# Imaging of Pulmonary Superinfections and Co-Infections in COVID-19

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New challenges in imaging and management of COVID-19 pneumonia emerge as the pandemic continues across the globe. These arise not only due to the COVID-19 pneumonia but also related to various superinfections and co-infections. Limited use of bronchoscopic and other aerosol generating procedures to obtain representative lower respiratory samples from these patient groups for accurate identification of organism, increases the responsibility of radiologists in suggesting the most likely cause of secondary infection. Imaging features of many of these infections overlap with features of COVID-19 pneumonia. In this review, we highlight imaging findings that can aid in the diagnosis of superinfections and co-infections in patients with COVID-19 pneumonia, and also help in predicting the likely causative organism.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially identified in December 2019 in Wuhan, China.[1] Since then, the virus has rapidly spread across the globe, predominantly transmitted through respiratory droplets or direct contact. After an interim decline in the number of cases in late 2020, there has been a surge in world-wide cases and deaths over the last 2 months especially the south-east Asia region, with over 2.6 million new weekly cases and over 72000 deaths reported in the second week of June 2021, with India accounting for 29% of weekly new global cases at present.[2] Co-infections and secondary infections are major contributors to mortality and extended hospital stay. Factors contributing to increased susceptibility to secondary infections in patients with COVID-19 pneumonia includes overuse of corticosteroids, immunomodulatory drugs like tocilizumab, prolonged ICU stay, pre-existing or acquired virus induced immunesuppression and overall poor hygiene practices. The term 'coinfection' refers to infection that occur simultaneously when the COVID-19 is active and are detected at the outset when a patient presents to the hospital. While superinfection/secondary infection is the one that occurs in succession to the primary COVID-19 infection and is the more common form encountered.

In non-COVID patients, obtaining lower respiratory tract samples were a common practice in an intubated patient, either as tracheal aspirate or bronchoscopic guided from a particular infected lobe for staining and culture/sensitivity. However, in COVID-19 pneumonia, this strategy needed to be modified due to the risk of these aerosol generating procedures posing a risk of increased transmission of the virus. Induced sputum in a non-intubated patient is also not routinely practiced. Hence, there is increased reliance on imaging (particularly CT chest) to predict the organism causing the secondary infection. In this review, we highlight the certain imaging features which are helpful in diagnosis of superinfections and co-infections in patients with COVID-19 pneumonia.

*Incidence* − A metanalysis of 30 studies published in August 2020 on co-infections in people with COVID-19, reported an overall 7% of bacterial co-infections in hospitalised patients, 3% were viral and 3 studies reported fungal coinfections[3]. In the setting of healthcare associated infections (HCAI), the gram negative bacteria(GNB) and fungi dominated the secondary infections. In another study of 3028 patients, overall rate of infection was 17% and 57% were caused by GNB and 19 % by fungi.[4]

## Causative Organisms

Organisms responsible for co-infections/secondary infections in COVID-19 patients include bacteria, viruses, fungi and rarely parasites. Table 1 enlists the common respiratory co-pathogens reported in COVID-19 according to likely timing of occurrence.[3-5] Polymicrobial infections may also occur.

## Imaging Features of Specific Infections

### Bacterial Infections

The incidence of bacterial co-infection and superinfection varies in different reported series in literature. It depends on various factors, such as clinical severity of SARS-CoV2 infection, steroid use, presence/ absence of lymphopenia and empiric use of antibiotics prior to hospital admission. The bacterial superinfection rate is higher in patients who are critically ill, in ICU settings, and have lymphopenia.[6]

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**TABLE 1**
Common respiratory co-pathogens reported in COVID-19

| Organism | Community acquired pneumonia/ Infections occurring within 48 hours | Hospital acquired pneumonia/ Infections occurring after 48 hours |
| --- | --- | --- |
| Bacteria | Mycoplasma pneumoniae | Gram-negative bacteria |
| | Pseudomonas aeruginosa | -Klebsiella spp. |
| | Streptococcus pyogenes | -Escherichia coli |
| | Haemophilus influenzae | Enterobacter sp |
| | Staphylococcus aureus | Acinetobacter baumannii |
| | Streptococcus pneumoniae | Serratia marcescens |
| | Proteus mirabilis | Staphylococcus aureus |
| | Chlamydia spp | Pseudomonas aeruginosa |
| Fungi | Pneumocystis jirovecii | Aspergillus flavus Aspergillus fumigatus |
| | Histoplasma capsulatum | Candida albicans Candida glabrata |
| | Cryptococcus neoformans | Rhizopus, Mucor |
| Viruses | Dengue virus | Respiratory syncitial virus |
| | | Influenza A |
| | | Rhinovirus/ enterovirus |
| | | Influenza B |
| | | Parainfluenza |
| | | Other coronaviridae |
| | | Adenovirus |
| | | Human Metapneumovirus |
| | | Epstein-Barr Virus |
| | | Coxsackievirus |
| | | Cytomegalovirus |
| Others | Mycobacterium tuberculosis | |
| | Plasmodium spp. | |
| | Strongyloidis stercoralis | |

Note-Some of the organisms can present as both Community acquired pneumonia and hospital acquired pneumonia.

The mechanism of bacterial superinfection in SARS-CoV2 is poorly understood; but thought to be similar, in a way, to influenza. The damage to the respiratory epithelial cells makes it easier for the nasopharyngeal commensal bacteria to be aspirated; and thereafter to penetrate the damaged mucosal lining.

Diagnosing a bacterial superinfection is challenging; as clinically differentiating the cause of respiratory distress is not easy. Worsening of SARS CoV2 itself can cause exacerbation of respiratory distress. Laboratory test reflective of a bacterial superinfection is a neutrophilic leukocytosis; whereas in COVID itself there is lymphopenia with no increase in neutrophil percentage. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may not always be very useful; especially in patients who are on anti-IL6 (Tocilizumab) treatment as these may be elevated even in absence of infection. Patients treated with Tocilizumab also may not manifest signs of sepsis.[6,7] Procalcitonin is a serum marker, which rises as early as 2-4 hours after infection, and peaks within 12-24 hours. Its levels are usually normal in mild COVID infection; however can be elevated in severe infections. Using procalcitonin as a marker of infection in the setting of COVID has fallacies, as it can be raised in severe COVID infection itself, acute respiratory distress syndrome (ARDS) and in other conditions such as end stage renal failure. Also, many authors have reported normal procalcitonin levels in proven bacterial superinfections; which is thought to be mediated by high TNF.[8,9] Hence the pointers to suspect a bacteria, superinfection are: new onset of fever, change in character of sputum, new onset of leukocytosis of neutrophilia, new increase in oxygen requirement, or appearance of new imaging findings.

Causative bacteria are also variable across various studies; mostly gram-positive cocci such as Staphylococcus aureus, Streptococcus pneumoniae and gram-negative bacteria (GNB) such as Haemophilus influenzae are the common pathogens to cause early superinfection. Late superinfections are commonly caused by Pseudomonas, Klebsiella pneumonia, Escherichia coli, Enterobacter spp. and Acinetobacter baumannii. Imaging features in bacterial superinfection can be variable, and may often be difficult to diagnose in presence of pre-existing COVID pneumonia, especially when bilateral. Serial chest radiographs (CXRs) are helpful in detection of new imaging findings.[10] However, presence of a lobar consolidation with air bronchogram can be highly suggestive of a bacterial superinfection. This is particularly so when it is unilateral, associated with necrosis with or without cavitation. (Fig 1) Hematogenous spread may result in multiple nodules with cavitation, as in septic emboli due to staphylococcus aureus (Fig 2). Unilateral pleural effusion also favors bacterial pneumonia. Adjoining pleural effusion that has empyema like features (loculations, thickened pleura, mottled air lucencies) favors superadded infection (bacterial or fungal).

