Chapter: Critical Care and Respiratory Medicine, Acute complications of COVID-19 infection, By Dr Harman Saman, Dr Hatem Mabrouk Taher Abusriwil and Dr Mohamad Yahya Khatib

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I. **COVID-19 pneumonia:**

Keywords: pneumonia, inflammatory pneumonia, cytokine storm/hyperinflammation, immunocompromised, superadded bacterial infection, tuberculosis, non-tuberculum mycobacterium, BCG, fungal infection, silent hypoxia, respiratory failure, high resolution CT scan, Tocilizumab, corticosteroids, antibiotics.

**a) COVID-19 pneumonia incidence rate and implications of disease severity:**

On 31 December 2019, a cluster of pneumonia cases of unknown aetiology were detected in Wuhan City, Hubei Province of China and were reported to World Health Organisation (WHO)(1). The causative organism was later identified as SARS-CoV-2, a novel virus belonging to the coronaviridae family(1).

The majority (about 81%) of individuals with COVID-19 infections have only mild disease (2). Patients who develop pneumonia, however, are more likely to suffer from severe illness, which represent about 14% of the cases(1) Important indications of severe disease are dyspnoea, hypoxia (with SpO2 <94%), and/or >50 percent lung involvement on imaging (3). Around 5% of individuals with COVID-19 pneumonia are expected to develop critical disease with features of respiratory failure, shock, and/or multiorgan dysfunction(3). In the state of Qatar, a large epidemiological study showed, 2.3% of patients had mild illness with pneumonia and 2% were severe or critically ill(4). In Qatar, during the pandemic, the majority of patients with pneumonia treated in hospital including those who required no oxygen supplementation(4).

As the commonest serious complication of COVID-19 infection, pneumonia causes fever, cough, dyspnoea, and bilateral infiltrates on chest x-rays(5, 6). Several cohorts showed that dyspnoea approximately one week after the onset of initial symptoms of COVID-19 infection might heralds the development of pneumonia which often led to further clinical deterioration(5-7). Moreover, there are several studies, showing that patients might be asymptomatic even in the presence of hypoxia and evidence of ground glass changes on chest CT scan (8, 9). In some cases lack of breathless in the presence of severe hypoxia (sometimes referred to as silent hypoxia) appears to proceed a rapidly issuing severe type 1 respiratory failure which is a medical emergency that requires prompt medical intervention(10). Besides the clinical features and chest imaging, raised inflammatory markers, such as white cell count, C reactive protein, ferritin and D-dimmer, aid the diagnosis of pneumonia. Normal serum procalcitonin levels are noted in majority of patients admitted to general wards, but procalcitonin levels are commonly raised in patients requiring ICU care and elevated procalcitonin levels usually indicates serious superimposed bacterial infection(6).

**b) COVID-19 pneumonia in immunocompromised:**

In immunosuppressed patients, as in the case of HIV coinfection or patients receiving cytotoxic or other immunosuppressing drugs, persistent pneumonia several weeks after the onset of the disease, has been reported. Such patients responded poorly to standard antimicrobial treatment(11). Therefore, patients with COVID-10 pneumonia who are immune deficient are better treated jointly by members of multidisciplinary teams (MDT), that include infectious diseases specialists, respiratory physicians and...
microbiologists. Members of MDT thoroughly investigate to detect and treat opportunistic microorganisms using extended culture and sensitivity tests to antibiotics, this to avoid misdiagnosis and inappropriate choice and prolonged use of antimicrobial drugs (9).

c) COVID-19 and superadded bacterial infection:
Similar to other common viral respiratory infections, such as influenza, infection with COVID-19 virus commonly leads to secondary bacterial superinfection due to disturbance to the physical barrier served by the respiratory epithelium and disruption to host antibacterial innate and adaptive defences (12). Superadded infection with *Streptococcus pneumoniae, Staphylococcus aureus* and *Acinetobacter baumannii*, is shown to be associated with severe disease and increased mortality in ICU (12, 13). The choice of antibiotic treatment should be guided by local antibiotic protocol(s) that usually take into account the incidence and prevalence of specific organisms and their sensitivity profile in local communities.

d) COVID-19 and inflammatory pneumonia:
In addition to bacterial coinfection, there's histological evidence of infiltration of the lungs with inflammatory cells and proinflammatory cytokines, ranging from oedema, proteinaceous exudate, vascular congestion, inflammatory clusters with multinucleated giant cells, interstitial fibroblastic proliferation, and reactive hyperplasia of pneumocytes in mild to moderate disease to diffuse alveolar damage with lymphocytic infiltrate, small thrombotic vessels, and foci of alveolar haemorrhage, in the critically unwell patients (14-16). Therefore, an important component of the ground glass changes that are seen on chest CT scans, is caused by inflammation of the lung interstitium. To tackle inflammatory pneumonia, corticosteroids and anti-interleukin 6 (Tocilizumab) in case of cytokine storm/hyperinflammation, are deployed and recommended in in several international guidelines and national guidelines (17, 18).

