

Fungal And Bacterial Sinusitis In Covid-19 Era; A Comprehensive Narrative Review

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Abstract

Generally, infection with respiratory tract viruses leads to secondary infections in which bacteria and fungi play an important role. One of the important secondary infections related to Covid-19 is sinusitis. Due to the complications of fungal and bacterial sinusitis, it is important to know the most substantive factors that predispose people to these diseases. Covid-19 treatment solutions and excessive use of steroids and immune system of infected people are effective in causing invasive fungal sinusitis related to COVID-19. Findings show that uncontrolled blood sugar levels are also effective in sinusitis. Corona virus affects immune system. The severe inflammatory response causes an increase in cytokines and a decrease in specific immune system function in these patients and causes a prolongation of disease period and sinus tissue inflammation. Clinically, fungal and bacterial sinusitis are very similar. In this article, the aspects of corona disease and subsequent bacterial and fungal sinusitis were discussed. According to available data, a high percentage of patients with SARS-CoV-2 infection have fungal sinusitis after disease. Bacterial sinusitis is generally not as common as acute viral rhinosinusitis and affects more women than men. By attacking and causing tissue inflammation and then using corticosteroids to reduce immune response, Covid-19 provides conditions for opportunistic fungi. Often items like allergies or an acute illness like covid-19 can affect immune system. Oral corticosteroids can cause serious side effects if used long-term, so their use is recommended only when necessary and to treat severe symptoms.

Keywords: Sinusitis, Bacterial Infection, Fungal Infection, Covid-19, Acute Sinusitis.

INTRODUCTION

Coronaviruses cause respiratory, intestinal, liver, and neurological diseases of varying severity in a wide range of animal species, including humans. Over the past two decades, coronaviruses have caused three epidemics, namely, acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19 (Coronavirus Disease 2019) [1]. Although Covid-19 preferentially affects respiratory and cardiovascular system, in patients with severe symptoms of neurological problems (such as headache, dizziness, reduced sense of smell and taste, and nerve pain) and complications such as encephalopathy, acute brain diseases, impaired consciousness, Musculoskeletal damage and sinusitis complications are also seen [2]. With the pandemic and increasing spread of Covid-19 globally, multi-modal therapeutic interventions have been identified, with immunosuppressants such as steroids and interleukin-6 inhibitors often being used. In addition, a significant percentage of patients receive broad-spectrum antibiotics during their treatment; particularly those admitted to intensive care units, those with long hospital stays, and those with superimposed bacterial infections such as ventilator-associated pneumonia [3, 4].

The nasal cavity also plays an important role in COVID-19 and in 85.6% of cases, olfactory disorders have been reported in patients with Covid-19 [5]. In fact, this is due to the binding of SARS-CoV-2 virus to two protein receptors, angiotensin-converting enzyme 2 (ACE2) and serine protease 2 (TMPRSS2), both of which are necessary to enter host cell (Figure 1). In addition, due to large number of these receptors in respiratory epithelium and subepithelial glands, olfactory dysfunction is probably induced due to excessive secretion and inflammatory cells increase. In general, respiratory tract infections (URTIs) such as COVID-19 are often due to generalized mucosal edema and include sinusitis. In fact, there is a possibility of mucus retention and infection in sinuses, which naturally increases the severity of disease and prolongs treatment period [6-9].

As mentioned, COVID-19 is associated with a wide variety of opportunistic infections. Recent evidence has shown an increase in co-infection during coronavirus disease, especially in people with severe inflammation. Indiscriminate use of antibiotics and therapeutic steroids during covid-19 pandemic period has led to unwanted consequences such as development of multi-drug resistant (MDR) bacterial infections or acute invasive fungal rhinosinusitis (IFRS) [9, 10]. Yeasts and bacteria are found in

natural flora of human body, and if environment is suitable, they can cause pathological conditions such as pneumonia and acute fungal rhinosinusitis. In most patients, viral upper respiratory tract syndromes generally subside within a week, while bacterial and fungal sinusitis can persist for 10 days or more and lead to possible additional complications[9]. According to studies, several factors such as immunodeficiency caused by long-term use of steroids, human immunodeficiency virus, or diabetes, as well as anatomical defects such as injuries or fractures in the face and jaw area can lead to sinusitis. Also, increased use of steroids and antibiotics during COVID-19 era may also predispose individuals to multidrug-resistant (MDR) bacterial and fungal infections[11, 12]. In addition, excessive expression of inflammatory cytokines and reduction of positive T-helper cells (CD4+ T and CD8+ T) due to reduced immune system function in patients with Covid-19 can be an important factor in occurrence of sinusitis complications [9].

