Review

Molecular pathogenesis of secondary bacterial infection associated to viral infections including SARS-CoV-2

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ABSTRACT

Secondary bacterial infections are commonly associated with prior or concomitant respiratory viral infections. Viral infections damage respiratory airways and simultaneously defects both innate and acquired immune response that provides a favorable environment for bacterial growth, adherence, and facilitates invasion into healthy sites of the respiratory tract. Understanding the molecular mechanism of viral-induced secondary bacterial infections will provide us a chance to develop novel and effective therapeutic approaches for disease prevention. The present study describes details about the secondary bacterial infection during viral infections and their immunological changes.The outcome of discussion avails an opportunity to understand possible secondary bacterial infections associated with novel SARS-CoV-2, presently causing pandemic outbreak COVID-19.

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Introduction

Bacteria and viruses often occupy the same niches, however, interest in their potential collaboration in promoting wellness or disease development has only recently gained attention. The interaction of some bacteria and viruses are well characterized and researchers are typically more interested in the location of the infection than the manner of cooperation [1]. There are two overarching types of bacteria-virus disease causing interactions by direct interactions that in some way aid the viruses, and indirect interactions of aiding bacteria. The virus-promoting direct interactions occur when the virus exploits a bacterial component to facilitate penetration into the host cell [2]. On the other hand, indirect interactions result in increased bacterial pathogenesis as a consequence of viral infection. Enteric viruses mainly utilize the direct pathway, while respiratory viruses indirectly affect bacteria [3]. The causative agent of the current pandemic outbreak, SARS-CoV-2 is also reported to associate with secondary bacterial and fungal coinfectionsas patients showed the symptoms of atypical bacterial pneumonia [1–3]. It has been known that SARS-CoV is the nearest virus to SARS-CoV-2 and their systemic comparison may further help in understanding the disease pathogenesis during COVID-19 and secondary bacterial infections [4]. However, SARS-CoV-2 is reported to evolve in the human body that might affect itsvirulence, infectivity, and transmissibility [5], thus the biology of SARS-CoV-2 further needs to be understood in detail, especially in case of secondary bacterial infections. This review focuses on some key examples of how virus-bacteria interactions impact the infection process across the two organ systems and provide evidence supporting this as an emerging premise in infectious disease pathogenesis.

Human body is inhabited by a diverse microbial community that is collectively coined as commensal microbiota. Recent research has greatly advanced our understanding of how commensal microbiota affects host health. Among the various kinds of pathogenic infections of the host, viral infections constitute one of the most serious public health problems worldwide. During the infection process, viruses may have substantial and intimate interactions with the commensal microbiota [4]. A plethora of evidence suggests that the commensal microbiota regulated by invading viruses through diverse mechanisms, thereby having stimulatory or suppressive roles in viral infections. Furthermore, the integrity of the commensal microbiota can be troubled by invading viruses, causing dysbiosis in the host, and further influencing virus infectivity. In the present article, we discuss current insights into the regulation of viral infection by the commensal microbiota. We also draw attention to the disruption of microbiota homeostasis by several viruses [5].

Viral infections predispose patients to secondary bacterial infections, which often have a more severe clinical course. The mechanisms underlying post-viral bacterial infections are complex and include multifactorial processes mediated by interactions between viruses, bacteria, and the host immune system [6]. Studies over the past 15 years have demonstrated that unique microbial communities reside on the mucosal surfaces of the gastrointestinal tract and the respiratory tract, which has both direct and indirect effects on host defense against viral infections [7]. The antiviral immune responses induced by acute respiratory infections such as influenza are associated with changes in microbial composition and function ("dysbiosis") in the respiratory and gastrointestinal tract, which in turn may alter subsequent immune function against secondary bacterial infection or alter the dynamics of inter-microbial interactions, thereby enhancing the proliferation of potentially pathogenic bacterial species [4]. Here, we summarize the literature on the interactions between host microbial communities and host defense, including how influenza and other acute respiratory viral infections disrupt these interactions, thereby contributing to the pathogenesis of secondary bacterial infections.