Infection with gram negative bacteria can present with a large area of consolidation with areas of breakdown (necrotizing pneumonia) (Fig 3). Pleural effusion or empyema may be associated. Extensive new onset bilateral consolidations may also be seen, often in non-dependent areas (Fig 4). Infection with mycoplasma pneumoniae may show bronchial wall thickening with centrilobular nodules and peribronchovascular distribution of consolidations/GGOs.[11]

Table 2 describes imaging differences between GPC and GNB infections.[12]

### Fungal Infections

Airway epithelial damage caused by SARS-Cov-2 virus increases susceptibility to invasion by various fungi, especially aspergillus and mucor. COVID-19 is recognized as one of the predisposing host factors, besides the additive factors discussed above under bacterial infections.[13] Superadded fungal infections significantly contribute to increased mortality amongst patients admitted in critical care units. Obtaining mycological evidence can be particularly challenging since the use of bronchoscopy techniques is limited in the setting of COVID-19 pneumonia, and CXRs and CT may be the initial investigations done which identify the abnormalities to raise suspicion of the invasive fungal disease.

### Mucormycosis

Mucormycosis refers to a group of infections caused by filamentous fungi which includes Rhizopus, Mucor and Lichtheimia (Absidia). COVID-19-associated mucormycosis (CAM) has been observed with increased prevalence as compared to pre-covid times, especially in some countries such as India. Apart from diabetes and corticosteroid
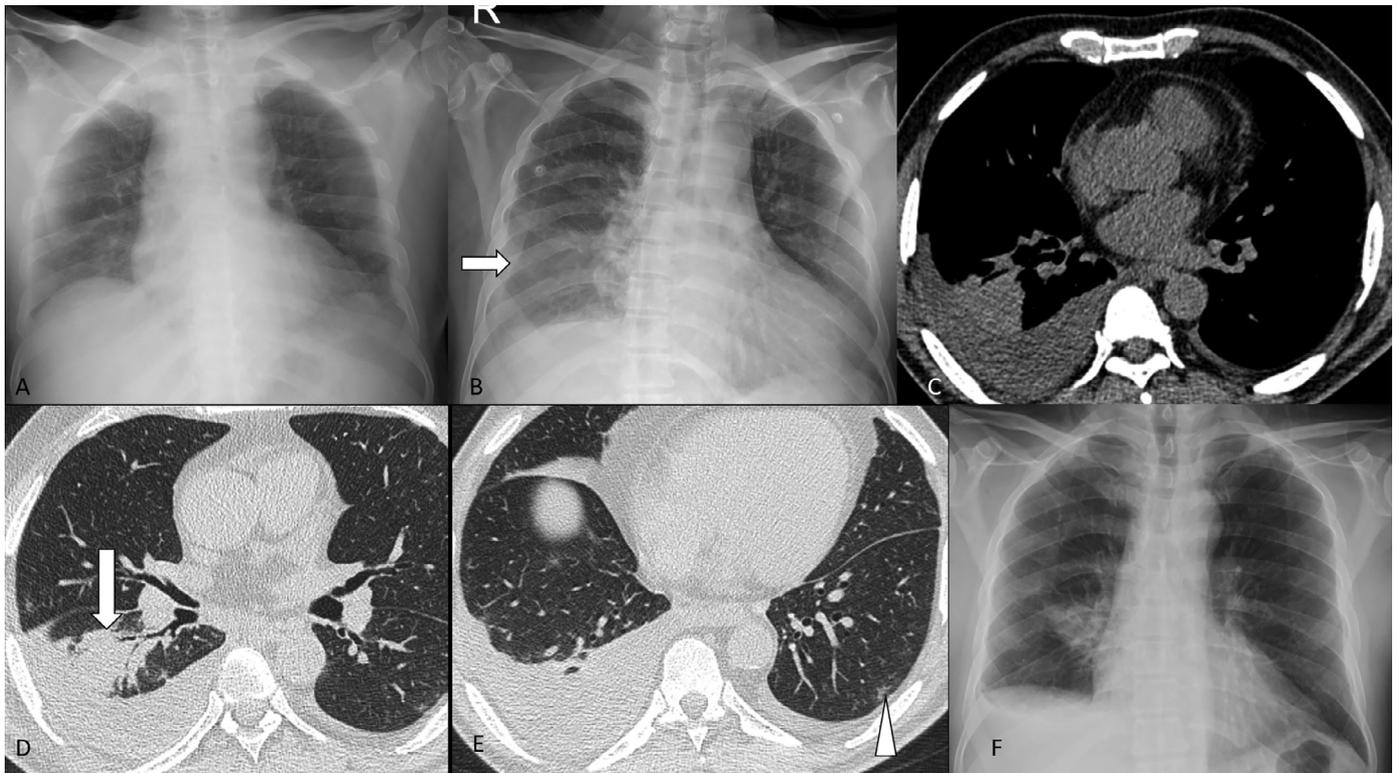
**FIG. 1. Bacterial superinfection in COVID-19.** A 55-year-old male affected with COVID-19. A,B. Chest radiograph (CXR) on the day of COVID positive report (A) showed no parenchymal changes. On day 5 of illness, patient developed right sided chest pain and CXR showed right lower zone consolidation with pleural effusion(arrow) (B). C,D. CT revealed subsegmental consolidation with air bronchograms in superior segment of right lower lobe (arrow in D) with mild parapneumonic effusion. Sputum culture grew Klebsiella pneumonie. E. Mild COVID related subpleural ground glass opacities were noted in left lower lobe (arrowhead). F. Follow-up CXR after 15 days of antibiotics showed resolution of effusion and residual organised area of consolidation and patient became asymptomatic.

use, COVID-19 itself has been recognized as important etiology predisposing patient to mucormycosis.[14]

Rhino-orbital-cerebral involvement is the predominant site for mucor infections in patients with COVID-19. Pulmonary involvement is less common, however is associated with rapid clinical deterioration and worse prognosis. Biomarkers for diagnosing invasive aspergillosis, such as beta-d-glucan and galactomannan, are typically negative in patients with mucormycosis.

On CT, presence of a large area of mass like consolidation with 'reversed halo sign' or 'bird nest sign' should raise the suspicion for

CAM.[15] Reversed halo sign, though is also reported with COVID-19 itself as well as IPA, its presence is more common in mucormycosis then IPA.[16] The large areas of consolidation tend to undergo central cavitation forming a thick wall cavity (Fig 5). Transfissural extensions and chest wall invasions are features for this aggressive nature of CAM (Fig 6). These are also prone to vascular complications such as pseudoaneurysm formation or thrombosis of pulmonary vessels. When a CT pulmonary angiogram is performed, thrombosed pulmonary vascular branches may be visualized within the area of mass like consolidation. Distinguishing CAM from a pulmonary infarct may
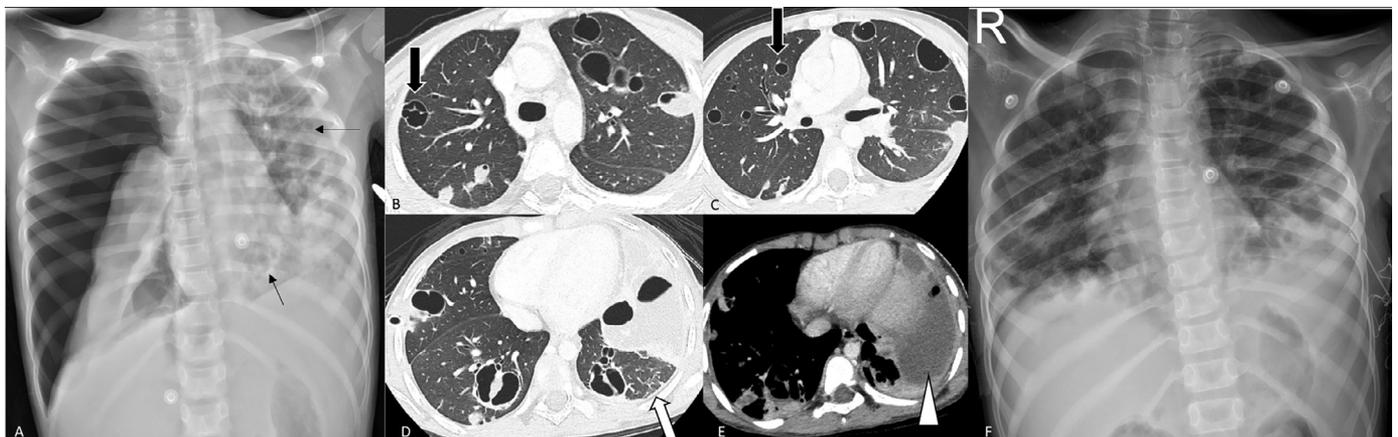


