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Review

Interplay between Multisystem Inflammatory Syndrome in Children, Interleukin 6, Microbiome, and Gut Barrier Integrity

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Abstract: A severe consequence of SARS-CoV-2 infection that manifests as systemic inflammation and multi-organ involvement is called Multisystem Inflammatory Syndrome in Children (MIS-C). This review examines the possible relationship between gut barrier integrity, the microbiome, dysregulation of interleukin 6 (IL-6) signaling, and MIS-C. Clinical and biochemical features of MIS-C are comparable to those of other hyper-inflammatory syndromes, suggesting a dysregulated immune response. One possible explanation for the systemic inflammation seen in MIS-C patients is the SARS-CoV-2-induced dysregulation of the IL-6 signaling pathway. In addition, new data suggest a reciprocal link between gut barrier integrity and IL-6. SARS-CoV-2 exhibits bacteriophage-like behavior, highlighting the role of bacteria as a reservoir for the virus and emphasizing the importance of understanding the bacteriophagic mechanism of the virus in fecal–oral transmission. The increased translocation of viral products and bacterial toxins may result from disrupting the intestinal barrier and cause systemic inflammation. On the other hand, systemic inflammation can weaken the integrity of the intestinal barrier, which feeds back into the loop of immunological dysregulation. In the context of MIS-C, understanding the interaction between SARS-CoV-2 infection, IL-6, and gut barrier integrity may shed light on the etiology of the disease and guide treatment options. Since children with gut dysbiosis may be more susceptible to MIS-C, it is critical to reinforce their microbiome through probiotics supplementation, and plant-fiber-rich diets (prebiotics). Early antibiotic treatment and the use of zonulin antagonists should also be considered.

Keywords: MIS-C; IL-6; gut barrier dysfunction; zonulin levels; microbiome; SARS-CoV-2 bacteriophage behavior; long COVID

1. Introduction

COVID-19 is not as severe in children as it is in adults in most situations. Children are the target of around 18% of coronavirus infections overall and 1% of COVID-19 cases. The 5–15 age group has a higher incidence of COVID-19. Children in the United States have a seropositivity rate of approximately 75%, which is greater than that of adults. Fortunately, the majority of pediatric patients (>90%) with SARS-CoV-2 infection are asymptomatic or only show moderate signs such as weakness, dry cough, and low fever. Inpatient and outpatient records from 2021 revealed that only 2% of all infected children in the United States required intensive care unit (ICU) care. A total of 27% had moderate symptoms similar to influenza, 5% had substantial pneumonic symptoms, and 66% of all infected children exhibited no symptoms at all [1].

Reports from the UK appeared in May 2020 about children who needed to be admitted to intensive care units because of an unexplained multisystem inflammatory condition that resembled toxic shock syndrome and Kawasaki disease [2]. Subsequent reports of comparable cases were made in both Europe and the US, and they were linked to COVID-19 outbreaks both geographically and temporally [3–5]. While most afflicted youngsters tested positive for antibodies, indicating prior infection, RT-PCR results for the SARS-CoV-2 virus were negative. A SARS-CoV-2 infection-related post-infectious inflammatory response was suggested as the source of the clinical condition [6]. Similar cases pertaining to this novel syndrome were reported by the UK, the US, and the World Health Organization, and the illness temporarily associated with COVID-19 was referred to as multisystemic inflammatory syndrome in children (MIS-C) [6].

MIS-C is different from acute severe COVID-19 infection in children in terms of both epidemiological and clinical characteristics. Young age, a history of co-morbidity, respiratory symptoms, and respiratory dysfunction are linked to acute severe COVID-19 infection in children [7]. On the other hand, most of the MIS-C cases that were presented had considerable cardiovascular dysfunction and gastrointestinal (GI) symptoms. They were also older and did not often have co-morbidities. Such clinical characteristics match those identified in the most extensive and well-researched MIS-C case series available to date (n = 99) [8]. According to that study, 63% of children had cardiovascular impairment and 80% of children were between the ages of 6 and 12 years [8].

In a review work, Banoun [9] reiterated the importance of the gut microbiome (GM) in the severity of COVID-19, as the GM and respiratory infections are strongly linked and may influence the host's response to pneumonia. The synthesis of short-chain fatty acids (SCFAs), the control of systemic inflammation, the establishment of oral immunological tolerance via regulatory T cells (Tregs), and the management of extra-intestinal T cell populations are some of the potential pathways [10]. Therefore, this paper hypothesizes that gut dysbiosis may also influence the pathogenesis of the MIS-C and clinical outcomes in affected children and presents evidence to support this proposal.

2. MIS-C Clinical Characteristics

COVID-19 and MIS-C are two distinct disorders caused by the SARS-CoV-2 virus [11]. MIS-C is an uncommon illness that may occur in children infected with SARS-CoV-2. It involves inflammation in various organs, including the brain, skin, eyes, heart, lungs, kidneys, and gastrointestinal tract. In total, 100% of the eight patients from the United Kingdom in the first correspondence to be published about MIS-C had GI issues [2]. Similarly, in an Italian study, GI problems affected 6 out of 10 children [4]. GI symptoms were reported in less than 10% to 15% of adult patients, but respiratory symptoms are the most prevalent presentation for them [12,13]. According to a study conducted in the USA, GI symptoms were reported in 84.1% of 44 children and were most frequently associated with rash (70.5%) and fever (100%) [14]. Other research found that 90% of 72 children had GI manifestations [15]. Although it can be life-threatening, most children recover with medical attention [11,16,17]. MIS-C was initially diagnosed as a form of Kawasaki disease due to their clinical similarities; however, subsequent research demonstrated that they are

different entities with distinct epidemiological, clinical, and immunological profiles [18,19]. According to a recent study on GI involvement linked to COVID-19, excrement from up to 41% of children without MIS-C tested positive for SARS-CoV-2 [20]. This result suggested that the elevated inflammatory response is probably the cause of the high frequency of GI symptoms in MIS-C cases [15]. This work proposes an inverse relationship: SARS-CoV-2 infects and replicates within gut bacteria. Afterwards, these bacteria are destroyed and release toxic molecules that together with elevated IL-6 levels cause gut barrier dysfunction, leading to leakage of viral antigens and bacterial toxins to the blood. In other words, the hyper-inflammatory response observed in MIS-C is not the cause but rather the consequence of the immune system response against viral and bacterial toxins. In all the mechanisms so far proposed in the literature, although some authors highlight the persistence and presence of the virus in all the different forms including COVID-19, MIS-C, and long COVID, no model has considered that individual, familial, or community variability in the microbiome may generate different toxin-like peptides dependent on its bacterial genetic content. This element would explain the diversity of some symptoms in some individuals in the presence of the same viral infection.