Mechanisms of viral predisposition to secondary bacterial infections

Respiratory viruses are often encouraged, secondary bacterial infections by supplementing the outgrowth opportunistic bacterial pathogens. Viral infections damage the respiratory airway by both histologically and functionally [8]. Cell loss, goblet cell hyperplasia, altered mucus secretion, reduced ciliary beat frequency, dis-coordinated mucociliary clearance function along with reduced oxygen exchange are characteristics of viral infection [9]. These effects are associated with different molecular mechanisms by which the predisposition of the virus occurs in the respiratory tract that facilitates the bacterial infection, simultaneously (Fig. 1).

Virus facilitates bacteria adherence and colonization

Epithelial cells of the respiratory tract facilitate bacterial adherence using different mechanisms during viral infection, while the disease severity varies upon virus, bacterial strain, and experimental model used. Respiratory syncytial virus (RSV) reported to bind directly with *Haemophilus influenzae* and *Staphylococcus pneumonia*, so enhancing bacterial proximity to the epithelial monolayer and supplementing attachment to the host cell receptors [10]. Interestingly, RSV glycoprotein expressed and localized on the host cell membrane upon infection that is further act as bacterial receptors for pneumococcal binding [11,12]. Respiratory viruses are also able to up-regulate the expression of host cell membrane protein to facilitate their binding [9,10]. Influenza virus, known to induce the production of type I interferons (IFNs) that results in reduced production of CCL2 (chemokine (C-C motif) ligand 2) and so decreased recruitment of macrophages thus results in enhanced colonization of *S. pneumonie* in mice [11]. Influenza virus also makes mice susceptible to pneumonia caused by *Staphylococcus aureus* where both virus and bacterial load increased during co-infection [12,13]. RSV, parainfluenzavirus-3, and influenza viruses reported increasing the bacterial adherence upon infection, in both primary and immortalized epithelial cells with different differences [9]. Recently, it has been reported that surface glycoprotein adhesion molecule-1 (ICAM-1) presents up-regulated expression during RSV and adenovirus infection. ICAM-1 presented as a cognate ligand for the Type IV pilus of non-typeable *H. influenza* induced secondary bacterial infection via adherence promotion [14]. RSV infections also confirmed to increase adherence for *S. pneumoniae* in human nasopharyngeal cells (HEp-2) and pneumocyte type II cells (A549). The enhanced pneumococcal adherence in epithelial cells results in bacterial accumulation and thus secondary bacterial infection may occur [15,16].

Impaired innate and adaptive immune response

Secondary bacterial infection with viral infections can drastically change the immunity level by the uncontrolled bacterial growth [17,18]. Viral infection impaired the phagocyte functions and induced alveolar macrophages (AM) depletion results in the facilitation of bacterial infection via apoptosis [19]. Infection in AM caused by the influenza virus reported to result in low-level production of cytokines and chemokines which is also required for recruitment and activation of neutrophils [18]. Influenza virus infection can diminish NADPH oxidase-dependent phagocytic bacterial clearance and so increase the chances of secondary bacterial infections [20]. Virus-induced dysregulation of proinflammatory cytokine response played a major role in promoting secondary bacterial infections [21,22]. While type I IFNs are well reported for
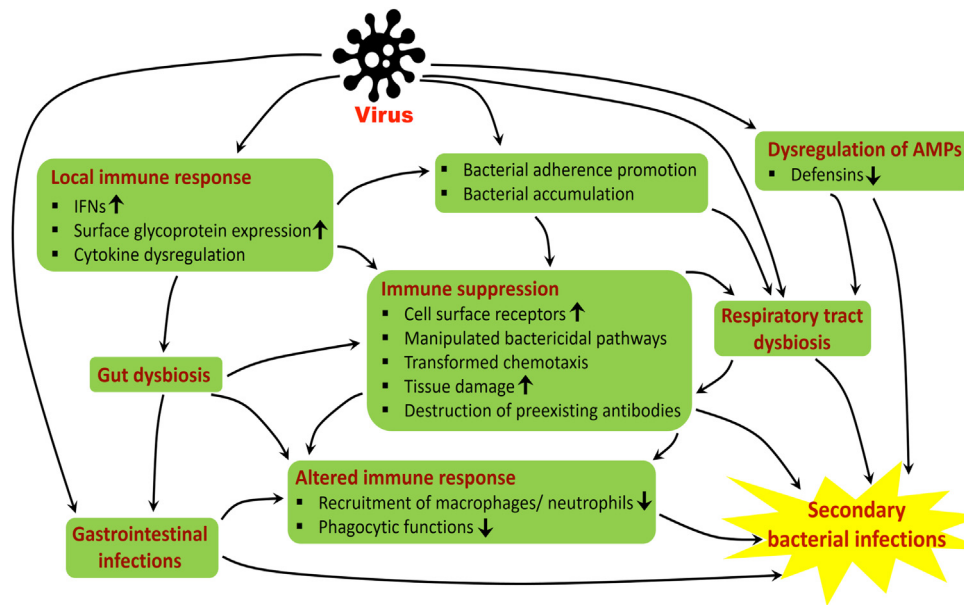
Fig. 1. Proposed model for viral-induced secondary bacterial infections.

