Implications of SARS-CoV-2 on patients with Common Respiratory Diseases

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Recently, both the Canadian Thoracic Society and the Canadian Society of Thoracic Radiology have recently published documents regarding management of patients with common respiratory diseases and imaging of patients with suspected or proven COVID-19. To benefit our local physician community we took on the task of summarizing the recent literature. We hope this is of benefit to all of you.

The document is divided into 3 sections:

A) Management of Common Respiratory Diseases in the setting of COVID-19 pandemic
B) Chest Imaging in the era of COVID-19
C) Algorithms for chest imaging in suspect and confirmed COVID-19 patients

Management of Common Respiratory Diseases in the setting of COVID-19

This section will be divided into 3 parts:

1) Inhaled salbutamol shortage – mitigation strategies for both asthma and COPD

2) Addressing therapeutic questions to help physicians optimize asthma management during COVIID-19 pandemic

3) Addressing therapeutic questions to help physicians optimize COPD management during COVID-19 pandemic

Inhaled salbutamol shortage

- As a result of a 3 fold increase in demand for salbutamol inhalers in the first 3 weeks of March 2020, health Canada identified a Tier 3 shortage for salbutamol (a situation when a manufacturer is unable to meet demand for the drug)
- Accordingly restrictions have been put in place by wholesalers and distributors to limit the supply of salbutamol which means that most patients will receive only one inhaler at a time.
- Mitigation strategies include:
    - Emphasize to patients the importance of well controlled asthma by ensuring patients use their controller inhaler, thereby, minimizing the need for prn salbutamol inhaler therapy.
    - Ensure patients use salbutamol only on a prn basis as opposed to regularly
    - Advise patients to not discard their recently expired inhalers (expired in the last 6 months) until they have obtained a replacement, advising patients that an expired inhaler may be less potent but in these exceptional circumstances perhaps OK to use.
    - Potential substitutions for salbutamol include: Salbutamol diskus, Terbutaline (bricanyl turbuhaler), Ipratropium (atrovent), Combivent Respimat, Formoterol 6mcg or 12mcg, Budesonide/Formoterol (Symbicort) or Mometasone/Formoterol (Zenhale)

Addressing therapeutic questions to help physicians optimize asthma management during COVID-19 pandemic

General Statement: it is highly recommended that maintenance and exacerbation management of asthma be continued according to current treatment guidelines. The best protection against a COVID-19 induced exacerbation is to maintain optimal asthma control. The risk of short- and long-term complications including mortality, can be significantly minimized by maintaining optimal asthma control.

Risk of acquiring COVID-19 by patients with asthma: There does not appear to be an increased risk for asthma patients to acquire SARS-CoV-2 infection compared to the generally population. 2 studies from China and a study from Korea did not find patients with asthma were over-represented in the group of hospitalized patients. However, a study looking at clinical characteristics of patients from a long term care facility in Seattle, revealed 31% of patients in that cohort with COVID-19 had pulmonary disease, however, given the age of the population it is likely (my own assumption) that the majority of those patients had COPD as opposed to asthma.

Risk and severity of asthma exacerbation caused by COVID-19: Any virus, including SARS-CoV-2, can trigger an asthma exacerbation. The severity of an exacerbation triggered by a virus (including SARS-CoV-2) is often influenced by the level of asthma control prior to developing a viral infection. Therefore, patients with asthma should be advised to restart or continue their prescribed inhaled corticosteroid or ICS/LABA regiment to improve asthma control and lessen the likelihood of a severe asthma exacerbation triggered by a viral infection.

Safety of using systemic corticosteroids to treat asthma exacerbations during COVID-19 pandemic: All local and international guidelines recommend using prednisone to treat a severe asthma exacerbation, including viral induced exacerbations. There is no available evidence of harm caused by using prednisone to treat asthma exacerbations during the pandemic. Also, a brief (5-7 day) course of prednisone is not expected to compromise the immune system sufficeiently to increase chances of acquiring SARS-CoV-2 and acquiring COVID-19. Although, there is no evidence to suggest the use of corticosteroid therapy in patients with COVID-19 induced ARDS, there is lack of data regarding the use of prednisone in patients with an asthma exacerbation triggered by COVID-19. The potential down sides of using prednisone in SARS-CoV-2 triggered exacerbation (prolong viral replication and shedding of virus) may, in some patients be worth the risk depending on the severity of their exacerbation. This is an individual decision based on the severity of a patient's exacerbation.

Safety of using inhaled steroids: There is no evidence that inhaled conrticosteroids increase the risk of acquiring SARS-CoV-2 infection or developing severe COVID-19 disease. It is likely, that inhaled corticosteroids, by improving asthma control will protect one against a severe asthma exacerbation. Therefore, it is strongly recommended that patients be advised to continue or restart inhaled corticosteroid therapy or ICS/LABA depending on the severity of their underlying disease.

Use of biologics to manage severe asthma: All patients on biologic therapies should continue their biologic therapy during COVID-19 pandemic. However, because of limitations to availability of staff to provide biologic injections, there is the potential that their therapy may be interrupted. During this period of interruption, increasing inhaled corticosteroid therapy or possibly low dose prednisone therapy may be required. There is no evidence that biologic therapy either increases the severity of COVID-19 or increases the likelihood of acquiring SARS-CoV-2 infection. In fact, previous studies had suggested that Omalizumab (Xolair) may protect against viral induced exacerbations.

Safety of nebulizer use in asthma: Because of the risk of aerosol generation, it is recommended that nebulizer therapy be replaced either with metered dose inhalers or dry powder inhaler therapies.

Addressing therapeutic questions to help physicians optimize COPD management during COVID-19 pandemic

General Statement: There is no evidence that the use of current inhaled COPD therapies impacts the severity of SARS-CoV-2 infection and thus maintenance and exacerbation management for COPD patients should be continued according to current CTS treatment guidelines. As maintenance inhaler therapy has been shown to reduce the risk of future exacerbations, optimal management of COPD is the best way to prevent and reduce the severity of exacerbations secondary to any viral illness, including SARS-CoV-2. This includes not only bronchodilator inhalers such as long acting anti-cholinergic bronchodilators (LAMA) and long acting beta-agonists (LABA), but also inhaled corticosteroid regimens.

