Oxygenation and Ventilation Strategies: COVID-19

This summary is based on the best available evidence, which is minimal, and anecdotal experience from countries with high disease burden. It may change as our understanding of the pathophysiology of COVID-19 evolves.

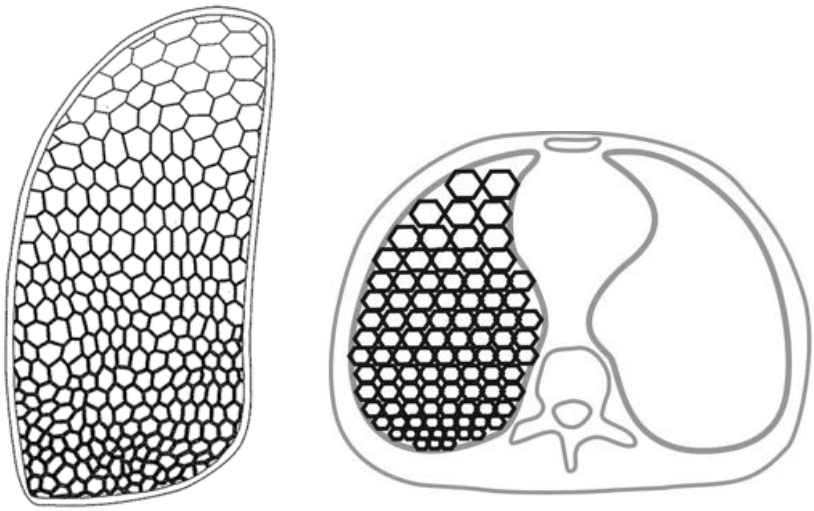
Normal Lung Physiology

Distribution of Pulmonary Blood Flow

Gravity has a significant effect on pulmonary blood flow:

- In the upright position, flow decreases linearly with height (more flow in the bases)
- In the supine position, flow to the posterior lung exceeds flow to the anterior regions

This occurs due to the low driving pressure of the pulmonary circulation, which means gravity has more of an effect on pulmonary blood flow than it does on systemic blood flow.

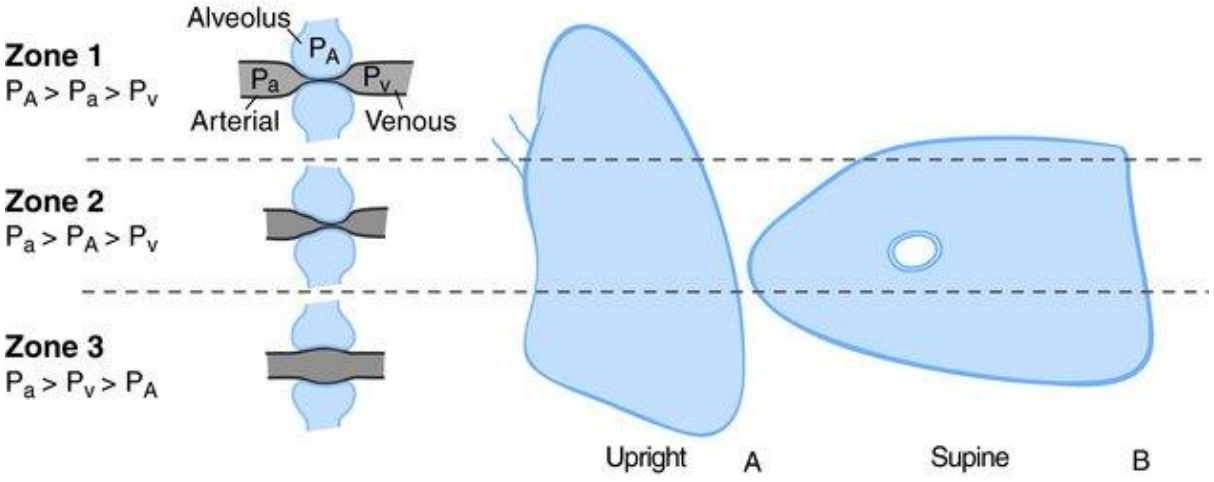


West's Zones of the Lungs

The lung is divided into four zones, based on the relationship between alveolar and vascular pressures.