antiviral and immuno-stimulatory properties, their, inappropriate or excessive production may have harmful effects. Results suggested that IFNs have an important role in the production of specific cytokines like immunosuppressive IL-10 and pro-inflammatory IL-6, suppression of which is key to the linkage between innate and adaptive immune response, involving IL-7 and IL-23, dendritic cells, macrophages, natural killer cells, CD4+ and CD8+, T cells, all these results in the reduced ability to efficiently eliminate bacterial co-infections and thus promote secondary bacterial infections. Dysregulation of antimicrobial peptides is another way used by the upper respiratory tract (URT) viruses to facilitate secondary bacterial infections. Expression of antimicrobial peptides lipocalin2, CAMP, REG3B, S100A8, and S100A9 found down-regulated during URT infections [23]. In another study, RSV infection reported to reduce the gene expression of chinchilla beta-defensin 1(an orthologue of human beta defensin3, hBD-3), and thus RSV infection found to induce 10–100 increase innasopharynx (NP) load of *H. influenza* [24].

Virus-induced immune suppression

Bacterial superinfections are associated with viral immune suppression condition which is not only limited to the respiratory tract but also related to several organ failures. These immunosuppressive viruses include especially HIV, cytomegalovirus (CMV), measles virus (MeV), and others. The prime characteristic of HIV infection is the severe reduction of CD4+ T cells that make the patient much more susceptible to develop bacterial superinfections like tuberculosis [25]. It has been reported that HIV infection ease the *Mycobacterium* infection along with various characteristics to macrophages that constrains bacterial clearance which promotes bacterial colonization with disease development. These HIV associated features to macrophages comprise the up-regulation of cell surface receptors for *Mycobacterium* entry, manipulation of bactericidal pathways used by macrophages, transformed chemotaxis, induction of immune response causing Th1/Th2 imbalance and apoptotic response that mediated by diminished tumor necrosis factor [26]. CMV infection is also connected with immune system paralysis that is characterized by enhanced IL-10 and NFkβ production, lymphopenia, reduction of IFN-γ producing T cells,

and increase tissue damage by dysregulated cytokine production. Immune response during CMV infection is generated a favorable environment for secondary bacterial infections [27–29]. MeV infection is another example of immunosuppressive characteristics that are associated with a secondary bacterial infection. MeV reported to have associated with several weeks of immune suppression, loss of delayed-type hypersensitivity responses, and thus increased susceptibility to secondary bacterial infections [30]. It has been reported that MeV infection destroys pre-existing antibodies that increase the vulnerability to pathogens that result in secondary bacterial infections [31].

Exploitation of bacteria through viral infection

The majority of reported direct bacteria-virus interactions are associated with infection in the gastrointestinal tract caused by viruses. In body system, commensal bacteria are considered the first line of defense against invading pathogens by out-competing their disease-promoting counterparts and limiting tissue accessibility. Undoubtedly, enteric viruses encounter these large numbers of diverse commensal bacteria, but rather than always preventing infection, some viruses evolved to exploit this contactfacilitating the disease developmental process [32].

Under in vitro conditions, viruses may able to directly bind to their target cells and undergo replication. However, this strategy may prove problematic in the gastrointestinal tract whereasa large number of bacteria occupy tissue surfaces, directly competing for receptor binding sites, and reducing the likelihood of pathogenic bacterial proliferation or virus attachment. Other components, like mucus or enzymatic secretions, may also interfere or assist the infection process. To circumvent this, rather than compete for host cell-binding sites, some viruses can utilize bacterial ligands to enhance their association with more accessible host cells, initiating infection. This same strategy may be employed by some viruses that may not exclusively target the host's epithelial cells rather uses bacteria to assist infection of other cell types in addition to or exclusive of epithelial cells [33,34].

