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Instant review

Seven secrets of COVID-19: fever, ACE2 receptors, gut-lung axis, metabolomics, microbiomics, probiotics, diet

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Abstract

The aim of this work is to investigate 7 secrets of COVID-19 (fever, ACE2 receptors, gut-lung axis, metabolomics, microbiomics, probiotics, diet), hoping to reveal a small part of some of these and to increase anyhow the knowledge on SARS-CoV-2 and its weaknesses to be able to defeat it.

In particular, in the opinion of the authors, significant improvements in contrasting the Coronavirus, and the pandemics that will follow, could derive from the use of "omics" disciplines, namely metabolomics (the stethoscope of the future) and microbiomics (an unrecognized player).

The discovery of new biomarkers using metabolomics could be used in clinical practice as predictive diagnostic tools or to evaluate the effectiveness and toxicity of a drug, in order to be able to provide the patient with a personalized, tailor-made medicine: precision medicine.

Our understanding of the role of the gut microbiome in COVID-19 infection remains in its infancy, but future research may potentially aid our understanding of viral infection, and create new ways in which we might treat and prevent it.

We strongly believe that the 3 M's (Metabolomics, Microbiomics and Machine learning [Artificial Intelligence]) will be the right route to the future for risk assessment, early diagnosis, patient management and decision-making.

By now, probiotics could help, fighting face to face against the virus. Moreover, the diet may be a key driver in determining the severity of COVID-19 and further studies are needed to explore the secret language between diet, bacteria, viruses and metabolites in determining individualized susceptibility or resilience to COVID-19.

Keywords

COVID-19, Coronavirus, fever, ACE2 receptors, gut-lung axis, metabolomics, microbiomics, probiotics, diet.

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Introduction

It is still unclear why coronavirus disease, similarly to other respitatory viral illnesses, is milder in the pediatric population. So, the question could be: "Pediatric COVID-19: what disease is this?" [1].

There are several potential reasons supporting the relatively milder illness in children: fewer outdoor activities, a healthier respiratory machinery, a different expression of receptors in the lower respiratory tract, a less vigorous adaptive system beside a preliminary potent innate response, the constitutional higher level of lymphocyte counts, the trained immunity with cross-reactive neutralizing antibodies, the lack of effects of aging, and the interaction between the immune system and the respiratory tract [2]. In this context we would like to add the magic of human milk [3, 4]. However, many unanswered questions remain, including the relationship with Kawasaki disease and the multisystem inflammatory syndrome [5-7].

By a general point of view, COVID-19 has brought the world to its knees and the final victory is not yet at hand. The achievement of the defeat of the Coronavirus must probably pass, not only through vaccines, but also through the research for possible connections between the different disciplines (systems theory), with the use of "omics" disciplines: genomics, transcriptomics, proteomics, metabolomics, microbiomics. The discovery of new biomarkers could be used in clinical practice as a predictive diagnostic tool or to evaluate the effectiveness and toxicity of a drug, in order to be able to provide the patient with a personalized, tailor-made medicine: precision medicine.

The aim of this work is to investigate 7 secrets of COVID-19 (fever, ACE2 receptors, gut-lung axis, metabolomics, microbiomics, probiotics and diet), hoping to reveal a small part of some of them and to increase anyhow the knowledge of the enemy and its weaknesses in order to be able to defeat it.

Fever in COVID-19: a two-faced Janus

Bats are known to be a vast reservoir of Coronavirus and SARS-CoV-2 seems to have originated from bats as well [8]. Perhaps, not everyone knows that, during flight, bats increase their metabolic rate by 15-16 times, and this situation is accompanied by high fever with profound activation of the immune system and the possibility of hosting pathogenic viruses [9]. In the literature, exhaustive reviews exist on phylogenomic distribution and evolutionary lineage of zoonotic viral cross-species transmission of the Coronaviridae family and the implications of bat microbiome in zoonotic viral transmission and infection [10].

In humans, the initial presentation of fever in COVID-19 in the first week, during the viral phase of the disease, is probably the evidence of the body's immune response to viral replication to increase immunity [11, 12]. Nevertheless, if the viral infection does not resolve at the proper time, the disease process is complicated by the activation state of inflammation triggered by the virus and described as a cytokine storm, anticipated by incessant fever. In these cases where extreme inflammation occurs, the fever can be counterproductive [13].

In a systematic review of 7,780 pediatric patients, fever was present in 59.1% of them (with a range of about 40-75%) [14].

In the first reports of the literature, the percentage of fever in pediatric patients was around 40% [15].

In more recent reports, the percentage was 76%, higher than that of seasonal flu (55%) [16].

An important difference between children and adults is the fever duration. In children, it tends to last less than 3 days and, generally, a high fever at the time of the admission is not an indicator of bad outcome. In adults, on the other hand, an elevated fever at the time of admission is associated with acute respiratory distress syndrome (ARDS) and death [17]. Moreover, the fever is always present in the inflammatory multisystemic syndrome [18].

A very important data to underline, is that the absence of fever at an initial screening does not exclude COVID-19 [19].

Furthermore, in the child, there may be a presentation of COVID-19 with acute respiratory distress without fever and cough [20]. Finally, it was reported that fever screening was lacking in sensitivity in the detection of patients with SARS-CoV-2 [21].

Several important questions arise about the autoimmune and autoinflammatory responses following COVID-19 infection, including its possible link with long-term sequelae [22].

ACE2 receptors: is it more important where or how many they are?

Angiotensin-converting enzyme 2 (ACE2) – a cell surface receptor that plays a key role in dietary amino acid homeostasis, innate immunity, and gut microbial ecology – is the target of SARS-CoV-2. Thus, the expression and distribution of ACE2 in the human body may indicate potential routes of infection of SARS-CoV-2 [23]. In general terms, children have less ACE2 expression in their tissues and lower binding affinity with the virus.

A high expression of ACE2 has been identified in alveolar type II cells (AT2) of the lung, upper esophagus and stratified epithelial cells, absorbing enterocytes from the ileum and colon, cholangiocytes, myocardial cells, proximal kidney tubular cells and urothelial bladder cells. These results indicated that those organs with cells expressing ACE2 should be considered at potential high risk of infection [24].