3. The GM Supports Barrier Protection Functionality

The pathophysiology of numerous inflammatory and immunological disorders is intimately linked to the integrity of the intestinal barrier [21–23], a dynamic structure that interacts with and responds to a range of stimuli. It is composed of surface mucus, the epithelial layer, and immunological defenses [22]. The mucosal and epithelial components of the physical barrier are closely associated with several cellular junctions, such as adherens junctions (AJs), tight junctions (TJs), and desmosomes [24]. Additionally, the normal GM controls the intestinal micro-ecological equilibrium [25]. The intestinal barrier typically blocks substances and microbes from moving from the lumen to the circulation. However, intestinal dysbiosis, or the dysregulation of the gut flora, may result in a disorder called "leaky gut syndrome", characterized by increased permeability that may trigger the innate immune system and promote low-grade inflammation. In recent times, GM dysbiosis has been linked to extra-intestinal as well as intestinal diseases. These include chronic diseases that are particularly prevalent in the elderly, such as diabetes [26–28], and other systemic side effects, such as oxidative stress, and increased inflammation [21,29,30].

4. The Link between Gut Microbiome Dysbiosis and MIS-C

Constant fever, vomiting, diarrhea, skin irritation, abdominal pain, and, in severe cases, hypotension and shock are the hallmarks of MIS-C [11,16,31]. One of the most common MIS-C symptoms is GI distress, raising the possibility that the GM may act as both a local and systemic inflammatory modulator [32,33]. The composition and activity of the GM have co-evolved with the host. It is influenced throughout life, from birth to old age, by a dynamic and complex interaction between the host genome and lifestyle variables, particularly nutrition, which is becoming recognized as the primary modulator of microbial activity [34,35].

This microbial population produces vitamins and ferments macromolecules including proteins, lipids, and carbohydrates. These metabolic effects are collectively known as co-metabolism [36]. Furthermore, the GM is primarily responsible for maintaining host homeostasis through the "training" of host immunity and structural/protective actions against commensal pathogens, specifically safeguarding the intestinal barrier [36]. Eubiosis is maintained by the GM when it is healthy. In pathological circumstances, the GM experiences an unbalanced state of dysbiosis wherein there is either a decrease in beneficial commensals, a proliferation of opportunistic pathogens, or both [37].

In adults, it is increasingly recognized that the gut acts as a reservoir for SARS-CoV-2 [38], and that dysbiosis and GI barrier disruption induce inflammatory activation in severe COVID-19 [39,40]. Several investigations have revealed that GM is also affected in adult patients with long COVID [41–43]. One study found that GM dysbiosis continued

for up to 30 days after disease resolution, which may be related to persistent symptoms of post-acute sequalae of COVID-19 (PASC), also referred to as long COVID [44]. It is known that angiotensin-converting enzyme 2 (ACE2) regulates the synthesis of neutral amino acid transporters in the gut [45], which regulate the composition of the GM and, ultimately, the immune responses in the body [46,47]. In COVID-19 patients who already had age-related disorders, ACE2 imbalance has been associated with poor outcomes (including increased disease severity and mortality rate) through its impact on intestinal dysbiosis [48].

In a 6-month follow-up, Liu et al. [43] confirmed that long COVID patients had different GM species than controls and a consistently decreased diversity. Remarkably, the dysbiosis pattern was different among those who initially had COVID-19 but did not have long COVID. In the latter subgroup, tiredness, respiratory, and neuropsychiatric problems were strongly correlated with increased fecal relative abundance of opportunistic microorganisms [43]. Additional research revealed that long COVID is associated with dysbiosis of the GM in patients who have recovered a year after being discharged, suggesting that the GM may be crucial in long COVID [49].

Although the aforementioned findings explicitly demonstrated that alterations in the microbiome have a deleterious effect on the extended clinical course of COVID-19 in adults, there has been a lack of research on this crucial topic in MIS-C. The composition, diversity, and abundance of the gut microbiome were found to be different in MIS-C cases compared to COVID-19 cases and healthy controls. At the phylum level, the MIS-C group had an abundance of Bacteroidetes, whereas the healthy children had Firmicutes. When MIS-C was compared to the SARS-CoV-2 group and the healthy control group, the relative abundance of Bacteroidetes increased, and the Firmicutes/Bacteroides ratio significantly dropped [50]. Romani et al. [51] investigated the GM of children with COVID-19, including four cases of MIS-C. *Veillonella*, *Ruminococcus*, *Clostridium*, *Dialister*, and *Streptococcus* were more prevalent in the GM of MIS-C patients, while *Bifidobacterium*, *Blautia, Granulicatella*, and *Prevotella* were less prevalent.

Pro-inflammatory taxa were more prevalent and anti-inflammatory taxa were less prevalent in children with MIS-C. Children with MIS-C and COVID-19 [50] had lower concentrations of *Faecalibacterium prausnitzii*, which has been demonstrated to use butyrate to reduce intestinal mucosal inflammation and maintain gut physiology [52,53]. Therefore, it has been proposed that "alterations of the intestinal microbiome may contribute to the pathophysiology of MIS-C predisposing factors" [50].

4.1. SARS-CoV-2 Infection Impairs Gut Barrier Integrity by Inducing Zonulin Release

Intestinal bacteria are secluded from the underlying lamina propria by the dynamic physical and biochemical barrier known as the intestinal mucosa, which also inhibits the infiltration of pathogenic and antigenic molecules [54]. Despite the presence of chemical and physical barriers in the intestines, some pathogens can cross through it and interact with intestinal epithelial cells (IECs). Several sensing pattern recognition receptors (PRRs) are expressed by IECs, which are essential for maintaining the intestinal mucosal immune response's homeostasis [55].

In response to bacterial signals, PRRs can initiate a physiological inflammatory response that promotes progenitor cell proliferation, epithelial cell survival, and pathogen elimination—all of which enhance intestinal integrity [56]. As was already mentioned, children with MIS-C frequently experience GI symptoms, which can lead to a severe hyperinflammatory reaction and cardiac problems. A SARS-CoV-2 infection is known to cause MIS-C several weeks later, and it is known that the viral load in respiratory secretions decreases for 7–10 days following infection [57–59]. It seems doubtful that the initial respiratory tract infection in children with MIS-C is related to the disease, as the majority of them have negative nasopharyngeal viral swabs [19,57]. Furthermore, several lines of evidence demonstrated that SARS-CoV-2 can establish robust infection and replication in human IECs, which may contribute to GI dysfunction and potential fecal–oral transmission in some patients [60–62].