**FIG. 2. Gram positive bacterial infection.** An 8-year boy in third week of COVID-19 illness, presented with sudden respiratory distress. A. CXR shows diffuse alveolar opacities in left lung with multiple cavities (arrows) and right sided pneumothorax. B,C,D. CT done after 6 days of drainage of pneumothorax, revealed multiple thin walled cavitary nodules in bilateral lungs with peripheral predominance (black arrows). COVID related lung background lung changes were also seen (white arrows). E. Infected left pleural fluid collection (arrowhead) was also noted with enhancing parietal pleura. F. Chest tube was inserted on left side and drained pus. Blood culture grew staphylococcus aureus.
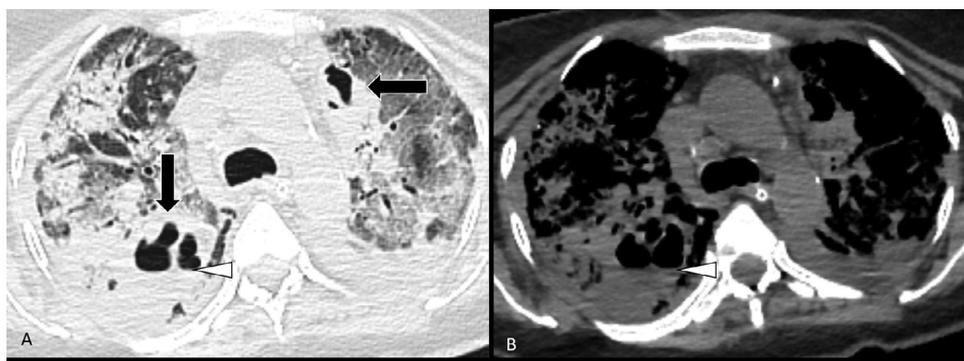
**FIG. 3. Gram negative bacterial infection.** A 48-year-old female presented with respiratory status worsening post 15 days of COVID-19 pneumonia. A,B. In the background of COVID lung, CT showed two large necrotizing consolidations in bilateral upper lobes (arrows). Air-fluid level was also identified in right upper lobe cavity (arrowhead). Serum Galactomannan was within normal limits. Endotracheal aspirate culture grew Acinetobacter baumannii and Burkholderia cepacia.

be difficult in such situations. CAM may also present as multiple cavitating nodules. Management in pulmonary CAM constitutes early initiation of antifungal therapy and surgical removal of involved lobe in case of single lobar disease. Drug of choice is intravenous liposomal amphotericin B; followed by posaconazole or isavuconazole as a step-down therapy or in those patients not responding to amphotericin. Surgical intervention, though recommended, is also limited in CAM due to underlying poor lung function caused by COVID-19 pneumonia.

*Aspergillosis*

Aspergillus infection in COVID-19 patients has been reported with species aspergillus fumigatus, aspergillus flavus or aspergillus terreus. Incidence varies between 19.6% to 33.3% in patients with COVID-19, with a high mortality rate of 64.7 %.[17,18] The invasive forms of aspergillosis includes airway invasive and angioinvasive types.The types of COVID-19-associated invasive pulmonary

aspergillosis (CAPA) are classified into two forms, pulmonary and tracheobronchial forms.[19] However, patients may have pre-existing non-invasive forms of aspergillosis such as aspergilloma, allergic bronchopulmonary pulmonary aspergillosis or colonization.

*Tracheobronchial form:* This form is usually defined on bronchoscopy by direct visualization of ulceration, pseudomembrane, plaque or eschar. On CT, the irregular thickening of the tracheobronchial walls, presence of extraluminal air pockets communicating with the airway lumen representing ulcerations or multifocal nodular mucosal thickening may be identified.

*Pulmonary form:* Recently, European Confederation of Medical Mycology and the International Society for Human and Animal Mycology Working Group (ECMM/ISHAM), have given guidelines wherein, in the background of typical ground glass opacities and areas of crazy-paving/ organizing pneumonia, the presence of nodular infiltrates, large nodules, nodules with halo sign/reversed halo sign, cavitation with air crescent sign should raise the suspicion for
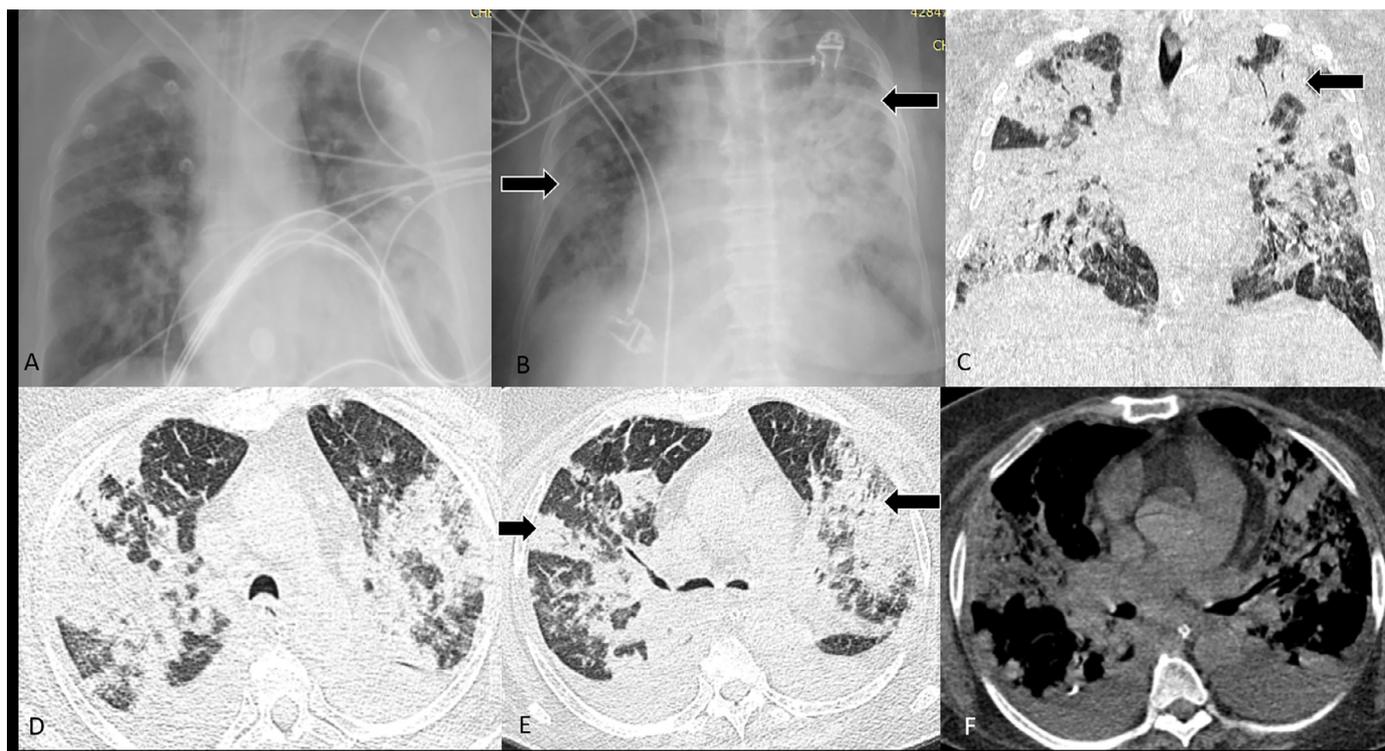