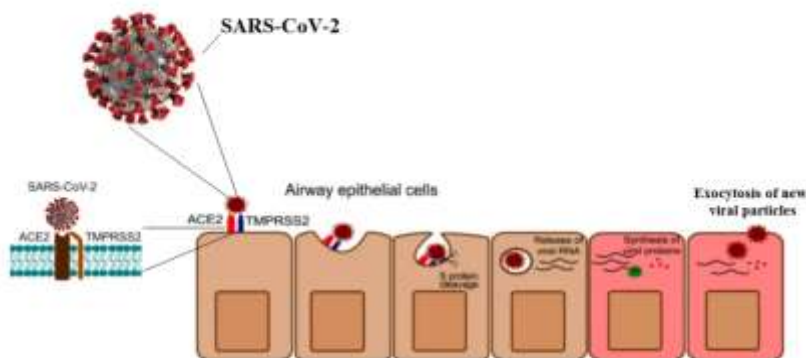


Figure 1: After entering airways, Covid-19 interacts with S protein to its ACE2 receptor. Cell proteases spread viral proteins in cell by creating proteolytic cleavage, and nucleic acid is transcribed. The cycle of protein synthesis and accumulation of new viral particles continues

Invasive fungal sinusitis, specifically caused by mucormycosis, is a life-threatening invasive fungal sinusitis that typically affects immunocompromised individuals. The exact association of IFRS infection with COVID-19 is also still unclear, and clinicians should consider the possibility of IFRS in patients with COVID-19 and underlying medical conditions, especially when they have nasal symptoms. Therefore, awareness of "red alert" signs of possible co-infection due to fungal and bacterial diseases in patients receiving immunosuppressive therapy for recent covid-19 infection should be increased [10-13]. This review study was also conducted with the aim of investigating the relationship between fungal and bacterial sinusitis in covid-19 era. In this article, we want to evaluate the aspects of covid-19 and subsequent bacterial and fungal sinusitis and examine the role of various factors, especially immune system, in bacterial and fungal sinusitis development.

CONNECTION BETWEEN SINUSITIS AND COVID-19

A sinus infection, or sinusitis, occurs when air-filled cavities in face, called sinuses, fill with fluid, inflaming sinuses lining and preventing them from draining. Trapped mucus can be a suitable environment for growth of bacteria and lead to infection [14]. Sinusitis can occur at any age. On average, children get 3 to 8 viral infections each year, and this increases the risk of developing acute bacterial sinusitis. Various factors such as local and systemic factors can trigger sinusitis. Upper respiratory infections, anatomical abnormalities, nasal polyps and tumors are local factors; While immunodeficiency, cystic fibrosis, ciliary disorder and Wegener's granulomatosis are in category of systemic factors [15].

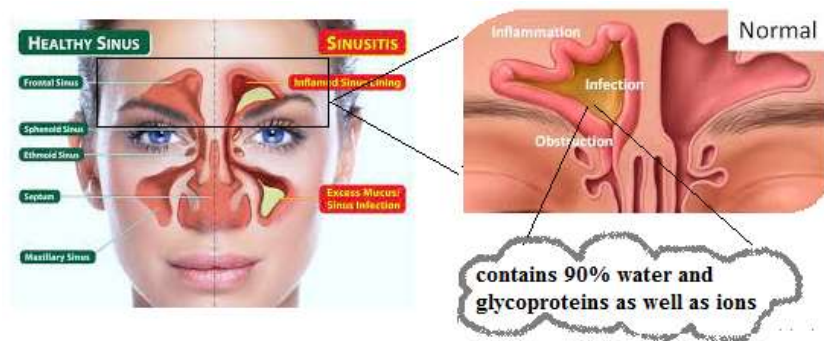


Figure 2: Inflamed sinus and healthy sinus, inflamed sinus becomes inflamed due to mucus accumulation and immune cells. The response of immune system to inflammation and increase of cells causes more intensity of inflammation

Both acute and chronic sinusitis are diseases that affect most people at some point in time. Typically, this disorder is classified as acute sinusitis lasting up to 4 weeks, subacute sinusitis lasting 4 to 12 weeks, and chronic infection lasting longer than 12 weeks. Based on epidemiological findings, secondary bacterial or fungal factors can be life-threatening with inflammation continuation and severity of sinusitis and cause acute or chronic complications for patients' lives for a long time. In addition to complications of disease, in severe sinusitis cases due to the use of broad-spectrum antibiotics, despite the treatment of disease, drug use complications have affected patients for a long time [16].

One of the common complications of sinusitis is occurrence of olfactory disorder, which occurs in 56 to 78% of patients with chronic sinusitis (CS). At the same time, as a disorder is also seen in covid-19 pandemic due to virus attack on mucous cells lining and depending on its type and country under investigation, 5 to 85% of olfactory disorders have been reported [17, 18]. According to available data, a high percentage of patients with SARS-CoV-2 infection have experienced CS after disease [19]; Most of them have fungal sinusitis and/or complications of mucormycosis related to SARS-CoV-2 infection. From clinical point of view, fungal and bacterial sinusitis are very similar, but laboratory findings have shown that a very small number of people have contracted bacterial sinusitis during the infection of Covid-19 [5, 20-24].