- Zone 1

    - Alveolar pressure exceeds arterial pressure
    - Little gas exchange takes placed
    - Blood flow is limited
    - Does not occur in normal conditions
    - May occur with: Haemorrhagic shock, positive pressure ventilation/high PEEP
- Zone 2
    - Flow is determined by the arterial-alveolar pressure gradient rather than the arterial-venous gradient
    - Flow is therefore independent of downstream pressure
- Zone 3
    - Occurs when alveolar pressure falls below venous pressure
    - Flow is dependent on the arterial-venous pressure gradient
    - Flow in this zone exceeds blood flow in all other zones
- Zone 4
    - Occurs at low lung volumes
    - Extra-alveolar vessels collapse and shunt occurs
    - This is the bulk of the atelectatic or oedematous lung at the very base of the chest cavity



Hypoxic Pulmonary Vasoconstriction

There are some differences in the blood and gas supply to different lung regions, i.e. some regions receive good ventilation and poor blood flow, whereas other regions are rich in blood supply but receive little air. This is known as ventilation/perfusion mismatch (VQ mismatch)

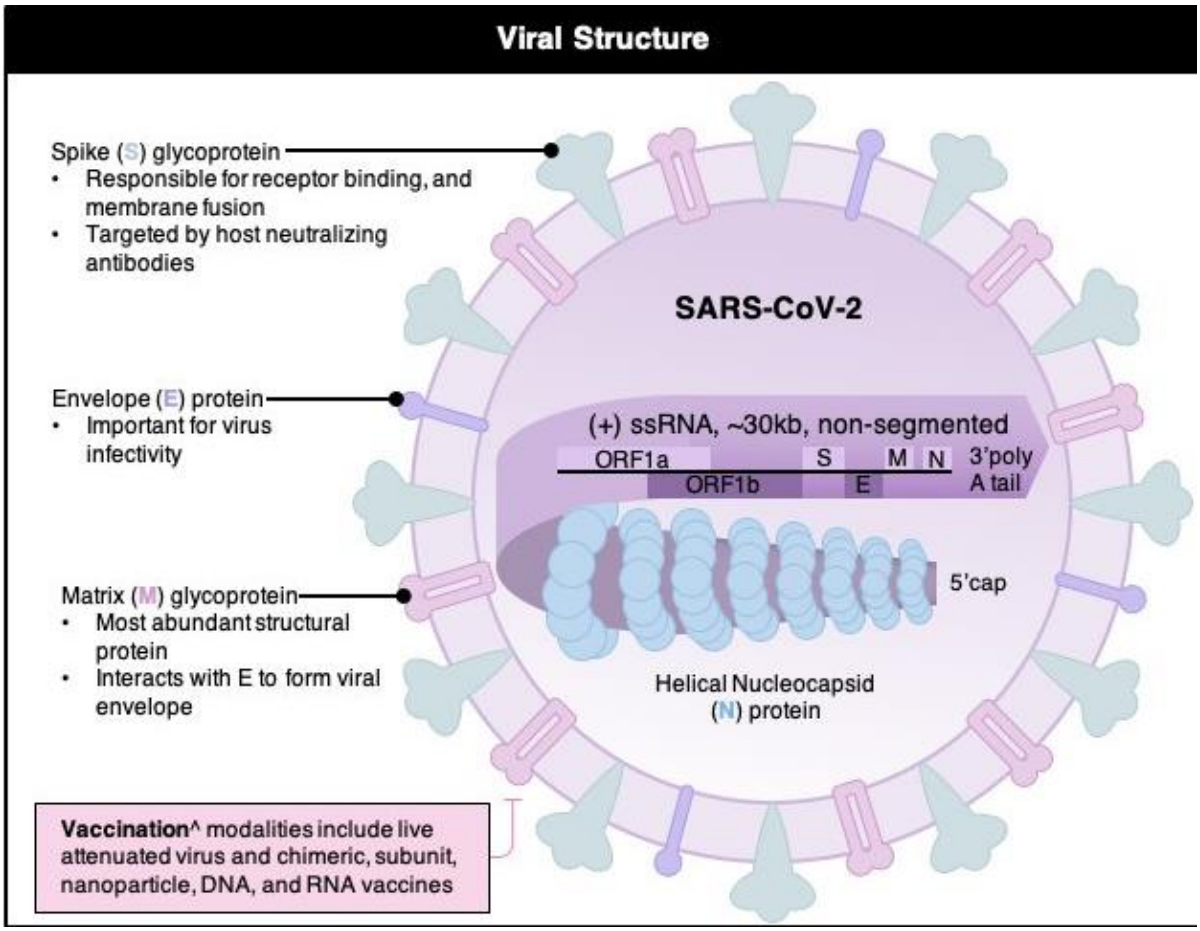
Hypoxic pulmonary vasoconstriction (HPV) allows redirection of blood flow from poorly ventilated regions of the lung in order to improve V/Q mismatching.