**FIG. 4. Gram negative bacterial infection.** 70-year-old female intubated due to COVID-19 pneumonia. A. CXR on the day of admission shows bilateral consolidations (Left > right). B. After initial improvement for 15 days, there was sudden onset respiratory worsening and CXR at this time revealed new consolidations in both lungs (arrows). C,D,E,F. Multifocal non-necrotizing consolidations seen in both lungs in non-dependent areas (arrows) with bilateral pleural effusions. Endotracheal aspirate yielded Acinetobacter baumannii.

| Gram-positive cocci infection | Gram-negative bacterial infection |
|---|---|
| • Lobar pneumonia (Usually unilobar) <br> • Round pneumonia <br> • Abscess formation common <br> • Cavitation/pneumatocele formation common <br> • Unilateral pleural effusion/empyema is more common | • Multilobar involvement with segmental consolidations <br> • Lobar consolidation with necrotizing areas <br> • Surrounding ground glass areas <br> • Pleural effusion, empyema or infected pleural fluid collection. |

CAPA[19] (Fig. 7 and 8). However, a recent study comparing influenza-associated pulmonary aspergillosis (IAPA) Vs CAPA showed that CAPA failed to show typical imaging features with none of the patients displaying well circumscribed nodules, cavitation, air-crescent sign or tree-in-bud sign.[20] In the author's experience, presence of centrilobular nodules, enlarging consolidation and halo sign should alert to CAPA. Further, any consolidation with or without cavitation not responding to antibiotics should be worked up for fungal infection as CAPA may not show classical signs of invasive pulmonary aspergillosis.

In addition to nodules, asymmetric, segmental areas of consolidation with central hypodensity may be seen. Multiple centrilobular clustered nodules and bronchial wall thickening and peribronchial ground glass opacities are seen in airway invasive forms (Fig 9). If serial imaging is available, the enlarging cavitary nodules or development of thick irregular walls may point towards diagnosis. Vascular complications such as pseudoaneurysm formation may also be seen (Fig 10).

There are no reports in literature of pre-existing aspergillus lung disease worsening or changing to invasive forms in COVID-19 patients. However, in the author's experience, patients with post tubercular sequelae and fibrobronchiectasis/ fibrocavitary changes have presented with enlarging masses in the area of the scar, subsequently proven as aspergillosis (Fig 11). It is hence possible that aspergillus present as colonizers in the walls of dilated bronchi/cavities have accelerated growth in response to COVID-19 and steroid induced immune suppression.

Supportive clinical and mycological evidence required to suggest appropriate probability of CAPA are summarized in Table 3. Imaging differences between pulmonary CAM and CAPA are described in Table 4.

*Candidiasis*

Unlike Aspergillosis, candidiasis is a relatively less common cause of co-infection in COVID-19. However, as in other immunocompromised states, hospitalized patients of COVID-19 are at higher risk of invasive candida infection. The predisposing conditions include presence of multiple intravenous catheters, parenteral nutrition, mechanical ventilation, steroid and broad-spectrum antibiotics use. Use of Tocilizumab has also been reported to be another predisposing factor in invasive candida infection. Causative species include *Candida albicans, Candida tropicalis, Candida glabrata, Candida parapsilosis.*[21,22]

Invasive candidiasis may either present as candidemia and multiple organ infection; or a much less common candida pneumonia. *Candida albicans* is the commonest causative organism, and occurs after colonization of the indwelling catheters. *Candida parapsilosis*, on the contrary, is a normal commensal of the human subungual space; and most transmission happens through contaminated hands of the caregivers. Candida pneumonia is much less commonly encountered; even though various candida spp. can be identified from respiratory tract samples due to colonization rather than true invasive candidiasis.[23,24]

Irrespective of the mode of acquisition; the pulmonary manifestations of candidiasis are protean. The CT imaging findings may be multiple random nodules, large cavitation nodules, or consolidation
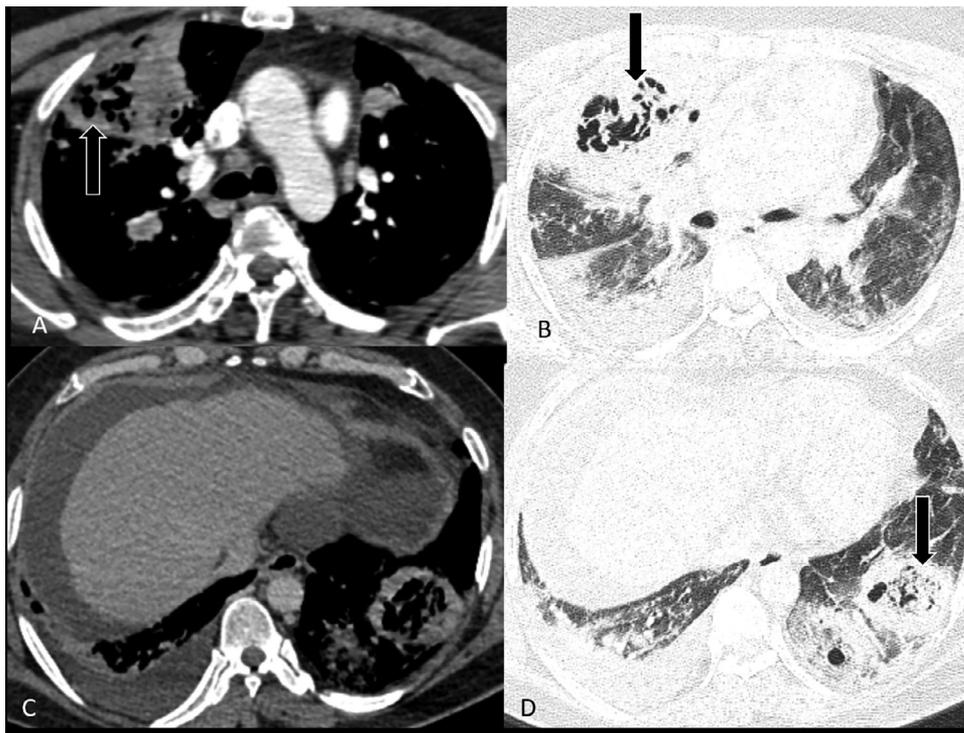