TREATMENTS FOR COVID-19 AND OPPORTUNISTIC INFECTIONS

As risk factors for opportunistic infections in COVID-19, steroid treatment, immunodeficiency status, and underlying diseases such as diabetes and diabetic ketoacidosis, malignancies, or malnutrition can be mentioned [5, 20, 21]. In fact, corticosteroids are usually prescribed in severe cases of SARS-CoV-2 (COVID-19) and despite their importance in reducing patient mortality, they can have harmful side effects, especially in immunocompromised patients, uncontrolled diabetes and have neutropenia with or without malignant diseases. By affecting the function of immune system, these drugs use can cause serious side effects such as a fungal infection that can damage lungs or attack sinuses and then quickly spread to eye orbit and even inside skull. Patients may lose vision or die from cavernous sinus thrombosis or other intracranial complications unless diagnosed early and managed properly [22-24].

The use of inappropriate antibiotics also leads to development of fungal and bacterial infections possibility in sinuses at the same time as covid-19 occurrence in a person. For example, Rhino-orbital mucormycosis has been well described as a consequence of COVID-19 infection treatment, demonstrating the effect of widespread steroids use and broad-spectrum antibiotics in promoting development of opportunistic fungal infections [25]. Of course, paying attention to various points such as antifungals and antibiotics use, limiting antibiotics use and duration of it in covid-19 infection management, and wise use of antibiotics and steroids may reduce high risk of bacterial infection. and colonization with MDR organisms may help [1, 26].

BACTERIAL SINUSITIS

Acute bacterial rhinosinusitis (ABRS) is an infection of nasal cavity and sinuses caused by bacteria. Normally, behind the nose, there is a large space that is filled with air. The sinuses are also part of this space enclosed by facial bones. Sometimes the infection caused by bacteria causes these spaces to become inflamed and a lot of mucus accumulates there. In such a situation, mucus is not easily discharged and this problem causes facial pain and other symptoms. ABRS is not as common as acute viral rhinosinusitis and affects more women than men. More middle-aged and elderly people are also reported to be affected. ABRS is caused by bacteria that infect nasal cavity and sinuses lining. Common bacteria that cause this inflammation are usually *Streptococcus pneumoniae* or *Haemophilus influenzae*. Most inflammations of nasal cavity are caused by a virus and occur in later stages of bacterial infection [27].

Acute bacterial sinusitis in children is difficult to diagnose because of clinical presentation similar to common viral URIs. Due

to this overlap, there is no consensus on sinusitis exact clinical definition in children. No specific clinical signs or symptoms are sensitive or specific for acute sinusitis, and general clinical impression should be used to guide management. Despite a thorough history and physical examination, treatment of presumed acute sinusitis is usually initiated on empirical grounds and results in treatment of common viral colds in 18% to 60% of cases. Discharge, cough, mouth breathing, snoring, halitosis, hypo-nasal speech, and nasal obstruction are also present in simple URIs and cannot be used alone to diagnose bacterial sinusitis. A history of purulent discharge, facial pain or pressure on affected sinus, toothache, or poor response to nasal decongestants suggests acute sinusitis in an adult, but is often difficult to diagnose in a young child. Perhaps the most important feature in history is duration of symptoms. Children have an average of 6 to 8 common colds per year, each lasting an average of 7 to 9 days [27, 28].

FUNGAL SINUSITIS

Fungi are ubiquitous organisms. They are widely distributed in air, water, soil and decaying matter. Spores are the reproductive cells of fungi that are airborne, so they easily reach the human airways. According to literature, the most common fungal species reported in nose and paranasal sinuses are *Mucor* and *Aspergillus* species. Disease presentation by fungi depends more on immune status of the host than on fungus itself. Fungi cause a spectrum of sinus disorders ranging from allergic fungal rhinosinusitis (AFRS) in atopic patient to "fungal balls" in immunocompromised host and finally invasive fungal rhinosinusitis in immunocompromised patient. Studies have compared the propensity of certain fungi to cause cranial and orbital nerve complications, i.e., *Mucor* versus *Aspergillus*, and found a higher prevalence with the former. Invasive fungal rhinosinusitis has made a resurgence during the current Covid-19 pandemic. This may be attributed to immunosuppression caused by depletion of CD4+ and CD8+ T cells caused by SARS COV 2 virus [28-30].

