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Review Article

Antibiotic use, gut microbiome and COVID-19 risk: a review

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Abstract

COVID-19 infection is caused by a betacoronavirus, SARS-CoV-2. It is highly variable in symptoms and clinical outcomes, ranging from mild to fatal forms. Hyperactivation of the immune system is potentially the factor precipitating the severe forms and mortalities of this infection. Both adaptive and innate immune responses to COVID-19 infection determine the natural history and progression of COVID-19. Microbiome (MB) often refers to the microbial taxa associated with man. Microbiome has many host-related functions. The gut has the largest population of microbes, and thus may have a vast impact on host health. Microbiome is involved in evolution of innate and adaptive immune system in humans, among other functions. Perturbations in composition of MB are referred to as dysbiosis. Dysbiosis can coincide with COVID-19 itself and be also drug-induced. Antibiotics commonly prescribed to COVID-19 patients often exert deleterious effects on composition of gut MB. In light of host-related microbiome functions, this possibly has consequences impacting severity and outcome of COVID-19. Gut microbiome integrity can be a crucial factor in COVID-19 patients, thus antibiotic use, in light of its impact on gut flora, may adversely affect disease outcome; however, the extent of these aspects is still unclear. A rational antibiotic use strategy should be an integral part in all COVID-19 therapeutic plans.

Keywords Antibiotic, COVID-19, dysbiosis, Microbiome, SARS-CoV-2

Introduction

SARS-CoV-2 and COVID-19 pathogenesis

Taxonomically, SARS-CoV-2, the causative agent of COVID-19 infection, is a betacoronavirus (Corman et al., 2020). It was first discovered in China (Hubei Province) in November 2019; later it spread through the entire world causing a pandemic (Heymann & Shindo, 2020). COVID-19 infection is associated with variability in symptoms and clinical outcomes, ranging from mild to fatal forms (Rabi et al., 2020). Many patients are asymptomatic or show only mild symptoms; on the other hand, others eventually develop a range of serious respiratory conditions (pneumonia and acute respiratory distress syndrome) which in many cases necessitate intubation and admission to intensive care units (ICUs), some of the critically ill patients die from complications (Chen et al., 2020).

Though knowledge of COVID-19 pathogenesis is still evolving, current evidence shows that hyperactivation of immune system is a factor behind the severe forms and mortalities of this infection (Abid et al., 2020). Both adaptive and innate immune response to COVID-19 infection determines the natural history and progression of COVID-19, and its outcome (Donati Zeppa et al., 2020). Additionally, the underlying chronic inflammatory state might also aggravate the disease course more than the direct viral cytopathic consequences themselves. Long after the virus is cleared from body, a state of post-COVID-19 auto-inflammatory conditions was noted underlining dysregulated immune system (Abid et al., 2020; Viner & Whittaker, 2020).

Microbiota and Microbiome

The term Microbiome (MB) refers collectively to different microbial species along with their genes and gene products, which coexist in a specific habitat (Marchesi et al., 2016;

Martin et al., 2019). A related term, microbiota, indicates the entire microorganism population colonizing a specific location (Sekirov et al., 2010). Microbiota in medical literature often refers to the microbial taxa associated with man; but the two terms are used interchangeably (Ursell et al., 2012).

Human MB species show regional differences, e.g. skin and gut microbiomes are not identical; however, together they functionally constitute the (greater) human MB (Marchesi et al., 2016). Though microorganisms colonize most body surfaces exposed to the external environment, the GIT remains the major habitat for human MB, constituting greater than 70 percent of the entire microorganism population living on the human body (Sekirov et al., 2010). The entire microbiota in humans is estimated to be 10-100 trillion cells per person (Turnbaugh et al., 2007), with gut bacteria estimated to be around 3.8×10^{13} , and close to 1000 bacterial species in healthy adult gut (Qin et al., 2010; Sender et al., 2016); hence, MB presumably exert a major impact on human health (Turnbaugh et al., 2007). In addition to bacteria, fungi, viruses and archaea bacteria also inhabit the human gut (Zhao & Elson, 2018). All these species in the gut live in a symbiotic co-existence with the human host (Schwartz et al., 2020).