**FIG. 5. COVID associated Mucormycosis.** A 33 year old male with COVID-19 pneumonia, presented to emergency with worsening respiratory distress and nasal blockage after 25days of illness. A-D. CT showed multiple large, thick-walled cavities with internal irregular septations giving a bird's nest appearance (arrows). Right mild pleural effusion was also noted. Culture from nasal mucosal biopsy grew *Rhizopus arrhizus (Mucor).*
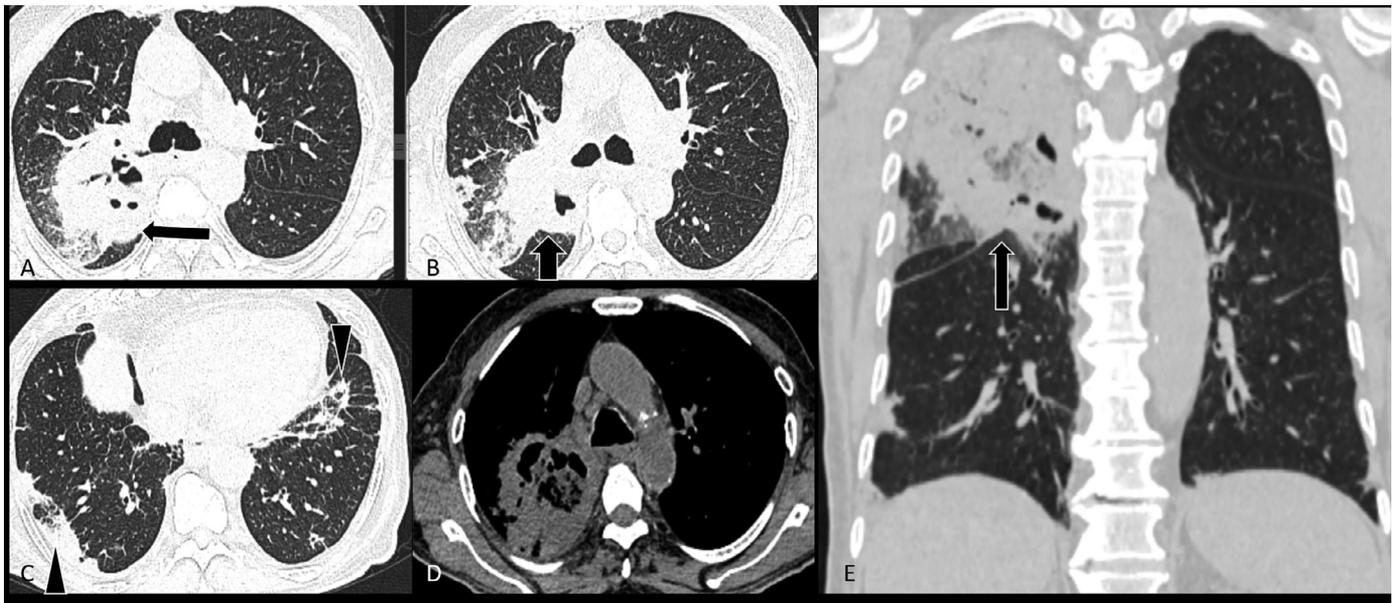
**FIG. 6. COVID associated Mucormycosis with fissural extension.** An 80-year-old male presented with persistent high-grade fever, not responding to antibiotics, after one month of being tested positive for COVID-19. A-E. CT shows large, cavitary mass-like consolidation in right upper lobe with surrounding ground-glass opacities. This was seen infiltrating the right major fissure medially and posteriorly (black arrows) and extending across to involve superior segment of right lower lobe. Lower lobes showed COVID-19 associated sub-pleural areas of organizing pneumonia (arrowhead).

(Fig 12.) [25] Candidemia requires antifungal treatment; but respiratory colonization does not warrant antifungal therapy; as candida pneumonia is a rare occurrence in patients with asymptomatic respiratory tract colonization by candida.[26]

### Pneumocystis Jirovecii Pneumonia (PJP or PCP)

Diagnosing PCP in a patient with COVID-19 is particularly challenging since both diseases show similar clinical presentation as well as imaging findings. Comorbidities such as cardiovascular disease in COVID-19 infected patients is recognised as an important risk factor for infection with *Pneumocystis jirovecii*.[27,28] In absence of pre-existing immunodeficiency, occurrence of PCP pneumonia is very uncommon; only 3 cases were detected in a study of 423 BAL samples in patients with severe COVID-19 in one of the studies.[29] Imaging features overlap with COVID-19 in the form of ground-glass opacities with interlobular septal thickening. Cyst formation may also be seen. Few reports also suggest HIV testing in all patients of COVID-19 pneumonia since other infectious etiologies are often overlooked and leads to delayed management of the potentially treatable causes.[30]

### Viral Infections

Viral pathogens reported are implicated in co-infections rather than superinfection with COVID-19, and the pathogens reported in



**FIG. 7. Aspergillus infection in COVID-19.** 60-year-old -female, post COVID-19 pneumonia, presented with new onset fever. A-D. CT showed presence of diffuse ground glass opacities with reticulations and bronchial dilatation secondary to COVID-19 pneumonia. A focal consolidation with eccentric cavitation was seen in left upper lobe in subpleural location (arrows). Sputum KOH showed hyaline septate hyphae suggestive of aspergillus, and patient was started on antifungals.
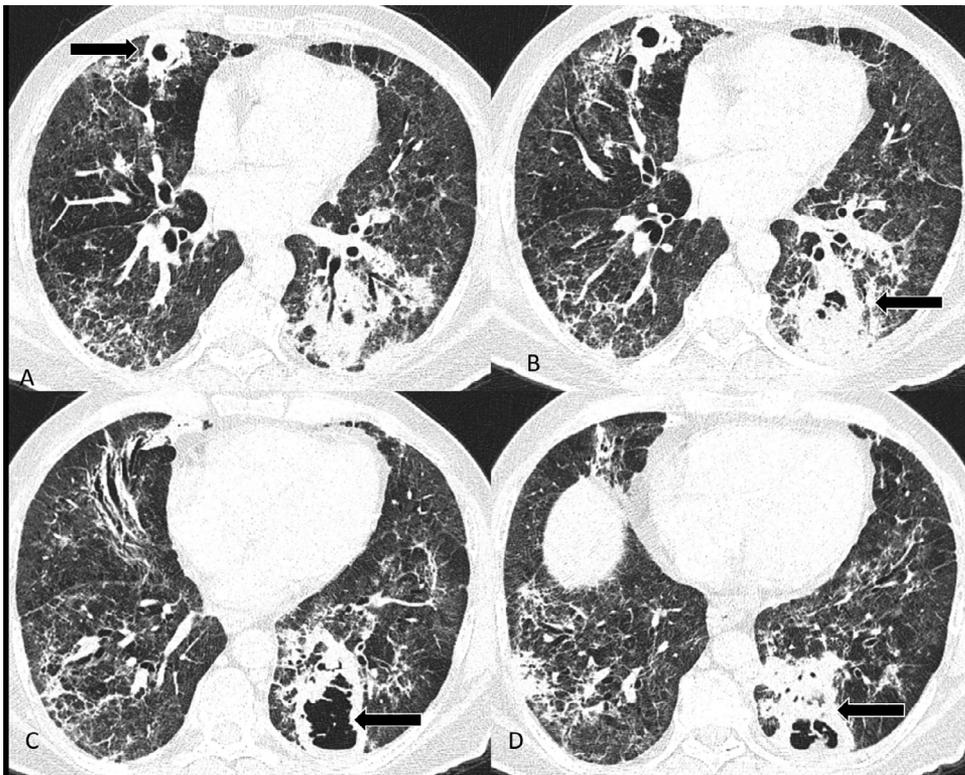
**FIG. 8. COVID-19-associated invasive pulmonary aspergillosis (CAPA).** 53-year male, developed increasing cough and new onset fever after 20 days of COVID-19 pneumonia. A-D. In the background of COVID-19 related lung changes of ground-glass opacities and reticulations, multiple cavitary nodules and consolidations were seen in bilateral lungs (arrows). Serum Galactomannan was negative; however, BAL culture yielded aspergillus fumigatus. This cavitary form is difficult to differentiate from mucormycosis on imaging.
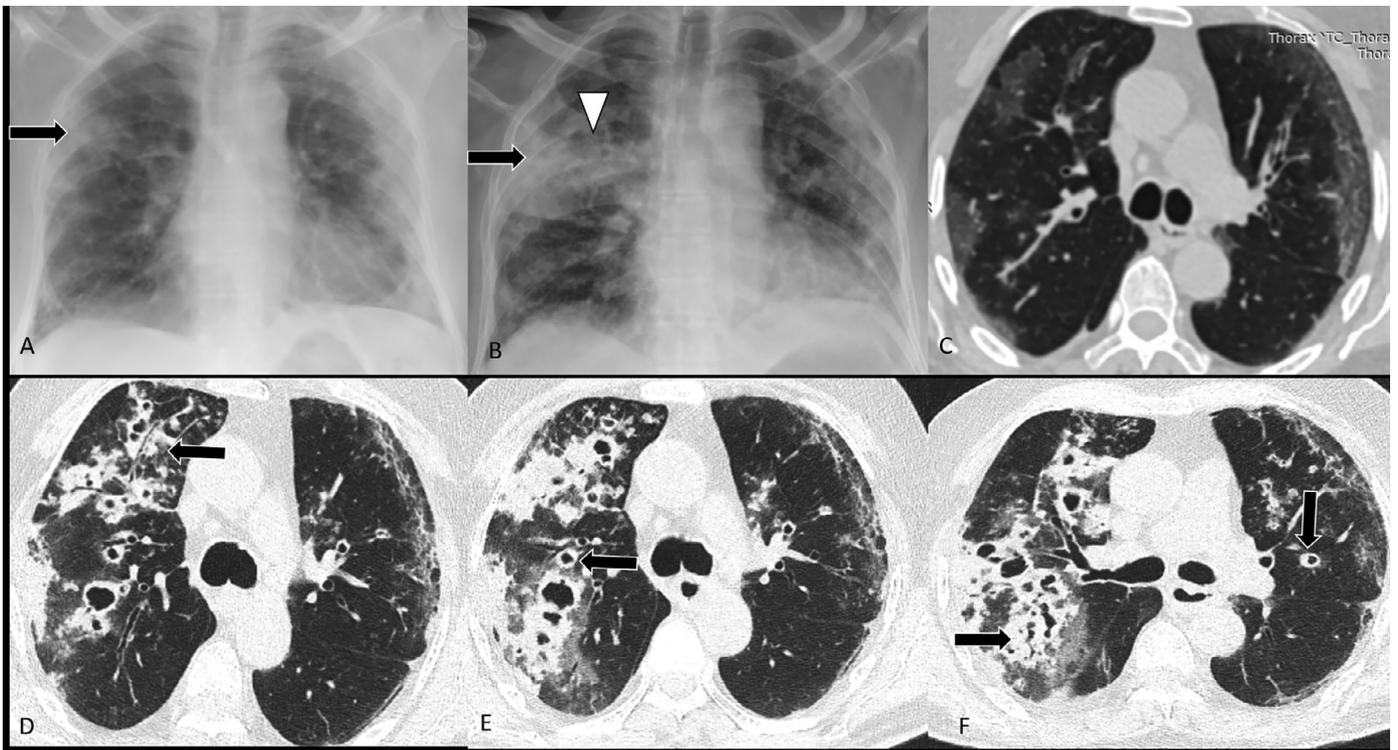