Zonulin is a member of a structurally and functionally similar family of proteins that modulate intercellular TJs to reversibly regulate intestinal permeability [63–65]. Large antigens, such as viral antigens generated from SARS-CoV-2 present in the GI tract, should not be able to pass through the gut lumen and into the bloodstream when the intestinal mucosal barrier is intact and functioning [38].

Patients with SARS-CoV-2 infection had elevated zonulin levels, which were linked to worse outcomes [33,66–69]. Furthermore, high serum zonulin levels disrupt the brain–blood barrier (BBB), allowing viruses to enter the brain and induce serious neurological symptoms [33,70]. Numerous autoimmune and hyper-inflammatory illnesses, including celiac disease [71], inflammatory bowel disease [72], and Kawasaki disease [73], have been linked to elevated circulating zonulin levels and increased intestinal permeability [72,74].

In 2021, Yonker et al. [33] examined bio-specimens from 100 children: 19 had acute COVID-19, 26 had MIS-C, and 55 were controls. Reverse transcription PCR (RT-PCR) was used to detect SARS-CoV-2 in stool samples, and zonulin and other indicators of mucosal barrier integrity were tested in plasma. According to this seminal research, the prolonged presence of undigested SARS-CoV-2 viruses causes the gastrointestinal tract to release more zonulin, which increases intestinal permeability [33].

Elevated zonulin levels suggest that intestinal epithelial TJs are failing, allowing SARS-CoV-2 antigens [33] and bacterial toxins [75,76] to penetrate the blood. It has been discovered that some strains of bacteria, mostly Gram-positive ones like *Bifidobacterium* and *Lactobacillus* spp., reduce intestinal zonulin levels while other strains, mostly Gram-negative ones like *Salmonella* spp., *Prevotella*, *Escherichia coli*, and *Pseudomonas*, induce zonulin release. These results are in line with earlier studies on animal models and cell lines (reviewed in [77]).

Several events, including gut dysbiosis [78], trigger the release of zonulin in a myeloid differentiation primary response 88 (MyD88)-dependent manner, which enables zonulin to bind to its target, protease-activated receptor 2 (PAR2), and subsequently transactivate the epidermal growth factor receptor (EGFR) [79]. This initiates a chain of events that results in the phosphorylation of TJ proteins, such as myosin 1c and zonula occludens 1 (ZO1), which in turn leads to the disintegration of TJs and an increase in the permeability of paracellular membranes to macromolecules [80]. This, in turn, accelerates the trafficking of viral and bacterial antigens into the bloodstream (Figure 1), resulting in hyper-inflammation [33].

The development of zonulin-dependent loss of gut integrity in infants affected with MIS-C suggests that chronic SARS-CoV-2 infection causes gut dysbiosis, leading to a progressive deterioration of mucosal barrier integrity. Viremia was not found in MIS-C [57], although antigenemia and viremia have been demonstrated to correlate with severe acute COVID-19 in adults [59,81].

Yonker et al. [33] found SARS-CoV-2 cleaved soluble components of spike (S1) and nucleocapsid antigens in the blood of children suffering from MIS-C, even though the children had been exposed to or had been infected with the virus weeks before. Compared to MIS-C patients and healthy controls ($p < 0.0001$), and children with acute COVID-19 ($p < 0.001$), SARS-CoV-2 spike protein levels were significantly higher. They also found that patients with MIS-C had significantly higher levels of SARS-CoV-2 S1 protein than healthy controls ($p = 0.004$) and children with acute COVID-19 ($p = 0.02$). Compared with healthy controls, the researchers found no discernible increase in blood levels of the SARS-CoV-2 antigen in children with acute COVID-19 [33].

It is known that a significant amount of blood that exits the gastrointestinal tract goes via the hepatic portal vein in the liver before entering the systemic circulation. As a result, it has long been understood that the liver is in control of immune surveillance against antigens coming from the gut [82]. It is important to mention that SARS-CoV-2 infection has been shown to impair liver immunity through several mechanisms, leading to liver injury and dysfunction. Hepatobiliary epithelial cells, cholangiocytes in particular, express the ACE2 receptor, which allows SARS-CoV-2 to infect these cells [83]. This direct infection can aggravate liver failure as the virus has been found in COVID-19 patients' liver

tissues, suggesting that this organ may be a target for viral replication [84,85]. A cytokine storm may result from the exacerbated immunological response that the infection sets off, which is defined by the release of pro-inflammatory cytokines. The liver's capacity to develop a successful immune response may be hampered by this systemic inflammation, aggravating liver dysfunction and damage in adults [86] and in children [87]. According to a 2020 study, younger children—those under three years old—were more likely than older children to develop liver damage from COVID-19. The likely cause was early-life liver immaturity [88]. Upon admission, children frequently had higher liver enzyme levels than adults, who typically had an increase in enzyme levels no earlier than the second week of hospitalization [89]. Similar findings were reported in other investigations, with MIS-C showing these findings more frequently than in COVID-19 [87]. Therefore, the liver immune surveillance against antigens coming from the gut may be compromised in MIS-C, allowing the antigens to enter systemic circulation.