Surprisingly, the expression in the colon is about 4 times higher than that of the lung. This journey of SARS-CoV-2 into the intestine is "thrilling" and the future clinical implications are anticipated by Scaldaferri et al. [25]. On the one hand, a presentation of the disease with only gastrointestinal symptoms is possible; on the other hand, this mode of presentation can lead to problems in the containment of COVID-19 pandemic. This observation is relevant if we consider the implications that we will see concerning the gastrointestinal symptoms [24].

A dysbiotic gut environment and epithelial inflammation increase the levels of ACE2. Elevated ACE2 expression was found in patients characterized by a (preexisting) proinflammatory gut microbiome and creates conditions favorable to infection by Coronaviruses like SARS-CoV-2 of the gut epithelium, from which it can further spread through the body [26, 27]. This is consistent with the development of gastrointestinal infections and detection of viral RNA in the feces of many COVID-19 patients, including those who tested negative to the PCR of their respiratory secretions [28].

An overview of current evidence on the involvement of gut alterations in human diseases including COVID-19 has been recently published [29].

In a recent metanalysis of 20 studies (4,265 patients), it was found that the prevalence of diarrhea, nausea and vomiting increased significantly in the severe form compared to the mild form of COVID-19. Moreover, COVID-19-related gastrointestinal symptoms were observed at higher rates in males than in females [30].

As previously stated, this primary presentation of COVID-19 solely with gastrointestinal symptoms could be a problem for the containment of the disease [31].

In more than 20% of patients with SARS-CoV-2 it was found that the test result for viral RNA remained positive in feces, even after the test results for viral RNA in the respiratory tract converted to negative, indicating that the viral gastrointestinal infection and potential fecal-oral transmission can last even after viral clearance in the respiratory tract [30].

Therefore, the authors strongly recommend that rRT-PCR testing for SARS-CoV-2 on feces should be performed routinely in infected patients with SARS-CoV-2 and that transmission-based precautions for hospitalized patients with SARS-CoV-2 should continue if feces test results are positive at rRT-PCR testing [30].

Viana et al. report that ACE2 has a trilogy of roles in COVID-19: 1) ACE2 is the SARS-CoV-2 receptor in humans; 2) ACE2 displays an important Renin-Angiotensin System (RAS) counter-regulatory activity of the pro-vasoconstrictor, pro-fibrotic, pro-oxidant and pro-inflammatory activities of Ang II via AT1R (reduced protective effects after viral infection); 3) ACE2 plays a major role in amino acid transport in the intestinal epithelium, a mechanism that is linked to the production of antimicrobial peptides, thus interfering with the gut microflora homeostasis. Thus, it is strictly related to gut microbiota dysbiosis [32]. Saleh et al., underlying the importance of microbiota dysbiosis, introduce also the role of mithocondria dysfunction in the pathogenesis of COVID-19, together with platelets dysfuction which plays a major role in blood clotting and coagulopathy events [33].

Iron overload may also affect extra- and intracellular mitochondria function, microbiota diversity (lungs and gut) and blood coagulation [34].

Recently, it has been reported that recombinant human ACE2 (rhACE2) could act as a potential therapy for hypertension, heart failure, kidney injury, and liver fibrosis [35].

"More gut in the lung" in COVID-19: unexpected always happen

For a very long time, until 2010, the sterility of the healthy lungs was given for certain. But the presence of a lung microbiota in normal conditions has been proven in the last 10 years [36]. It is much less numerous than the gut microbiota, but it can impact the health of an individual. Data show that the gut microbiota and the lung microbiota may develop together right after birth. Furthermore, various factors can affect the composition of the lung microbiota, such as micro-aspiration and inhalation, meaning the microbial migration [37]. It is thought that the immunity of the lungs depends on the interactions between the lung microbiota and the respiratory epithelia [38]. Hence, the investigators assumed a gut and lung cross-talk [39]. Following the "more gut in the lung" phenomenon, some bacterial strains show up in the gut before their emergence in the lung [40]. In fact, in cases of respiratory diseases, gastrointestinal disorders generally occur, leading to a more severe clinical course. The presence of a dysbiosis in the lung microbiota could cause the admission of the patient to intensive care.

We refer to our previous work for the complete discussion of this topic [40]. Here, we would like to emphasize that both adult and pediatric patients received few antibiotics in percentage, since COVID-19 is a viral disease, and a macrolide (which does not cover gastrointestinal bacteria) was used [41, 42]. Only 17% received azithromycin, despite the clinical severity of the patients and the presence of important comorbidities [41]. This data could or should be revised in the light of the above-mentioned concept of "more gut in the lung". Moreover, for unclear reasons, the use of antibiotics decreases the virus entry into the gut [43]. We redirect you to our previous paper totally dedicated to this argument [40].

Furthermore, it has been provided a conceptual framework on the potential impact of SARS-CoV-2 oral infection on the local and distant microbiomes across the respiratory and gastrointestinal tracts ("oral-tract axes"), which remains largely unexplored [44].

Although the gut-lung axis is only beginning to be understood, there is an emerging evidence that indicates that there is potential for manipulation of the gut microbiota in the treatment of lung diseases [45].

Metabolomics and early diagnosis of COVID-19: the right route?

The urgent need for diagnostics and therapeutics against the COVID-19 pandemic has shown the great potential of antibodies, proteomics and metabolomics in this direction [46]. The inter-individual differences in the activation of the receptors that allow the harmful pulmonary and systemic effects in the course of COVID-19 may be due to the microbiota. Therefore, the lung microbiota and COVID-19 could be strongly correlated in children as well [47]. In this context, metabolomics could be a very promising tool for an early diagnosis, to investigate drugs responses in patients and to predict mortality. It is important to highlight that metabolomics, given its ability to provide a metabolic snap-shot of an individual, is considered to be the Rosetta Stone of the microbiomics. More recently, metabolomics has been defined as the stethoscope of the 21st century [48]. The metabolites broken down in the human body through the process of metabolism could act as excellent biomarkers for COVID-19. Finally, metabolomics could provide us a legend to understand the status of the microbiota in case of COVID-19 and help in reducing the mortality [49, 50].

