

## **Retrospective study of Covid-19 associated co-infections and super infections from bacteria, fungi and viruses, their molecular pathogenesis, etiology and immune dysregulation- current global challenges-A critical review**

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### **Abstract**

A broad spectrum of different kinds of viral, bacterial and fungal pathogenic infections is significantly reported among Covid-19 patients. Most of these infections shoot up the incidences of morbidity and mortality and results in community spread. To review in detail about various co-infections, super infections, etiology, diagnosis, molecular pathogenesis, immune dysregulation and appropriate treatment methods in Covid-19 patients. The Science direct, PubMed and web resources were surfed with different keywords including: "Covid-19"; "SARS-CoV-2"; "viral co-infection"; "bacterial co-infection"; "fungal co-infection" "Interferon"; "Transforming Growth Factor"; "CAPA"; "ROCM"; "Mucormycosis"; "Black fungus infection"; "white fungus" "yellow fungus" "OPC". It has been about 18 months since the entire world is fighting to control Covid-19, even since it stipulates many associated diseases to cope up with; one such is the microbial co-infection. The co-infection is the current challenge in treating the Covid-19 patients as it majorly intensifies the morbidity and mortality ratio. Besides some common bacterial and viral pathogenesis, highly virulent fungal infections like Rhino-orbital-cerebral mucormycosis, Zygomycosis, Black fungus, White fungus and yellow fungus infection which were reported recently has been detailed. A timely diagnosis, proper medications and treatments can help to overcome the severe implications; hence this review also emphasized on the symptoms of infections, molecular pathogenesis, sample collections with diagnosis, immune dysregulation and available treatment methods. Either it isn't possible to ignore the co-infections or to misinterpret the diagnosis in order to ensure the proper pandemic management. Better understanding of co-infections, diagnosis, effective treatment, prevention and root cause identification is thus critical for the effective patient management, treatment and

containment of SARS-CoV-2. Hence, this review discussed everything in detail and hence it provides the reader a crystal clear detail on Covid-19 associated microbial co-infections. This study may also enlighten the necessary precautionary measures to look forwarding to combat the severe impacts.

**Key words :** SARS-CoV-2; Zygomycosis; Pulmonary aspergillosis; Oropharyngeal candidiasis; *Pneumocystis jirovecii* Pulmonary Co-infection, Bacterial and viral co-infection.

A novel  $\beta$  enveloped RNA virus is ought to be the main causative agent of rapidly spreading Coronavirus disease 2019 (COVID-19) named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This specific virus is reported to be highly virulent compared to previously reported SARS-CoV and Middle East respiratory syndrome (MERS-CoV). The disease reported in 2019 and spreads around the world, the pathology and proper treatment still unknown in detail<sup>19,43</sup>. This viral pathogen causes upper respiratory infections in adults and severe respiratory infections in both children and adults. So far, the reported strains for this kind of infections are severe acute respiratory syndrome (SARS) virus, Middle East respiratory syndrome (MERS) virus and recently SARS-CoV-2 virus, this one initially reported<sup>5,9</sup> as 2019-nCoV. Symptoms of Covid-19 infections are grouped as follows: fever, dry cough and tiredness and aches, sore throat, headache, loss of taste and smell, rashes on skin and diarrhea. Similarly, serious symptoms include shortness of breath, discomforts or pressure in chest, loss of speech and arresting of movement. Food and Drug Administration (FDA) released the statement regarding Emergency Use Authorization (EUA), established guideline for treatment in adults' Covid-19 patients as follows :

- 1) Use of either baricitinib or tocilizumab combination with dexamethasone alone or dexamethasone and remdesivir for treating Covid-19 positive patients those who admitted at hospitals with ventilation or intensified markers of inflammation
- 2) When corticosteroids ought not preferred, baricitinib jointly with remdesivir can use for the patients who were admitted in hospital
- 3) Panel recommends against using baricitinib along with tocilizumab for the treatment, because both are immunosuppressant

Till date there are many different variant strains of Covid-19 with significant alterations like gene addition or deletion from SARS-CoV-2 has been reported round the globe. For instance, Bal *et al.*,<sup>5</sup> reported a case of Covid-19 from France and revealed the presence of amino acid nsp2; three-nucleotide deletion in open reading frame 1a (ORF1a). This was the first genetic characterization of COVID-19 cluster in Europe and concluded that high depth of coverage in sequences. In another report molecular characterization of covid-19 virus from Italy was first time reported by Capobianchi *et al.*,<sup>8</sup> according to their report, two non-synonymous changes (at ORF 1a and ORF 3a) with respect to the

Wuhan-Hu-1 NCBI Reference Genome (Accession number: MN908947.3). These variants are even potent than the earlier strains in case of virulence and other associated infections.