Risk of acquiring SARS-CoV-2 infections in patients with COPD: Although the initial trials from China and Korea failed to show an increased risk of COPD patients acquiring COVID-19, a recent trial from a long term care facility in the state of Washington showed that 32% of patients had a pulmonary disease, the vast majority of it, likely COPD. Although COPD is likely a slight risk factor for SARS-CoV-2 infection, there are many other well defined risk factors for severe COVID-19 disease (age, hypertension, diabetes) that often co-exist in patients with COPD.

Severity of Acute Exacerbation of COPD caused by COVID-19: Patients with COPD are at higher risk of developing severe COVID-19 disease compared to the general population with a HR= 2.7. A meta-analysis published in the Journal of Respiratory Disease, indicated a 5 fold increase risk of having severe COVID-19. Accordingly, patients with COPD need to strictly follow all public health recommendations (social distancing, hand washing, etc.) in addition to optimizing the management of COPD.

Safety of using systemic corticosteroids to treat AECOPD during COVID-19 pandemic: Prednisone is recommended for the treatment of COPD exacerbations and should continue to be used during the COVID-19 pandemic to treat these exacerbations. There is no available evidence of harm caused by using prednisone to treat a AECOPD. Although prednisone therapy has not been proven to manage ARDS secondary to COVID-19, the use of prednisone to treat an exacerbation caused by SARS-CoV-2 has to made on a case by case basis, with the suggestion that a short course of prednisone is unlikely to cause harm even in the setting of an AECOPD caused by SARS-CoV-2.

Safety of nebulizer use in COPD: Because of the risk of nebullizer therapies increasing aerosolization of SARS-CoV-2, nebulized inhaler therapy should be avoided during the COVID-19 pandemic. Nebulized inhaler therapy should be switched to either MDI, tubuhaler or respimate devices in all clinical circumstances. This includes at home and inside healthcare facilities.

The Role of Chest Imaging During the COVID-19 Pandemic

The value of chest imaging in COVID-19 lies in its ability to render actionable results either for establishing a diagnosis, guiding management algorithms, triaging patients or starting therapy. This value needs to be balanced against the costs of imaging, namely radiation exposure, risk of transmission of COVID-19 to health care personnel, consumption of PPE and the down-time required to clean and disinfect radiological equipment.

CXR is an insensitive modality in mild or early COVID-19 infection [1]. It has minimal value in the early course of the disease however it is often abnormal once patients develop more advanced symptoms. The overall sensitivity is approximately 69%. The majority of patients (~80%) however will have an abnormality on CXR at some point during the course of their illness.

CT is more sensitive, however a slight majority of scans are also negative early (within the first two days after symptom onset) in the course of disease. CT abnormalities usually develop between day 0 and 4 after symptom onset and peak by day 6-13 [2-6]. Overall CT has a range of sensitivities and specificities, 60-98% and 25-53%, respectively [7-10]. The positive and negative predictive value of chest CT for COVID-19 is estimated to be 92% and 42%, respectively, in a population with high pre-test probability of disease [8]. CT is more sensitive than CXR in determining disease progression and alternative diagnoses including heart failure from COVID-19 myocardial injury and pulmonary embolism, if contrast is introduced. These superior attributes should be leveraged against the availability of CT capacity during the pandemic, as additional time must be taken to clean and disinfect equipment used for suspected COVID-19 cases.

The following endeavors to present clinical scenarios where thoracic imaging may be of value to the patient with presenting features consistent with COVID-19 infection. These are summarized from a multinational consensus statement from the Fleischner Society and the Canadian Society of Thoracic Radiology and Canadian Association of Radiologists published in April of 2020 [11,12]. **Table 1** describes the definitions used as it pertains to severity of illness, pre-test probability of the disease, risk factors for progression and resource-constrained environments.

Patients with mild features of COVID-19

This scenario describes the patient presenting for evaluation in the outpatient setting with mild respiratory features of COVID-19, in other words they are normoxic without dyspnea or have at most mild dyspnea. Imaging is advised for those patients at risk of progression with either confirmed COVID-19 positivity or with moderate to high pre-test probability in the absence of testing (**see Table 1**). The role of imaging here is to act as a baseline for future comparison, establish manifestations of comorbidities that increase the risk of disease progression and influence the intensity of monitoring for clinical deterioration. Imaging is not required in those with mild features and without risk factors for progression. However, for all patients who develop clinical worsening, imaging is suggested.

Immunosuppressed patients are generally at risk of infection, including viral infections. COVID-19 positive patients in Wuhan, China with solid malignant tumors on chemotherapy, immunotherapy or radiation therapy had worse outcomes [13]. In contrast more recent data from Italy suggest that the immune response to COVID-19 infection is what drives the acute lung injury and subsequently, immunosuppressed patients do not have more serious disease [14]. Due to the high risk of lung infection in immune suppressed patients in general, performing a CT chest is reasonable if the initial CXR is normal [15].

Patients with moderate to severe features of COVID-19

Imaging is recommended in essentially all patients presenting with moderate to severe features consistent with COVID-19, assuming no significant resource constraints.

For confirmed COVID-19 positive patients, imaging establishes a baseline and facilitates risk stratification. If there is clinical worsening, repeat imaging is again recommended to assess for COVID-19 progression and other cardiopulmonary abnormalities such as pulmonary embolism, superimposed bacterial pneumonia or heart failure as a result of COVID-19 myocardial injury.

For COVID-19 negative or unknown patients, imaging can importantly lead to an alternative diagnosis. If no alternative diagnosis is established or imaging is consistent with features of COVID-19, then COVID-19 testing (either initial or repeat) versus other investigations should be carried out depending on the pre-test probability of COVID-19.

Patients with moderate to severe features of COVID-19 in a resource-constrained environment
This describes the scenarios such as those that took place in Wuhan and regions in Italy, Spain and New York City where highly prevalent disease resulted in an overwhelmed health care infrastructure due to the influx of new patients.