**FIG. 9. Airway invasive COVID-19-associated invasive pulmonary aspergillosis (CAPA).** 81-year-old male with COVID-19 pneumonia developed fever and respiratory distress one month post COVID illness. A,B. CXRs acquired 15 days apart shows a progressive consolidation in right upper zone (arrows) with internal cavitations (arrowhead). C. Initial CT during COVID illness showed typical subpleural GGOs in bilateral lungs. D,E,F. CT done 20 days later revealed peribronchial thickening and peribronchial consolidations (arrows), with cavitations and surrounding ground glass opacities suggestive of airway invasive aspergillosis.
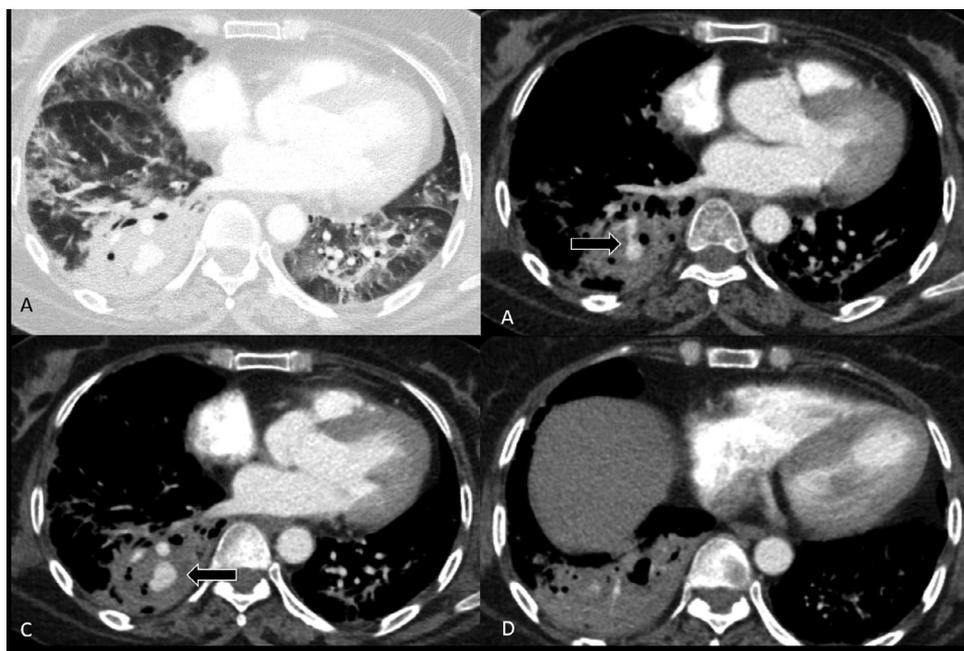
**FIG. 10. Vascular complications in fungal infections.** 40-year male with COVID-19 pneumonia presented with hemoptysis. A-D. CT angiography showed necrotizing consolidation in right lower lobe with pseudoaneurysm arising from segmental branch of right descending pulmonary artery (arrows). Sputum culture yielded aspergillus fumigatus.

various studies are variable. While Lansbury et al reported influenza virus A and B, and Respiratory syncytial virus (RSV) to be the commonest viruses causing coinfection; other studies have shown entero/rhinovirus or non-SARS CoV2 coronavirus to be more common.[31] Because of the overlapping clinical and imaging features of other viral coinfection, COVID infection may not be diagnosed at an early stage.[18] Other than elderly patients; even children and middle-aged adults are also at risk of coinfections.[32] The causes of viral coinfection may be multifactorial: damage to the respiratory epithelium, or overall lowered immunity in viral infections.

Several laboratory markers such as D-dimer, lactate dehydrogenase (LDH), ferritin and troponin are elevated in severe SARS CoV2; lymphopenia is also encountered. However, some other viral infections may cause confounding results. Adenovirus coinfection can cause increased D-dimer, ferritin and LDH. Lymphopenia and thrombocytopenia can be associated with other viral infection such as dengue fever.