The SARS-CoV-2 infections risks the patient with the concurrent co-infections and super infections and these were mainly considered as the prime reason behind the increased mortality notably during the second wave<sup>35</sup> of Covid-19. Many viruses, bacteria and fungi were reported along with Covid-19 virus and it is very difficult to diagnose either and/or to provide proper treatment. Many of the causative agents of co-infections were reported as opportunistic microorganism and

due to the collapsed immune system after Covid-19 infection, favor the growth of these microbes inside the body comparatively higher than their normal flora resulting in severe infectious conditions. Commonly isolated and reported bacterial pathogens among Covid-19 patients are *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus* sp. Similarly, for fungus, *Candida* spp. and *Aspergillus* spp. associated infection were highly recorded. Human metapneumovirus (hMPV), Influenza A, Enterorhinovirus (hRV), Chlamydia pneumoniae were the major viral strains reported from Covid-19 patients. Few commonly isolated and reported co-infectious microbes from Covid-19-patients are given in the Figure. 1.

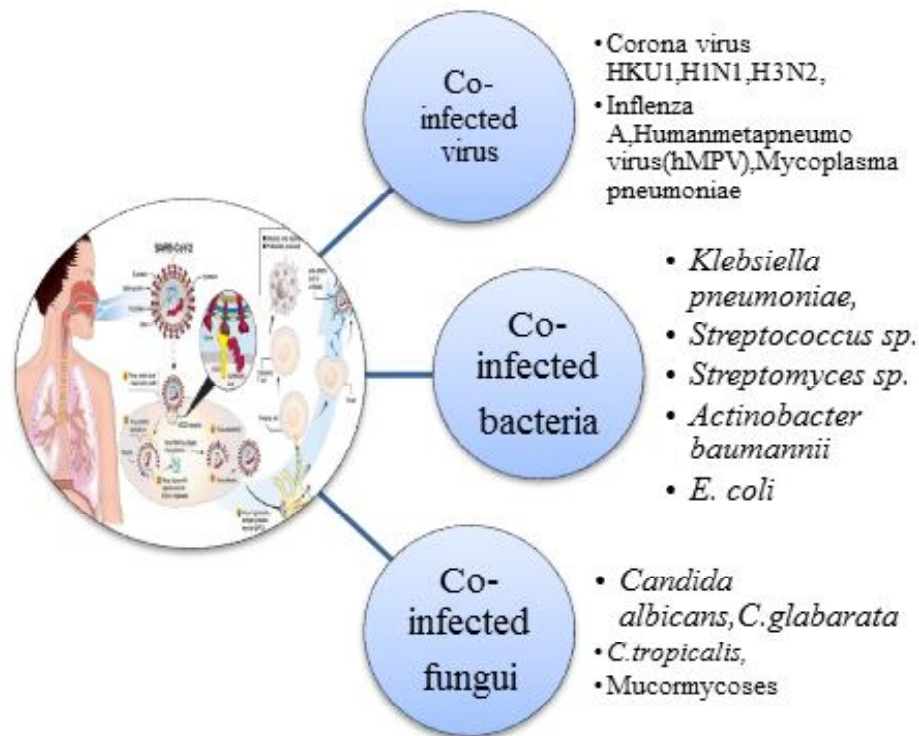


Figure 1. Precisely depicts the major associated co-infections in the Covid-19 patients.

Poor immunity, mechanical ventilation, intake of steroids and antibiotics are the main reasons for severity in co-infections. The best treatment method for controlling any co-infections strongly rely on targeted isolation of pathogens and appropriate selection of antibiotics. Few indicators that are present in can easily categorize the infectious agents which in turn favoring the effective diagnosis. For bacterial and fungal co-infections, the indicators to be focused are pro-inflammatory cytokines, calcitonin, tumor necrosis factor  $\alpha$  and interleukin  $1\beta$ . Similarly, for viral co-infections, the indicators like lymphopenia, prothrombin, neutrophils, troponin, C-reactive protein, lactate dehydrogease and alanine aminotransferase are to be emphasized. The detection of viral infection is mainly by means of Real Time Polymerized Chain Reaction (RT-PCR) and for the bacterial and fungal infections it may be identified by using microbiological methods of analysis and more precisely by molecular methods.

In this review, we discussed about the various case studies reported with different fungal infections (Covid-19 associated invasive pulmonary aspergillosis, Rhino-orbito-cerebral mucormycosis, Mucormycosis or Zygomycosis-Black fungus infection, White fungus and yellow fungus infection, Covid-19 associated oropharyngeal candidiasis, Covid-19 Associated Candidiasis, *Pneumocystis jirovecii* Pulmonary coinfection), bacterial infections from (*E. coli*, *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, *Streptococcus* sp. *Streptococcus* sp.) and viral infections (Human Immunodeficiency Viruses, Hepatitis Virus, influenza A virus, influenza A H3N2, Respiratory Syncytial Virus (RSV), Human Rhinoviruses (HRV), Human metapneumo Virus (HMPV), Parainfluenza

Virus type2 (PIV2), and Human Coronavirus HKU1) in detail. Similarly, symptoms of infections, molecular pathogenesis, sample collections with diagnosis and available treatment methods are also well discussed.