Commensal bacteria (the microbiota inhabiting the gut) are located throughout the entire length of GIT, with heaviest population situated in the caecum and colon, together with their genes and products (Martin et al., 2019). In healthy human adults, the two dominant microbial phyla are the Firmicutes and Bacteroidetes, mainly comprised of clostridia and Gram-negative bacteria like *B. fragilis*, respectively, although other phyla may also contribute to MB functionality. Viral, protozoal and fungal species may also contribute, but were not studied extensively to reveal their true contribution (Marchesi et al., 2016).

Factors shaping and affecting the microbiome

Evidence suggests that MB begins to colonize the gut prenatally (Aagaard et al., 2014). Previous studies revealed a direct mother-to-child transmission mode (Lagier et al., 2012), with infants showing a microbial profile related to the vaginal MB (Dominguez-Bello et al., 2010). While colonization of gut initiates from maternal bacteria which are acquired at birth and later through breast milk, it continues throughout later stages of life (Ferreira et al., 2014). Studies conducted on twins revealed a hereditary component as a determinant for composition of gut microbiota; however, other factors, including diet, exposure to drugs, and some anthropometric determinants probably play a vastly greater modulatory effect on the composition (Goodrich et al., 2014; Rothschild et al., 2018). Adult's microbiota were shown to have notable stability and resilience when no extreme external factors exist like diet change or treatment with antibiotics. Even when challenged with such stressors, it was resilient sufficiently as to return to a pre-stress state (Derrien et al., 2019).

Microbiome host-related functions

Microbiome's survival depends on utilizing the host as a habitat and a nutrient source; in return, it supports host organ functions by supplying many essential compounds (Hasan & Yang, 2019). While a multitude of microbiota species exist in the human large intestine (Rajilić-Stojanović & De Vos, 2014), only a few species are shared and actually, there is a large inter-individual variation in MB composition. However, this contrasts with the MB functional similarity between individuals, suggesting the function is more relevant than the composition of organisms. Nevertheless, species differences/changes do impact functions, an example of this is the short-chain fatty acid (SCFA) synthesis. It is a function maintained universally by gut MB (Louis et al., 2010), yet amounts of SCFA produced vary individually (Marchesi et al., 2016), thus it probably impacts host functions to variable extents. In contrast to the human genome, which is comprised of around 23000 genes, the MB genetic pool is huge, comprising greater than three million genes, which in turn encode thousands of metabolic products, supporting many functions in the host (Bull & Plummer, 2014; Vyas & Ranganathan, 2012), which translates into a huge impact of host's well-being, phenotypic expression, and overall health (Rath & Dorrestein, 2012). Gut MB is involved in functions like absorption of nutritional substances (Belkaid & Hand, 2014), digestion and metabolism (Rothschild et al., 2018), modulating resistance to insulin and its secretion (Kelly et al., 2015), affecting proliferative and differentiative aspects of epithelial cells (Sekirov et al., 2010) as well as impacting host behavioral and neurological aspects (Hasan & Yang, 2019).

Gut microbiome and antiviral immunity

In addition to functions mentioned earlier, gut MB has host-defensive functions, involving combating pathogens and co-evolving host immune system (Arpaia et al., 2013; Chung et al., 2012). Gut MB blocks pathogenic organisms from colonizing the gut (Belkaid & Hand, 2014). Additionally, it has a vital role in immune system maturation, of particular importance is the role it plays in post-natal shaping and maturation of host immune system. Acquiring proper gut microbiota coincides with forming fully-developed host adaptive and innate immune systems, together with immune tolerance, and thus is a prerequisite for antiviral immune competence (Donati Zeppa et al., 2020). Host adaptive immunity is initially triggered postnatally by the first encounter with diets and microorganisms. Later on, host immune tolerance to microbial and food antigens occurs (Ferreira et al., 2014). While microbial population presents a genomic/enzymatic reserve that is vital for inducing, developing and functionality of the host immune system; the latter in turn supports microbiota by combating pathogenic species and developing tolerance to certain antigenic products (Donati Zeppa et al., 2020). This mutual relationship regulates the threshold at which immune cells /tissues are activated to combat infections (Belkaid & Harrison, 2017). Given that GIT, by virtue of its microbiota, is considered the largest