HPV is relevant in disease states, as well as specific physiologic circumstances (altitude, at birth)

Proposed Respiratory Pathophysiology of COVID-19

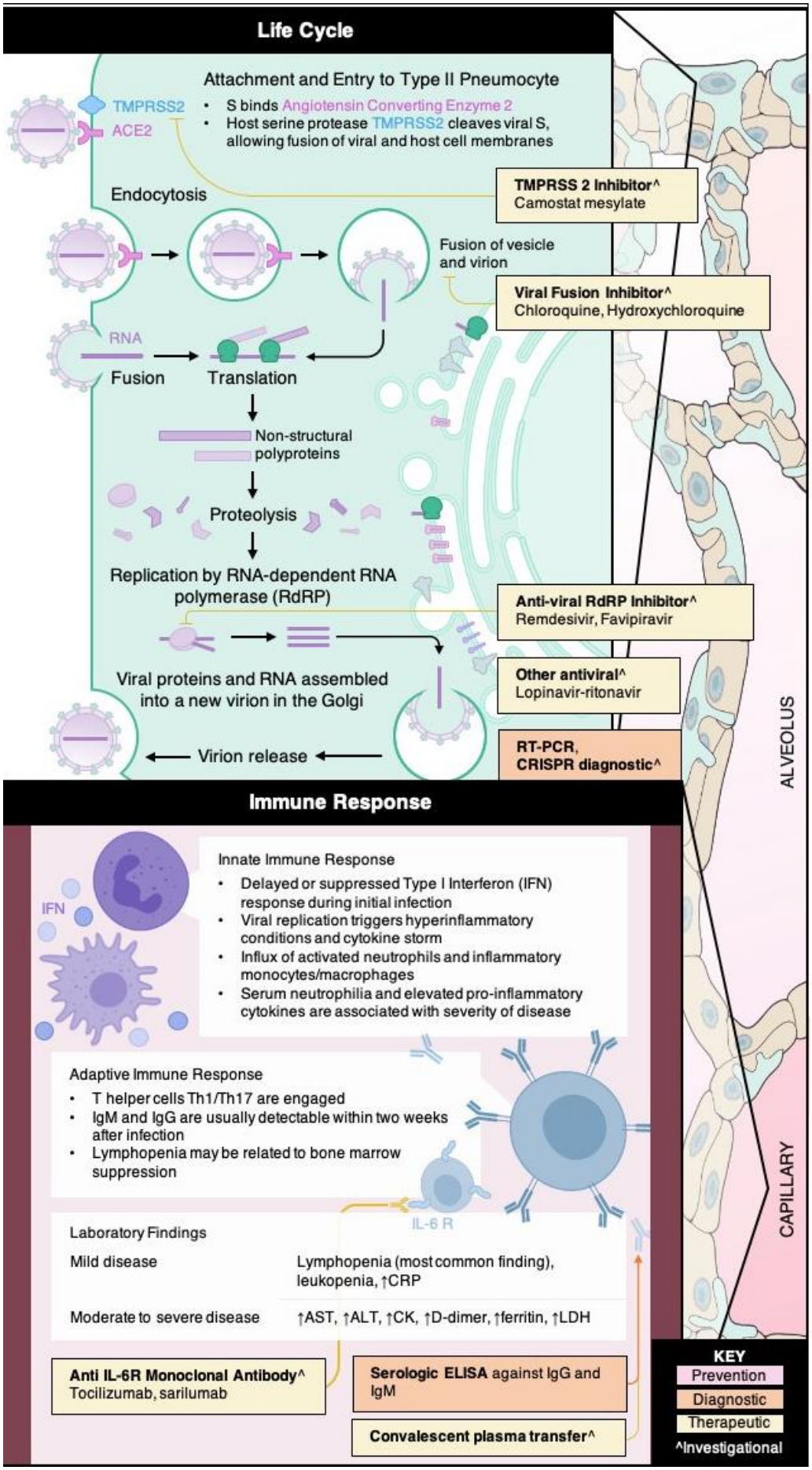
General underlying process

The SARS-CoV-2 virus enters cells via attachment of its virion spike protein (S-protein) to the ACE-2 receptor. This receptor is commonly found on alveolar cells (Type 2 pneumocyte) of the lung epithelium, hence the commonest presentation of COVID-19 as primarily a disease with respiratory symptoms. It is thought that the mediation of the les common CVS effects is also via the same ACE-2 receptor.



The high turnover of virus within the pneumocyte leads to cell stress and apoptosis. There is also an associated chemokine surge with neutrophil recruitment. At a microscopic level, the above events lead to a loss in the interface between the alveolar space and surrounding stroma, with fluid leakage and filling of alveolar sacs.

The respiratory changes seen in COVID-19 are amplified by multiple 'indirect' insults to the pulmonary vasculature, which raise resistance to blood flow and cause a patchy VQ mismatch throughout the lungs.