#### *Corona associated viral infection :*

In general, the Covid-19 patients are very much susceptible to various kinds of viral infections. The literatures majorly documented the frequent viral associated co-infections, the proper diagnosis and treatment methods have also been well discussed as well which in turn favors the effective handling of pandemic situation. Many reports concluded that the presence of different viral strains in Covid-19 patients with SARS-Cov-2, and commented that poor immunity is the one main reason for co-infection. The accumulated reports and their outcome data are discussed here; most of these studies were conducted during first wave of Covid-19. Lin *et al.*,<sup>28</sup> analyzed 186 Covid-19 patients samples collected from Shenzhen Third People's Hospital, during January 20 to February 1, 2020 and reported that 3.2% of Covid-19 patients been infected with other viruses as well as 2.2% showed mild viral infections other than Covid-19 virus. Normal respiratory viruses viz. Respiratory Syncytial Virus (RSV), Human Rhinoviruses (HRV), Human metapneumo Virus (HMPV), Parainfluenza Virus type2 (PIV2), and Human Coronavirus HKU1 (HKU1) were also rarely observed in few samples.

A report by two researchers Wang *et al.*,<sup>41</sup>; Zhang *et al.*,<sup>46</sup> also documented similar kind of viral co-infections, predominantly by influenza A virus, HRV, and influenza A H3N2 in almost 5.8% out of 2745 SARS-CoV-2

patients studied. Another report says, in North California, 20.7% of Covid-19 patients were having other viral co-infections.<sup>24</sup> Rarely in critically ill patients with the survivors of Human Immunodeficiency Viruses (HIV) as well as Hepatitis Virus were also reported in detail Bengoechea *et al.*,<sup>6</sup>; Kiley *et al.*,<sup>23</sup>. The presence of influenza viruses in Covid-19 patients from United States were reported by Cuaradro *et al.*,<sup>15</sup>; Chen *et al.*<sup>10</sup> In another study conducted by two researchers Wang *et al.*,<sup>41</sup> and Zhang *et al.*,<sup>45</sup> also reported the presence of Influenza viruses in 9 out of 242 samples collected from Covid-19 patients. Burrell and colleagues<sup>7</sup> studied 1423 Covid-19 patients (677 male and 746 females) and reported the existence of other respiratory viruses in 1.5% samples they are especially infecting the upper and lower respiratory tract besides SARS-CoV-2 infection.

Normally, the blood cultures and bronchoalveolar lavage fluid, sputum or endotracheal aspirate are the main choices of samples for diagnosis. In general, the viral co-infection significantly increases the C-reactive protein and procalcitonin levels. During the infection, air pathway is highly damaged by viruses followed by the reduction of mucociliary clearance which in turn results in the collapsing of immune system by destroyed epithelium Vareille *et al.*,<sup>40</sup>

#### *Bacterial co-infections :*

Often the bacterial co-infections are much observed to be associated with the Covid-19 patients round the globe. Nori and colleagues<sup>32</sup> reported bacterial infection in Covid-19 patients admitted at US hospital.

Similarly, in UK the nosocomial bacterial pathogenic infections were generally observed in the samples collected from Covid-19 patients; approximately the patients who were hospitalized for more than 5 days found to turn positive for nosocomial infections<sup>18</sup>. From two London hospitals, sampling was done during first wave of COVID-19 Hughes *et al.*,<sup>20</sup> Out of 836 Covid-19 patients, 27 people are reported with bacterial infection within 5 days of hospital admission. It was reported that *Staphylococcus aureus* and *Klebsiella pneumoniae* were predominantly observed among Covid-19 patients and the rate of infection as 55.8 and 40.1% respectively. However, so far from the records, it was observed that the bacterial pathogen *Streptococcus pneumoniae* is predominantly infecting the Covid-19 patients causing critical illness<sup>22,38</sup>. There were found to be many methods adopted for sampling and analysis; for instance, Chen and colleagues discussed about the various microbiological methods for collecting samples from Covid-19 patients; this includes the throat swab, sputum collection and endotracheal aspirates for detecting the bacterial co-infections<sup>11</sup>.