immune-modulating organ in humans, gut microorganisms orchestrate mucosal immunity, and have a recognized regulatory role on host immune response (Abid, 2019; Zmora et al., 2019). Gut microbes can regulate immune response in extra-intestinal sites, through byproducts they release reaching other sites through blood stream, e.g., SCFAs, these would regulate immunoglobulin and anti-inflammatory functions (Zhang et al., 2020). Latest evidence shows that they modulate the inflammatory and immune processes in the lungs (Dang & Marsland, 2019; McAleer & Kolls, 2018). Gut microbiota is probably protective against viral infections through regulating immune response to combat infections (Donati Zeppa et al., 2020). Alterations in the microbiota (Dysbiosis) potentially degrade the symbiotic state between host and microbes and some recent evidence suggests a negative impact on viral immunity secondary to changes in function and structure of MB (Harper et al., 2021). Healthy microbiota can be vital in viral respiratory tract infections, especially through modulating alveolar macrophages and neutrophils (Bradley et al., 2019; Steed et al., 2017). Gut microbiota were shown to be major regulators for virus-targeting T cells (CD4 and CD8) and antibody response following respiratory viral infections (Ichinohe et al., 2011).

Antibiotic use and gut dysbiosis

Dysbiosis, by definition, refers to changes observed in the composition of commensal microbial species, compared to microbial community in healthy host (Petersen & Round, 2014). Available evidence suggests antibiotic (AB) use produces a state of dysbiosis in the gut, manifested as disturbed microbial function and composition. About a third of gut microbiota is removed by broad-spectrum antibiotics, resulting in loss of taxonomic biodiversity and evenness (Dethlefsen et al., 2008; Dethlefsen & Relman, 2011). Vich Vila et al. (2020) studied the impact of 41 drugs on gut microbiota, and found that 19 of the studied drugs were associated with significant MB composition alterations, and the use of multiple medications (i.e. polypharmacy) e.g. laxatives, proton pump inhibitors, antibiotics and metformine, caused the highest detrimental effect on microbial composition, with reduction in *Bifidobacterium* genus in association with polypharmacy; however, this was independent of AB use. Despite the negative impact, a post-antibiotic recovery of microbial composition occurs, reflecting bacterial resilience; however, the recovery is often partial, and drug-induced changes in microbiota usually last for long periods (months to years) (De La Cochetière et al., 2005; Dethlefsen et al., 2008; Dethlefsen & Relman, 2011).

Gut Dysbiosis, antibiotics, and impact on infections

Antibiotic-induced disruption in gut microbiota (dysbiosis) may modulate/affect extra-GIT viral infection in other distant organs (Ichinohe et al., 2011). Notably, depleting beneficial gut microbiota in association with antibiotic use was shown in murine studies to be linked to lung disease (Trompette et al., 2014). Gut dysbiosis, especially secondary to the use of drugs,

maybe a pathogenic factor in respiratory tract diseases, as both the lung and gut appear to be linked together in modulating immune responses (Fanous et al., 2020). Conflicting evidence points to either enhancing /or suppressing the impact of commensal microbes in viral infections, which indicates a pathogenic role of microbiota in viral infections (Donati Zeppa et al., 2020). In a study by Ichinohe et al. (2011), Neomycin-sensitive gut commensal bacteria were found to regulate/induce respiratory tract-specific immune responses to influenza virus; administration of antibiotics enhanced mice susceptibility to lung infection with influenza, probably by modulating the adaptive immune response, hence establishing a gut-lung link (axis).