Although the nature of the interaction remains the same, there may be additional benefits to viruses with bacteria interactions other than direct disease progression. Studies have also shown

that association with fecalmicrobiota increased poliovirus environmental fitness and stability, as exposure to bacteria or their polysaccharides decreased the efficacy of virus inactivation by heat and bleach, potentially aiding viral survival in the environment [35]. This observation was further supported by the higher susceptibility to inactivation with heat observed in a poliovirus mutant that did not bind LPS as efficiently. Furthermore, the introduction of these bacterial polysaccharide components has been found to enhance wild type poliovirus binding to its host cells expressing its receptor [35]. In short, gastrointestinal microbiota not only increase poliovirus infectivity but may also promote virus transfer to the next host. Thus, there are numerous ways that direct viral interaction with bacteria aid viral pathogenesis, and this topic is an emerging area of study in microbiology.

Bacterial species often benefit from viral infections, the virus-induced disease state can allow normally harmless bacteria to become opportunistically pathogenic. Under normal, healthy circumstances, direct competition between microbes limits pathogen invasion by saturating colonization sites, priming barrier immunity to produce antimicrobials, and increasing the immune response to invading microorganisms [36]. When microbial populations are disrupted, niches previously inaccessible to invading pathogens become available, and the microenvironment where native microbiota previously was outcompeted their disease-causing counterparts are compromised. The overall ways viruses aid bacteria pathogenesis include a complex combination of cellular receptor up-regulation, disruption of the epithelial layers, displacement of commensal bacteria, and immune system suppression [37]. Arguably, the interactions between influenza viruses and pathogenic bacteria (i.e., *S. pneumoniae*, *S. aureus*, and *H. influenzae*) remain the best-studied within the human body, and they exemplify some of these mechanisms with both viruses and bacteria benefitting from the relationship. Influenza viruses not only damage the host epithelium (e.g., apoptosis), they also provide potential binding sites for bacteria through three mechanisms such as neuraminidase cleavage of sialic acid from host cells, bacterial host receptor up-regulation, and host regeneration of the common bacterial receptors fibrin and fibrinogen [38,39]. This pattern of host damage is common amongst upper respiratory tract viruses and bacteria [40,41], and these interactions are summarized in Table 1. Thus, these numerous dynamics that exist between the influenza virus and bacteria exemplify the multiple complex ways of viral infection that can indirectly assist bacterial infection [42,43].

Secondary infection of bacteria for viral infection

Epidemiological and clinical research clearly says that bacterial secondary infection can significantly increase after viral infections [44]. As an example, Up to 75% of that influenza-infected patient that goes on to acquire pneumonia, and they are establishedthat have bacterial co-infection [45]. Bacterial secondary infection after influenza infectionlooks to occur normally. Data revealed that upto 65% of the laboratory establishedthat cases of influenza infection showed bacterial secondary infection. However, Klein et al. [46] established through a meta-analysis that this figure ranged between 11 and 35%. In the site of influenza epidemic or pandemic bacterial secondary infection can have an alarming situation that is predominantly risk to immune-compromised or immune-suppressed patients. Immunosuppression is related to more severe illness and much of a higher risk of mortality from a secondary bacterial infection [47]. During pandemic Swine influenza in 2009, there was an arising patient in hospital pneumonia cases as a consequence of secondary bacterial pneumonia, which was recognized in 29–55% of mortalities [48–50].