For COVID-19 positive patients, imaging is advised, again to establish a baseline and facilitate risk stratification. CXR may be preferred if access to CT is limited. However, imaging with CT is advised with subsequent clinical worsening, again to recognize progression or super-imposed complications.

For COVID-19 negative or status unknown patients, imaging is advised to support more rapid triage. COVID-19 testing has a higher likelihood of a false negative result in an environment of high baseline prevalence. Therefore, if CT features are strongly suggestive, a presumptive diagnosis can be made despite the negative testing.

Patients who have recovered from COVID-19
There is obviously no long-term follow up studies of survivors of the disease as of yet. Postmortem evaluation of a single patient with severe COVID-19 disease showed pathological findings of diffuse alveolar damage (pathological correlate of Acute Respiratory Distress Syndrome), similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [16]. Those patients who have functional impairment following recovery should undergo imaging to differentiate between the expected anatomical sequelae of infection and/or mechanical ventilation from a different potentially treatable entity.

Incidental finding of typical COVID-19 features on CT chest
Although CT findings of COVID-19 are non-specific, their presence in an environment of known community transmission is concerning, even in the absence of symptoms, particularly if there is not an obvious alternative diagnosis. Asymptomatic carriers of COVID-19 are estimated to comprise 17.9-33.3% of all infected cases [17,18]. RT-PCR testing is therefore suggested in this scenario. It is not clear whether CT is a viable screening tool in highly prevalent areas, however the low estimated negative predictive value suggests it may not be. Chest CT is currently not recommended as a screening modality.

Table 1. Definitions and criteria for key components of common clinical scenarios.

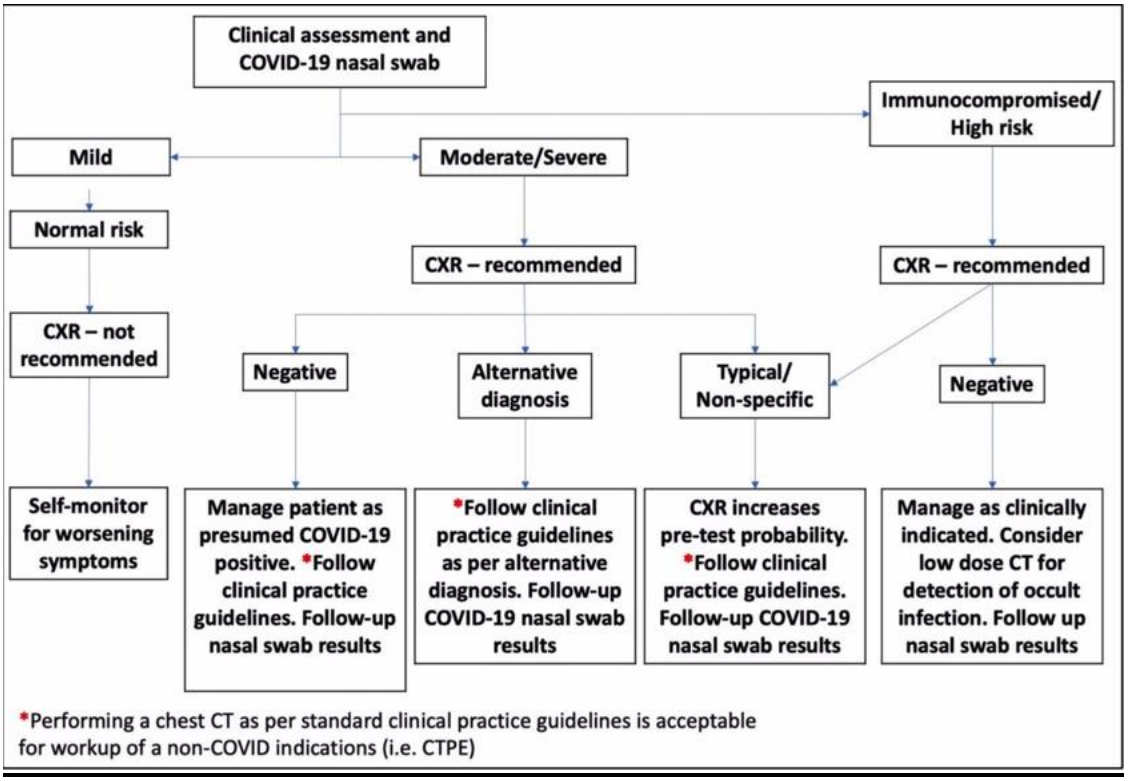
Severity of respiratory disease • Mild: No evidence of significant pulmonary dysfunction or damage (e.g., absence of hypoxemia, no or mild dyspnea) • Moderate-to-severe: Evidence of significant pulmonary dysfunction or damage (e.g., hypoxemia, moderate-to-severe dyspnea)

Pre-test probability
• Based upon background prevalence of disease as estimated by observed transmission patterns. May be further modified by individual's exposure risk. Sub-categorized as:
  o Low: Sporadic transmission
  o Medium: Clustered transmission
  o High: Community transmission