In previous studies in 2003-2007, fungal infections were one of the main causes of death in patients with SARS. Lung damage, persistent hypoxemia, hyperglycemia, excessive use of corticosteroids had led to secondary infections. It seems that the same thing happened in the current epidemic. Inflammation and the development of pneumonia in covid-19 patients and then the use of corticosteroids to reduce the immune response provide conditions for opportunistic fungi. As a result, the SARS COV virus can be a predisposing factor for the invasive fungal infection of aspergillosis as well as other fungal infections. Hence, in patients presenting with minimal complaints, a high suspicion of fungal infection should be raised for early diagnosis and intervention to prevent spread of infection[31, 32].

IMMUNE SYSTEM AND SINUSITIS

According to National Institute of Allergy and Infectious Diseases, 37 million Americans develop sinusitis each year, which is characterized by sinuses inflammation. This disease can be caused by several factors in this population, but the immune system is an important influencing factor in the severity of the disease. Inflammation constricts the nasal passages so mucus cannot drain properly, leading to pain, discomfort and potentially infection. The sinusitis causes vary from viral infections and allergies to environmental triggers such as smoke or hair spray. Other predisposing factors include deviated septum, nasal polyps, cystic fibrosis, dental infections, reflux disease, autoimmune disease, and facial trauma. It is noteworthy that immune system deficiency is one of the main influencing factors in sinusitis. IgG deficiency, IgA deficiency, and antibody deficiency can present with sinusitis. The breakdown of the immune system is not the cause of sinusitis in itself, but often things like allergies or the occurrence of an acute disease like Covid-19 can affect the immune system. Because the severe inflammatory response causes an increase in cytokines and a decrease in the function of the specific immune system in these patients. In the specific immune system, lymphocytes directly destroy the pathogenic agent and this helps to quickly recover from the disease, but excessive secretion of inflammatory factors in people with a weaker immune system causes a prolongation of the disease period and inflammation of the sinus tissue. becomes[33, 34].

TREATMENT SOLUTIONS TO REDUCE SINUSITIS

Nasal corticosteroids such as fluticasone drops and sprays, triamcinolone, budesonide, mometasone, and beclomethasone help prevent and treat sinus inflammation. Of course, there are also injectable types of them, which are generally used in special cases such as nasal polyps. Oral corticosteroids can also cause serious side effects if used long-term, so their use is recommended only when necessary and to treat severe symptoms. Also, rinsing the nose with salt, nasal sprays or solutions, reduces drainage and washes away irritants and allergies. If infection is caused by bacteria, sometimes the use of antibiotics can be necessary for sinusitis, and if it has a fungal origin, the use of antifungal treatments is considered a suitable solution for treatment [35]. In cases refractory to treatment or medication, endoscopic sinus surgery may be an option. For this procedure, your doctor uses a thin, flexible tube with an attached light (endoscope) to explore your sinus passages. Depending on the source of the blockage, the doctor may use different tools to remove the tissue or shave the polyp that is causing the nasal obstruction. Enlargement of the narrow sinus opening may also be an option to promote drainage[35].

SUMMARY AND CONCLUSION

In this article, the aspects of Covid-19 disease and subsequent sinusitis were discussed. The role of various factors, especially the immune system, in people suffering from bacterial and fungal sinusitis was investigated. According to the WHO report, until December 2022, about 7 million people have died due to the covid-19 infection; Meanwhile, about 13 million doses of vaccine have been used worldwide [36]. Many patients with covid-19 have died due to secondary infections. According to the available data, a high percentage of patients with SARS-CoV-2 infection have experienced CS after the disease[19]; Most of them have fungal sinusitis and/or complications of mucormycosis related to SARS-CoV-2 infection. From the clinical point of view, fungal and bacterial sinusitis are very similar, but laboratory findings have shown that a very small number of people have contracted bacterial sinusitis during the infection of Covid-19 [22-24]. Bacterial sinusitis is generally not as common as acute viral rhinosinusitis and affects more women than men. More middle-aged and elderly people are also reported to be affected. Inflammation and the development of pneumonia in covid-19 patients and then the use of corticosteroids to reduce the immune response provide conditions for opportunistic fungi. As a result, SARS COV virus can be a predisposing factor for invasive fungal infection. It is noteworthy that immune system deficiency is one of the main influencing factors in sinusitis. The breakdown of the immune system is not the cause of sinusitis in itself, but often things like allergies or the occurrence of an acute disease like Covid-19 can affect the immune system. Because the severe inflammatory response causes an increase in cytokines and a decrease in the function of the specific immune system in these patients. In the specific immune system, lymphocytes directly destroy the pathogenic agent and this helps to quickly recover from the disease, but excessive secretion of inflammatory factors in people with a weaker immune system causes a prolongation of the disease period and inflammation of the sinus tissue. will be Oral corticosteroids can cause serious side effects if used long-term, so their use is recommended only when necessary and to treat severe symptoms.

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