Relationship between pathological changes and host responses

Viral infections are different with specific characteristics those are developed in the infected area and for that reason, bacterial colonization occurs. Bacteria can easily adhere and penetrated the infected region of the host cell [51]. Influenza virus produces neuraminidase, which also helps to increase the adhesion of some bacterial species by eliminating sialic acid which helps to depict the host cell receptors [39,52]. Some other bacteria such as *Streptococci* have sialic acid which allows for direct attachment with the viral hemagglutinin (HA) and this is expressed by influenza-infected host cells [52,53]. When the viral infection occurs they damaged the host cell by directly or inflammation of immune cell responses. The wound or damaged tissue welcomes the bacterial cells which can easily adhere and this viral infection increased by bacterial adhesion. For example, the contacts of apical receptors like integrins help the adhesion of bacteria such as *S. aureus* and *Pseudomonas aeruginosa* [54–57]. At the onset of viral infection, the host inflammatory responses are the reason for the up-regulation in the expression of host receptor molecules and other molecules that bacteria can use as a receptor [52,58]. As an example, Cundell et al. [59] reported that increased performance of the G-protein-coupled platelet-activating factor (PAF) is utilized by some bacteria such as *S. pneumoniae*, for their attachment and colonization in the endothelial cells [59,60]. In difference, it has been recommended that the platelet-activating factor (PAF) receptor does not disturb the preliminary bacterial adherence and colonization but is more involved with secondary bacterial transition or spread into the blood and facilitates the growth of invasive disease [61].

The respiratory viruses enter through the upper respiratory tract and these virus-infected in the acute infection of the respiratory tract. When the influenza virus or other viral infections are beginning in the respiratory tract than they might influence the secondary bacterial infection such as pneumonia by changing the microbial composition in the upper respiratory tract. For that secondary infection, there is developed the growth of pathogens and large bacterial loads has occurred in the lower respiratory tract [61]. Acute viral infection and secondary bacterial colonization have a bidirectional relationship.

Viral factors implicated in severity of infection

Humans are constantly exposed to viral agents with endogenous or exogenous in origin, but few of them are the cause of significant pathogenecity or severity of the diseases. Viruses are require host cells to replicate and assemble infectious offspring. The character of the viral factors are more important which imparted in the disease progression and tissue damage [62]. Recently, Miller et al. [63], demonstrated the role of viral factors showed their severity in infant respiratory tract illness. Both, host and viral risk factors are necessary to understand which may help to develop the disease prevention strategies. When a viral strain move between hosts is accountable to new symptoms appearance or stably adapted to new hosts. Viruses are able to initiate infection, and strat their replication by the help of specific **v**irulence factors [64]. It is well documented that different viral strains posses variable viral factors and therefore different degree of patheogenecity observed with different virulence [65]. One of the most important viral factor is located in their genome to defeat the host barriers, such as a point mutation in 5′ untranslated region (5′ UTR) of polio vaccine strain but the strain without mutation shows the greater pathogenecity in hosts [64]. Thus, viral genome is important factor to control the tropism, virus entry to host, shedding and transmission.

Table 1
List of secondary bacterial infections and their immune responses during viral infection.

Viral infection	Secondary bacterial disease	Bacterial name	Immune response
Influenza	Pneumonia, Otitis media, Sinusitis, meningitis	*S. pneumonia, S. aureus, S. pyrogenes, M.catarrhalis, N.meningitids*	loss of ciliary function, produce INF, Mucus response.Destroy phagocytic cell, produce cytokines including TNF-α, IL-6, and pro-IL-1β,
Coronavirus	Pneumonia	*H. influenzae*	activate the innate immune response or induce costimulatory signals for adaptive immunity
Adenovirus	Pneumonia	*S. pneumonia, H. influenza,S. aureus, M.catarrhalis*	Produce cytokines, loss of ciliary function, produce INF, Mucus response.
Measles virus	Otitis media, Pneumonia, Tracheobronchitis.	*S. pneumonia, H. influenzae,S. aureus,*	activate the innate immune response, produce cytokines including TNF-α, IL-6, and pro-IL-1β, Mucus response.
Human rhinovirus	Pneumonia, Otitis media, Sinusitis,	*S. pneumonia, H. influenzae,S. aureus*	Alters in pulmonary immune response, produce cytokines, inflammatory cell recruitment.
Parainfluenza virus	Pneumonia	*S. pneumoniae*	Destroy phagocytic cell, produce cytokines including TNF-α, IL-6, and pro-IL-1β.
Respiratory tract viral infection	Pneumonia, lungs problem	*S. pneumonia,S. aureus,H. influenzae, pseudomonas.*	Mucus response, IFN secretion, epithelial cell death, cytokine release, loss of ciliary function.
UTI viral infection BK Virus, Herpes virus	UTI infection is occur	*E. Coli, K. pneumoniae, P. aeruginosa*	chemokines and cytokines such as CXCL8, CCL2, interleukins (IL-6, IL-8, IL-10, IL-17A), and granulocyte colony stimulating factor (G-CSF) are release.