e) COVID-19 and fungal coinfection:
Autopsy studies of lung tissue obtained from patients deceased as the result of COVID-19 pneumonia, suggest predominance of coinfection with fungal species, such as *Cryptococcus spp., Cladosporium spp., Alternaria spp., Aspergillus spp.,* and *Candida spp* (19). Diagnosing and treating fungal coinfection can be very challenging, especially in intubated patients with severe COVID-19 pneumonia (20). We, however, do not recommend routine treatment with antifungal therapies. Fungal coinfection should be suspected in immunocompromised and invasively ventilated patients, who continue to show signs of infection, such as ongoing fever and high inflammatory makers and persistence of lung infiltrates on chest imaging, despite adequate treatment with parenteral broad-spectrum antibiotics. Such patients, therefore, should be considered for antifungal treatment, after sending appropriate samples, such as respiratory aspirates, including samples obtained by bronchoscopy, to fungal culture and fungal DNA analysis.

f) COVID-19 and tuberculosis (TB):
Infection with *Mycobacterium tuberculosis* remains a leading cause of death in low and middle income countries (21). There’s a resurgence in the number of new TB cases in the developed economies. For example, in the UK there are 4500 new cases reported every year. These patients are predominantly located in large metropolitan cities with high immigrant and homeless population, such as London (22). In Qatar, the prevalence of both

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pulmonary and extra-pulmonary TB, is high, especially among male workers that immigrated from low income courtiers(23, 24) Therefore, clinicians need to be aware of the interaction between COVID-19 and TB infections, especially as diagnosis of such co-infection can be challenging due to shared common symptoms such as cough, malaise and fever as well as common risk factors for transmission like crowded living conditions such as in hostels and prisons. In addition, patients with both conditions can suffer stigmatisation, which in itself can hinder early presentation for medical care which in turn delays diagnosis and treatment. In a cohort of 49 patients with COVID-19 and TB coinfection, treatment of TB appeared to have offered no protection against infection with COVID-19. Patients with severe COVID-19 and TB coinfection were more likely to be older, with cavitating lung lesions and to suffer from comorbidities namely COPD, hypertension, HIV and kidney disease(25).

**g) COVID-19 pneumonia and non-tuberculous mycobacterial (NTM) infections:** There is a global rise in the numbers of patients with chronic lung diseases diagnosed with NTM infection. NTM pulmonary infection is notoriously difficult to diagnose and its treatment is complicated by resistance to common antibiotics, prolonged duration of treatment (on average 2 years), patients' treatment adherence and treatment toxicity profile (26). It is expected that an important proportion of individuals recovered from acute COVID-19 pneumonia but ended up with chronic lung destruction such as chronic cavities and interstitial lung disease, to be infected with NTM in the future. Clinically infection with NTM often presents with insidious onset but a prolonged (weeks to months) history of cough productive of mucopurulent sputum, weight loss, breathlessness and fatigue. These symptoms often do not or partially respond to antibacterial antibiotics. The Canadian Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control (PIDAC-IPC) provides a set of comprehensive review and guidelines of managing NTM infection. The authors of this chapter recommend utilising algorithm 1 to aid in making a diagnosis of infection with NTM.

**h) COVID-19 and Bacillus Calmette–Guérin (BCG) vaccine:** In the middle of the pandemic, a debate regarding the potential protective effect of BCG vaccination against severe COVID-19 pneumonia, through the stimulation of innate immune system, drew the attention of the public and scientific communities alike. This debate was largely triggered by the findings of a few ecological studies that showed lower incidence and mortality rates of COVID-19 infection in countries that mandated vaccination with BCG(27, 28). But such association is hard to prove due to presence of a number of important confounding factors that affected these ecological studies and the lack of high quality randomised controlled trials to investigate the protective effect of BCG(27).
Algorithm 1: An algorithm for the investigation of individuals with clinical suspicion of NTM-pulmonary disease (AFB, acid-fast bacilli; HRCT, high-resolution CT; NTM-PD, non-tuberculous mycobacterial pulmonary disease).

Charles S Haworth et al. Thorax 2017;72:i61-i64
2. COVID-19 and Pulmonary Embolism/Venous thromboembolism (VTE):

Keywords: pulmonary embolism, PE, hypercoagulable state, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, Venous thromboembolism (VTE), Adult Respiratory Distress Syndrome (ARDS), D-dimer, platelet activation, CT Pulmonary Angiogram (CTPA), Hamad General Hospital Anticoagulation Clinic, Thromboembolic Pulmonary Hypertension (CTEPH), Cor pulmonale, Qatar’s Communicable Diseases Centre (CDC) Treatment Protocol for confirmed COVID-19 Infection, right ventricular strain, right ventricular strain, massive PE, thrombolysis.

i) Pathogenesis of VTE/PE in COVID-19 infection:
The exact pathogenesis of COVID-19 associated hypercoagulable state is poorly understood. There is evidence that the following changes are likely to contribute significantly to the prothrombotic state of COVID-19 infected patients (29-31):

I. Elevated fibrinogen
II. Elevated factor VIII
III. Hyperviscosity
IV. Neutrophil extracellular traps (NETs)
V. Circulating prothrombotic microparticles

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus directly invading endothelial cells, is another potential risk factor to develop Venous thromboembolism (VTE). Such endothelial injury that causes microvascular inflammation, endothelial exocytosis, and/or endotheliitis, is likely to be a critical step in the pathogenesis of Adult Respiratory Distress Syndrome (ARDS) (32-34).