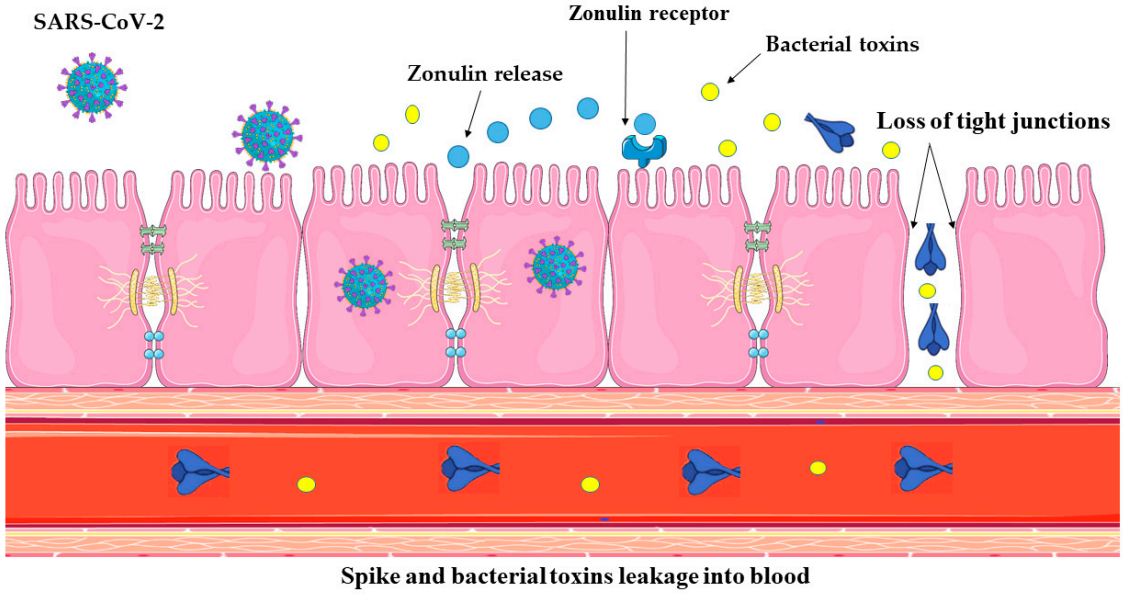

Figure 1. Zonulin is a molecular gatekeeper that regulates TJs between intestinal epithelial cells. Normally, these TJs serve as a selective barrier, preventing chemicals and pathogens from entering the bloodstream from the intestines. SARS-CoV-2 infection in the GI tract causes localized inflammation of the mucosa, which in turn triggers zonulin release. This, in turn, enhances gut permeability, allowing SARS-CoV-2 antigens and bacterial toxins to pass through mucosal barriers and enter the bloodstream. Parts of the figure were drawn using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

4.2. Bacteriophage-like Behavior of SARS-CoV-2 and MIS-C

Other important research performed by Brogna and colleagues revealed that this virus is capable of infecting intestinal bacteria, acting like a bacteriophage [90–94]. According to a previous study by that group, the blood, feces, and urine of COVID-19 patients contained toxin-like peptides that were almost identical to the poisonous elements of animal venoms, including conotoxin, phospholipases A2, phosphodiesterases, zinc metal proteinases, and bradykinins [75]. Later research revealed that SARS-CoV-2 might replicate autonomously in bacterial cultures derived from patient feces for up to 30 days and longer [95]. Viral-like structures ranging in size from 25 to 100 nm were observed by electron microscopy interacting with and within bacterial cell walls (Figure 2). The presence of SARS-CoV-2 nucleocapsid protein both inside and outside of the bacteria was verified by immunolabeling, specifically in two anti-inflammatory gut bacterial species normally present in a healthy human GM (*Faecalibacterium prausnitzii* and *Dorea formicigenerans*) [92]. These species were previously found to be considerably reduced in severe COVID-19 cases [96,97] and in

children with MIS-C [50]. Importantly, both bacteria have been shown to use butyrate, thereby preserving gut physiology and reducing gut mucosal inflammation [52,53].

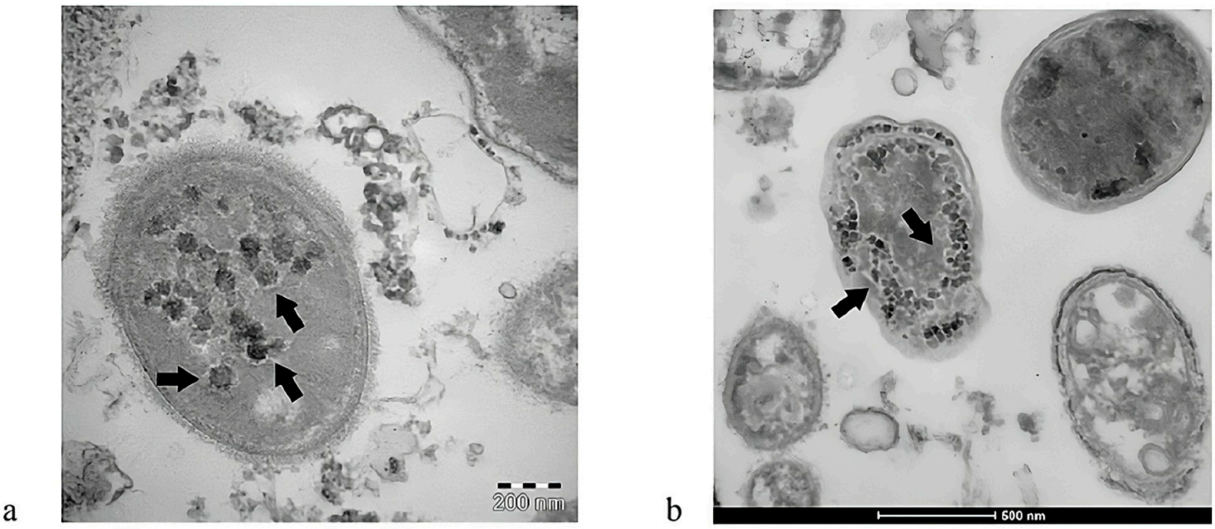

Figure 2. SARS-CoV-2 can infect intestinal bacteria, thus showing a bacteriophage-like behavior. Panels (**a**,**b**): Images from a transmission electron microscope revealed the presence of SARS-CoV-2 inside two bacteria, marked by black arrows. Source: [91]. This figure is open access and is distributed under the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license.

In addition, de novo synthesis of SARS-CoV-2 spike protein was detected in the bacterial cultures using 15N-labeled nitrogen as a source, accompanied by an increase in viral RNA load [92]. The discovery that SARS-CoV-2 can infect bacteria cells that are a component of the normal human GM and synthesize both nucleic acid and viral peptides has major consequences for human health, especially concerning the regulation and control of the virus spread. For example, the ability of SARS-CoV-2 to infect and replicate in human gut bacteria may lead to a scenario in which infected bacteria continue to harbor the virus for prolonged periods, possibly even after the systemic infection of the human host has resolved [92]. Epidemiological studies have shown that this may result in prolonged viral shedding through the intestinal tract, potentially increasing the likelihood of subsequent transmission. Furthermore, prolonged survival due to the continuous replication of the virus in the intestinal lumen could allow recurrent revival of systemic SARS-CoV-2 infection in the person, leading to COVID-19 relapse without the need for external reinfection [92].

The combined deleterious effects of SARS-CoV-2 infection reflected as increased zonulin release [33] and the decrease in commensal bacterial populations due to the bacteriophage-like effect of SARS-CoV-2 [90–94] could further compromise the integrity of the intestinal barrier, allowing the passage of the spike protein and toxins released by infected bacteria.