The severity as well the prolonged hospitalization were found to be the basic reasons for getting infection with the bacterial pathogens for Covid-19 patients. Respiratory samples were taken from the Covid-19 patients for diagnosing co-infections, it was revealed that even within 24 hrs of observation 13 patients (~28%) were contracted bacterial co-infections Kretimann *et al.*,<sup>27</sup> Another report analyzed the possible bacterial co-infections among the patients under critical care unit (ICU) at Spanish hospital and identified 32 different kinds of pathogenic bacteria from 24

patients out of 92 cases within 48hrs. These includes *S. aureus*, *S. pneumoniae* and *Pseudomonas aeruginosa*, further they found that the severity is high among those are in ICU for more than nine days. Bacterial pathogens like *K. pneumoniae* and *Moraxella catarrhalis* were found to be common in SARS-CoV-2 patients admitted in hospitals. Contou and colleagues reported that samples collected within 48 hrs from Covid-19 patients admitted at ICU were observed with 28% of bacterial co-infection includes *S. aureus*, *S. pneumoniae*, and *Enterobacteriaceae*<sup>12</sup>. Methicillin resistant *S.aureus* was isolated from samples of ICU admitted Covid-19 patients and reported as 47% people were affected by the same<sup>39</sup>.

Case study of 289 people revealed that

48 (16.6%) inherited co-infection with in 72 hrs and 25 (8.7%) among found to bacterial co-infection Zhu and colleagues Zhu *et al.*,<sup>47</sup> collected 257 samples (blood and sputum) from adult and children those who were suffered from Covid-19; their report said that approximately 94% (242) of the patients having co-infections with 11 different bacterial strains including *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Enterococcus*. Similarly, *P. aeruginosa*, *Enterococcus* spp. *Enterobacter cloacae* were found in these samples of Covid-19 patients<sup>20</sup>. Crisan and colleagues<sup>14</sup> even reported the tuberculosis (TB), infection in SARS CoV1, SARS CoV2 and MERS CoV patients. The interlinking pathway of diseases and immune condition is well depicted in this Figure. 2.

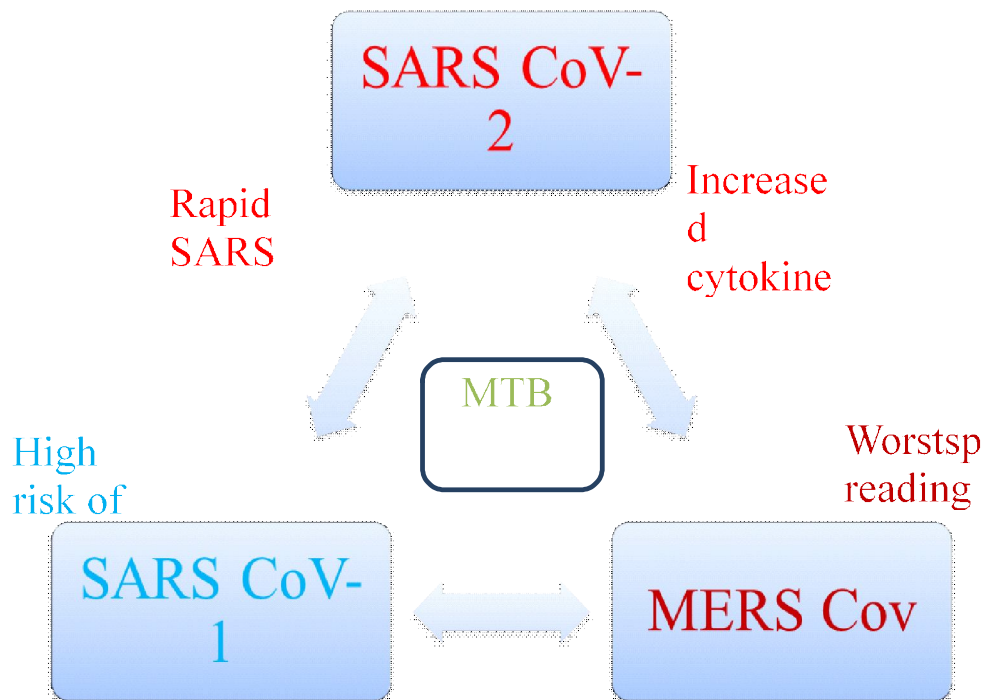


Figure 2. The interlinking pathway and immune conditions

The possible mechanisms of bacterial infections are as follows

- a) Destruction of the respiratory epithelium and infection of the basement membrane
- b) Up regulation bacterial receptor molecules
- c) Attachment of bacterial cells and damage of immune cells including neutrophils and macrophages.

During bacterial infection, interferon (IFN) normally gets damaged, accumulation and attachment of more bacterial cells will take place followed by invasion towards healthy body sites. Down regulation of type 1, IFN and alveolar macrophages are also the reason for increased bacterial co-infection. Immunosuppression and immunosuppression are also being the main reason for co-infection in Covid-19 patients. Platelet derived immunosuppression also found to enhance the chance of bacterial infection. The enzyme 2 (ACE2) from megakaryocytes interacts with spike protein of SARS-CoV-2, followed by activation of platelets. This leads to the cellular aggregation, upregulation and expression of the adhesion molecule, CD62P (P-selectin), activation of the integrin, GP11b/111a, mobilization of both  $\alpha$ -granule and dense granules, and platelet spreading. Increased pro-inflammatory/ pro-thrombotic platelets cause thrombocytopenia.<sup>45</sup> Procalcitonin level normally get too increased with bacterial infection in Covid-19 patients whereas, their normal range to be found is  $< 0.5 \mu\text{g/L}$ <sup>43</sup> Platelet derived immunosuppression will cause the following problems to the immune system.