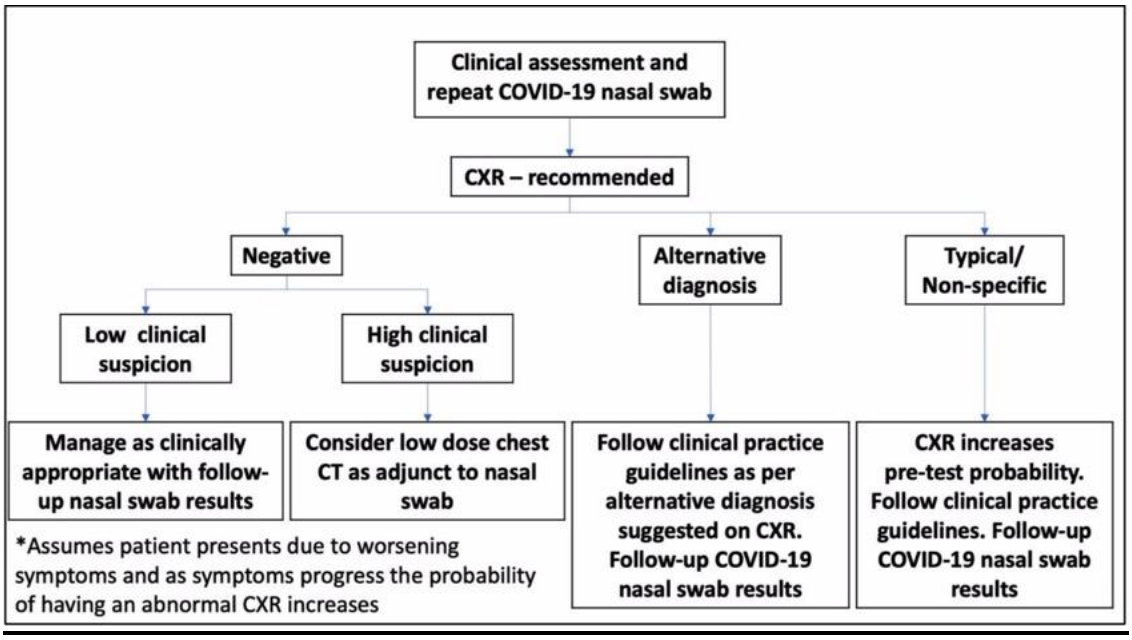
Risk factors for disease progression • Present: Clinical judgement regarding combination of age > 65 years and presence of comorbidities (e.g., cardiovascular disease, diabetes, chronic respiratory disease, hypertension, immune-compromised) • Absent: Defined by the absence of risk factors for disease progression
Disease progression • Progression of mild disease to moderate-to-severe disease as defined above. • Progression of moderate-to-severe disease with worsening objective measures of hypoxemia.
Resource constraints • Limited access to personnel, personal protective equipment, COVID-19 testing ability (including swabs, reagent, or personnel), hospital beds, and/or ventilators with the need to rapidly triage patients.

Chest Imaging in Suspected and Confirmed COVID-19 – Summary Algorithms

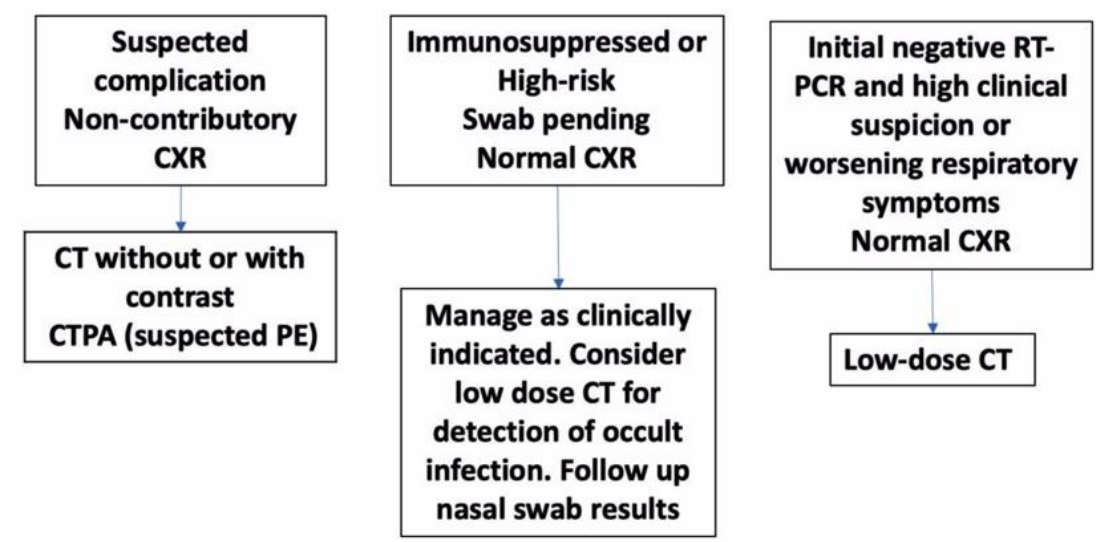
COVID-19 Chest Imaging algorithm for initial presentation



COVID-19 Imaging algorithm for repeat presentation and initial negative COVID-19 swab



Potential Clinical Scenarios in which CT Chest may be helpful



Imaging Findings Related to COVID-19

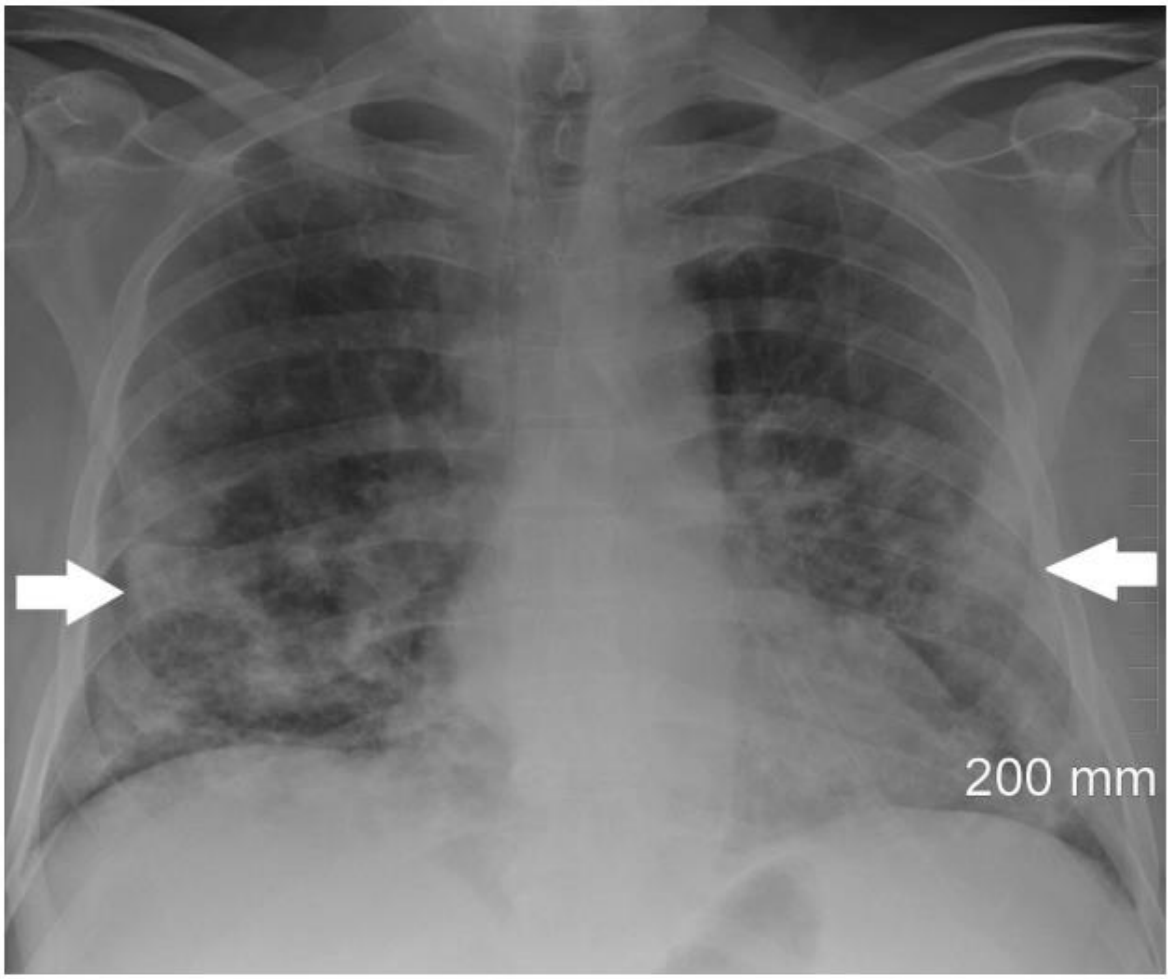
The CXR findings in COVID-19 include most commonly consolidative changes followed by ground glass opacity (GGO). The distribution is usually peripheral and lower zone and most patients have bilateral involvement. Pleural effusions are rare (~3%). CT findings of COVID-19 can be non-specific however there have been some patterns that have been found to be more typical of the underlying pulmonary disease [19].