4.3. The Superantigen Hypothesis of SARS-CoV-2 Spike Protein

The proposed superantigen (Sag) activity of the SARS-CoV-2 spike protein has been a topic of investigation, particularly in relation to MIS-C. On one hand, the study by Sacco et al. [19] identified distinct immunopathologic signatures in pediatric COVID-19 and MIS-C and pointed out that MIS-C is characterized by prominent type II IFN and NF-κB-dependent signatures, matrisome activation, and increased levels of circulating spike protein. Only 2 of these 15 MIS-C patients showed a positive PCR on a nasopharyngeal swab within 7 days of the hospitalization, indicating that elevated spike protein levels were not caused by a prolonged respiratory tract infection, even though they did not look into the presence of SARS-CoV-2 mRNA in stool samples [19]. The study by Noval Rivas [98] suggests that "continuous and prolonged exposure to superantigen-like

and neurotoxin-like viral motifs of the SARS-CoV-2 spike may promote autoimmunity leading to the development of post-acute COVID-19 syndromes, including MIS-C and long COVID, as well as neurological complications resulting from SARS-CoV-2 infection". A study found that at the junction between the S1 and S2 subunits, the SARS-CoV-2 spike component S1 includes an insertion of four amino acids, P681RRA684 (PRRA), next to the cleavage site R685↑S686 [99]. Only SARS-CoV-2 and the β-coronaviruses in the SARS-like subfamily possess the polybasic segment PRRA [99]. The PRRA insert was discovered to be a component of the E661–R685 motif, a group of 25 amino acids with sequence and structural similarities to a portion of the SAg from SEB [100].

On the other hand, some studies also highlight that the SARS-CoV-2 spike protein does not exhibit superantigen-like activity [101,102]. In experimental setups, the spike protein was compared to staphylococcal enterotoxin B (SEB), a well-known superantigen. The study showed that while SEB induced a significant production of pro-inflammatory cytokines, the SARS-CoV-2 spike did not trigger a similar response in T cells, indicating that it lacks the intrinsic ability to function as a superantigen [101].

Another study examined the T cell response to SARS-CoV-2 peptide pools in children in the subacute phase of MIS-C in order to corroborate this observation. Despite their abundance, Vβ21.3-bearing CD4+ and CD8+ T cells did not belong to the SARS-CoV-2-specific T cell population. According to this research, most children's T cell repertoire grew in response to an antigen unrelated to SARS-CoV-2 [103]. Although the antigen that triggers MIS-C is unknown, it might come from the associated leaky gut [33].

Burns [102] wrote: "If spike peptides are not superantigens, then what is the role of the spike protein in MIS-C pathogenesis?" Several groups reported the persistence of the spike antigen in the circulation of patients with acute MIS-C. However, Sigal et al. [104] used a sensitive electro-chemiluminescent immunoassay in patients with MIS-C and showed no persistence of the spike antigen in the plasma.

In 2022, reports from different countries reported a decrease in the prevalence of MIS-C in association with Omicron variant waves of SARS-CoV-2 infection. This questioned again the spike superantigen theory significance in the pathophysiology of MIS-C. Research conducted in 12 Israeli hospitals over a 16-week period during each of the three pandemic waves (Alpha, Delta, and Omicron) found that during the Omicron wave, there were fewer admissions to critical care and less severe cardiac outcomes. According to national data, there were 54.5 MIS-C incidents per 100,000 people under the age of 18 during Alpha, 49.2 during Delta, and 3.8 during Omicron. The reduced frequency of MIS-C during the Omicron wave may have been caused by vaccination, prior SARS-CoV-2 infection acting as a protective factor, or changes in the spike protein that resulted in diminished pathogenesis [105].

It is crucial to keep in mind that the furin-like cleavage site R685↑S686 is located next to this SAg-like motif [99]. Because the furin cleavage site (FCS) contains the SAg-like motif, it is essential for the acidic furin epitope to recognize it. In fact, viral mutations that eliminated the furin cleavage site have been shown to significantly decrease SARS-CoV-2-induced pathogenesis in the animal model [106]. It is important to clarify that the Delta variant did not lose the FCS. In that variant, a P681R mutation occurred near the FCS, and as a consequence, a glycosylation site was lost [107], leaving the FCS uncovered (Figure 3), thus promoting syncytia formation and a greater pathogenicity [108].

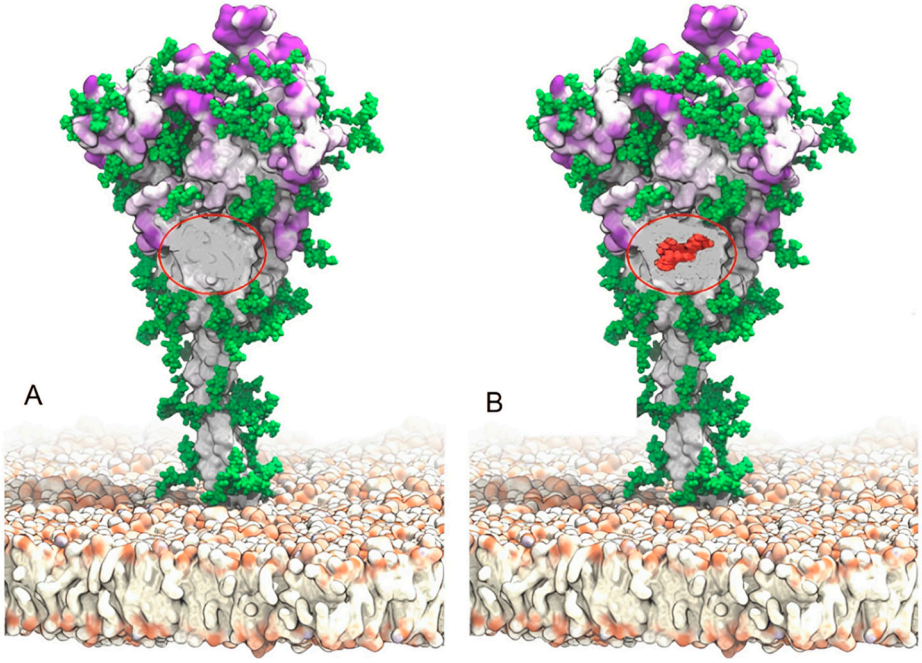

Figure 3. (**A**) Spike protein from the Delta variant displaying the location of the FCS and the glycan hole (a region with no glycans indicated by a red oval). There were glycans covering this specific area in the original Wuhan strain. The Delta variant's P681 mutation, on the other hand, caused glycans to be lost, which increased cell-to-cell fusion and syncytia formation, with increased pathogenicity as a result. (**B**) A Thr376 mutation in the Omicron variation led to the insertion of O-glycans (shown in red), whose structure blocks the FCS and prevents cell-to-cell fusion and the formation of syncytia. Source: [109].