Elevation of D-dimer, a degradation product of cross-linked fibrin, appears to correlate well with disease severity (35). Although, D-dimer is a nonspecific indicator often raise in a wide range of infective and inflammatory conditions. In addition, some data suggest that platelet activation might be another causal factor to COVID-19 associated VTE (36, 37). COVID-19 associated VTE (sometimes referred to as COVID-19-associated coagulopathy (CAC)) is distinct from disseminated intravascular coagulation (DIC) (37).

j) Incidence rate of VTE/PE in COVID-19 infection:
PE appears to be a common complication in patients with moderate to severe COVID-19 pneumonia. A metaanalysis of 23 studies that included 7178 COVID-19 patients [mean age 60.4 years] of hospitalized in general wards and ICU; the incidence of PE was 14.7% of cases (95% CI: 9.9-21.3%, I²=95.0%, p<0.0001) and 23.4% (95% CI:16.7-31.8%, I²=88.7%, p<0.0001) respectively. Segmental/sub-segmental pulmonary arteries were more frequently involved compared to main/lobar arteries (6.8% vs18.8%, p<0.001)(38). A large French retrospective multicentre observational study of 1240 patients (58.1% men, mean age 64 ± 17 years), 103 (8.3%) patients had PE confirmed by CT Pulmonary Angiogram (CTPA). The same study concluded that PE risk factors in the COVID-19 context do not include traditional thrombo-embolic risk factors but rather independent clinical and biological findings at admission, including a major contribution to inflammation (39). In a single-center study evaluated 62 COVID-19 patients who underwent CTPA, 37.1% had PE, of those who had PE, 40% receiving prophylactic anticoagulation. This study noted that D-dimer can be used to stratify patients regarding PE risk and severity (40). The thrombotic complications in ICU patients with COVID-19 is particularly high. In a retrospective observational study of 184 ICU patients with COVID-19 pneumonia all of whom received at least one form VTE prophylaxis; 31% (95%CI 20-41) developed a thrombotic event. Of which CTPA and/or ultrasonography confirmed...
VTE in 27% (95%CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). PE was the most frequent thrombotic complication (n = 25, 81%)\(^{[41]}\).

In another retrospective analysis of >6500 non-ICU hospitalised patients with COVID-19 found a VTE rate of approximately 3 percent \(^{[42]}\). The data regarding the rate of PE in COVID-19 pneumonia treated as outpatient is more limited. One study of 72 outpatients with COVID-19 pneumonia showed a rate of 18% as confirmed by CTPA\(^{[43]}\).

K) Diagnosis of VTE/PE in COVID-19 infection:

Clinically patients with COVID-19 pneumonia who complicated by PE may have no additional symptoms. Indicators that might point towards PE in such patients include increased respiratory and heart rate and hypoxia out of proportion to the severity of pneumonia or development of pleuritic chest pain or less commonly new pleural effusion incongruent to the location of the consolidation on chest imaging. Biochemical evaluation should include: Complete blood count (CBC) including platelet count.

Coagulation studies (prothrombin time [PT] and activated partial thromboplastin time [aPTT]), Fibrinogen and D-dimer. A daily measurement of these blood rests can aid in making a diagnosis of PE. Of note mild thrombocytopenia or thrombocytosis, or normal platelet count are all documented in COVID-19 associated PE. Some of these values, especially D-dimer have prognostic value and may impact decision-making about the escalation of the level of care. A study of 343 patients enrolled from Wuhan Asia General Hospital showed D-dimer on admission greater than 2.0µg/mL (fourfold increase) could effectively predict in-hospital mortality in patients with Covid-19, and that D-dimer could be an early and helpful marker to improve management of Covid-19 patients\(^{[44]}\). Electrocardiogram (ECG), albeit none sensitive test and may be normal, can be of value in making a diagnosis of PE especially in the presence of ECG signs of right ventricular strain in patients suspected of PE.

CTPA, and in special situations V/Q scan, are gold standard image modalities of choice to diagnose PE. In patients with high pertest probability of PE with elevated D-dimer in whom CTPA or V/Q scan are not feasible, treatment with anticoagulation is recommended without delay, unless there are absolute contraindications for anticoagulation such as life threatening or intracranial bleeding. Echocardiogram is another alternative none radiation emitting scan to look for evidence of right ventricular strain and/or blood clots in pulmonary trunk right or left pulmonary arteries. Although, echocardiogram has lower sensitivity for detecting segmental and none segmental blood clots.

I) Service set up and treatment of VTE/PE during the pandemic:

During the pandemic in the state of Qatar, Hamad Medical Corporation launched Hamad General Hospital Anticoagulation Virtual Clinic for patients diagnosed PE and discharged from hospital to minimize the exposure of patients and healthcare providers to and to promote social distancing\(^{[45]}\). This service promotes early and regular follow up of discharged patients and with the view of managing any complications from anticoagulation and early detection of chronic complications such Chronic Thromboembolic Pulmonary Hypertension (CTEPH) and Cor pulmonale.

We recommend the use of European Society of Cardiology Guideline of management of Acute PE for a comprehensive assessment of patients with PE. A special attention needs to be paid risk stratification of PE (table 1) for early detection and prompt treatment of...
massive PE, as the latter is a life-threatening medical emergency that require urgent intervention.