- a) Heterotypic aggregates form between platelets with neutrophils, monocytes, and T cells, this will lead to inappropriate leukocyte activation<sup>18,30</sup>.

- b) Platelets will bind with cell surface expressed platelet factor 4 and leukocyte integrin, CR3 (Lishko *et al.*)<sup>29</sup>
- c) Mobilization of platelet granules will increase neutrophil/ monocyte-activating pro-inflammatory reaction
- d) Chemokines and transforming growth factor (TGF)- $\beta$  level will get increase<sup>17</sup>
- e) Release of pro-inflammatory/pro-thrombotic, cytosolic group box 1 (HMGB1) protein (Kim *et al.*)<sup>24</sup>
- f) The increased (TGF)- $\beta$  will increase IL-6 by hepatic endothelial cells results in increased thrombopoietin and thrombocytosis and platelet activation<sup>44</sup>

#### *Fungal co-infections associated with Covid-19 patients :*

Fungal co infection is very common in patients of SARS-Cov-2. Zhang *et al.*,<sup>46</sup> reported that among 221 patients with Covid-19 infection, 3.2% were diagnosed with fungal co-infections. A study by Huttner *et al.*,<sup>21</sup> documented 11% of patients associated with fungal co infection. Sample analysis by Chen *et al.*,<sup>11</sup> in 99 Covid-19 patients reported the common fungi found were *Aspergillus flavus*, *Candidaglabrata*, and *Candida albicans*. Samples (Blood, sputum, and broncho-alveolar discharges) were collected from Covid-19 patients between 20 February 2020 and 30 April 2020 from the hospitals of UK for diagnosing fungal co-infections. These samples were tested for the presence of clinical deterioration in acute physiology, upward trend in inflammatory markers and new infiltrates on chest radiography. Along with these, standard microbiological methods were also preferred and confirmation was done by using

matrix assisted laser desorption/ ionisation-time of flight (MALDI-TOF). The results revealed that 21.4% candida co-infection was found with mild oropharyngeal thrush or pulmonary candidiasis and *Aspergillus fumigatus* reported with three patients<sup>20</sup>.

*COVID-19 associated invasive pulmonary aspergillosis (CAPA) :*

COVID-19 associated invasive pulmonary aspergillosis (CAPA) is another threatening infection in the Covid-19 patients. Immune dysregulation in patients leads to T-helper cells Th2 and Th1 responses; including the cytokine release syndrome which normally increases the risk of fungal co-infection in patients. The patients with Invasive Pulmonary Aspergillosis (IPA) or Invasive Candidiasis (IC) were reported to have higher pro-inflammatory (IL-1, IL-2, IL-6, tumor necrosis alpha) and anti-inflammatory (IL-4, IL-10) cytokine levels whereas there observed a drop in CD4 interferon-gamma expression, and lesser number of CD4 and CD8 cells. Samples collected from Covid-19 patients who were admitted at three Spanish hospitals were taken for lab study; many of these patients were reported with COVID-19 associated invasive pulmonary aspergillosis. The diagnosis is mainly by the detection of Galactomannan (GM) in both Broncho-alveolar lavage (BAL) serum and sputum. Those who reported with CAPA were also observed with intra-alveolar neutrophilic infiltration and vascular congestion. *Aspergillus fumigates* and *Aspergillus flavus* are the common causative agents of infection related with CAPA. Histopathological examination confirmed with bronchial wall ulceration, necrotizing pneumonia, and septate branching hyphae; the PCR-amplification helps in the

identification of the causative agent.

Case study of CAPA affected people reported at different countries was assessed by Armstrong *et al.*,<sup>4</sup>. The total number of patients infected with CAPA as follows; 8 from Belgium, 9 in France, 10 at Netherlands and 11 from Germany, these patients were intubated for speedy recovery. The same research group conducted one more case study and concluded that out of 33 people reported with CAPA, the age of people was around 55-75. Among these 33 people, few reported with many other co-morbidity issues and/or having weak immune system; this includes 16 (48%) had corticosteroids, 10 (30%) with diabetes, 9 with (27%) lung disease including asthma, bullous emphysema, pulmonary fibrosis, lung cancer. The mortality rate was found to be 63.6% (21 out of 33).