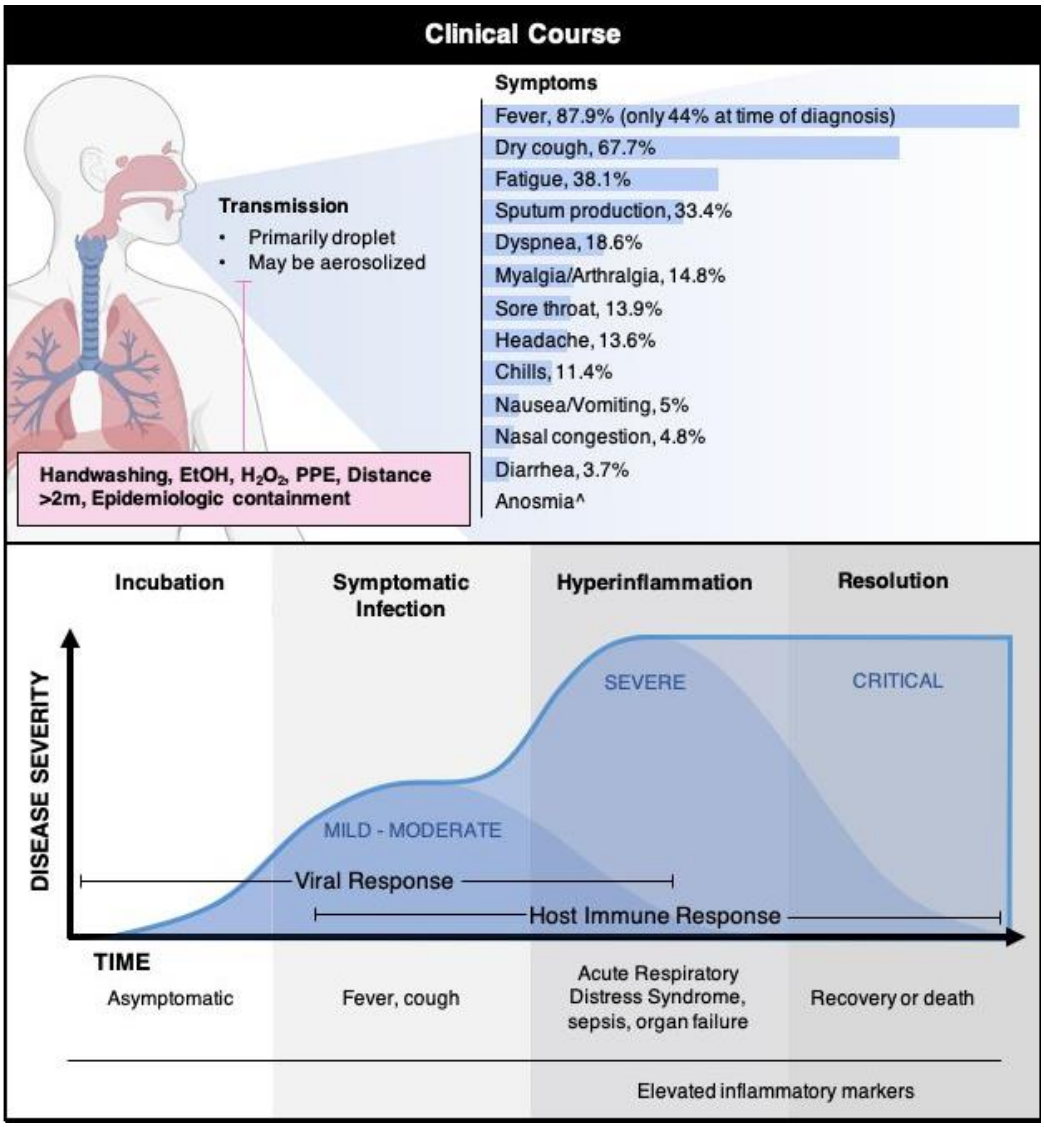

Life Cycle
Attachment and Entry to Type II Pneumocyte
TMPRSS2
ACE2
S binds Angiotensin Converting Enzyme 2
Host serine protease TMPRSS2 cleaves viral S, allowing fusion of viral and host cell membranes
TMPRSS 2 Inhibitor^
Camostat mesylate
Endocytosis
Fusion of vesicle and virion
Viral Fusion Inhibitor^
Chloroquine, Hydroxychloroquine
RNA
Fusion
Translation
Non-structural polyproteins
Proteolysis
Replication by RNA-dependent RNA polymerase (RdRP)
Anti-viral RdRP Inhibitor^
Remdesivir, Favipiravir
Other antiviral^
Lopinavir-ritonavir
Viral proteins and RNA assembled into a new virion in the Golgi
RT-PCR,
CRISPR diagnostic^
Virion release
ALVEOLUS
Immune Response
IFN
Innate Immune Response
Delayed or suppressed Type I Interferon (IFN) response during initial infection
Viral replication triggers hyperinflammatory conditions and cytokine storm
Influx of activated neutrophils and inflammatory monocytes/macrophages
Serum neutrophilia and elevated pro-inflammatory cytokines are associated with severity of disease
Adaptive Immune Response
T helper cells Th1/Th17 are engaged
IgM and IgG are usually detectable within two weeks after infection
Lymphopenia may be related to bone marrow suppression
IL-6 R
Laboratory Findings
Mild disease
Lymphopenia (most common finding), leukopenia, ↑CRP
Moderate to severe disease
↑AST, ↑ALT, ↑CK, ↑D-dimer, ↑ferritin, ↑LDH
Anti IL-6R Monoclonal Antibody^
Tocilizumab, sarilumab
Serologic ELISA against IgG and IgM