The following presents a summary of these patterns followed by imaging examples and comparisons to non-SARS-CoV-2 entities.

COVID-19 Chest XRAY Findings

COVID-19 pneumonia imaging classification	**Rationale**	**CXR Findings**
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia	- Bilateral, peripheral multifocal opacities or consolidation -Lower lung zone predominant
Non-Specific appearance	Not commonly reported features of COVID-19 pneumonia	-Unilateral and/or perihilar opacities or consolidation -No zonal predominance or are upper lung zone predominant -Cavitation, Kerley B lines with pleural effusion, lymphadenopathy
Negative for pneumonia	Findings are either absent or do not contribute towards an infectious diagnosis	-No features to suggest pneumonia (note CXR does not exclude COVID-19

		infection, particularly early disease)



Chest radiograph depicting "*typical appearance"*. This 66-year-old man with chronic lymphocytic leukemia presented to the Emergency Department with a history of fever, worsening shortness of breath, night sweats, myalgia and diarrhea. He had tested positive for COVID-19 seven days earlier. Chest radiographic findings include lower zone predominant bilateral, peripheral opacities (arrows). There is no pleural fluid.

Chest radiograph depicting “non-specific appearance”. This 55-year-old woman with chronic renal insufficiency presented to hospital with a one-week history of cough, shortness of breath, malaise and low-grade fever. RT-PCR was positive for COVID-19. Chest radiographic findings include diffuse bilateral opacities with no zonal predominance.

COVID-19 Chest CT Findings

COVID-19 pneumonia imaging classification	**Rationale**	**CT Findings**
Typical appearance	Commonly reported features of greater specificity for COVID-19 pneumonia	-Peripheral, bilateral GGO with or without consolidation or visible intralobular septal lines (‘crazy-paving’) -Multifocal GGO of rounded morphology with or without consolidation or crazy-paving -Reverse halo sign or other findings of organizing pneumonia (seen in later stages of disease)
Indeterminate appearance	Non-specific imaging features of COVID-19 pneumonia	Absence of typical features AND *Presence of:*

		-Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral -Few very small GGO with a non-rounded and non-peripheral distribution
Atypical appearance	Uncommonly or not reported features of COVID-19 pneumonia	Absence of typical or indeterminate features AND *Presence of:* -Isolated lobar or segmental consolidation without GGO -Discrete small nodules (centrilobular, 'tree-in-bud') -Lung cavitation -Smooth interlobular septal thickening with pleural effusions
Negative for pneumonia	No features of pneumonia	No CT features of pneumonia (note that CT can be normal in early disease)