There are reports for the CAPA infections among the patients, samples collected across Asian hospitals<sup>10</sup>. The samples collected from 221 patients admitted at China hospitals also reported with CAPA; besides, 99 patients from the same hospital were identified to had infection with *A. flavus* from respiratory tract<sup>45</sup>. *Aspergillus* DNA was isolated from respiratory samples of patients admitted at Jiangsu Province of China<sup>46</sup>. Nasir *et al.*,<sup>31</sup> isolated *Aspergillus* sp. from tracheal aspirates (TA) of 9 patients and CAPA pathogens from 5 patients. The patients those who have CAPA are reported positive for galactomannan (GM) serological test. The detection of GM and 1,3- $\beta$ -d-glucan, as well as the fungal DNA in serum or in respiratory secretions gives information about CAPA. Observations are given in the following table (Table-1).



Table-1. Case study of CAPA with observed results and suggested medicines

Author	Patients with CAPA	Total No.of Patients	Total days at ICU	Culture reported	Treatment
2	9	27	5	<i>A. fumigatus</i>	CAS, VOR
24	1	5	2	<i>A. flavus</i>	ISA
27	1	1	3	<i>A. fumigatus</i>	VOR+CAS, AMB
30	9	23	16	<i>A. flavus</i> , <i>A. flavus</i> + <i>A. fumigatus</i> <i>A. fumigatus</i> + <i>A. niger</i>	VOR,AMB

Voriconazole (VOR), Capsfungin(CAS), Posaconazole, Isavuconazole (ISA), Echinocandins, amphotericin B(AMB) in combination with anti-mold azoles.

Diagnosis of CAPA includes different method and traditional practices such as collection of samples from the site of infection followed by microbiological and microscopic observation is time consuming as well as very challenging with respect to accuracy. Considering this, serological assays are most preferable method of diagnosis which includes specific assay for fungal antigens, including (1,3)-b-D-glucan (G), galactomannan (GM), and mannan (Mn). Detection of glucan (G) antigen and galactomannan (GM) antigen reported with 70-80% sensitivity for the conformation of CAPA belongs to serological tests and the sensitivity of mannan detection is 93%. Computed tomography (CT) chest imaging with *Aspergillus* antigen identification is one of the best method. Serum or BAL samples can also be checked for the detection and confirmation of antigen using Enzyme Linked Immuno Sorbent Assay (ELISA) or flow tests or PCR methods. A (1-3)- $\beta$ -D-glucan (BDG) test on a serum sample also used for diagnostic purposes.<sup>4</sup>

*Rhino-orbito-cerebral mucormycosis (ROCM):*

Rhino-orbito-cerebral mucormycosis

(ROCM) is a type of fungal infection which affects the eyes of people especially the Covid-19 patients. These are common opportunistic fungi in our body and the active immune system generally regulates the number of this flora. With the obstruction in the immune system or in immunogenic individual, these fungi commonly induce the opportunistic infections leading to severe complications. Usually, the mode of attack is they invade by surrounding blood vessels and resulting tissue necrosis and severity results in death. These causative agents are well existing in the air and will get deposit at nasal cavity and adjoining sinuses. The spores when germinates develops the hyphal (filamentous processes) outgrowth as well releases destructive enzymes which normally digest the host tissue, thereby providing nutrition to the rapidly growing fungi. When it grows through nasal cavity it destroys the surrounding cavity and sinuses. It also destroys hard palate, the orbital bones, and the skull base bones and produces black discharges at nasal and oral cavity. Once it made entry to eye socket, it results in bulging of the eyes, pain, frozen eye movements, and

blindness. If it invades the major arteries and venous, it may end up in major health problems by inducing brain strokes and other life threatening issues. This infection is not very highly contagious; however, personal hygiene and protection is most important. The ROCM are accurately diagnosed by Magnetic Resonance Imaging (MRI) and CT scans. Delaying the treatment as well as improper care may result in the mortality that ranges between 25 to 90%.

Now reports also documented the high possibility of acquiring this infection in Covid-19 patients during hospitalization or after discharge in an unclean atmosphere. However, the major reasons for ROCM in Covid-19 patients are as follows:

- 1) Damaged airway mucosa and blood vessels favoring the entry of fungus
- 2) After Covid-19 infection, increased iron content of blood will favor the fungal growth
- 3) Intake of steroids will enhance sugar level in the body and increase the chance of infection
- 4) Continuous intake of antibiotics will kill the useful microflora which provide immunity
- 5) During artificial ventilation, the humidifier water that present along with oxygen may result in transmission of fungus

Common treatment includes removal of affected region through surgery and decompression will prefer if it is spread to brain. Amphotericin B is the first choice of drug and if patient cannot tolerate posaconazole or isavuconazole tablets may be given.

Recently reported Mucormycosis or

Zygomycosis-Black fungus infection, white fungus and yellow fungus with Covid-19 patients.

In India, second wave of SARS-Cov-2 infection reported with different co-infections mainly with black fungus and white fungus. This is called as mucormycosis and earlier it was reported as zygomycosis. The spores normally present in soil, leaves and decayed woody items. Besides the regular skin darkening, inflammatory responses, redness, ulceration and fever, it also invades the major functioning organs like eyes, lungs, skin and brain which need special attention and proper treatments.