Influenza is one of the common coinfection in SARS CoV2. The possibility of a protracted course is common in influenza and SARS-CoV2 co-infection; rather than influenza alone. While the symptoms of both are overlapping; influenza has a much less mortality
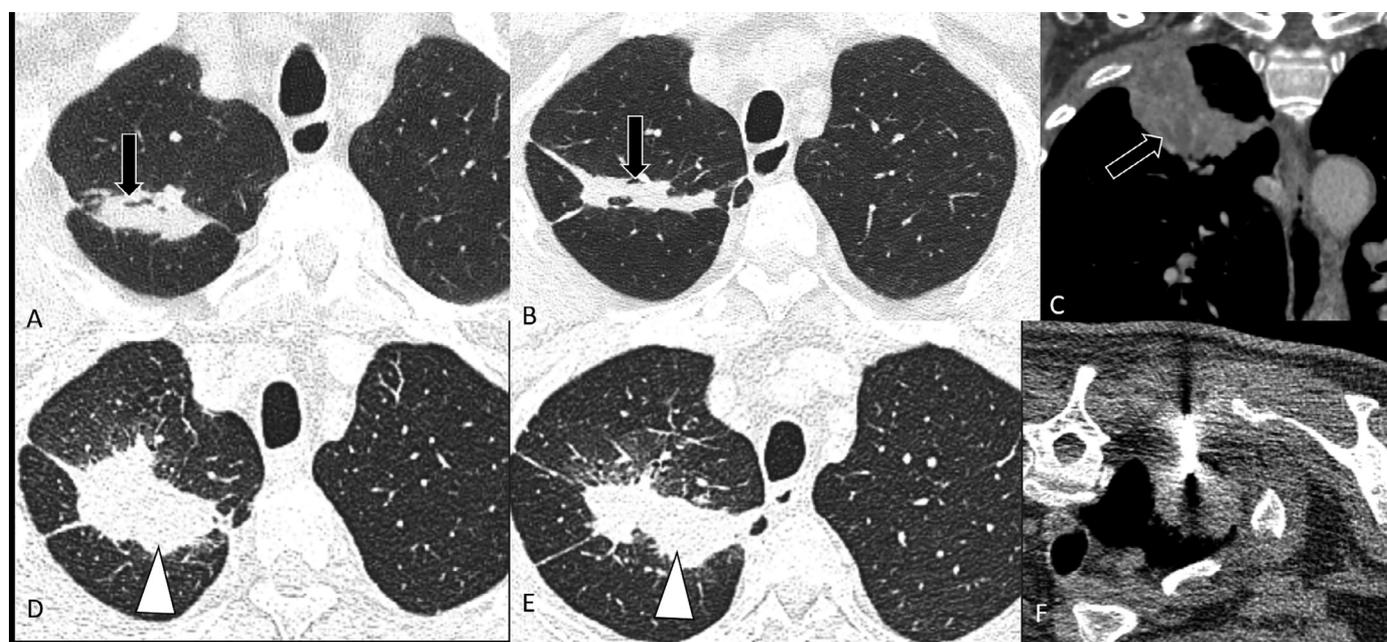


**FIG. 11. Subacute invasive aspergillosis.** A 59-year male with COVID-19 positive status, presented with persistent fever after 2 months of illness. A,B. CT performed in revealed post tubercular fibrobronchiectasis in right upper lobe (arrows). C,D,E. CT was repeated due to persistent fever 2 months after the initial illness. It showed enlargement of the area of the scar giving mass-like appearance(arrowheads). Mediastinal window revealed multiple dilated fluid-filled bronchi (arrow in C). This area was PET avid and a CT guided biopsy was performed from the apical component abutting the pleura (F) which revealed necrotizing granulomas and blood RTPCR was positive for aspergillus fumigatus. This hence represented rapid proliferation of aspergillus colonization in the tubercular scar.

**TABLE 3**
Diagnostic probability grades of CAPA

| Possible | Probable | | Proven | |
|---|---|---|---|---|
| Pulmonary form | Pulmonary form | Tracheobronchitis | Pulmonary form | Tracheo-bronchitis |
| Pulmonary infiltrate *or* cavitating infiltrate *or* nodules | Pulmonary infiltrate *or* cavitating infiltrate *or* nodules | No radiology Bronchoscopically-ulceration, nodule, pseudo-membrane, plaque or eschar | - Histopathological/microscopic detection of fungal hyphae showing invasive growth with tissue damage. <br> - Aspiration or biopsy from pulmonary site detected aspergillus by culture/ histology/ microscopy | |
| + one of the following In a non-bronchoscopic lavage only* <br> 1. Detection of fungal elements indicating a mould on microscopy <br> 2. Positive culture <br> 3. Single GM >4·5 <br> 4. GM index >1·2 twice or more <br><br> 5. GM >1·2 plus another mycology test positive (PCR or LFA) | + one of the following (BAL/ Serum samples) <br> 1. BAL- microscopy/culture positive or Single positive asp PCR <br> 2. BAL GM >=1.0 <br> 3. Serum GM >0.5 <br> 4. Two or more positive PCR in plasma, serum or whole blood <br> 5. One BAL PCR+ 1 Blood PCR | + one of the following (BAL/ Serum samples) <br> 1. BAL- microscopy/culture positive <br> 2. BAL GM >=1.0 <br> 3. Serum GM >0.5 | | |

GM, Galactomannan; BAL, Bronchoalveolar lavage; PCR, Polymerase chain reaction.

**TABLE 4**
Imaging features of pulmonary CAM Vs CAPA

| Imaging findings favoring Mucormycosis | Imaging findings favoring invasive Aspergillosis |
|---|---|
| Concomitant sinusitis <br> Mass like consolidation <br> Presence of multiple (≥10) nodules <br> Reversed halo sign/ Bird's nest sign <br> Pleural effusion <br> Transfissural extension | Clusters of centrilobular nodules <br> Peribronchial consolidations <br> Bronchial wall thickening |

(approx 1%) compared to SARS-CoV2; and the virus shedding is also prolonged in the latter. The identification of influenza infection in the background of COVID is difficult; as both of them can present with bilateral peripheral GGO and consolidation on CT. However, a few imaging findings are reported to be helpful in differentiating them0[33] Bronchiectasis and pleural effusion are more often associated in influenza, whereas crazy paving appearance, linear opacification, vascular enlargement are more common in COVID-19. One case report also suggested that influenza coinfections may result in higher incidence of spontaneous pneumomediastinum[34] One of the studies have shown that peribronchovascular distribution of pulmonary opacities, centrilobular nodules, consolidation and bronchiectasis or bronchial wall thickening on imaging are more suggestive of H1N1 pneumonia over COVID-19 pneumonia.[35]
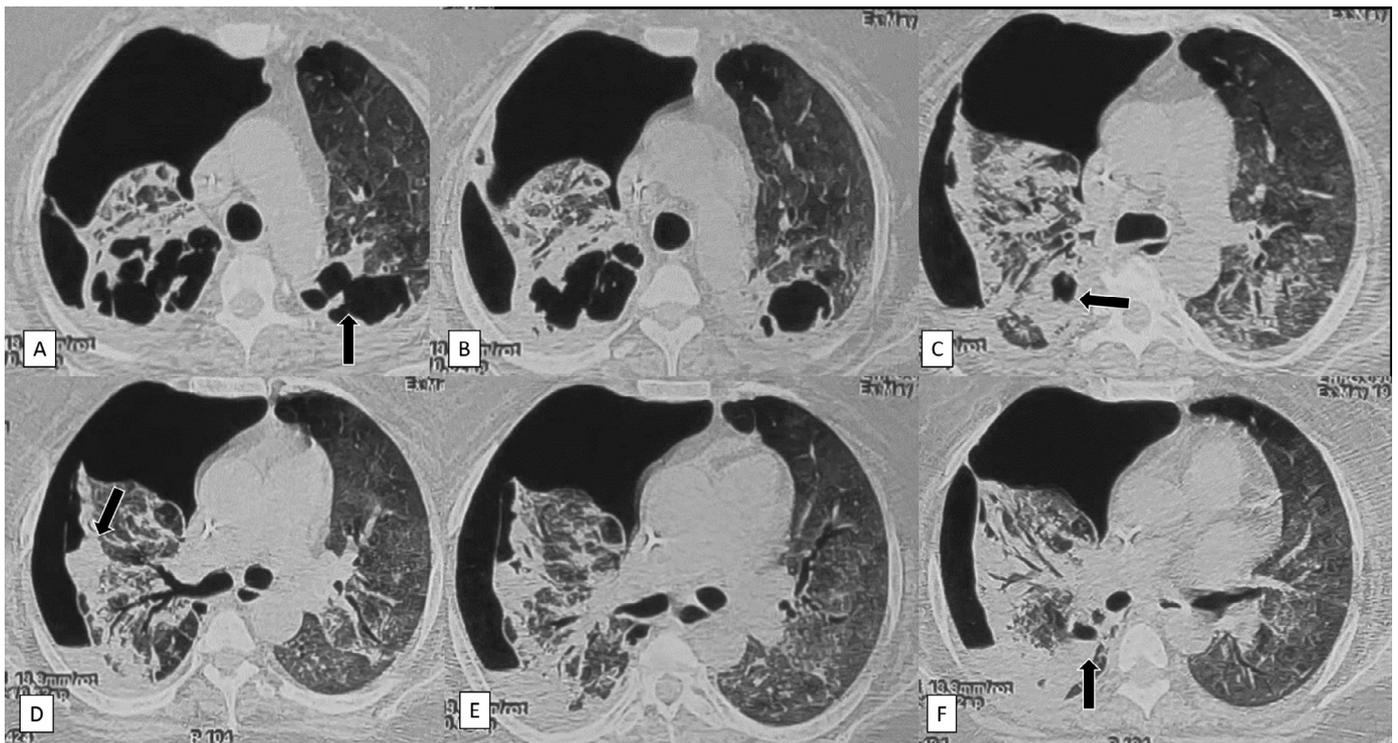