Convalescent plasma transfer^
CAPILLARY
KEY
Prevention
Diagnostic
Therapeutic
^Investigational

These indirect insults include:

- Microthrombi
- Hypoxaemic vasoconstriction
- Hypercapnia
- Interstitial oedema

Of note, when lung stress is abnormally high, over-distention of inhomogenous lung (i.e. from over-use of PEEP) will result in excessive West Zone 1, particularly during inflation, which raises transmural pressure in corner blood vessels and favours interstitial oedema, especially when vessels are already particularly "leaky". This can then compound the underlying problem.

Clinical Course and Correlation with Management Principles



Course of the Disease

There are four proposed phases of disease:

(1) Mild disease
    a. Generally can be managed as an outpatient
(2) Hypoxaemia
    a. Often severe (SpO2 50-60%)
    b. Low to no increased WOB
    c. Normal mentation
    d. Other vital signs often within normal limits
    e. May progress to the next stage due to natural disease progression or as a result of the way the disease was managed through the hypoxaemic phase, or a combination of both
(3) Indolent disease
    a. After 4-5 days in the hypoxic phase these patients enter a hyperactue inflammatory stage
    b. Rapid deterioration
    c. Requirement for critical care and invasive ventilation (if not already)
(4) Hyperacute progression
    a. Rapid decompensation, often soon after arrival in ED
    b. Require immediate critical care
    c. May progress to cardiac arrest rapidly