In a recent experimental study, the authors created a murine model of SARS-CoV-2-induced severe systemic toxicity and multi-organ involvement. The animals developed within 7 days severe weight loss, morbidity and failure to thrive, associated to metabolic suppression of oxidative phosphorylation and the tri-carboxylic acid (TCA) cycle in multiple organs with neutrophilia, lymphopenia and splenic atrophy, mirroring human COVID-19 phenotypes. This model suggests that SARS-CoV-2-induced metabolic reprogramming and epigenetic changes in internal organs could contribute to systemic toxicity and lethality in COVID-19 [51].

To date, very few metabolomic studies have been conducted in adult patients with COVID-19.

Shen et al. performed a proteomic and untargeted metabolomic characterization of COVID-19 patient sera in 99 participants (46 COVID-19 patients and 53 controls) [52]. The authors identified molecular changes in the sera of COVID-19 patients compared to other groups, implicating dysregulation of macrophages, platelet degranulation, complement system pathways, and massive metabolic suppression [52].

Song et al. studied the plasma metabolomic and lipidomic profile of healthy subjects and patients with COVID-19, which resulted to be clearly distinct. The role of exosomes (GM3-enriched) was also important [53].

Blasco et al. analyzed the plasma metabolome of 55 patients infected with SARS-CoV-2 and 45 controls by LC-HRMS at the time of viral diagnosis

[54]. Plasma metabolome allowed to generate a discriminant multivariate model to predict the diagnosis of SARS-CoV-2 in an independent population (accuracy > 74%, sensitivity and specificity > 75%).

Volcano plot analysis highlighted two main metabolites: cytosine and indole-3-acetic acid (indoleacetate or IAA).

Cytosine is known as a coordinator of cell metabolism in SARS-CoV-2 and tryptophan-nicotinamide pathways is clearly linked to inflammatory signals and microbiota [54].

The indole-3-acetic acid is a breakdown product of tryptophan metabolism.

Interestingly, tryptophan represents a metabolic node that involves serotonine synthesis, kynurenine pathway and the indole/aryl hydrocarbon receptor (AHR) pathway. The indole-3-acetic acid is a ligand of AHR that has been involved in many diseases involving immune and inflammatory processes, including the connection with gut microbiota and mucosal immunity. Finally, the tryptophan-nicotinamide pathway can also act on mTOR activation, which is involved in cell proliferation, survival, transcription and expression of intestinal antimicrobial peptides.

The tryptophan-nicotinamide pathway consists of two parts. The first part is from tryptophan to quinolinic acid, and the second is from quinolinic acid to nicotinamide catabolism [54]. Nicotinamide, an amide derivative of nicotinic acid, is a precursor for generation of the coenzymes NAD+ and NADP+, which are essential for many metabolic pathways.

Omics findings by Shen et al. and, more recently, by Thomas et al. also reported the activation of kynurenine pathway in COVID-19 patients [52, 55]. They suggested that NAD synthetized from tryptophan modulates macrophage activity such as the release of interleukin-6 (IL-6) and tumor necrosis factor alpha. Interestingly, similarly cytosine was the main discriminant metabolite between COVID-19-positive and COVID-19-negative patients. Cytosine belongs to the pyrimidine class and is one of the four main bases found in DNA and RNA. Viral infections are known to cause significant metabolic changes in host cells, such as upregulation of pyrimidine nucleotide biosynthesis. It has been hypothized that the increased plasma cytosine levels in COVID-19 patients may correspond to the coupling between synthesis of viral particles, the host cell metabolism and cell lysis inherent to infection. However, in this paper, metabolomic exploration modestly explained long-term disease evolution [54].

As previously reported, Thomas et al. performed targeted and untargeted metabolomic analyzes of COVID-19 patients and identified impaired tryptophan metabolism in the kynurenine pathway, which regulates inflammation and immunity [55].

Indeed, these changes in tryptophan metabolism were related to IL-6 levels. Widespread dysregulation of nitrogen metabolism was also observed in infected patients, with altered levels of most amino acids, along with an increase in markers of oxidative stress, proteolysis and renal dysfunction. Increased circulating levels of glucose and free fatty acids have also been observed.

The metabolomic signatures in COVID-19 patients suggest metabolic suppression, platelet degranulation and dysregulated macrophage function [46].

In another study by Doğan et al., the serum samples were obtained from 44 COVID-19 patients and 41 healthy controls. Untargeted metabolomics revealed significant differences between patients and healthy controls in terms of purine, glutamine, leukotriene D4 (LTD4) and glutathione metabolisms. Down-regulations were determined in R-S lactoglutathione and glutamine [56]. This could be explained by the hypothesis of Polonikov that endogenous deficiency of glutathione is the most likely cause of serious manifestation and death in COVID-19 patients [57]. At this regard it is well known the relevant role of oxydative stress on COVID-19 [58, 59]. It must also be remembered that paracetamol and its metabolites decreased, in healthy volunteers, glutathione levels also when given at low doses and it is possible a link with the severity of COVID-19 illness [60].

Up-regulations were detected in hypoxanthine, inosine, and LTD4. The identified metabolites indicate roles for purine, glutamine, LTD4, and glutathione metabolisms in the pathogenesis of COVID-19. The use of selective LTD4 receptor antagonists, targeting purinergic signaling as a therapeutic approach and glutamine supplementation may decrease the severity and mortality of COVID-19 [56]. An extensive review discusses the relationship between intestinal purine metabolism and the use of *L. gasseri* and low-purine diets, particularly in individuals with hyperuricemia, as adjuvant nutritional therapies to improve the immune system and weaken viral replication, assisting in the treatment of COVID-19. Probably, people with hyperuricemia or gout can be considered a risk group in case of COVID-19 [61].

When infected by viruses, human cells increase the demand for purine nucleotides, which are needed for the synthesis of viral RNA and DNA:

thus probiotics, namely *L. gasseri*, can influence the metabolism of purine, breaking down inosine and guanosine to directly influence the reduction of acid uric levels. Moreover, colchicine, an anti-inflammatory drug widely used to treat patients with acute attack of gout, is undergoing clinical trials for the treatment of COVID-19 [61].