In acute and hospital settings, Qatar’s Communicable Diseases Centre (CDC) version 11 Treatment Protocol for confirmed COVID-19 Infection, table 2, recommends routine VTE prophylaxis via anticoagulation, mechanical compression and early mobilisation. The protocol advises adjustment in the dose of anticoagulation according to the level of rise in D-dimer. Emergency resuscitation including thrombolysis by using tissue plasminogen activator (tPA), table 3, is indicated in massive PE (PE with haemodynamic instability). Thrombolysis can also be used, albeit more controversially, for intermediate-high risk PE (Abnormal RV function AND elevated BNP or troponin).
Table 1: classification and risk stratification of acute PE as per European Society of Cardiology Guideline

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Indicators of risk</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Haemodynamic instability(^a)</td>
<td>Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td>(+)(^d)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate–high</td>
<td>-</td>
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<tr>
<td></td>
<td>Intermediate–low</td>
<td>-</td>
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<tr>
<td>Low</td>
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\(^{a}\) PESI: Pulmonary Embolism Severity Index; \(^{b}\) TTE: transthoracic echocardiogram; CTPA: computed tomography angiography; \(^{c}\) Cardiac troponin: specific markers for myocardial injury.

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Table 2: Qatar’s Communicable Diseases Centre (CDC) version 11 recommendation of prophylaxis against VTE and dose adjustment of anticoagulation according to D-dimer level.

- Adopted from HMGH local protocol for Management of Anticoagulation in COVID19 pneumonia patients admitted to Intensive Care Unit May 2020
- All patients should be routinely placed on routine standard LMWH prophylaxis, with the exception of pregnant women >>>20 weeks gestation who should receive unfractionated heparin.

❖ Suggested oral anticoagulation for severely ill patient with COVID19 Pneumonia and high-risk patients for VTE:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>note</th>
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<tbody>
<tr>
<td>Rivaroxaban</td>
<td>10 mg</td>
<td>once daily</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>220 mg</td>
<td>once daily</td>
<td>Preferred in patients with chronic liver disease</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5 mg</td>
<td>twice daily</td>
<td>Preferred in patients with renal impairment</td>
</tr>
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</table>

✓ For severely ill patient’s oral anticoagulation is advised for 35±4 days as VTE prophylaxis unless there is contraindication

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Table 3: emergency resuscitation of massive PE, as defined by the presence of haemodynamic instability: hypotension is defined as a systolic blood pressure (BP) <90 mmHg for a period >15 minutes or a drop in systolic blood pressure substantially below baseline (generally a drop of >40 mmHg

Massive PE – Initial resuscitation

- **Fluid-conservative strategy**
  - Rarely helpful (venous pressure generally already excessively high)
  - Don’t give fluid unless evidence of low filling pressure (e.g. small IVC or collapsed jugular veins)

- **Pressor-aggressive strategy**
  - Epinephrine good front-line agent, titrate for MAP > 65 mm
  - Vasopressin as second-line agent

- **Inhaled pulmonary vasodilators**
  - Epoprostanol or nitric oxide – whatever you can get fastest.
  - If refractory may consider combination of nitric oxide plus epoprostanol.

- **Thrombolysis**
  - No contraindication: 100 mg alteplase.
  - Relative contraindication & actively dying: 100 mg alteplase.
  - Relative contraindication & stabilized: may start with 50 mg alteplase.

- **Other PE-directed therapies (tPA failure/contraindication)**
  - Interventional radiology clot extraction (e.g. FlowTriever)
  - Cardiothoracic surgical extraction
  - VA ECMO

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3- COVID-19 and Pneumothorax/pneumomediastinum:

Keywords: Pneumothorax, barotrauma, pneumomediastinum, positive end expiratory pressure, subcutaneous emphysema, tension pneumothorax.

Pneumothorax can be the presenting complication of COVID-19 infection or develop in hospital in patients on room air or receiving oxygen therapy via O2 mask, none invasive or invasive positive pressure ventilation (46). Nonetheless, the majority cases of pneumomediastinum and pneumothorax complications occur as the result of barotrauma caused by invasive mechanical ventilation (47). Spontaneous pneumothorax commonly presents with sudden onset pleuritic chest pain, tachypnoea and/or dry cough and are occasionally detected incidentally on chest x-rays, figure 1 (48). Iatrogenic pneumothorax related to mechanical ventilation is more common in patients with pre-existing lung disease(49). The mechanism of ventilation related alveolar rapture is poorly understood. High positive end expiratory pressure (PEEP) used for maximum alveolar recruitment to improve oxygenation in adult respiratory distress syndrome is associated with higher rate of pneumothorax (50). However several studies failed to confirm this correlation (51). Human and animal studies suggested deployment of low tidal volume lung protective ventilation might reduce the risk of barotrauma and consequent development of pneumothorax, pneumomediastinum and surgical emphysema(52-54). Other studies showed that low lung compliance, as a surrogate for lung damage, not ventilator settings, are more accurate predictor of barotrauma(55-57).

In majority of patients, severe mediastinal emphysema, pneumothorax are self-limiting and require no invasive intervention. Subcutaneous emphysema usually tracks superiorly and in extremely severe cases may constrict the main airway and impede blood flow in head and neck vessels. The British Thoracic Society Guidelines of management of pneumothorax provides important practical advice, figure 2, depending the size of the air leak as well as how to manage acute medical emergencies such as tension pneumothorax. This guideline describes different interventions such as needle aspiration, portable chest drains, Seldinger technique to more invasive surgical chest drain insertion in cases of large air leak.