Viruses are able to developed immunomodulation pathway to undermine the host immune response. The virus-encoded decoy receptors are targeted to cytokines and chemokines of host cells [66]. Usually, primary bacterial clearance needs innate immunity with bacterial phagocytosis by local AM. The phagocytic activity of CD11c + alveolar macrophages in broncho alveolar lavage fluid was lower. To define the effect of interferon c (IFNc) were immunized with exogenous IFNc which inhibited alveolar macrophage-mediated phagocytosis of pneumococci both in vitro and in vivo. There was also repressed the external expression of the scavenger receptor which is responsible for phagocytosis of pneumococci by alveolar macrophages. Thirdly, interferon improved the surface expression of MHC class II antigen for that region interferon c inhibits bacterial phagocytosis and destroys innate defense against pneumococcal infection. in vivo treatment with the interferon c specific antibody had little consequence on the progress of viral infection but prohibited increased susceptibility to pneumococcal infection by developed macrophage expression of inflammatory cytokines and inhibiting pre-regulation of MHC class II expression [67]. The post-viral bacterial infection mechanism is very complex because different multifunctional interaction occurs between the virus, bacteria, and also host immune system. The pathogenesis of the respiratory super-infection has been endorsed by the direct mucosal or epithelial damage by the influenza virus. This viral infection increased the bacterial colonization of the upper and lower respiratory tracts. The host immune responses are the main cause of increased susceptibility to secondary bacterial infections. Another way, modern research suggests that our microbial populations be present in on our mucosal surfaces and probably affect our immune responses which create the characters of ecological relations among hosts and pathogens. The past 10 years result revealed the complex relationship of secondary microbial infections in the host body during viral infection [68]. In the time of secondary infection, different bacteria affect the physical substance in the host body, number of genes, and metabolic activities in different organ systems. Actually, respiratory viral infections can decrease the host immune responses, for that reason microbial growth conditions in the URT, LRT is high. When the influenza virus attacks host, body induced antiviral interferon pathways but this immune system is inadequate during host defense against secondary bacterial infections, therefore the pathogenic bacteria can easily proliferate and infected the host cell. Thus, molecular basis of virulence is polygenic in nature by consideration of viral factors. Therefore, viruses are efficiently altering the host cell response and exhibit greater pathogenicity [69].

Role of inflammatory responses in disease severity

The epithelial cells and mucosal immune cells in lung airway are the hotspot of respiratory viruses. These primary cells are getting first infected with viral agents and immediately strat to produce a range of mediators such as type I interferon (IFN), proinflammatory cytokines, and chemokines, which are the major molecules for the development of inflammation process in infected area. These are key factors in virus control molecules until vaccines are not available. It is well documented that infections induce the excessive production of reactive oxidative species (ROS), which are one of the importantat inflammatory mediators [70]. and consequences of several adverse physiological responses [71]. The expression of genes involved in respiratory process in host, their biogenesis signalling and antioxidant enzymes are regulated at the onset of viral infection. Overproduction of ROS along with mitochondrial damage increase the imflammation process in infected zone [72]. The entry of viral agents into lung and their colonization trigger for acute exacerbations of chronic obstructive pulmonary disease (AECOPD). A details study on patients with AECOPD revealed the elevation level of IL-6, TNF-α, and MCP-1 which are also increased several folds during coinfection [73].

Co-infections of viral and bacterial pathogens increase the disease susceptibility and outcome is more severe with higher mortality. In healthy lung tissue, neutrophils, monocytes, macrophages, dendritic cells, natural killer (NK), and other innate lymphocyte (ILC), B and T cells are found in abundance where AM are mostly abundant. After establishment of infection both pathogen-associated molecular pattern (PAMPs) and damage-associated molecular patterns (DAMPs) can engage in pattern recognition receptors (PRRs) to active the cellular signalling process for the production of soluble interferons (IFNs) to limit the replication process of invading pathogens. Interestingly, this PRR ligation [e.g., toll-like receptors (TLRs) 2 and 4] start to induce the overproduction of cytokines and chemokines which regulate the activation and recruitment of inflammatory molecules in the lung [74]. Recognition of PAMPs by specific PRRs have substantial impact on disease susceptibility and increased pathogen transmission. Therefore, it is important to accurately tune the immune and inflammatory mechanisms to restore the lung tissues from maximum damage [75].