Microbiota status, Inflammation and COVID-19

COVID-19 severity and outcome are probably host-determined. An intense pro-inflammatory response that precedes/coincides with the severe form of COVID-19 is not seen in a subset of patients. This heterogenous, patient-specific severity variation is unlikely due to less virulent viral strains, and more probably the product of variation in host response (Hussain et al., 2021). Those with pre-existing hyperinflammatory state and/ or abnormal immune response were shown to be more at risk of COVID-19 complications (Donati Zeppa et al., 2020).

A direct correlation between severity of the disease and gut dysbiosis is already established (Yeoh et al., 2021; Zhang, et al., 2020). Microbiome is essential for development of immune system, and in return, the latter regulates microbiota function and composition. When this balance is disrupted, inflammatory diseases (Crohn's disease and ulcerative colitis for example) may consequently ensue (Aktas, 2021; Duboc et al., 2013).

Dysbiosis status may contribute to COVID-19 severity, as a possible factor behind many of pro-inflammatory conditions could be the axis of microbiota-host immune system (Gou et al. 2020). Pro-inflammatory markers (IL-1, IL-6, TNF- α) are characteristically high in severe COVID-19 (Han et al., 2020; Zhou et al., 2020) and constitute the hallmark of severe COVID-19 disease; these in turn induce a state of gut dysbiosis with altered gut permeability, a state that has been termed "leaky gut". As entry of bacterial products like toxins is enhanced, this further exacerbates pro-inflammatory status (Hussain et al., 2021). In those with gut dysbiosis, the further inflammatory burden of the resulting leaky gut adds to the worsened outcome. Furthermore, increased severity of COVID-19 was linked to worsening GI symptoms (Pan et al., 2020), as more severe forms of COVID-19 showed higher GI symptoms and inflammation. This establishes the role of Gut MB as a moderator for immune crosstalk between respiratory and GI tracts (Hussain et al., 2021).

To date, no direct evidence links any gut-residing microbe species to SARS-CoV-2 (Han et al., 2020; Troisi et al., 2021); still, gut microbiota may have a pathogenic role in COVID-19

(Hussain et al., 2021); and probably SARS-CoV-2 infections may be moderated by gut microbiota immune-modulating effects (Hussain et al., 2021) as gut MB composition was linked to cytokine and inflammatory markers levels in COVID-19 patients. This suggests that MB may titrate the infection severity through regulating the host viral immune response (Yeoh et al., 2021) especially since the GIT is the largest immune-related organ (Schirmer et al., 2016); hence the gut MB was thought of as theoretically controlling the host inflammatory response to the SARS-CoV-2 infection (Yeoh et al., 2021). Which pattern of gut MB is protective against inflammatory sequelae is still unclear; yet factors probably associated with more diverse gut MB, like rural environmental microbiota pattern, a higher ratio of slum-residing population, and a lower score for water sanitation and quality, were all associated with less disease mortality (Kumar & Chander, 2020).