According to Indian Council of Medical Research (ICMR) guidelines, here are the major risk factors associated with mucormycosis infections in Covid-19 patients:

- i. People with diabetes mellitus
- ii. Patients taking steroids to control Covid-19 infection or preexisting infections
- iii. Admission in ICU for prolonged time
- iv. Those who undergone organ transplantation and any surgery
- v. Already taking antifungal or antibiotic drugs

The symptoms of the black fungus infection reported as

- i. Sinusitis and clogging of nasal tract with bloody or blackish fluid from nose
- ii. Pain at one side of face or cheek bone and lack of sensation
- iii. Black colour appearance on the nose bridge
- iv. Blurred vision with eye pain
- v. Abnormal thrombosis of tissue with

- necrosis of dermal cells
- vi. Improper respiratory function, chest pain, coughing and bleeding

How to control or prevent mucormycosis

- i. Hygienic practices
- ii. Wearing protective items while going out or interacting with outside people
- iii. Avoid accumulation of moisture in the body
- iv. Oral administration of antifungal drugs as well as intravenous dosages if it needed

The fungal mould belongs to white and black present in the environment and cause infection called as “Mucormycetes”. Recently, an infection called white fungus has also been found to affect some people those who are suffered with Covid-19. This was first reported at Patna, Bihar, India, and the physicians reported that this particular infection is more dangerous than black fungus infection. The persons with weak immunity and those who get contact with the objects carrying the moulds are well at possible risks of getting infections; normally the infections appears in nail, skin, private parts and mouth and spread to various internal organs like kidneys and brain even. A detailed CT-Scan or X-ray is however suggested for proper diagnosis. If the patient is showing negative for Covid-19 test but having infections at lungs and similar symptoms of Covid-19, then it may be due to the fungal infections; in this case serological test are required for the patient for further treatment. The patients under intubation and those who are with weak immunity and co-morbidity such as diabetes, cancer and those under steroids are at high risk of infection. First case of yellow fungus has been reported from Ghaziabad, in India. Symptoms are weight loss and formation of

pus. More details aren't very clear for this infection.

Covid-19 associated oropharyngeal candidiasis (OPC)

The Covid-19 patients who are immune compromised or with poor immune functioning are probably at the high risk of getting infections with *Candida albicans*; besides being severe, the chances for mortality is very high. The people those admitted for mechanical ventilation acquire this infection through denture wearers to oral region. *C. albicans* is normally considered as opportunistic pathogen; however, their virulence depends on the chances of developing multidrug resistance. Considering these points, it is imperative for prevention measures and much attention should be focused in avoiding this infection among Covid-19 patients. The accumulation of *Candida* sp. at lower respiratory tract in Covid-19 patients of critical care unit was reported by few researchers<sup>16,34</sup>. Another study reported that OPC is the main reason for nosocomial pneumonia in Covid-19 patients<sup>36</sup>.

This infection normally starts with colonization of pathogens at oral mucosa and the common symptoms includes discomfort, change in taste, oral burning, glossodynia, dysphagia and difficulties in breathing<sup>37</sup> and this infection was found in 70.7% of Covid-19 patients who were in the age group of 50. The Infection starts from oropharynx to the esophagus or systematically through the bloodstream or upper gastrointestinal tract. Different forms of OPC were observed includes acute pseudo-membranous candidiasis, acute atrophic candidiasis, chronic form, as chronic hyperplastic candidiasis, chronic atrophic candidiasis and the details are given in the following table (Table-2).

Table-2. Types of candidiasis infection, symptoms and suggested treatments

Type of candidiasis	Clinical features	Symptoms	Treatment
Acute pseudomembranous Candidiasis	Attack on the surface of lip and buccal mucosa, tongue, periodontal tissues, and oropharynx Yellow or white plaque formation	Burning and dysphagia	Topical antifungal application according to patients' health
Acute atrophic candidiasis	Attack on mucosa and back of tongue	Burning while eating of acidic or hot food	Topical antifungal application based on the health of patients
Chronic hyperplastic candidiasis	Attack on mucosa and border of tongue	Burning while eating	Topical antifungal application
Chronic atrophic candidiasis	Stony appearance with red colour inside mouth	Pain, Irritation and discomfort in saliva secretion	Topical antifungal application
Median rhomboid glossitis	Tongue and anterior papilla		Topical antifungal application
Angular cheilitis	Symmetrical area of mouth		Topical antifungal application

Choice of treatment is topical antifungals such as nystatin, disinfectant agents such as 0.12 or 0.2% chlorhexidine<sup>3</sup>. Those who are at high risk of infection the preference of antifungal includes combination of 2 drugs: clotrimazole, in the form of an oral tablet or 10 mg pills, administered 5 times a day for 14 days, or fluconazole, at a dosage of 50–100 mg daily for 7–14 days<sup>1</sup>. Nystatin recommended with less side effect<sup>42</sup>. The personal hygiene is very much appreciable like cleaning of tooth, cavity, and tongue, dentures, cleaning of cavity with smooth brush using 0.5% sodium hypochlorite solution or 0.12% chlorhexidine for 10 min in order to overcome or minimize the infection.