Bruzzone et al. found an increase in succinic acid, citric acid, glutamic acid, and pyruvic acid by 156%, 12%, 33%, and 67%, respectively, in sera of COVID-19 patients [62]. These modifications are consistent with impaired central metabolic and/or mitochodrial dysfunction. The accumulation of succinic acid has been shown in acute experimental asphyxia as a negative prognostic factor [63]. Moreover, it further creates a pseudohypoxic environment that facilitates cancer development and progression [62]. Again, there is a reduction in the essential amino acids namely methionine, isoleucine, histidine, and lysine by 19%, 11%, 16%, and 34%, respectively, together with the reduction of tyrosine and glutamine by 4%, and 19%, respectively.

Furthermore, substantially increased levels of phenylalanine (an essential amino acid precursor of tyrosine) and 2-hydroxybutiryc acid (a readout of hepatic oxidative stress) were observed by 81%, and 628%, respectively. Finally, the authors also found an excess of ketone bodies (acetone, acetoacetic acid, and 3-hydroxybutyric acid) as an alternative energy source due to a "sort of diabetic ketoacidosis". Taken together, all these results support the existence of a general metabolic stress condition in COVID-19 patients.

Interestingly, in the unique paper regarding the milk of mothers with COVID-19, there is a reduction of different metabolites such as tryptophan, tyrosine, and also phenylalanine (the latter in other papers is increased in sera of COVID-19 patients) [64].

In the largest published study on metabolomics (161 patients, 103 of which were positive for COVID-19), Barberis et al. found alterations of lipidomics, namely a global down-regulation of phospholipids. Moreover, they found a downregulation of several amino acids, including histidine, L-valine (which can be considered a potential marker of the infection) and L-proline in COVID-19 patients [65]. Tryptophan was also reduced, confirming the results of other studies. The levels of succinic acid was also increased. In addition, the level of pyroglutamic acid, which can be converted into glutamic acid and enter the TCA cycle for further energy production or substance synthesis, was increased in infected patients, as a marker of oxidative stress [65].

A dysregulation of porphyrin metabolism was also observed, since the levels of glycine, a precursor in the first step of production of porphyrin, were shown to be upregulated in COVID-19 patients admitted to Intensive Care Unit (ICU) [65]. It has recently been shown that the increased viral proteins and decreased hemoglobin in severe patients lead to the formation of porphyrin, which plays a very important role in the progress of the COVID-19 infection, suggesting the hypothesis that COVID-19 is an acquired acute porphyria [66].

Migaud et al. described the metabolites predicting mortality in adult subjects, trying to delineate the drugs response as well [67, 68]. Even in this paper, the relevant role of tryptophan and its metabolites is underlined, together with the metabolites of Krebs cycle [67].

An excellent review on the central role of tryptophan metabolism in microbiota-host cross-talk in health and disease is available: deciphering the complex equilibrium between these pathways will facilitate a better understanding of the pathogenesis of human diseases, including COVID-19, and open therapeutic opportunities [69-71].

Fraser et al. identified in critically ill COVID-19 patients the top-performing metabolites for identifying COVID-19-positive patients from healthy control subjects: increased kynurenine and decreased arginine, sarcosine, and lysophosphatidylcholines [72]. Arginine/kynurenine ratio alone provided 100% classification accuracy between COVID-19-positive patients and healthy control subjects ($p = 0.0002$). Creatinine was the top metabolite for predicting COVID-19-associated mortality on both ICU days 1 and 3, and both creatinine and creatinine/arginine ratio accurately predicted COVID-19-associated death with 100% accuracy ($p = 0.01$) [72].

Paez-Franco et al., in a preprint, identified the main changes in serum metabolites associated with severe ($n = 46$) and mild ($n = 19$) COVID-19 patients by gas chromatography coupled to mass spectrometry. The modified metabolic profiles were associated to an altered amino acid catabolism in hypoxic conditions. Noteworthy, three α-hydroxyl acids of amino acid origin increased with disease severity and correlated with altered oxygen saturation levels and clinical markers of lung damage. These data highlight the potential relevance of amino acid supplementation during SARS-CoV-2 infection [73].

Finally, in the preprint by Meoni et al., despite the heterogeneity of the clinical symptoms, COVID-19 patients were characterized by specific plasma metabolomic and lipidomic signatures (91.7% and

87.5% accuracy, respectively, when compared to controls) [74]. Tocilizumab treatment resulted in at least partial reversion of the metabolic alterations due to SARS-CoV-2 infection, confirming the role of pharmametabolomics in monitoring treatments [75].

Interesting data have been published on metabolomics in exhaled breath and saliva in patients with COVID-19 [76-78].

A list of relevant metabolites discriminating healthy controls and COVID-19 patients and suggesting a bad oucome is presented in **Tab. 1**.

Microbiomics in COVID-19: an unrecognized player?

There is evidence that the gut microbiome influences ACE2 receptor expression, and hence, it may play a role in influencing COVID-19 infectivity and disease severity. Furthermore, the gut microbiome plays a significant role in immune regulation, and hence may be pivotal in influencing the immune response to COVID-19, as well as the response to treatment [80-82].

More and more information are available about the relationships between microbiota, immune system and viral infections including, in particular, Coronavirus [83-86]. A common observation, that can be very useful, is that gastrointestinal symptoms seem to precede respiratory ones [87].

Gut microbiota diversity declines in the elderly, and COVID-19 was mainly fatal in elderly patients, indicating again the role that gut microbiota may play in this disease. Maintaining and improving the gut microbiota eubiosis through personalized nutrition

Table 1. Relevant metabolites in COVID-19 and critical COVID-19 patients compared with controls [67, 62, 65, 72, 73,74, 79].