SARS-CoV-2 and secondary bacterial infection

Like other well studied respiratory viral infections including the 1918 influenza outbreak [76] and 2009 H1N1 pandemic [77], the current pandemic outbreak of SARS-CoV-2 is also reported to

associate with secondary bacterial infections, thus poor outcomes and fatalities [2,78]. Recent studies reported a low rate of associated secondary bacterial and fungal infections with COVID-19 [3], however, SARS-CoV-2 is a novel coronavirus that suggested as proximally originated [79] and thus we can't ignore the fact that our current knowledge SARS-CoV-2 is very limited. Very recently, cohort studies of tuberculosis, sequelae, and COVID-19 co-infection revealed SARS-CoV-2 associated infection in patients with TB, however, the number of patients were less and no associated disease pathogenesis need to be determined [80,81]. Further investigation and detailed studies are needed to explore the role of latent or active TB associated with COVID-19 disease severity and progression [82]. Another cohort study of 11 patients suggested that the cases with pre-existing chronic obstructive pulmonarydisease or complicated with secondary bacterial pneumonia as the most severe outcome cases of COVID-19 [83].

SARS-CoV-2 is very much similar to the SARS-CoV, though it caused ongoing pandemic outbreak COVID-2. SARS-CoV has been already reported to regulate immune function-related gene expression in human monocytes. Immune-related gene expression suggested that SARS-CoV infection downregulatesIFN-α/β-inducible and cathepsin/proteasome geneswhile differential regulated genes include, TLR/TLR-signaling, cytokine/cytokine receptor-related, chemokine/chemokine receptor-related, lysosome-related, MHC/chaperon-related, and fibrosis-related genes [84]. In a different study, SARS-CoV also reported suppressing type 1 IFN production [85]. Downregulation and differential regulation of immune genes suggested a possible encouraging environment for secondary bacterial infections. Additionally, SARS patients has been reported to have secondary bacterial infections and confirmed the presence of different bacteria in various human samples, including *Escherichia coli*, *K. pneumoniae, P. aeruginosa*, Methicillin-Resistant *S. aureus* (MRSA), etc. [86]. During the SARS outbreak, increased rates of MRSA infections have been reported in SARS patients that further suggested the role of secondary bacterial infections in viral disease pathogenesis [87].

A recent study, confirmed SARS-CoV-2 infection in pregnant women and studied the clinical features and neonatal outcomes. The study suggested timely use of antibiotics might prevent COVID-19 associated secondary bacterial infections and can reduce mortality and complications during pregnancy [88].

SARS-CoV-2 RNA has also been found in stool samples ofCOVID-19 patients [89]. This raises the question of gastrointestinal infection of SARS-CoV-2 and also suggested a possible fecal-oral route of disease transmission. Further, high expression levels of ACE2 mRNA in the gastrointestinal system, avail indirect evidence of SARS-CoV-2 infection [90,91]. Preliminary studies suggested gastrointestinal infection [92,93] and strong interaction of SARS-CoV-2 with the gastrointestinal system that has high microbiome diversity and possible chances of immune suppression and secondary bacterial infections. Additionally, a recent study reviewed the secondary bacterial and fungal infection in coronavirus patients and suggested guidelines for the use and prescription of antimicrobial in SARS-CoV, SARS-CoV-2, and related viral infections [3]. However, further, clinical studies may provide future directions for SARS-CoV-2 and related secondary bacterial infections.

Conclusion

Viral infections avail bacterial infections by using multiple strategies, including providing a more susceptible site for adhesion, altering immune response, and invasive infection by cell and tissue damage. Secondary bacterial infections then make the clinical outcomes more severe that is an alarming situation in concern of public health. However, antibiotics can diminish the effect of secondary bacterial infections, in-depth understanding of the viral-host, bacterial-host, and viral-bacterial interaction is important to fight against these infections. Especially in the focus of rapid increasing antibiotic resistance and adaptation of microbes may lead to escape from vaccine-induced immunity. The eventual goal of understanding the molecular pathogenesis of viral infection associated secondary bacterial infections is to development of more efficient diagnostics and therapeutic strategies. Further, it becomes an important fight against the current or future potential of pandemics and the emergence of novel viruses like SARS-CoV-2.

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