A case study in 2020 for the identification of candidacies in Covid-19 patients and the observed study results are presented below for deeper understanding: Medical report of patient at the age of 76 with SARS-CoV-2 infection who admitted at ICU showed that leukocytosis (12,000/mm<sup>3</sup>) with neutrophilia (10,000/mm<sup>3</sup>) and lymphocytopenia (500/mm<sup>3</sup>). Results showed elevated inflammatory markers C-reactive protein (CRP) of 199 mg/l, d-dimer of 80, ferritin of 1240 µg/l, lactate dehydrogenase (LDH) of 565 IU/l and Ca of (1.94 mmol/l). The blood culture of this patient was reported with the presence of *C. albicans*. Similarly, another patient in the age of 68 died due to Covid-19

and candidiasis with estimated glomerular filtration rate (GFR) of 53.

#### *Covid-19 Associated Candidiasis (CAC):*

Multi drug resistant *C. auris* and *C. glabrata* was isolated by Arastehfar *et al.*,<sup>2</sup>. Fluconazole-resistant *C. parapsilosis* and *C. tropicalis* and *C. krusei* were also reported by the same researcher and colleagues. In general the sharp drop in the Neutrophils, monocytes or macrophages in Covid-19 patients enhances the chances of candidiasis. Increased peripheral neutrophil-to-lymphocyte was also reported and reason for this is *Candida* infection. The study also discussed that extracorporeal membrane oxygenation (ECMO) is required for patients and which connected with vascular catheters. The common diagnosis for candida infections and associated mannan antigens are D-Glucan (BDG) and mannan antigen testing, Enzyme-linked immunosorbent assay (ELISA) kits, T2 *Candida* Panel (T2 Biosystems) and Echinocandins. The common medication choice for invasive *Candida* infections are fluconazole, liposomal amphotericin B, voriconazole, posaconazole and isavuconazole<sup>13,26,33</sup>.

#### *Pneumocystis jirovecii Pulmonary Coinfection in Covid-19 patients :*

Infection in Covid-19 patients with *Pneumocystis jirovecii* was reported by some researchers Cornely *et al.*,<sup>13</sup>; Koehler *et al.*,<sup>26</sup>; Pappas *et al.*,<sup>33</sup>. A 52-year-old male patient reported with infection and confirmed with RT-PCR, after 17 hrs patient passed away. Lab observation and examination of samples were reported with preexisting lesion because of

comorbidities, massive lung thromboses, alveolar exudate rich in foam cells, suprapleural and intra-alveolar *Pneumocystis jirovecii* cystic forms and bilateral adrenal hemorrhage. Cough, chest pain and fever was reported for the patient with other health risk includes heart disease, hypertension. Chest X-ray confirmed a pulmonary condensation in lungs. Laboratory tests revealed leukopenia with lymphopenia (white blood cells 1110/ $\mu$ L, lymphocytes 190/ $\mu$ L), thrombocytopenia (127.000/ $\mu$ L), prolonged prothrombin time (PT) (15.6 s), international normalized ratio (INR) 1.15, hepatocytolysis (aspartate aminotransferase 88.8 units/L, alanine aminotransferase 82.8 units/L), total bilirubin 2.88 mg/dL, reduced creatinine clearance (63.8 mL/min), nitrogen retention (creatinine 1.82 mg/dL), inflammatory syndrome (C-reactive protein 450 mg/L).

The Covid-19 and associated microbial co-infections generally impede the host immune system and their synergism causes much complicated clinical problems. Despite the rapid increase of mortality in covid-19 patients, proper data collection is required for the treatment and control. This review clearly discussed about possible microbial co-infections in SARS-CoV2 patients. Many reasons were reported for co-infections including disturbed or weak immunity of person, intake of steroids, antibiotics and mechanical ventilation. Still there are no proper treatments defined for co-infections, however, many physicians have discussed about number of guidelines for the treatment as well for the selection of antibiotics to managing people with SARS-CoV-2 infection and to control the pandemic situations. Few reports are available about covid-19 associated co-infections from global level, collection of clinical data is imperative

in developing appropriate guideline for further treatment to reduce the chances co-infection and mortality. Proper sample collections, diagnosis and effective serological tests will favor the identification and selection of appropriate spectrum of medicines. In addition, proper hygienic conditions may also help in containment of Covid-19 and associated co-infections. Further clinical studies should incorporate the rapid detection and treatment methodologies which can favor the effective management of pandemics.

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### Conflicts of Interest

There are no conflicts of interests

### Author contributions

Both the authors equally contributed to investigation, data curation, review and editing the article

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