Polypharmacy, antibiotics and COVID-19

Empirical use of AB to combat secondary bacterial infections has been rising, especially in the hospital setting. Occasionally, patients may suffer from several medical conditions which entails use of multiple medications, a condition referred to as “polypharmacy”, and often these are chronically used (Ticinesi et al., 2017). Scant evidence exists on the relationship between COVID-19, polypharmacy and microbiota. Some studies (Ticinesi et al., 2017; Vich Vila et al., 2020) found that composition of gut microbiota is severely affected by polypharmacy, with more changes occurring when the number of drugs is increased. Number of co-prescribed drugs and biodiversity index of MB were found to be inversely correlated, those with lowest index were at a higher mortality risk (Ticinesi et al., 2017). Of critical importance is the finding that COVID-19 mortality was increased in association with lower MB diversity index (Donati Zeppa et al., 2020). This puts overuse/ misuse of ABs, commonly encountered in COVID-19 patients, as a major modifiable factor improving patient survival. In hospitalized COVID-19 patients, the probiotic bacteria populations (e.g. *Faecalibacterium prausnitzii*) and *Firmicute/Bacteroidetes* ratio were both minimized, along with increased proportion of Actinobacteria (pathogenic) species. This species imbalance was shown to be linked to increased pro-inflammatory markers, ultimately leading to untoward COVID-19 outcomes (Abreu et al., 2022). The elderly in particular, are more at risk since more pathogenic bacteria prevail in old age together with shrinking of beneficial microbial populations like *Lachnospiraceae* and *Succinivibrionaceae* (Ticinesi et al., 2017). These species are likely vital for maintaining cardiorespiratory integrity, and keeping inflammation in check, the absence of both of these aspects can aggravate COVID-19 outcome (Sestili & Stocchi, 2020; Siddiqi & Mehra, 2020). The elderly, among the most COVID-19-vulnerable populations, require multiple, chronically administered medications, such polypharmacy impacts negatively the gut MB, especially given the decreased biodiversity and increasing abundance of opportunistic

pathogens in gut MB in the elderly, which downgrades host’s ability to combat invading viruses (Ticinesi et al., 2017). This, together with other old age-related health concerns may be a principal factor for COVID-19 serious consequences in the elderly (Donati Zeppa et al., 2020).

SARS-CoV-2-induced dysbiosis

The importance of a good antibiotic usage policy, especially for those already at risk, is highlighted in the case of COVID-19, as substantial changes in gut MB were observed during and following recovery from COVID-19. Compared to healthy adults, COVID-19 patients exhibit reduced microbial diversity, increased pathogens abundance, and much fewer symbiotic microbial species (Hussain et al., 2021). Increased population of opportunistic pathogens was seen in some COVID-19 patients (Liu et al., 2022). Additionally, diminished gut commensal bacteria like *Faecalibacterium prausnitzii*, *Lactobacillus* and *Bifidobacterium* were also reported. These commensals exert host-supportive functions like preventing intestinal infections, augmenting immune response, as well as exerting anti-inflammatory effects; in addition, they minimize the antibiotic-induced overgrowth of certain species e.g. *Candida*, *Pseudomonas*, *Staphylococcus*, and *Escherichia coli* (Liu et al., 2022; Xu et al., 2020). Importantly, inflammation and viral replication (consequences of COVID-19) in the gut may contribute to gut dysbiotic state seen (Hussain et al., 2021). Reciprocally, an altered microbiota profile is itself risk factor for the infection and an aggravating factor for disease severity, hence establishing a vicious cycle. Gut dysbiosis was linked to COVID-19 severity in a recent study on infected patients (Zhang, et al., 2020) in line with another multi-center study on COVID-19 patients, which showed a similar link between dysbiosis and severity of systemic inflammation as per elevated inflammatory status markers (Yeoh et al., 2021).

Antibiotics, dysbiosis and impact on COVID-19

Since associated/ secondary super infections are commonly encountered in COVID-19 patients, preventing and treating them via broad-spectrum antibiotics is common practice (Knight et al., 2021). Over 60 percent of hospitalized COVID-19 patients were on empirical therapy with broad-spectrum antibiotics (Rawson et al., 2020), and about 58 percent of COVID-19 patients received antibiotics, according to one study in China. This massive-scale use pattern was postulated to disrupt host-microbiome balance (Chen et al., 2020; Guan et al., 2020); which is already disrupted in such patients.

Loss of biodiversity is a hallmark of gut dysbiosis, and usually enhances the likelihood of metabolic anomalies and hyperinflammatory states (Le Chatelier et al., 2013). Gut dysbiosis was proportional to the severity of COVID-19, and despite clearance of SARS-CoV-2 nucleic acid after recovery, dysbiosis persisted in some patients (Kariyawasam et al., 2021; Zhan, et al., 2020). Antibiotics given to COVID-19 patients may be responsible such effects (Zuo et al., 2020).