The impact of barotrauma on mortality rate and ICU stay is controversial. A case series of 71 patients from 16 centres, of whom 60 had pneumothoraces (6 with pneumomediastinum in addition); showed 28 days survival was not significantly different following pneumothorax (63.1±6.5%) or isolated pneumomediastinum (53.0±18.7%; p=0.854). Therefore, this study suggested that a diagnosis of pneumothorax/pneumomediastinum did not signify as a marker of poor prognosis(46). However, a prospective cohort of 361 intensive care units from 20 countries showed that barotrauma was associated with a significant increase in the ICU length of stay and mortality(58).
COVID-19 and pleural effusion and empyema:
Keywords: pleural thickening, pleural effusion, empyema, thoracocentesis, chest drain

Pleural effusion and empyema caused directly by COVID-19 infection is rare. Pleural effusion is more likely to be secondary to superadded bacterial infection and/or pleural inflammation. Therefore, the same principles of managing parapneumonic effusion and empyema must be applied in patients with COVID-19 and pleural effusion. In an observational study, high-resolution CT features of 42 patients (26–75 years, 25 males) with COVID-19 were examined. 5/42 (12%) scans showed pleural effusion. In follow up HRCT performed to monitor glass ground changes a higher rate of pleural effusion was detected (16/42, 38%)(59). Management of parapneumonic pleural effusion has changed significantly in the past few years as indications for pleural fluid drainage are becoming more specific and guideline based. The distinction between transudative and exudative based on the Light’s criteria remains an important step in deciding whether pleural intervention is required or not. The British Thoracic Society provides a practical diagnostic and therapeutic algorithm to manage suspected infected pleural effusion.
Figure 1: Spontaneous right pneumothorax with small pleural effusion (red arrows). The patient had COVID-19 but no respiratory symptoms at presentation. The pneumothorax was an incidental finding on the chest x-rays.
Figure 2: British Thoracic Society flowchart of managing spontaneous pneumothorax.

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Algorithm: BTS diagnostic and management of infected pleural effusion

**Diagnostic algorithm for the management of patients with pleural infection**

1. **History, examination & Chest X Ray**
2. **Pleural effusion and evidence of infection?**
   - **YES**
     - **INVOLVE RESPIRATORY PHYSICIAN**
     - Nutrition and DVT prophylaxis
     - Start antibiotics
     - Diagnostic pleural aspiration using Ultrasound guidance
   - **NO**
     - **Failed Sampling?**
     - **Small, loculated effusion?**
     - **YES**
       - Consider CT scan and further image guided aspiration
     - **NO**
       - **Pu's?**
       - **YES**
         - Fluid pH
         - Send M.C & S
         - **Gram stain &/or culture positive &/or pH <7.2**
         - **YES**
           - Observations unless clinical indication for chest tube
         - **NO**
           - **Repeat fluid sampling**
           - **Poor clinical response**
       - **NO**
         - **Insert chest tube**
         - **Is the patient better?**
         - **(CXR fluid drained & sepsis improved) Day 5-7**
         - **YES**
           - **Remove tube**
         - **NO**
           - **1. Check tube position on chest X ray**
           - **2. Assess tube, residual collection with contrast enhanced CT imaging**
           - **3. Early liaison with thoracic surgeons**
           - **Is the patient fit for radical treatment?**
           - **YES**
             - Surgical therapy
           - **NO**
             - **Consider large bore drain insertion; less radical surgical techniques, palliative care measures**

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COVID-19 diagnostic chest imaging,

Keywords: chest radiograph, chest x-rays, COVID-19 pneumonia, ground-glass opacities, consolidation, spontaneous pneumothorax, Computed tomography (CT) of the chest, high resolution chest scan, HRCT, CT pulmonary angiogram, CTPA, machine learning method for image-based diagnosis of COVID-19, crazy paving pattern, lung/pleural ultrasound, pleural effusion, chest drain.

A- Chest radiograph (x-rays):
As the first line chest imaging, chest radiograph (x-rays) is an easily accessible and cheap modality that emit low dose radiation. However, it can be normal in COVID-19 pneumonia, for example, a review of chest x-rays of 64 patients with documented COVID-19 in Hong Kong showed no abnormalities (60). Therefore, normal chest x-rays, figure 1, does not exclude COVID-19 pneumonia. In early stages of the disease, up to 63% of patients with covid-19 pneumonia may have normal chest x-rays (61, 62). The appearance of ground glass appearance commonly proceeds consolidation in majority of cases (60, 63). A systematic literature review with meta-analysis of 27% showed that bilateral lung changes are more common than unilateral lung involvement, 72.9% and 25% respectively (64)

In keeping with the natural clinical progression of COVID-19 pneumonia, most patients develop signs on their chest x-rays between 10 to 14 days after the onset of their symptoms (65). There is no one specific signs that is diagnostic of COVID-19 pneumonia on chest radiograph; it is rather a constellation of signs that are seen on chest x-rays, congruent with clinical features and results from blood tests that leads to a diagnosis of covid-19 pneumonia. Validation of the British Society of Thoracic Imaging guidelines for COVID-19 chest radiograph reporting, box 1, states that consolidation and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions; lung involvement increased over the course of illness are common radiographic findings, figure 2, of COVID-19 pneumonia (62).