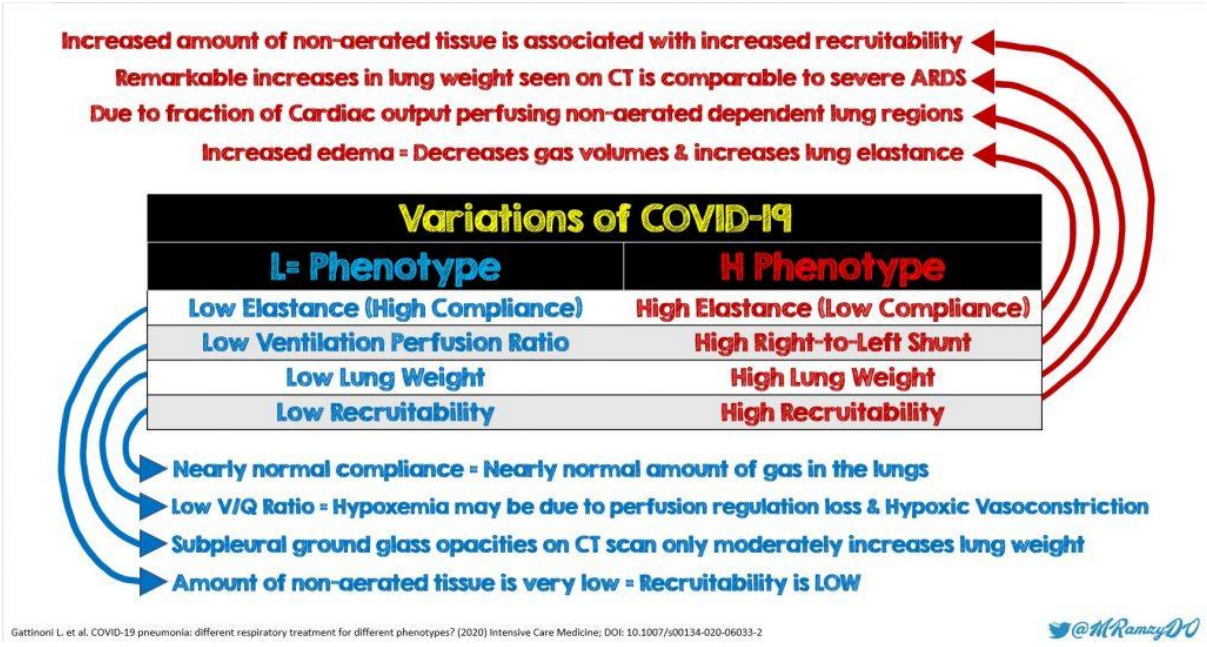
The phases are more likely on a spectrum, than clearly distinct from each other.

Proposed Phenotypes for COVID-19

There have been two phenotypes, COVID-L and COVID-H, described- this classification is preliminary and has been created from an ICU perspective. Each of the two phenotypes appears to be at a different stage in the underlying pathophysiological processes. Accordingly, treatment should relate to the particular stage or phenotype that the patient is at.

COVID L	COVID H
"Viral pneumonitis"	"ARDS-like"
Dysregulation of pulmonary perfusion	Occurs later in the illness
Loss of hypoxic vasoconstriction	Increased lung stroma permeability
Underlying pulmonary microthrombosis	Underlying lung oedema & atelectasis
LOW elastance	**H**IGH elastance
Normal compliance	Low compliance ("stiff" lungs)
Low recruitability	High recruitability

Limited "PEEP response"	Higher "PEEP response"
Low V/Q	High left → right shunt
Best managed with: High FiO2, titrated PEEP, and delayed invasive ventilation	Best managed with: Invasive ventilation and traditional ARDSNet ventilation strategy http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf



The key issue in Type L stage appears to be disruption of the vasoregulatory system, where the pulmonary vasoconstriction that normally occurs in response to hypoxia fails to occur. This seems to result in the profound hypoxaemia that is seen.

Whilst recruitabilty is low in Type L because non-aerated tissue is low, compliance is high and this increases the risk of volumetric trauma.

General Approach to Management

1. Infection Control
2. Rapid assessment and management of immediate life threats
3. Consider specific therapies
    a. Antimicrobials
    b. Oxygen and ventilation strategies (see below)
4. Supportive care (including but not limited to)
    a. Fluids
    b. Analgesia
    c. Sedation

    d. Thromboprophylaxis
    e. Head up position
    f. Glycaemic control
5. Psychosocial support to patients, staff, family
6. Seek and treat complications
    a. Myocarditis
    b. AKI
    c. DIC
    d. Secondary bacterial infection
    e. Acute liver injury (rare)
    f. Rhabdomyolsis

Approach to Oxygenation of the COVID-19 Patient

Keep in mind when determining management for these patients that patients can have severe hypoxaemia with minimal respiratory distress. This may not correlate with their other symptoms. Pulse oximetry therefor may not be the reliable guide to respiratory therapy choice that we are used to having.