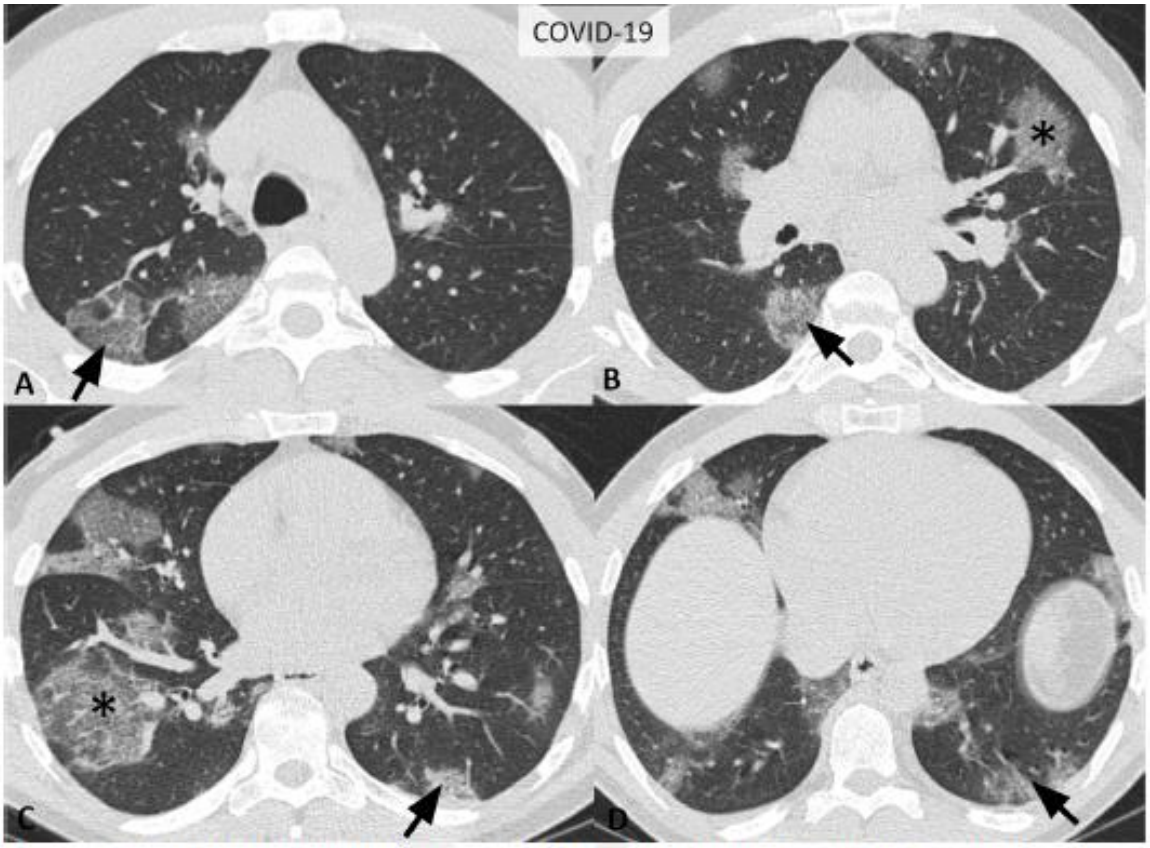


Figure 1: Typical CT imaging features for COVID-19. Unenhanced, thin-section axial images of the lungs in a 52-year-old man with a positive RT-PCR (A-D) show bilateral, multifocal rounded (asterisks) and peripheral GGO (arrows) with superimposed interlobular septal thickening and visible intralobular lines ("crazy-paving").

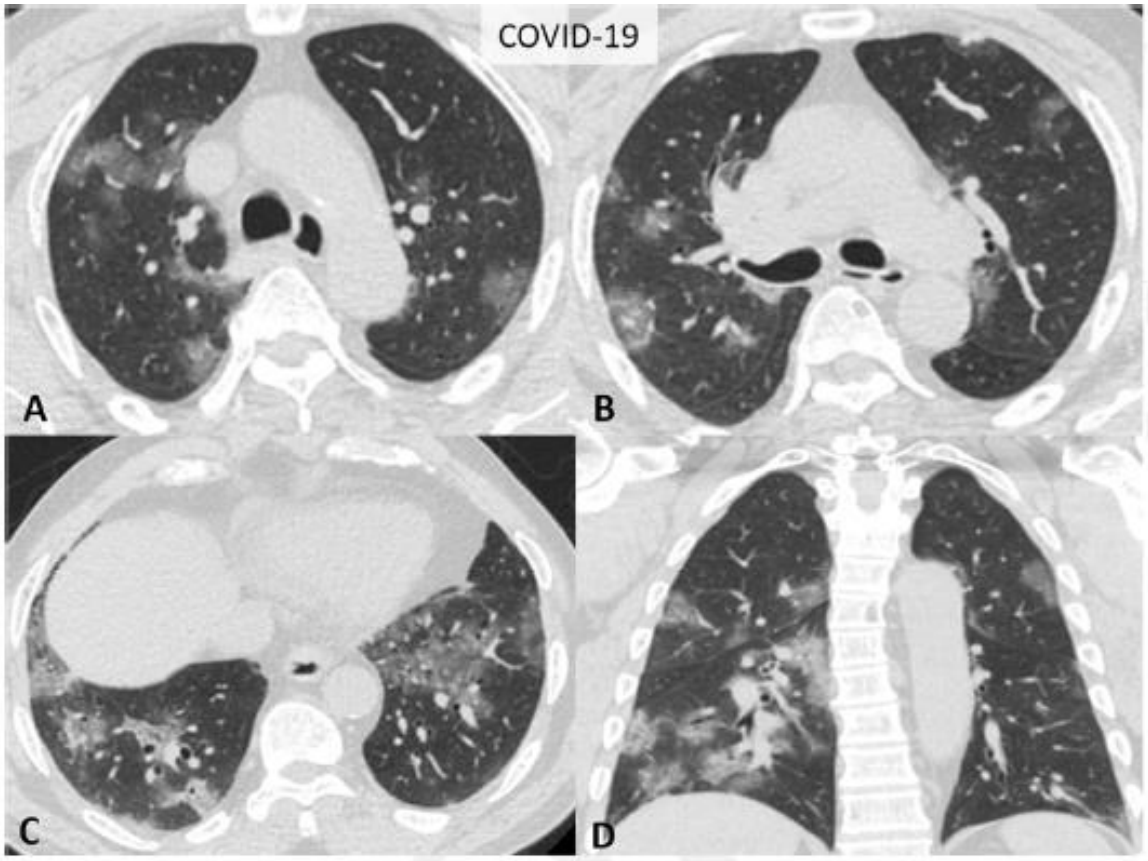


Figure 2: Typical CT imaging features for COVID-19. Unenhanced, thin-section axial (A-C) and coronal multiplanar reformatted (MPR) images (D) of the lungs in a 77-year-old man with a positive RT-PCR show bilateral, multifocal rounded and peripheral GGO.