5. The Link between IL-6 Levels, Gut Barrier Integrity, and MIS-C

During the COVID-19 pandemic, several meta-analyses demonstrated that high levels of IL-6 have been linked to some adverse health effects, including acute respiratory distress syndrome, death, and ICU hospitalization. Serum IL-6 levels were almost three times greater in patients with such complex types of COVID-19 than in patients with less severe disease [110–114]. It has been demonstrated that the SARS-CoV-2 spike and nucleocapsid proteins alone can cause monocytes and macrophages to produce IL-6. Of interest, children with MIS-C exhibit hyper-phagocytosis and enhanced monocyte recruitment [19,115]. In certain COVID-19 patients, this IL-6 overexpression may be the catalyst that starts the dysregulated immune response [116,117]. However, extensive research allows us to understand that, depending on the specific circumstances of the immune response, IL-6 is a cytokine with multiple functions, having both pro- and anti-inflammatory effects [118]. Initially discovered as B cell stimulatory factor 2 (BSF-2), IL-6 stimulates activated B cells to produce immunoglobulin (Ig) [119]. At low, physiological concentrations, it regulates many important immune functions. Innate and adaptive immune systems are largely developed and activated in large part by IL-6. This cytokine induces monocytes to differentiate into macrophages rather than dendritic cells (DCs) in the innate immune system [120].

Moreover, the increase in anti-apoptotic proteins that support T cell survival is associated with IL-6 signaling [121–123]. Furthermore, IL-6 inhibits the transforming growth factor beta (TGF-β)-mediated maturation of Tregs and promotes the development of untrained CD4+ T cells into effector T cell subgroups, such as pathogen-specific effector Th17 cells [124,125]. Therefore, an increase in IL-6 levels causes immune dysregulation, as in COVID-19's cytokine storm, and in other autoimmune disorders and cancer [124,126–131]. IL-6 is also essential for epithelial proliferation and wound repair [132] and for immune–epithelial–bacteria communication in both beneficial as well as harmful processes. For

example, *Pediococcus acidilactici* K15, a lactic acid bacterial strain, promotes the secretion of IL-6 in BDCA1+ DCs (mDC1) via its double-stranded RNA and enhances the synthesis of protective IgA antibodies [133].

On the other hand, high levels of IL-6 can cause inflammation, and many probiotics work to lower these levels to treat intestinal disease [134]. In the context of ulcerative colitis (UC), a study found that at physiological levels, IL-6 controls epithelial barrier function by modulating the expression of TJ-related proteins. In contrast, IL-6 levels in the plasma of UC patients were elevated and increased as the disease worsened. The overproduction of IL-6 has also been shown to damage the intestinal epithelial cell barrier and control barrier function by increasing zonulin release. Conversely, when an anti-IL-6 antibody was added, the amount of zonulin was lower than in the control group [135].

It was discovered that long-term SARS-CoV-2 infection in the GI tract triggered zonulin release in children with MIS-C, with subsequent trafficking of SARS-CoV-2 antigens into the circulation, resulting in hyper-inflammation and signs of a cytokine storm, including significantly higher levels of tumor necrosis factor- α (TNF-α), IL-6, IL-10, and IL-1β [33]. Scientists demonstrated that SARS-CoV-2 RNA is still present in the GI tract for weeks after initial infection and viral antigenemia is correlated with zonulin-induced increased permeability (leaky gut) of the mucosal barrier [33].

Thus, it is likely that the high zonulin levels found in children with MIS-C [33] are due to excessive concentrations of IL-6 released by SARS-CoV-2-infected cells at the GI. In addition, several works have demonstrated that in MIS-C, impairment of the innate and adaptive immune responses is responsible for the prolonged presence of the virus in the GI tract [77,136–140].

6. Preventive and Therapeutic Strategies for MIS-C

Yonker et al. [33] used larazotide, a zonulin antagonist, to treat children with MIS-C and evaluated the impact on antigenemia and the children's clinical outcomes. After receiving larazotide treatment for MIS-C, the patient's plasma SARS-CoV-2 spike antigen levels and inflammatory markers decreased concurrently, leading to a greater clinical improvement than what was currently possible with known treatments. In adults with COVID-19 and long COVID, Brogna et al. [141] discovered that patients who started early antibiotic treatment showed a statistically significant decrease in recovery time, and such treatment was critical for maintaining high blood oxygen saturation levels. Delayed antibiotic initiation within the first 3 days increased the risk of pneumonia in both vaccinated and unvaccinated patients.

Furthermore, it is noteworthy that a considerable proportion of patients who were administered antibiotics within the initial three days and throughout the full seven days of the acute phase did not experience long COVID. One of the main contributing factors to the development of the disease appears to be the bacteriophage behavior of SARS-CoV-2 during the acute and post-COVID-19 phases. Early antibiotic treatment appears to be essential for halting the progression of disease, possibly controlling toxin release from infected bacteria, and preventing viral replication in the GM [141]. Severe streptococcal infections that mimic MIS-C were highlighted in a recent report [142]. Since MIS-C is an excluding diagnosis, the differential diagnosis needs to be carefully considered. Treatment is difficult for the physician because it overlaps with other prevalent disorders. Empirical antibiotic therapy for possible bacterial agents should be initiated in those with fever, organ involvement, and increased inflammatory markers. In fact, antibiotic therapy may be continued if clinical suspicion is high [142].

Another potential approach could involve employing anti-IL-6 antibodies such as tocilizumab or sarilumab. However, it has been shown that IL-6 suppression in COVID-19 patients affects the neutralizing capacity of anti-SARS-CoV-2 antibodies [143]. Considering that the neutralizing activity of anti-SARS-CoV-2 antibodies determines protection against symptomatic infection [144], the study conducted by Della-Torre calls for a rigorous re-evaluation of the risk of reinfection and severe illness in patients receiving anti-IL-6 anti-

bodies [143]. It is also important to discuss the phenomena of COVID-19 rebound, which has been documented in individuals treated with antiviral medications after their initial infection [145]. In particular, it has been demonstrated that nirmatrelvir therapy during SARS-CoV-2 infection diminishes the likelihood of developing severe COVID-19, but it also inhibits the production of T cells and antibodies specific to SARS-CoV-2 [146]. This causes some patients' viral loads to rebound and their COVID-19 symptoms to recur quickly following the completion of prompt and efficient nirmatrelvir treatment. Furthermore, the development of efficient long-term immunity may be hampered by this process [146].