COVID-19 patients using concomitant antibiotic therapy showed less bacterial biodiversity; some species were heavily depleted like *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Collinsella aerofaciens* (Cao et al., 2021; Yeoh et al., 2021; Zuo et al., 2020). Loss of gut biodiversity is commonly encountered in those undergoing AB therapy, which sometimes may eradicate entire taxa, leading to several deleterious effects like enhanced gut colonization susceptibility, developing antibiotic resistance (ABR) and metabolic shifts (Lange et al., 2016), this is especially true for broad-spectrum ABs (Menees & Chey, 2018). In this respect, azithromycin, widely prescribed for COVID-19 patients, caused a significant decline in bacterial richness and diversity, with a shift towards the *Actinobacteria* phylum, and shrinking of the genus *Bifidobacterium* – this may lead to drug-induced weakening of already-disrupted microbiota of (mostly elderly) patients (Donati Zeppa et al., 2020). Likewise, administration of meropenem, gentamicin and vancomycin shifted gut microbial diversity toward enhanced prevalence of *Enterobacteriaceae* and other pathogenic species, together with reduced *Bifidobacterium* and microbial species with host-beneficial merits (Palleja et al., 2018). Semi-complete restoration of baseline microbiota composition less than 2 months later, while other species were not restored through 6 months (Palleja et al., 2018).

Immune response against respiratory pathogens appears to be regulated by gut MB. It follows that antibiotic impact on microbiota may diminish the host antiviral immunity (Robinson & Pfeiffer, 2014). The use of antibiotics in mice was associated with impaired innate and adaptive antiviral immunity in antibiotic-induced dysbiosis in mice (Abt et al.,

2012). Attenuated antibody response was observed in mice pre-treated with an oral course of 4-week broad-spectrum antibiotic, when a viral respiratory infection occurred; with less production of specific CD8+ T-cells (Abt et al., 2012; Ichinohe et al., 2011) and higher titer of virus in respiratory tract (Ichinohe et al., 2011). Alveolar macrophages immune responses were suppressed likewise in AB-treated mice. Profiling of macrophage showed decreased expression of antiviral immunity-related genes after exposure; damaged airway epithelium as well as retarded viral clearance after viral infections were also reported (Abt et al., 2012). A similar impaired antibody response to influenza vaccine was registered in mice treated with oral antibiotics; and was restored with orally administered flagellated *E. coli* (Oh et al., 2014).

Priming innate immune response toward respiratory viral infections depends on gut microbiome. It was suggested that the latter apparently send tonic signals that regulate threshold and sensitivity of innate antiviral immunity, these immune-activating signals were suppressed secondary to use of AB (Abt et al., 2012). Through such signals gut microbiota protect lung from viral infection by priming lung stromal cells which eventually interrupts pathogen's life cycle (Bradley et al., 2019). Likewise, treatment with antibiotics in rodents impaired antiviral immune response, thus augmenting susceptibility to invading viruses, this antibiotic effect was reversed by transplanting microbiota from control rodents (Bradley et al., 2019). Ultimately the antibiotics deplete and thus probably interrupt the microbiota regulatory function titrating innate/adaptive antiviral immunity (Robinson & Pfeiffer, 2014).

