gastroenterology 2020; 159: 1302-1310.e5.
37. Fan J, Li X, Gao Y, Zhou J, Wang S, Huang B, Wu J, Cao Q, Chen Y, Wang Z, Luo D, Zhou T, Li R, Shang Y, Nie X. The lung tissue microbiota features of 20 deceased patients with COVID-19. J Infect 2020; 81: e64-e67.