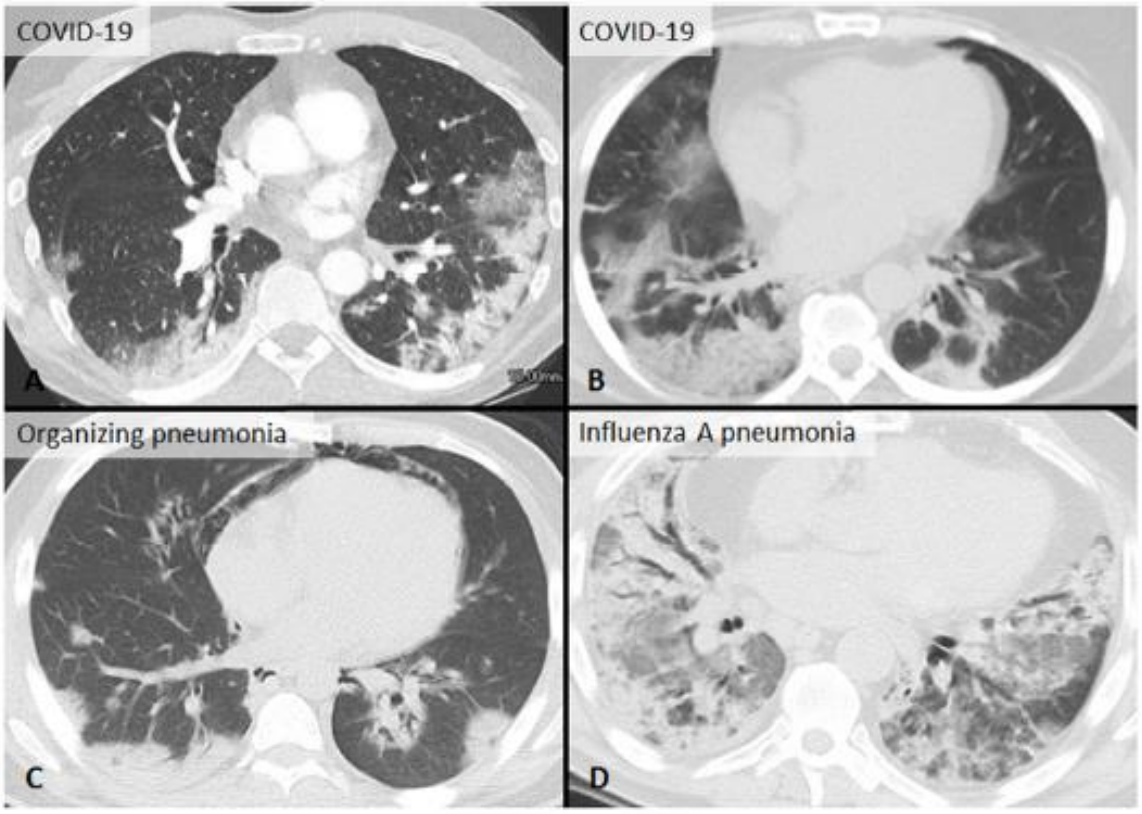


Figure 4: Typical CT imaging features for COVID-19 and other diseases with similar findings . Posterior, peripheral, and rounded GGO and consolidation in axial images of four patients; COVID-19 (A,B), organizing pneumonia secondary to dermatomyositis (C) and influenza A pneumonia (D). Organizing pneumonia and influenza pneumonia can be indistinguishable from COVID-19 by CT.

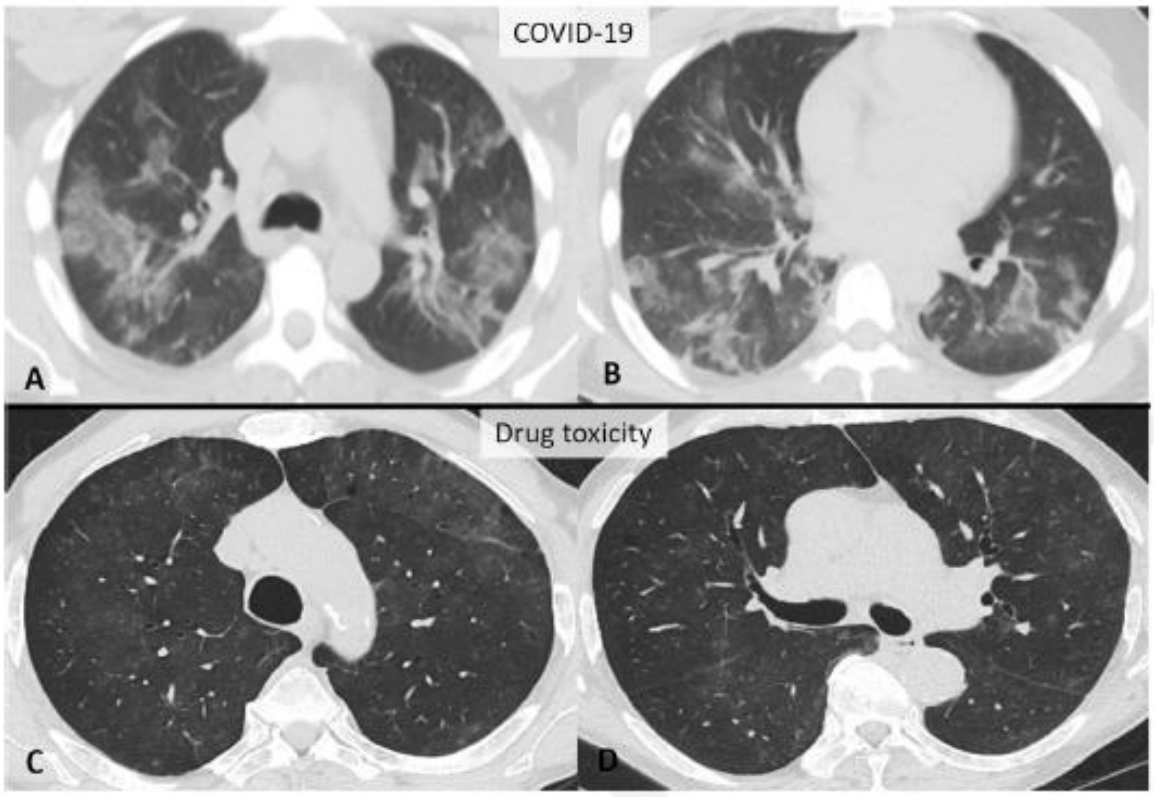


Figure 5: Indeterminate CT imaging features for COVID-19. Unenhanced axial images in two patients showing patchy GGO with nonrounded morphology and no specific distribution, in a case of COVID-19 pneumonia (A,B) and acute lung injury from presumed drug toxicity (C,D).