Mortality in patients that have been intubated seems to be >50% in most studies. A gradual escalation of oxygen, followed by a gradual escalation of respiratory support, seems appropriate. The aim is to prevent invasive ventilation if possible by titrated management of the L-phenotype stage of disease.

The goal should be to maintain saturations at >90%. Unlike conventional approaches, in the L-phenotype stage focus should be on provision of oxygen, rather than PEEP. Reassess response to oxygen therapy at least every 30 minutes for the first hour, and then hourly for the next few hours. Monitor closely for clinical deterioration.

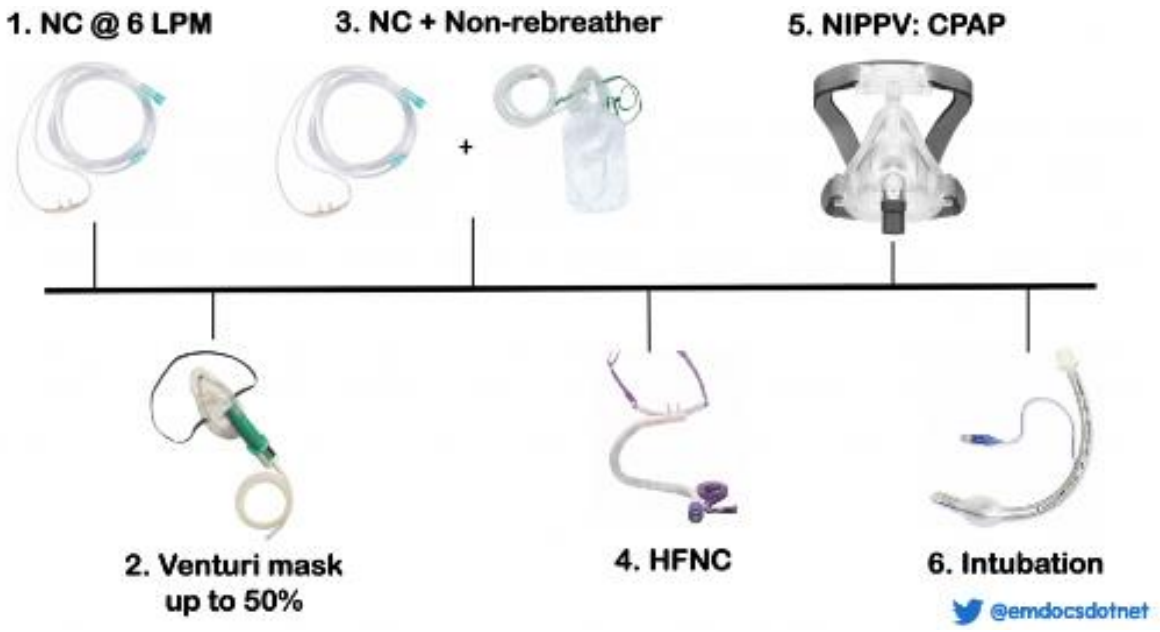
Consider intubation for patients that do not respond to high flow oxygen therapy in the first two hours. See below section for more details.

Patients receiving high flow oxygen should preferentially be managed in a single room. Patients on BiPap should preferentially be managed in a negative pressure room, if BiPap is unavoidable.