Spontaneous pneumothorax, albeit not common, but can be the presenting manifestation of COVID-19 infection. Spontaneous pneumothorax was detected in 40 patients (0.56%) in a retrospective analysis of over 70,000 patients with COVID-19 presented to Spanish emergency rooms(66). There are only very few reports of bilateral pneumothorax caused by COVID-19 without a history of pre-existing lung disease such as chronic obstructive airway disease, including one case report from Qatar, (67). Several investigators around the world, including from Qatar, have published interesting data showing the role of automated and machine learning algorithm to diagnose COVID-19 pneumonia on chest x-rays (68-70)
B- **Computed tomography (CT) of the chest:**
Routine use of chest CT is not recommended for screening or to make a diagnosis of COVID-19 pneumonia; as findings from history, physical examination, blood tests and chest x-rays are sufficient, in the majority of cases, to diagnose COVID-19 pneumonia. the American College of Radiology (ACR) recommend chest CT only for hospitalized patients to advise management.

Chest CT might be normal in early disease or in patients with no COVID-19 pneumonia, on the other hands, chest CT can be abnormal in a symptomatic or preclinical patient during the prodromal phase of the infection(71, 72). By enlarge, CT chest is considered to be more sensitive compared to chest radiograph in detecting early changes within the lung interstitium, pleural and the mediastinum(72, 73). Although none of the CT findings are specific to COVID-19 pneumonia as they can occur in most viral, inflammatory or bacterial causes of pneumonia.(72, 73).

The CT findings are bilateral in the majority of cases of COVID-19 pneumonia. Ground glass changes (GGC), a feature of viral pneumonia, is the commonest CT finding(72, 74, 75). Other less common CT features (of no specific order) are: **a crazy paving pattern** (ground-glass opacifications with superimposed septal thickening), lymphadenopathy, pericardial effusion, pleural effusion, , and bronchiectasis.

Bao C et al, carried out a systematic review and metanalysis of 2700 patients with acute COVID-19 infection, and produced the following list of commonest CT features(76):
1. Ground-glass opacifications – 83%
2. Ground-glass opacifications with mixed consolidation – 58%
3. Adjacent pleural thickening – 52%
4. Interlobular septal thickening – 48%
5. Air bronchograms – 46%

**High resolution CT scan (HRCT),** which uses no contrast, hence causes no contrast related complications such as nephrotoxicity or anaphylaxis, not CT pulmonary angiogram (CTPA), is the modality of choice to be used if CT chest is required. CTPA is recommended if there’s a clinical suspicion of pulmonary embolism that requires radiological confirmation.

To prevent inconsistencies and to standardize the language of radiological reporting, the ACR produced a useful table that is encouraged to be used by health systems, **table 1.**

C- **Lung/pleural ultrasound:**
Ultrasound of the lung and or pleura has limited tole in the diagnosis of COVID-19 infection.

Lung ultrasound findings in COVID-19 pneumonia includes non-specific changes, for example: multifocal, or confluent; patchy, strip, and nodular consolidations; thickening, discontinuation, and interruption of the pleural line and air bronchogram if consolidation is present(77-79).

Pleural ultrasound is particularly to assess pleural effusion and to guide pleural procedures such as diagnostic and/or therapeutic pleural needle aspiration or insertion of intercostal tube to drain pleural effusion.
Figure 1: A: normal chest x-rays in a patient with COVID-19 pneumonia. B: CT chest of the same patient, within 1 hour of the chest x-rays, showing infective infiltrates (ground glass changes) in the right lower lobe (red arrows).

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Figure 2: Examples of the COVID BSTI categories for plain films, in each case all radiologists agreed on the categorisation. (a) Anteroposterior (AP) erect radiograph demonstrating “Classic COVID-19”. (b) AP erect chest radiograph “Indeterminate for COVID-19”. (c) AP erect radiograph classified as “COVID normal”. (d) AP erect radiograph classified as “Non-COVID”.

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Box 1: The British Society of Thoracic Imaging chest radiography reporting criteria.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>COVID-19 not excluded, please correlate with PCR</td>
</tr>
<tr>
<td>Classic/probable COVID-19</td>
<td>Lower lobe and peripheral predominant multiple opacities that are bilateral (&gt;&gt; unilateral)</td>
</tr>
<tr>
<td>Indeterminate for COVID-19</td>
<td>Does not fit Classic or Non-COVID-19 descriptors” or “poor quality film</td>
</tr>
<tr>
<td>Non-COVID-19</td>
<td>Pneumothorax/lobar pneumonia/pleural effusion(s)/pulmonary oedema/other</td>
</tr>
</tbody>
</table>

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Table 1: American College of Radiology (ACR) suggested corresponding language for the interpretation report and has categorized features as typical, indeterminate, or atypical for COVID-19(80).

<table>
<thead>
<tr>
<th>COVID-19 pneumonia imaging classification</th>
<th>Rationale</th>
<th>CT findings</th>
<th>Suggested reporting language</th>
</tr>
</thead>
</table>
| Typical appearance | Commonly reported imaging features of greater specificity for COVID-19 pneumonia. | - Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving")
- Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving")
- Reverse halo sign or other findings of organizing pneumonia (seen later in the disease) | "Commonly reported imaging features of COVID-19 pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern." |
| Indeterminate appearance | Nonspecific 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. | "Imaging features can be seen with COVID-19 pneumonia, though are nonspecific and can occur with a variety of infectious and noninfectious processes." |
| 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 cavitition
  - Smooth interlobular septal thickening with pleural effusion | "Imaging features are atypical or uncommonly reported for COVID-19 pneumonia. Alternative diagnoses should be considered." |
| Negative for pneumonia | No features of pneumonia. | - No CT features to suggest pneumonia. | "No CT findings present to indicate pneumonia. (NOTE: CT may be negative in the early stages of COVID-19.)" |

Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA.