Metabolite	COVID-19	Critical COVID-19	Comment
Tryptophan	↓	↓↓	Adjunctive therapy?
Indole-3-acetic acid (indoleacetate, IAA)	↑	↑	
Kynurenine		↑↑	Brain involvement
Kynurenate		↑↑	Brain involvement
Quinolinate		↑↑	Brain involvement
Picolinate		↑↑	Brain involvement
Succinic acid	↑↑ (156%)	↑↑	Hypoxia
Fumaric acid	↑		Hypoxia
Pyruvic acid	↑↑ (67%)		
Citrate		↓	Hypoxia
Pyroglutamic acid		↑	Oxidative stress
Lactic acid	↑	↑	Hypoxia
Glycine	↑	↑	Acute porphyria-like
Tyrosine	↓		
Arginine		↓	Adjunctive therapy? Arginine/kynurenine ratio predicts diagnosis
Hystidine	↑	↓	
Proline	↑	↓	
Glutamine	↑	↓	Adjunctive therapy?
Phenylalanine	↑↑ (81%)		
2-hydroxybutyric acid	↑↑ (628%)	↑↑	Readout of hepatic oxidative stress
3-hydroxybutyric acid	↑		Ketoacidosis-like
Acetone	↑		Ketoacidosis-like
Acetoacetic acid	↑		Ketoacidosis-like
Sarcosine	↑	↓	Adjunctive therapy?
Hypoxantine	↑		
Inosine	↑		
Purine	↑		Patients with gout at risk?
Valine	↓		Marker of infection
Phospholipids		↑	
Oleic acid		↑	
Arachidonic acid		↑	
Glycerol		↑	
Lysophosphatidilcholine		↓	Adjunctive therapy?
Creatinine		↑	Creatinine/arginine ratio predicts mortality

↑: increased concentration; ↓: decreased concentration.

and supplementation may improve host immunity and is one of the prophylactic ways by which the impact of this disease can be minimized in the elderly, immuno-compromised patients and, more in general, in patients at risk [88].

"Is a healthy microbiome responsible for lower mortality in COVID-19?" This is the title of an article from the literature where a close relationship between a good microbiota and the best outcome in patients with COVID-19 is hypothesized [89]. What it means a balanced microbiota ecosystem (namely eubiosis) and its opposite (dysbiosis) is well clarified in an elegant review [90]. The quantitative and qualitative impact of the flu infection on the microbiota is known both in experimental studies on animal models and in studies on humans [91, 92].

A growing body of the literature highlights possible clinical implications between gut microbiota and COVID-19 [87, 88, 93].

Hence, the microbiota pre-existing health status and its eventual modifications in the course of COVID-19 are likely to play an important, still underscored role in determining individual susceptibility and resilience to COVID-19. The vast majority of COVID-19 worst clinical conditions and fatalities develop in subjects with risk factors such as aging, inflammation (inflammaging) and comorbidities. Intriguingly, these risk factors are also characterized by an unhealthy microbiome status. Finally, these high-risk subjects require complex pharmacological regimens known as "polypharmacy" (for example antibiotics, glucocorticoids, antiviral drugs) that may further negatively affect microbiota integrity and worsen the resilience to viral infections [81].

In COVID-19, there is an interplay between the gut microbiota triad (dysbiosis – immune hyperresponse – inflammation) and the putative influence on disease progression. Rather than being merely restricted to the lower respiratory tract, severe acute infection of SARS-CoV-2 spreads to other organs, namely the gastrointestinal tract (multi-tissue infection), with the relevant contribution of the microbiome.

In particular, in patients with COVID-19 there is a reduction of good bacteria such as *F. prausnitzii*. Furthermore, the following situations were observed.

- Increased levels of *Lactobacillus spp.* correlated to higher levels of anti-inflammatory IL-10 and improved disease prognosis.
- Increased levels of proinflammatory bacterial species, including *Klebsiella spp.*, *Streptococcus spp.*, and *R. gnavus* correlated with elevated levels of proinflammatory cytokines and increased disease severity.
- These species were previously found as enriched in the proinflammatory gut environment of patients suffering from a range of conditions, including diabetes, obesity, irritable bowel disease, and high blood pressure [94].
- Moreover, in hospitalized patients with COVID-19, the gut bacteriome was characterized by a significant decrease in bacterial diversity, depletion of beneficial bacterial symbionts, and enrichment of opportunistic pathogens (e.g., *Streptococcus spp, Rothia spp.*, *Actinomyces spp.*), which may correlate with the gastrointestinal complaints (e.g., abdominal pain, nausea, vomiting, diarrhoea) of the acute phase of the infection [95]. Interestingly, these symptoms often occur in the onset of the infection and may precede respiratory complaint [96].

Considering the microbiome of the bronchoalveolar lavage fluid (BALF), several studies revealed that higher frequencies of *Capnocytophaga gingivalis*, *Veillonella spp.*, *Leptotrichia buccalis*, *Veillonella parvula* and *Prevotella melaninogenica* exacerbated COVID-19 patients' conditions. Conversely, *Fusobacterium periodonticum* is protective.

Considering the microbiome of the gut, *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, *Morganella morganii* are preeminent commensals in gut microbiome of severely infected COVID-19 patients [97]. In contrast, a few bacteria such as *Parabacteroides merdae*, *Bacteroides stercoris*, *Alistipes onderdonkii* and *Lachnospiraceae bacterium* of intestinal microbiota have the competence to reduce ACE2 expression. They are able to produce short-chain fatty acids (butyrate, acetate). *Alistipes onderdonkii* is involved in tryptophan and melatonin metabolism [97].

We must add the importance of the human gut virome, a real dark matter [98]. It shares important information with all microbial components and may influence overall human health by molding gut community structure and function [96]. Finally, in a pilot study, Zuo et al. found heterogeneous configurations of the fecal mycobiome, with enrichment of fungal pathogens such as *Candida spp.* and *Aspergillus spp.*, during hospitalization of 30 patients with COVID-19 compared to controls [93]. Unstable gut mycobiomes and prolonged dysbiosis persisted in a subset of patients with COVID-19 up to 12 days after nasopharyngeal clearance of SARS-CoV-2 [93].

The dream of the physician could be to have a predictive index not only for a health status using species-level gut microbiome profiling, but also for specific diseases, including COVID-19 [99].

Preliminary data on 990 subjects suggest that gut microbiota may depict the predisposition of normal individuals to severe COVID-19 [100].

In 972 microbial samples from hospitalized ICU patients with COVID-19, their health care providers, and hospital surfaces before, during, and after admission, community profiles allowed for high classifier accuracy for SARS-CoV-2 status in not only nares, but also forehead, stool and floor samples. In particular the genus *Rothia* was highly predictive of SARS-CoV-2 across sample types, and had higher prevalence in positive surface and human samples, even when compared to samples from patients in another ICU prior to the COVID-19 pandemic [101].