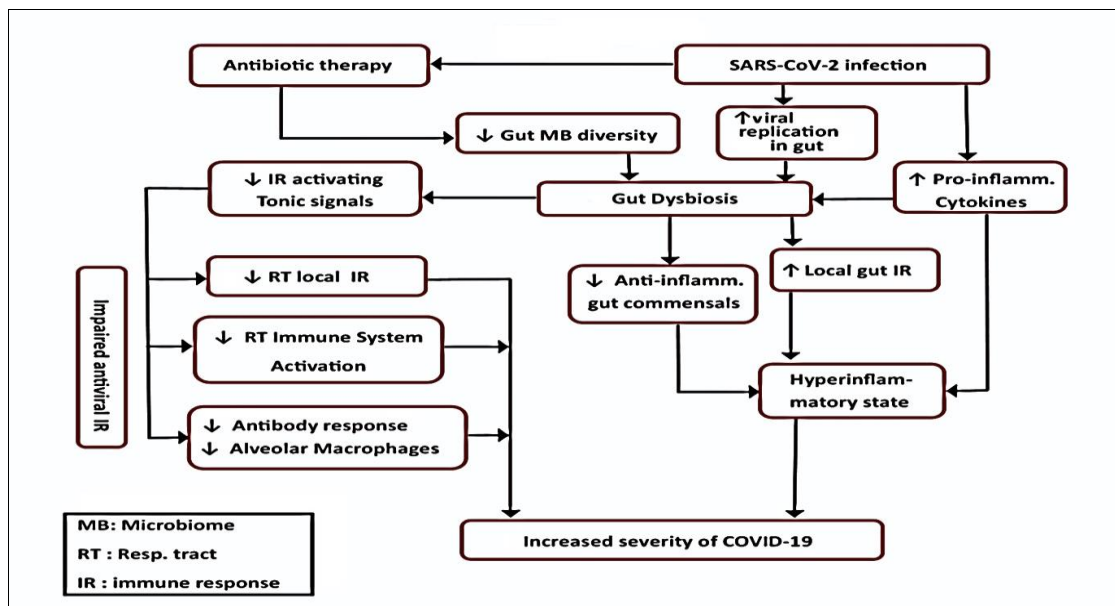


Fig. 1 Potential mechanisms by which antibiotic administration may modulate COVID-19 severity

Antibiotic use may alter many aspects of host response toward respiratory pathogens (Hanada et al., 2018). The so-called gut-lung axis concept (Enaud et al., 2020) emphasizes that both tracts (GIT and respiratory) share a common mucosal immune apparatus, and that microbiota of both tracts modulate immune responses to external pathogens (Kraft et al., 1976) in a bi-directional manner (i.e. an attack on one site modulates responses on the other tract) (Hussain et al., 2021). Co-incident with drug-altered gut microbiota, antibiotic administration impacts respiratory tract local immune responses (Ichinohe et al., 2011), probably via disrupting this axis. Under such circumstances, respiratory immune system activation, secondary to antibiotic-induced gut dysbiosis is a very likely mechanism for some grave outcomes in viral infections in general (Hussain et al., 2021) and in COVID-19 specifically. Recent or past use of certain AB classes like the tetracyclines and the macrolides, were found to associate with inflammatory conditions (Villarreal et al., 2012), it is hypothesized that AB-induced imbalance in microbial populations (dysbiosis) activates the immune system locally in the gut and favors a low-grade inflammatory state (Menees & Chey, 2018), with adverse consequences in COVID-19 patients to be expected. Based on available evidence, it can be assumed that AB usage may alter COVID-19 disease course through the disturbing lung-gut axis, but the exact magnitude of the effect is still unclear. Fig.1 shows the potential mechanisms by which antibiotic administration may modulate COVID-19 severity.

Conclusion

A potential link exists between gut MB status and COVID-19 immune response. Gut dysbiosis resulting both in the context of COVID-19, and via antibiotic administration, is a factor that potentially aggravates severity and clinical outcome of the disease. Underlying mechanisms linking dysbiosis to untoward outcome in the viral infection are still unclear. However, Intestinal MB health may be an overlooked yet crucial factor for the clinical outcome of this disease, in light of the impact dysbiosis has, through the gut-lung axis, on antiviral immunity and hence the severity of the disease. The possibility of therapeutic strategies to either preserve the microbial population, through rational antibiotic use and perhaps even the use of probiotics, to improve disease outcomes, are promising aspects that need further consideration. Therapeutic manipulation of gut MB to modulate COVID-19 course and outcome is an aspect that merits further in-depth consideration.

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