Chapter: Critical Care and Respiratory Medicine.
Chapter: Critical Care and Respiratory Medicine

Keywords:
Critical care medicine and COVID-19 infection

Intensive care unit (ICU), invasive mechanical ventilation (IMV), adult respiratory distress syndrome (ARDS), ventilation mode, tidal volume, positive end expiratory pressure, tracheostomy, weaning from mechanical ventilation.

A: Epidemiology:

Of the 20% of patients with COVID-19 infection requiring hospitalisation, up to one-quarter need intensive care unit (ICU) admission, which is 5 to 8% of all infected patients(5). Patients who received ventilation varies from between regions, reflecting differences in population mean age and different ICU protocols for ventilation. For example, 5700 patients hospitalized with COVID-19 in New York, 1151 (20 percent) required mechanical ventilation(81). Younger populations with fewer somebodies are likely to require ICU admission and mechanical ventilation. A good example is that in the State of Qatar 2.0% of confirmed COVID-19 patients had severe or critical illness, in a sample of 5685 cases of COVID-19 (4). In term of sex distribution of ICU admitted patients, results are mixed. In Chinese cohort, ¾ of critically ill cases were male, however other studies showed equal male to female distribution and some studies showed more male preponderance (82-85)

B: Risk factors for critical and rapid progression of disease:

I) Age: Older age is also associated with more risk of critical illness and increased mortality(3, 85). A seminal report by Chinese CDC case stated that fatality rates were 8 and 15 percent among those aged 70 to 79 years and 80 years or older, respectively, in contrast to the 2.3 percent case fatality rate among the entire cohort(3). A large data analysis of from the UK showed that individuals 80 years and older was 20-fold that among individuals 50 to 59 years old(86). By contrast <2 percent of children and adolescent suffered from a fatal disease (86).

II) Comorbidities: the following conditions are likely to be associated with more critical illness(3, 87-89):

- Chronic lung diseases.
- Cardiovascular diseases
- Diabetes
- Obesity
- Chronic kidney diseases
- Hypertension
- Smoking

III) Demographic features: Data from the United States indicates that patients of non-white background have higher incidences of Critical Care illness and admission to ICU. This is likely be due to inequality in healthcare and lack of adequate medical support to individuals from disadvantaged social economic backgrounds(86, 90).

IV) Laboratory findings: the following laboratory abnormalities seem to be associated with more critical illness and higher risk of admission to ICU(91-94).

[Type here]
• Lymphopenia
• Thrombocytopenia
• Acute kidney injury
• Elevated liver enzymes
• Elevated troponin level
• Elevated D-dimer (>1 mcg/mL)
• Elevated inflammatory markers (eg, C-reactive protein [CRP], ferritin) and inflammatory cytokines (ie, interleukin 6 [IL-6] and tumor necrosis factor [TNF]-alpha)
• Elevated lactate dehydrogenase (LDH)
• Elevated prothrombin time (PT)
• Elevated creatine phosphokinase (CPK)

V) Genetic factors: there are reports of severe illnesses and increased mortality clustering in certain families which gives rise to the possibility of genetic predisposition for severe disease(95, 96). A genome-wide association study identified a relationship between polymorphisms in the genes encoding the ABO blood group and respiratory failure from COVID-19 (type A associated with a higher risk and type B associated with lower risk of infection and severe disease)(97).

VI) Viral load: a higher viral RNA levels in respiratory specimens than those with milder disease(98, 99). However other reports showed conflicting data in relation to the correlation between viral load and disease severity(100, 101). Some studies showed that the detection of viral RNA in the plasma has a higher association with end organ damage (lungs, kidneys and heart), coagulopathy and mortality(102-104).
C: Clinical features of critically unwell patients:

The range of need for invasive mechanical ventilation (IMV) in ICU ranges from 30 to 100% (83, 84). Severe hypoxia associated with Adult Respiratory Distress Syndrome (ARDS) and very rarely hypercapnia are markers of respiratory failure (5, 6, 83, 87). Patients in ICU commonly have fever of wax and wane pattern (87, 105, 106). The following are commonly seen complications of patients admitted to ICU:

I. ARDS:

An acute, diffuse, inflammatory form of lung injury. ARDS is a frequent complication of COVID-19 infection in ICU patients (92). The degree of hypoxemia determines the severity of ARDS to mild, moderate and severe, as per Berlin classification, table 1. Moderate and severe ARDS mandate IMV.

In ARDS there’s excessive fluid leak to lung parenchyma and alveolar space. This is resulted from endothelial injury caused by the release inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8. This fluid leak leads to impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure (107, 108). ARDS results in impairment/dysfunction and three main domains:

i. Impaired gas exchange: Fluid leakage to the lung parenchyma and the alveolar space causes increases V/Q mismatch and increased physiological dead space.

ii. Decreased lung compliance: the non-aerated or poorly aerated lung becomes stiff and therefore reduce lung compliance. A small raise in tidal volume will lead to a dramatic rise in airway pressures.

iii. Pulmonary hypertension – Pulmonary hypertension (PH) occurs in up to 25 percent of patients with ARDS who undergo mechanical ventilation (109, 110)

II. Special consideration of IMV in ARDS:

- Low tidal volume ventilation (LTVV): LTVV is recommended with a target of less than 6ml/kg predicted body weight. A volume-limited assist control mode is a commonly used mode of ventilation.