In children it was demonstrated that COVID-19 alters the respiratory and gut microbiome. Alteration of the microbiome was divergent between the respiratory tract and gut, albeit the dysbiosis was dominated by genus *Pseudomonas* and sustained for up to 25-58 days in different individuals. The respiratory microbiome distortion persisted in 7/8 children for at least 19-24 days after discharge from the hospital. The gut microbiota showed early dysbiosis towards later restoration in some children, but not others. These data imply possible long-term complications after clinical recovery from COVID-19, such as predisposition to an increased health risk in the post-COVID-19 era [102].

The functional profiling of COVID-19 respiratory tract microbiomes was also studied by Haiminen et al. [103].

The upper respiratory tract microbiota in COVID-19 patients differed from that in healthy controls, while deceased patients possessed a more distinct microbiota. *Streptococcus spp.* was enriched in recovered patients, whereas potential pathogens, including *Candida spp.* and *Enterococcus spp.*, were more abundant in deceased patients. A higher abundance of *S. parasanguis* on admission in oropharyngeal swabs predicted a better outcome [104].

Finally, the lung tissue microbiota features of 20 deceased patients with COVID-19 were reported with peculiar results, both for bacteria and fungi [105].

A list of relevant bacteria, present in the gut and in the lung, favoring or contrasting COVID-19 is presented in **Tab. 2**.

Table 2. Different commensal microbiome between SARS-CoV-2 sensitivity and resistance (based mainly on Shelly et al., mod. [97]).

Microbiomes	Favoring infection	Protective against infection
Bacteria	*Acinetobacter baumannii* (P): GUT *Actinomyces viscosus* (A): GUT *Bacteroides nordi* (B): GUT *Capnocytophaga gingivalis* (B): BALF *Capnocytophaga spp.* (B): GUT *Clostridium hathewayi* (F): GUT *Clostridium ramosum* (F): GUT *Collinsella aerofaciens* (A): GUT *Collinsella tanakaei* (A): GUT *Corynebacterium spp.* (A): GUT *Enterococcus avium* (F): GUT *Erysipelotrichaceae bacterium* (F): GUT *Klebsiella pneumoniae* (P): GUT *Leptotrichia buccalis* (Fu): GUT *Morganella morganii* (P): GUT *Prevotella melaninogenica* (B): BALF *Ruminococcus gnavus* (F): GUT *Ruthenibacterium lactatiformans* (F): GUT *Streptococcus infantis* (F): BALF; GUT *Veillonella parvula* (F): BALF *Veillonella spp.* (F): GUT	*Alistipes onderdonkii* [a, b] (B): GUT *Bacteroides dorei* (B): GUT *Bacteroides massiliensis* (B): GUT *Bacteroides ovatus* (B): GUT *Bacteroides stercoris* [a, b] (B): GUT *Bacteroides thetaiotaomicron* (B): GUT *Bifidobacterium spp.* (A): GUT *Dorea formicigenerans* (F): GUT *Eubacterium rectale* (F): GUT *Faecalibacterium prausnitzii* (F): GUT *Fusobacterium periodonticum* (Fu): GUT *Lachnospiraceae bacterium* [a, b] (F): GUT *Lactobacillus spp.* (F): GUT *Parabacteroides merdae* [a, b] (B): GUT *Roseburia intestinalis* (F): GUT *Ruminococcus obeum* (F): GUT
Fungi	*Aspergillus flavus* (Fun): GUT *Aspergillus nifer* (Fun): GUT *Candida albicans* (Fun): GUT *Candida auris* (Fun): GUT *Candida glabrata* (Fun): GUT	-

A: *Actinibacteria*; B: *Bacteroidetes*; F: *Firmicutes*; Fu: *Fusobacteria*; Fun: Fungi; P: *Proteobacteria*.
BALF: presence in the bronchoalveolar lavage fluid; GUT: presence in the intestine.
[a] Competence to reduce ACE2 expression in the gut epithelial cells; [b] producing short-chain fatty acids (butyrate, acetate).

Probiotics at war against COVID-19

What about probiotics at war against viruses [106]? In particular what about probiotics and COVID-19? Not only there is a link, but we must think about the link [88, 107].

It was suggested that the possibility to improve the gut microbiota eubiosis and the immune system efficacy minimizes the impact of the disease. Indeed, many authors suggest the modulation of gut microbiota among the approaches to COVID-19 prevention and treatment [108]. Probiotics are potential candidates to be tested in moderate and severe cases of COVID-19 due to several beneficial effects, including the fact that they are easily available, easy to administer, and safe and economical to use.

In Janda et al.'s study, especially in people at high risk, the oral supplement with *L. rhamnosus* and *B. animalis ssp. lactis*, or *B. subtilis* peptidoglycans (which reduces the infectivity of Coronaviruses), or *L. gasseri TMC0356* both as living organisms or cell lysates, is hypotesized [89].

There are wide reviews on the use of probiotics in viral respiratory infection; the application in clinical practice of probiotics and prebiotics in the prevention and treatment of COVID-19 seems promising, although further studies are needed [109-111]. Gastrointestinal and respiratory tracts share the same embryonic origin, and thus they are structurally alike and interact similarly in physiological and pathological conditions [110]. Moreover, some anti-viral, anti-inflammatory and antimalarial drugs have been applied to treat COVID-19. However, none of these medications have been approved as effective curative treatments against COVID-19. Therefore, other safe strategies such as probiotics and prebiotics could be applied to prevent or treat COVID-19 [110].

Some suggestions of probiotics used in viral infections are presented in **Tab. 3**.

Table 3. Some suggestions of probiotics used in viral infections [112-114].