Certain Gram-negative bacterial strains, such as *Escherichia coli*, *Prevotella*, *Pseudomonas*, and *Salmonella* spp., have been found to induce intestinal zonulin release, while other strains, primarily Gram-positive ones, like *Bifidobacterium* and *Lactobacillus* spp., have been found to decrease zonulin levels. These findings are consistent with previous research conducted on cell lines and animal models (reviewed in [147]). Probiotics are live microorganisms that, when administered in the right quantities and for the right length of time, benefit the health of the host [148]. Through their surface molecules and metabolites, probiotics and intestinal symbionts can alter the host's intestinal barrier function [149]. Several studies have shown that probiotics reduce both intestinal permeability and epithelial barrier dysfunction in gastrointestinal disorders, thereby demonstrating the role of GM in improving intestinal barrier function and protection (Figure 4) against pathogens [150–152].

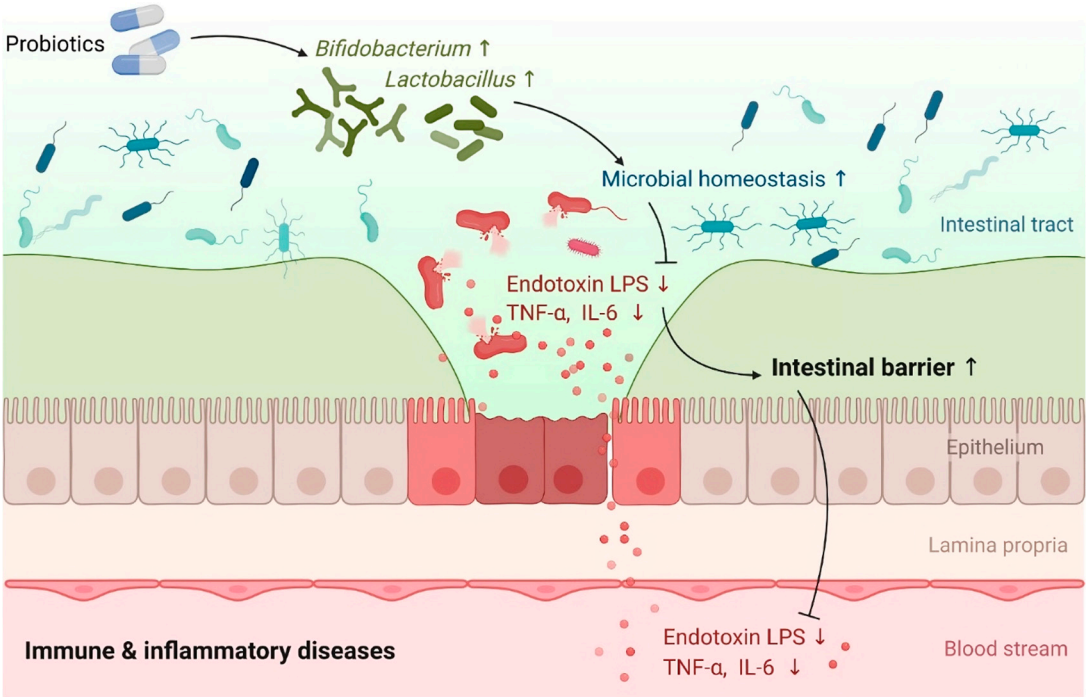

Figure 4. A graphical representation shows the influence of probiotics on intestinal barrier function in immunological and inflammatory conditions. Source: [152]. This figure is open access and is distributed under the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license.

At present, there is no doubt about the link between GM and the regulation of zonulin release, as some probiotic strains have been shown to improve gut barrier function by affecting the expression of zonulin and TJ proteins [147,153–155]. Probiotics dramatically enhanced gut barrier functioning, according to a meta-analysis of data from a total of 26 randomized controlled trials (n = 1891). Specifically, the trans-epithelial resistance (TER) was significantly enhanced, while serum zonulin, endotoxin, and lipopolysaccharide levels were importantly reduced. Moreover, probiotic groups outperformed control groups in lowering inflammatory markers like IL-6,TNF-α, and C reactive protein. Additionally, pro-

biotics can regulate the composition of the GM by increasing the enrichment of *Lactobacillus* and *Bifidobacterium* [152].

Oral probiotic therapy has also been utilized in pediatric and adult populations to reduce the incidence and severity of respiratory infections. By strengthening the gut–lung axis and controlling the host inflammatory response, probiotics can elicit antiviral effects [156]. In a pediatric experiment (n = 31 prebiotics, 31 probiotics, and 32 placebos), preterm infants were given a prebiotic combination of galacto-oligosaccharide and polydextrose or the probiotic *Lactobacillus rhamnosus* GG mixed with breast milk throughout the first 60 days of life. There were fewer cases of virus-associated respiratory tract infections in the probiotic and prebiotic groups (p = 0.022 and $p < 0.001$, respectively) [157]. Probiotics may lessen symptoms of upper respiratory tract infections and stabilize GM diversity, according to a study that supplied Lab4P probiotics (comprising lactobacilli and bifidobacteria) daily to 220 overweight and obese adults [156,158]. This may be especially important for COVID-19 disease, where obesity is linked to worse outcomes [159,160].

Research into the treatment of COVID-19 in children using oral microbial interventions is scarce, despite its potential [32,161]. Probiotics have only been tested in a small number of adult patients with COVID-19, but the results were encouraging, showing reductions in viral load, hospitalization duration, death, and diarrhea frequency [161–167]. Adults with moderate-to-severe COVID-19 were given a supplementary oral dose of the *Bifidobacterium animalis* sp. Lactis strain (n = 20 probiotic, 24 non-probiotic). The probiotic group experienced a five-day reduction in hospital stay ($p < 0.001$) and a corresponding decrease in IL-6 levels ($p < 0.001$) [164].