- Prone ventilation: seems to be more effective in COVID-19 associated ARDS in comparison to the causes of ARDS. Criteria for prone ventilation includes: partial arterial pressure of oxygen/fraction of inspired oxygen [PaO₂:FiO₂] ratio <150 mmHg, a FiO₂ ≥0.6, and PEEP ≥5 cm H₂O; excessively high airway pressures; or recalcitrant hypoxemia

- Recruitment manoeuvres and high PEEP are often used to improve oxygenation.

- Neuromuscular blockade: muscle relaxants are used in patients with refractory hypoxaemia and/or poor patient ventilator synchrony.

- Extracorporeal membrane oxygenation (ECMO): ECMO is used as a rescue strategy in patients with refractory hypoxaemia with or without hypercapnia who failed to respond to the above interventions. ECMO is not widely available and requires special expertise to be implemented effectively and safely.
III: Extubation and weaning from IMV:
The same criteria of exhibition and weaning from IMV due to other pathologies are applied. However, patients are still considered contagious therefore standard precautions for aerosol generated procedures should be deployed. Initial weaning trials of pressure support ventilation (PSV) is the standard. Once the patient successfully breath spontaneously for 16 to 24 hours on PSV, then he/she can progress to spontaneous breathing trials (SBTs). This process might take few days or a few weeks.

IV: Tracheostomy: it’s commonly used for patients who are expected to be ventilated for more than one week. Other common indications are failed extubation, secretion management, airway oedema, neurological impairment such as that impairs airway protection. There is no strong evidence to guide the exact timing of tracheostomy, however 7 to 10 days following incubation is a feasible option, this is extrapolated from studies of non-COVID intubated patients(111).

V: Sedation and analgesia:
There is no evidence to guide the use of sedation and analgesia in intubate patients. There is anecdotal evidence indicating that COVID-19 intubated patients seem to require larger doses of sedation to achieve optimum ventilation. Both propofol and fentanyl are used regularly in most ITU units worldwide.

VI: Nutrition and bowel care:
There is no evidence to guide the use of a specific nutritional supplementation to COVID-intubated patients. Early administration of nutritional supplement via nasal gastric tube is encouraged. There is no strong evidence to support the use of high protein formulas or supplementation with specific vitamins or minerals that is different from non-COVID-19 intubated patients. Adequate monitoring of sluggish bowel movement or poor absorption is required; prokinetics such as metoclopramide or domperidone can be administered to improve bowel motion and absorption.

VII: Daily monitoring:
Patients treated in ITU should be regularly monitored for common and important complications. Daily physical examination, reviewing fluid balance, glucose chart, arterial/venous blood gas analysis, ECG and baseline blood investigations are recommended. The aim is to identify complications and intervening promptly. Special attention should be paid to detect DVT, hypoglycaemia, electrolyte disturbances, transaminitis, fluid imbalance, pericarditis/pericardial effusion, plural effusion and barotrauma.

VIII: Management of hospital acquired or ventilation associated infection/pneumonia (HAP and VAP respectively) and other comorbidities:
Patient care for in ITU are at high risk of HAP and in intubated patients VAP. Antibiotic use should be rationalised based on results from culture and sensitivities with advice from clinical microbiologists and infectious diseases specialists. Special attention must be paid to early detection of Central line and other catheter associated infections. Hypothermia and hypothermia should be detected early and corrected according to patient’s clinical needs. Important complications such as pressure sores and formation of peripheral ischaemia and gangrene have to be treated aggressively with members of the multidisciplinary team.
Chronic medical conditions, such as chronic obstructive airways disease/asthma, diabetes mellitus, ischaemic heart disease, hypertension, chronic kidney disease and others have to be managed by respective specialities to optimise standard biological outcomes.

XI: Long-term complications:
Early data and anecdotal experience suggest that a significant proportion of COVID-19 intubated patients suffer from long-term sequels of prolonged incubation, use of nerve blockade and corticosteroid therapy. Critical illness myopathy, psychological and cognitive trauma have to be addressed by specialised rehabilitation units that involves physiotherapists, occupational therapists, counsellors and psychologists.
Table 1: Berlin grades of severity of ARDS:
PEEP: positive end expiratory pressure.

<table>
<thead>
<tr>
<th>ARDS Severity</th>
<th>( \text{PaO}_2/\text{FiO}_2 \text{ Ratio} ) (mmHg)</th>
<th>PEEP (cmH}_2\text{O})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>(200 &lt; \text{PaO}_2/\text{FiO}_2 \leq 300)</td>
<td>(\geq 5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>(100 &lt; \text{PaO}_2/\text{FiO}_2 \leq 200)</td>
<td>(\geq 5)</td>
</tr>
<tr>
<td>Severe</td>
<td>(\text{PaO}_2/\text{FiO}_2 \leq 100)</td>
<td>(\geq 5)</td>
</tr>
</tbody>
</table>
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54. Miller MP, Sagy M. Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung

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