Probiotic strain	Basis for inclusion	Mode of action
Bacillus subtilis OKB105	Gastroenteritis due to Coronavirus	Block of viral adherence by competitive inhibition
Bifidobacterium animalis ssp. lactis BB-12	RTI	Reduction of the viral titer
Bifidobacterium bifidum MF 20/5	Flu-like illness	Lowering duration and severity
Bifidobacterium breve BbrY	Ventilatory-associated pneumonia	Lowering incidence
Bifidobacterium longum BB536	H1N1	Increase of IFNγ and IL-6
Bifidobacterium longum SP 07/3	Flu-like illness	Lowering duration and severity
Bifidobacterium infantis BB-12	URTI	IL-17 inhibitory effect
Lactobacillus casei DN-114001	RTI, rhinopharingitis, influenza	Enhance defensin expression and innate immunity
Lactobacillus casei Shirota	Ventilatory-associated pneumonia	Lowering incidence
Lactobacillus gasseri TMC0356	H1N1	Decrease in the severity of symptoms and viral titer. Stimulation of IL-12, IL-6, IFNγ and IgA production
Lactobacillus gasseri PA 16/8	Flu-like illness	Lowering duration and severity
Lactobacillus paracasei ssp. paracasei 19	SIRS, infections, sepsis	Reduction of days of stay in ICU, days in MV and mortality
Lactobacillus plantarum 2362	SIRS, infections, sepsis	Reduction of days of stay in ICU, days in MV and mortality
Lactobacillus plantarum CRL1506	Gastroenteritis due to Coronavirus	Reduction of inflammatory-mediated tissue damage
Lactobacillus plantarum DK119	Influenza virus A	Increase of IFNγ and IL-2
Lactobacillus plantarum DR7	Prevention of URTI	Immune modulation
Lactobacillus plantarum L137	Influenza virus A, H1N1	Proinflammatory activity
Lactobacillus plantarum NCIMB 8826	RSV, pneumovirus	TLR-dependent inflammatory response
Lactobacillus rhamnosus CRL1505	RSV	Innate immunity stimulation and induction of IFN-α production via TLR3/RIG-I-triggered antiviral respiratory immune response
Lactobacillus rhamnosus GG	Prevention of viral RTI	Promotion of digestive health and gut barrier integrity
Lactobacillus rhamnosus M21	Pneumonia, flu	Increase of IFNγ and IL-2
Lactococcus lactis JCM 5805	RTI, common infectious diseases	Activation of plasmacytoid dendritic cell
Leuconostoc mesenteroides 32-77:1	SIRS, infections, sepsis	Reduction of days of stay in ICU, days in MV and mortality
Pediococcus pentosaceus 5-33:3	SIRS, infections, sepsis	Reduction of days of stay in ICU, days in MV and mortality

RTI: respiratory tract infections; URTI: upper respiratory tract infections; IFNγ: interferon γ; IL: interleukin; ICU: Intensive Care Unit; RSV: respiratory syncytial virus; SIRS: systemic inflammatory response syndrome; MV: mechanical ventilation.

Diet

A related topic is the relationship among diet, gut microbiota and COVID-19.

Improving the composition of the microbiota and the proportion of its metabolites through probiotics and personalized diet could be a potential strategy to prevent and treat COVID-19 [115].

In fact, the diet may be a key driver in determining the severity of COVID-19 [116]. The World Health Organization (WHO) provides advice on nutrition during this pandemic to include plenty of fruit and vegetables [117]. Indeed, there is a large evidence on the impact of diet on the gut microbiota [118].

We were very impressed by the data presented by Rishi et al. [119]. In particular in India, on an average, only 12 infected cases per 100,000 people were observed during the lockdown period and the fatality rate was the lowest, compared to the worst affected Western countries. The authors hypothesize that a plant-based high-fiber diet, which is consumed by the majority of the Indian population, appears to be advantageous, as it replenishes the host gut microbiota with beneficial microbes, thereby leading to health benefits to the host, including enhanced immunity. This might have resulted in better prognosis for COVID-19 patients in India in comparison to that observed in the Western countries. Death rate are very low in many Sud-Saharian African Countries, in the Middle East and in Pakistan, as well. Furthermore, the recent COVID-19 second wave outbreak in Europe and in the USA does not appear to happen in many Asian or African Countries.

Raw and fermented vegetables and several spices are associated with the activation of the most potent antioxidant in humans, the antioxidant transcription factor Nrf2 (nuclear factor [erytroid-derived 2]-like 2). Additionally, Nrf2 downregulates the oxidative stress from the AT1R axis, limits the overproduction of IL-6, proinflammatory cytochines and chemokines and inhibits the activation of nuclear factor kappa B (NFkB), which is involved in oxidative stress [120, 121]. Furthermore, several spices desensitize the receptor potential ankirin 1 and vanillin 1 (TRPA1/V1). Since TRPA1 causes inflammation, while TRPV1 detects and regulates body temperature, it seems that the sinergy between the activation of Nrf2 and the desensitization of TRPA1/V1 channels may explain the role of the diet in COVID-19.

There are many spices with benefical effects on human health, like allicin garlic (present in leek and onion) that interacts with TRPA1 and TRPV1 [122]. Other spices, like capsaicin (contained in red pepper), cinnamaldehyde (cinnamon), curcumin (turmeric), gingerol (ginger), mustard oil (mustard seeds), piperine (black and long pepper), wasabi (Japanese horseradish) interact with Nrf2, TRPA1, and TRPV1 [123-140]. Recently, it was suggested that spices can also interfere with the entry of SARS-CoV-2 into the cell and in the autophagy processes [120, 141]. There are many other Nrf2-interacting nutrients like quercetin and resveratrol that can reduce insulin resistance, endothelial damage, lung injury, and cytokine storm. Finally, a few COVID-19 patients have been studied in order to assess their response to either broccoli and paracetamol or broccoli with TRPA1/V1 and paracetamol during the first 2 phases of the infection. The authors hypothesized that Nrf2-interacting foods and nutrients can re-balance insulin resistance and have a significant effect on COVID-19 severity. As a result, these nutrients reduced cough, gastrointestinal symptoms, and nasal symptoms within minutes and fatigue was improved 1 h after ingestion. They concluded that the intake of these foods may restore an optimal balance for the Nrf2 pathway and mitigate COVID-19 severity [121, 142].

Evidence suggests that epigenetics is more important than genetics, even in this field: the major genetic risk factor for severe COVID-19 is inherited from Neanderthals [143].

Some authors suggest enhancing intestinal butyrate production by dietary changes as for promoting a healthy microbiome in general. One relevant explanation should link to the finding of negative correlations of two beneficial commensals, *A. muciniphila* and *F. prausnitzii*, with viral load and disease severity, respectively [144]. This has been suggested also by other authors [145].