**FIG. 12. Candida superinfection in COVID-19.** A 40 year female presenting with increasing respiratory distress after 10 days of being tested positive for COVID-19. A-F. CT shows cavitary nodules and consolidations in both lungs (arrows) in background of COVID-19 associated GGOs with pneumothorax on right side. Candida parapsilosis was isolated from sputum culture.
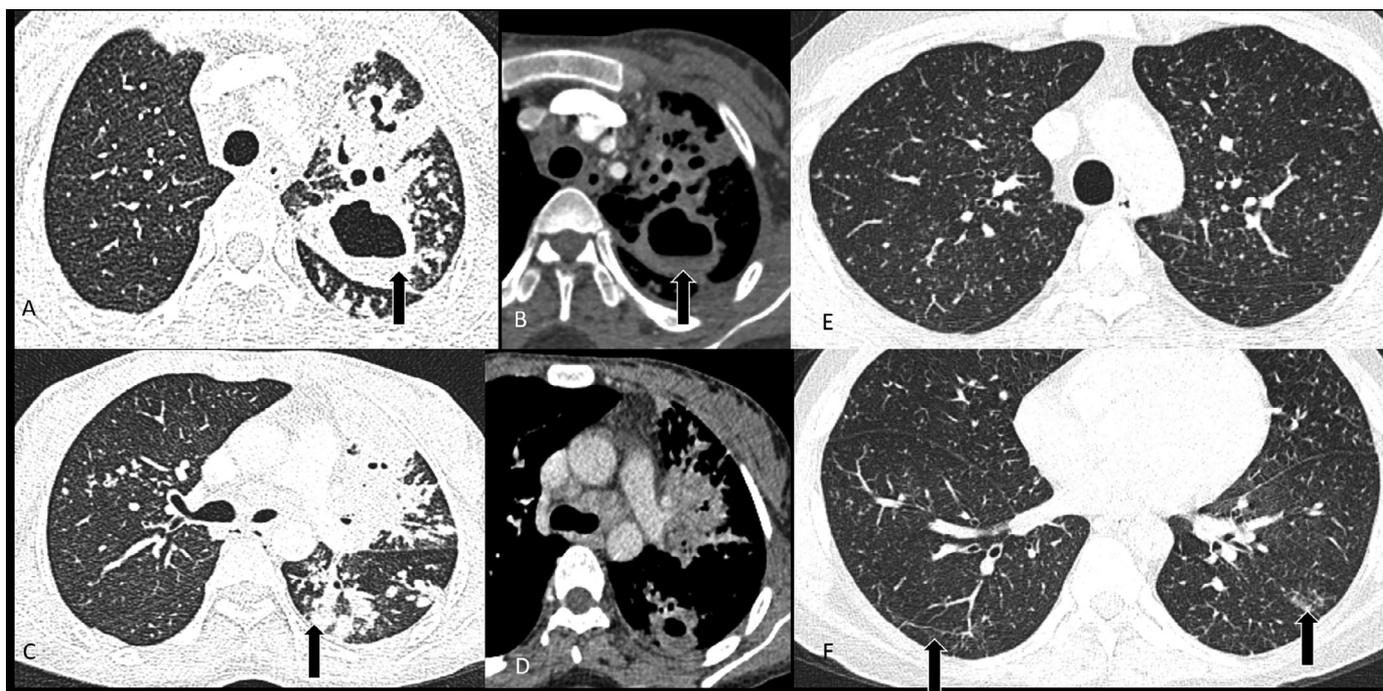
**FIG. 13. Tubercular co-infections in COVID-19 (Different patients).** 25 yr patient presented with massive hemoptysis. A-D. CT revealed active tubercular infection in the form of consolidation and cavities in left upper lobe with tree-in-bud nodules (arrows) and necrotic mediastinal lymphadenopathy. COVID RT-PCR was positive; however, no CT features of COVID-19 pneumonia was identified. E-F. Different patient- A 30 year-old-male presented with weight loss and loss of appetite. CT revealed miliary nodules in both lungs in the background COVID-19 related subpleural ground glass opacities and linear bands in lower lobes (arrows).

**TABLE 5**
Imaging pattern of pulmonary findings Vs likely organism

| Pattern | Most probable causative organism |
| --- | --- |
| Unilobar consolidation | Bacterial pneumonia |
| | Non-necrotizing - GPC |
| | Necrotizing - GNB, Aspergillosis |
| Cavitation | GNB |
| | Mucormycosis/ Aspergillosis |
| Pneumatocele | Staphylococcus pneumonia |
| | COVID-19 pneumonia |
| Peribronchial consolidation | Airway invasive fungal infection (Aspergillus spp) |
| | GNB |
| Centrilobular nodules | MTB |
| | Airway invasive aspergillosis |
| Random nodules | Bacterial septic emboli |
| Nodules with halo sign | Aspergillosis |
| | GNB |
| | COVID-19 pneumonia |
| Reverse halo sign | Mucormycosis |
| | COVID-19 pneumonia |
| Bird's nest sign | Mucormycosis |

GNB, Gram-negative bacteria; GPC, Gram positive cocci; MTB, Mycobacterium tuberculosis

*Dengue co-infection-* Dengue is endemic in tropical and subtropical regions. Antibody cross-reactivity between dengue and COVID-19 has been reported and overlapping clinical feature of fever and rash raises the concern of missing the diagnosis of co-infection. Thrombocytopenia and coagulopathy are some of the shared features[36]. Thoracic involvement in dengue may occur in the form of pulmonary hemmorhage or pleural effusions.[37]

*Other Uncommon Pathogens*

*Mycobacterium Tuberculosis (MTB)*

Co-infections with MTB are usually present at the time of admission in patients with COVID-19. Superinfections with MTB and reactivation of latent TB are also potential complications in patients receiving prolonged corticosteroids.[38,39] Imaging helps to avoid diagnostic delay when typical CT features of pulmonary TB (PTB) are identified such as clusters of centrilobular nodules, upper lobe cavitary consolidations, miliary nodules and mediastinal necrotic lymphadenopathy (Fig 13). Unilateral pleural effusion are also reported as presenting feature.[40] Hence, COVID-19 and MTB have a distinct imaging features enabling differentiation most of the time.

*Parasites*

Coinfections with other parasites such as Plasmodium spp. or intestinal parasitic infestations such as Entamoeba spp. Ascaris, Giardia, Strongyloides stercoralis and other helminths are reported with COVID-19 and usually present with gastrointestinal manifestations.[41] Pulmonary involvement is uncommon and we could not find any reports on literature search.

**Pattern Approach**

In summary, an imaging pattern-based approach is essential to short-list the possible causative organisms and direct further investigations, or at times even empirical therapy. This approach is summarized in Table 5.

**Conclusion**

A broad spectrum of organisms are responsible for coinfections and secondary infections in patients with COVID-19 pneumonia. Clinically persistent fever, worsening shortness of breath raises the suspicion for secondary infections. CT acts as a useful modality to predict the likely organism since the routine bronchoscopy sampling techniques are limited utilized in COVID-19 patients. Systematic assessment of the morphology of lung involvement on CT helps to narrow the differential diagnosis.

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## Conflict of Interest

None.

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