A single-center, quadruple-blinded, randomized trial was carried out by other researchers on adult outpatients with symptomatic COVID-19. For 30 days, subjects were randomly assigned to either a probiotic formula (including *Lactiplantibacillus plantarum* KABP022, KABP023, and KAPB033, as well as *Pediococcus acidilactici* KABP021) or a placebo [163]. In total, 78 of 147 (53.1%) patients in the probiotic group accomplished complete remission, as opposed to 41 of 146 (28.1%) in the placebo group. There were no hospitalizations or deaths during the research, and the nasopharyngeal viral load, lung infiltrates, and duration of both digestive and non-digestive symptoms were all reduced when compared to the placebo. There were no significant differences in fecal microbiome composition between probiotic and placebo groups, although probiotic treatment boosted specific IgM and IgG antibodies against SARS-CoV-2 when compared to the placebo. Therefore, rather than altering the diversity of the colonic microbiome, it is assumed that probiotics predominantly enhance the host´s immune system [163]. They promote the synthesis of immunoglobulins, specifically IgA and type I interferons, and boost the induction of interleukins and the activation of macrophages, natural killer cells, and T-helper cells [168,169].

Probiotic supplementation may therefore help to restore gut health by enhancing immune responses, reducing inflammation, and reinforcing the epithelial barrier, thus possibly decreasing susceptibility to severe SARS-CoV-2 infection. It is suggested that probiotics should be used as a prophylactic rather than a treatment for severe cases of MIS-C, as once a cytokine storm is activated, it is very difficult to control.

7. Conclusions

A severe hyper-inflammatory illness known as MIS-C is linked to infection with the SARS-CoV-2 virus. After contracting COVID-19, children and adolescents can develop this uncommon but potentially dangerous syndrome, which is characterized by fever, increased inflammatory markers, and predominant gastrointestinal symptoms [6]. After the acute sickness passes, immunological dysregulation is thought to be the cause, with a genetic susceptibility in some cases [19]. Although the complex relationship between invasive viruses and host physiology is not yet fully understood, increasing data suggest that the GM may influence the course of viral diseases [169]. Research also identified autoantibodies against endothelial cells and cardiomyocytes, suggesting that MIS-C may

be an autoimmune response triggered by the viral infection [170,171]. The superantigen hypothesis proposed that a domain within the SARS-CoV-2 protein could excessively stimulate the immune system and contribute to the hyper-inflammatory state observed in MIS-C [100]. However, experimental work demonstrated that the spike protein lacks superantigen activity [101].

This work has delved into the multifaceted interactions between MIS-C, elevated levels of IL-6 induced by SARS-CoV-2 infection, the microbiome, and gut barrier integrity. A significant aspect of our pathogenic model is the mechanism by which the virus impairs gut barrier integrity. In addition to the infection and destruction of beneficial bacteria by SARS-CoV-2 [90–95], this virus also induces an excessive IL-6-mediated zonulin release that increases intestinal permeability (leaky gut), so the spike protein and toxins released by the bacteria pass into the bloodstream, causing MIS-C [33]. Although some researchers discovered the presence of the spike antigen in blood from children with acute MIS-C, subsequent work showed no persistence of the spike antigen in the plasma, and more detailed analysis is needed to determine if the circulating spike protein in patients with MIS-C is involved in disease pathogenesis [104]. In our model, the initial pathogenic stimulus is provided by the virus inducing IL-6 release and damaging the gut barrier. SARS-CoV-2 infects and destroys beneficial bacteria in the gut, favoring the growth of pathogenic bacteria that release toxic products into the blood [90,92,93]. This probably triggers a hyper-inflammatory response resembling the toxic shock syndrome. Interestingly, the prevalence of beneficial bacteria like *Bifidobacterium*, *Faecalibacterium prausnitzii*, and *Dorea formicigenerans* was found to be much lower in severe COVID-19 cases [96,97], in PACS [43,44], and in children with MIS-C [50]. Such a reduction in the number of these bacteria could be due to the destruction caused by the lytic phase of SARS-CoV-2 [90].

The presence of the FCS located in the spike protein [99] could cause further damage to the integrity of the gut barrier. Research demonstrated that syncytium formation was related to severe disease outcomes in COVID-19, as it led to extensive tissue damage in the lungs. The ability of the virus to induce syncytia is also thought to contribute to the inflammatory response observed in infected patients, as the released S1 subunit from the spike protein can activate immune receptors, further exacerbating the disease [172,173]. Interestingly, in 2022, several countries reported a significant reduction in the incidence of MIS-C cases in association with Omicron waves. A study found that during the Omicron wave, there were fewer admissions to the critical care ward, with 54.5 MIS-C cases per 100,000 children under the age of 18 during Alpha, 49.2 during Delta, and 3.8 during Omicron [105]. We suggest that such reduced incidence was caused by a mutation that added O-glycans to the FCS in Omicron, since such mutation has been shown to significantly decrease SARS-CoV-2-induced pathogenesis in the animal model [106]. It is possible that the Alpha and Delta strains induced greater damage to the gut barrier by forming syncytia, thus causing an enhanced leakage of bacterial toxins to the blood.

Due to the acknowledged relevance of the GM in MIS-C, COVID-19, and long COVID, preventive and therapeutic strategies should prioritize restoring and maintaining GM balance and enhancing gut barrier integrity. There is evidence that if damage to the mucosal epithelium is prevented and treated early in the disease, MIS-C may not develop [33]. Given that gut dysbiosis may predispose children to MIS-C, it is important to strengthen their microbiome by consuming probiotics, and diets high in plant fiber (prebiotics). Therapeutic agents like larazotide [33] and antibiotics [95,141] constitute the best options. An experimental strategy was created to culture in vitro fecal microbiota from adult infected persons, monitor the presence of SARS-CoV-2, and compare the effects of various antibiotics. It was discovered that viral replication parallels bacterial growth and is affected by the use of particular antibiotics. In the four aliquots treated with metronidazole, vancomycin, amoxicillin, and azithromycin, respectively, the viral load was decreased to undetectable levels (100% efficacy), while Cefixime reduced viral load by 85%, ciprofloxacin by 61%, and teicoplanin by 56% [95]. Since metronidazole and amoxicillin are frequently used in children, they could be safely used to treat severe MIS-C cases.

The use of anti-IL-6 antibodies can lead to immune suppression, increasing the risk of infections [143]. The use of antivirals like nirmatrelvir could cause a COVID-19 rebound by inhibiting the production of T cells and antibodies specific to SARS-CoV-2, and hampering the development of efficient long-term immunity [145,146]. In conclusion, given that gut dysbiosis appears to be the predisposing factor to MIS-C development, strengthening the microbiome by consuming probiotics, particularly butyrate-producing *Bifidobacterium*, and diets high in plant fiber (prebiotics) should be a strategy for further research as a preventative measure, and the use of specific antibiotics to help restore the beneficial GM makeup post disease development to curb the viral ability to dysregulate the gut flora in afflicted children.

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