Our understanding of the role of the gut microbiome in COVID-19 infection remains in its infancy, but future research may potentially aid our understanding of viral infection, and new ways in which we might treat it and prevent it [80].

Thus, we can conclude claiming that the gut microbiome is an under-recognised contributor to the COVID-19 pandemic [80].

Conclusions

In **Tab. 4**, take-home messages are presented on what we know and some practical final considerations.

When we talk about COVID-19 there are so many things we don't know, despite being overwhelmed

Table 4. Take-home messages on the 7 secrets of COVID-19: what we know and some practical final considerations.

The 7 secrets of COVID-19	What we know	Practical considerations
Fever	• In children, there may be a presentation of COVID-19 with acute respiratory distress without fever and cough. • In children, fever tends to last less than 3 days and, generally, a high fever at the time of the admission is not an indicator of bad outcome.	• The absence of fever at an initial screening does not exclude COVID-19. • Fever duration is different in children and adults.
ACE2 receptors	• ACE2 is the target of SARS-CoV-2. • The expression of ACE2 in the colon is about 4 times higher than that of the lung. • Elevated ACE2 expression in the gut creates conditions favorable to infection by Coronaviruses like SARS-CoV-2 of the gut epithelium, from which it can further spread through the body.	• A presentation of COVID-19 with only gastrointestinal symptoms is possible.
Gut-lung axis	• Lung microbiota is present in healthy lungs. • Following the "more gut in the lung" phenomenon, some bacterial strains show up in the gut before their emergence in the lung. • In cases of respiratory diseases, gastrointestinal disorders generally occur, leading to a more severe clinical course. • There is potential for manipulation of the gut microbiota in the treatment of lung diseases. • In COVID-19, both adult and pediatric patients receive few antibiotics in percentage (since COVID-19 is a viral disease), despite the clinical severity of the patients and the presence of important comorbidities.	• The use of antibiotics in COVID-19 should be revised in the light of the concept of "more gut in the lung".
Metabolomics	• The inter-individual differences in the activation of the receptors that allow the harmful pulmonary and systemic effects in the course of COVID-19 may be due to the microbiota. Metabolomics, given its ability to provide a metabolic snap-shot of an individual, is considered to be the Rosetta Stone of the microbiomics. • Many metabolites were found to be up- or downregulated in COVID-19 patients and critical COVID-19 patients, discriminating them from healthy controls. These metabolites could act as biomarkers for COVID-19: they are presented in **Tab. 1**.	• Metabolomics could be a tool for an early diagnosis, to investigate drugs responses in patients and to predict mortality in COVID-19. • Influencing the metabolism of specific metabolites through a therapeutic approach and dietary supplementation may decrease the severity and mortality of COVID-19.
Microbiomics	• The gut microbiome influences ACE2 receptor expression, so it may play a role in influencing COVID-19 infectivity and disease severity. • The gut microbiome plays a significant role in immune regulation, so it may be pivotal in influencing the immune response to COVID-19, as well as the response to treatment. • Rather than being merely restricted to the lower respiratory tract, severe acute infection of SARS-CoV-2 spreads to other organs, namely the gastrointestinal tract, with the relevant contribution of the microbiome. • The vast majority of COVID-19 worst clinical conditions and fatalities develop in subjects with risk factors such as aging, inflammation (inflammaging) and comorbidities. These risk factors are also characterized by an unhealthy microbiome status. • High-risk subjects require complex pharmacological regimens known as "polypharmacy", that may further negatively affect microbiota integrity and worsen the resilience to viral infections. • A list of relevant bacteria, present in the gut and in the lung, favoring or contrasting COVID-19 is presented in **Tab. 2**.	• The microbiota pre-existing health status and its modifications in the course of COVID-19 are likely to play an important role in determining individual susceptibility and resilience to COVID-19. • Maintaining and improving the gut microbiota eubiosis through personalized nutrition and supplementation may improve host immunity and is one of the prophylactic ways by which the impact of COVID-19 can be minimized in the elderly, immuno-compromised patients and, more in general, in patients at risk.
Probiotics	• Modulation of gut microbiota could be one of the approaches to COVID-19 prevention and treatment. Probiotics are potential candidates to be tested in moderate and severe cases of COVID-19 due to several beneficial effects, including the fact that they are easily available, easy to administer, and safe and economical to use. • Some suggestions of probiotics used in viral infections are presented in **Tab. 3**.	• The administration of probiotics could be beneficial to prevent and treat COVID-19.
Diet	• Maternal milk is highly protective. • Improving the composition of the microbiota and the proportion of its metabolites through probiotics and personalized diet could be a potential strategy to prevent and treat COVID-19. • The diet may be a key driver in determining the severity of COVID-19. • The WHO provides advice on nutrition during this pandemic to include plenty of fruit and vegetables. • A plant-based high-fiber diet appears to be advantageous, as it replenishes the host gut microbiota with beneficial microbes, thereby leading to health benefits to the host, including enhanced immunity. • Raw and fermented vegetables and several spices are associated with the activation of the most potent antioxidant in humans and could have benefical effects on human health, mitigating COVID-19 severity.	• The right diet could be beneficial to prevent and treat COVID-19.

ACE2: angiotensin-converting enzyme 2; IAA: indole-3-acetic acid; LTD4: leukotriene D4; WHO: World Health Organization.

by the number of articles that come out about COVID-19: up to 25 every hour. An information overload, an impossible undertaking to read them all.

We strongly believe that the 3 M's (Metabolomics, Microbiomics and Machine learning [Artificial Intelligence]) will be the right route to the future for risk assessment, early diagnosis, patient management and decision-making [146-148]. We presented in December 2020 our ideas and projects on this topic in the 12th European Innovation Summit of the European Parliament ("Towards a European Innovation Area") [149]. In this article we have tried to deepen 7 points, meaning a small step towards the final victory against the virus. A recent paper has this title: "The future is now? Clinical and translational aspects of 'Omics' technologies" [148]. The future is now. We would like to finish with a sentence of Gerd Leonhard: "*I do not predict the future, but I observe it, because the future is here*".

Declaration of interest

The Authors declare that there is no conflict of interest.

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