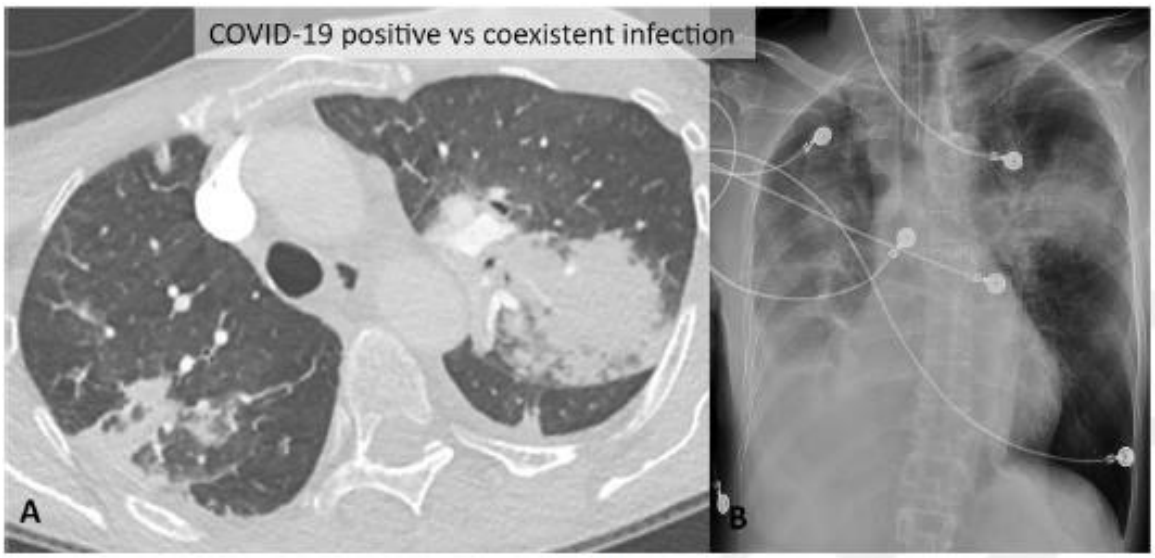


Figure 7: Atypical CT imaging features for COVID-19. Contrast-enhanced axial CT image (A) and frontal chest radiograph (B) showing segmental consolidation without significant GGO. Although this patient tested positive for COVID-19, the imaging features are not typical and could represent pneumonia related to COVID-19 or a secondary infectious process.

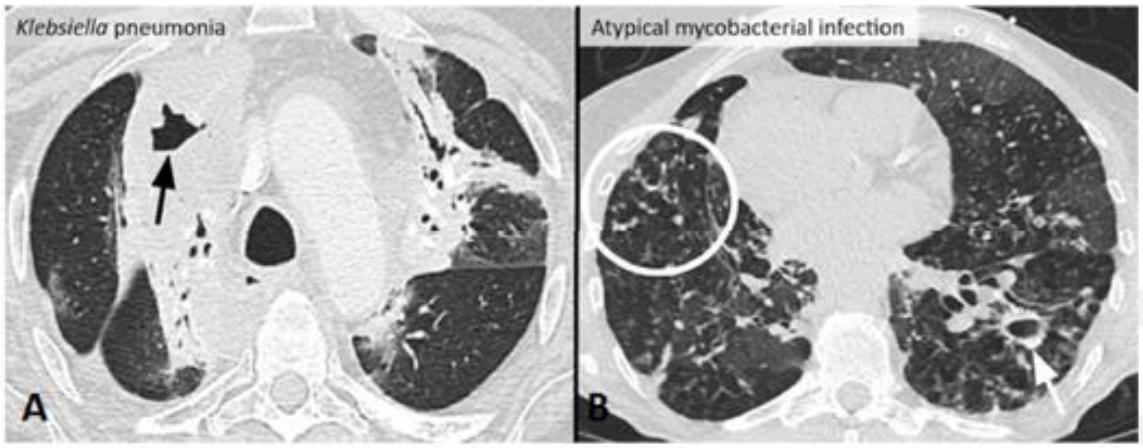


Figure 8: Atypical CT imaging features for COVID-19. Axial images of the lungs of two patients showing cavitation (*arrow*) in *Klebsiella* pneumonia (A) and tree and bud opacities (*circle*) and a cavity (*arrow*) in nontuberculous mycobacterial infection (B).

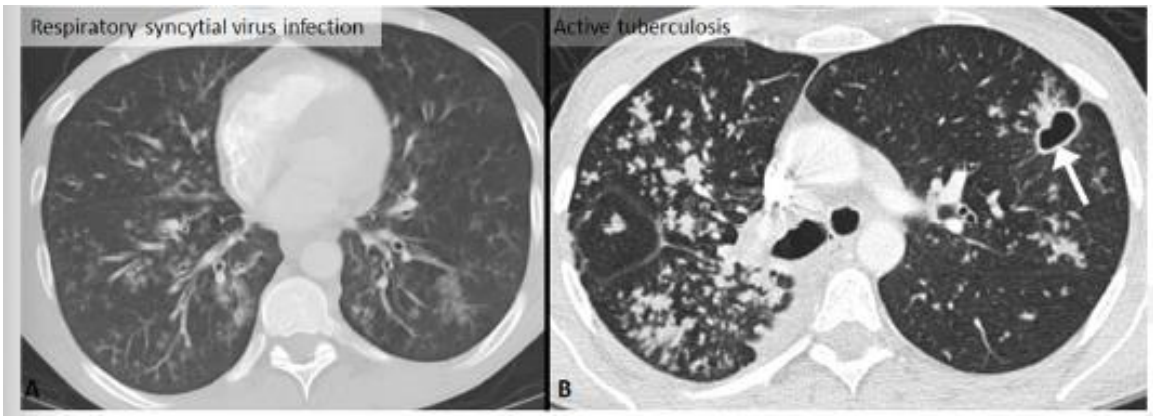


Figure 9: Atypical CT imaging features for COVID-19. Axial CT images from two different patients showing tree-in-bud opacities and centrilobular nodules, caused by respiratory syncytial virus A) and active tuberculosis (B). A small cavity (*arrow*) is also present in (B)

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