Oxygen Supply Choices

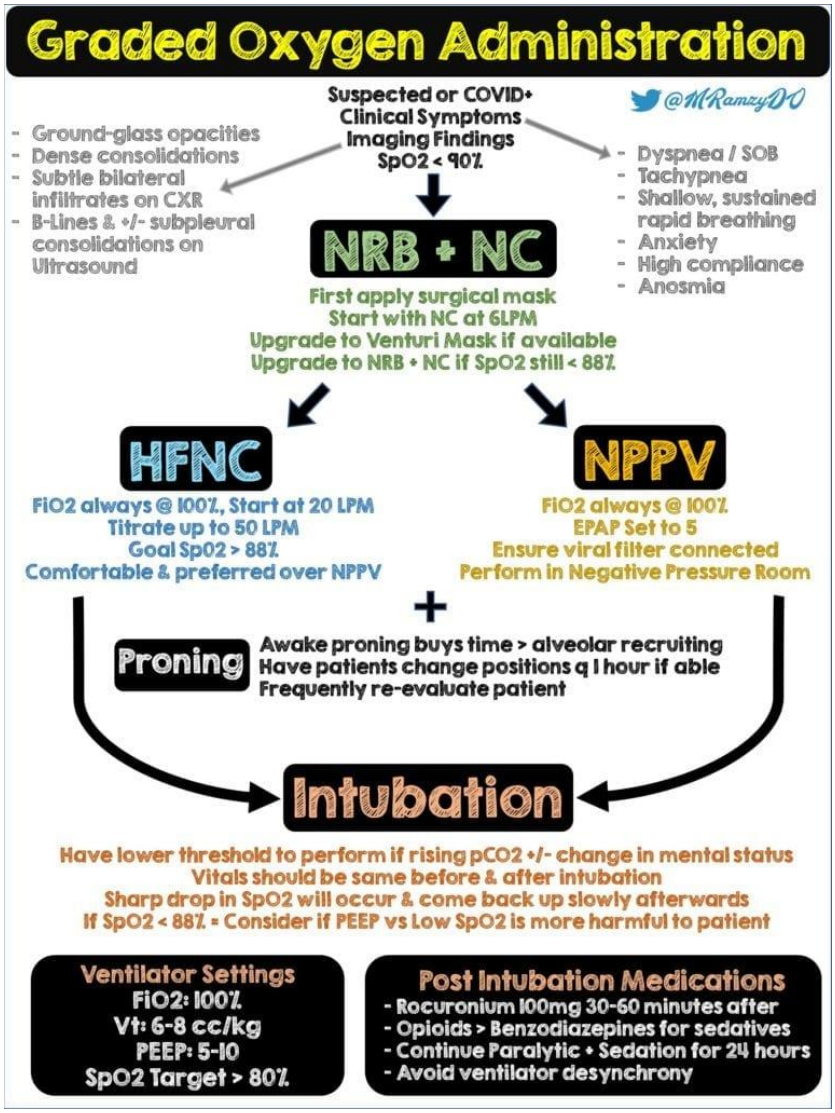
1. Simple Nasal Cannulae (NC)
2. Simple Mask
3. Venturi Mask
4. Non-rebreather Mask
5. HHFNP
6. CPAP
7. BiPAP
8. Mechanical Ventilation

Method	Max Flow Rate	FiO2	Maximal exhaled dispersion distance	
Nasal Cannulae (NC)	6L/min	~45%	50cm	Inadequate humidification can be problematic
Simple Mask	10L/min	Not much more than NC	40cm	
Venturi mask	2-15L/min	24-60%	40cm	Highly titratable FiO_2 depending on flow rates
Non-rebreather mask	15L/min	90%	<10cm at 10L/min	Reservoir bag must remain inflated at all times
HHFNP	60L/min	Determined by patient need	17cm	
CPAP		100% on a closed circuit		Use with attachment of viral filter between the mask and the exhalation tubing
BiPAP		100% on a closed circuit	64cm on 10cmH2O IP increased up to 85-95cm at 18cmH2O IP	Use with attachment of viral filter between the mask and the exhalation tubing
Invasive Ventilation				



Oxygen Escalation Therapy

One suggested schematic is shown below.



Awake Prone Positioning in COVID-19

Overview

The evidence for awake proning in COVID-19 is not robust. Previous studies have shown that prone positioning can improve the PaO2/FiO2 ratio by +35mmHg and help reduce mortality in moderate to severe ARDS patients.

Early use of non-invasive ventilation (NIV) and high flow nasal cannula (HFNC) could potentially reduce the need for intubation of mild to moderate ARDS patients. NIV applies end-expiratory positive airway pressure (PEEP) and pressure support (PS) to help improve functional residual capacity, open collapsed alveoli, improve ventilation-perfusion mismatching, and reduce intrapulmonary shunting.

Anecdotal evidence from North America in particular suggests that awake proning can help improve saturations. In theory, this could prevent intubation.

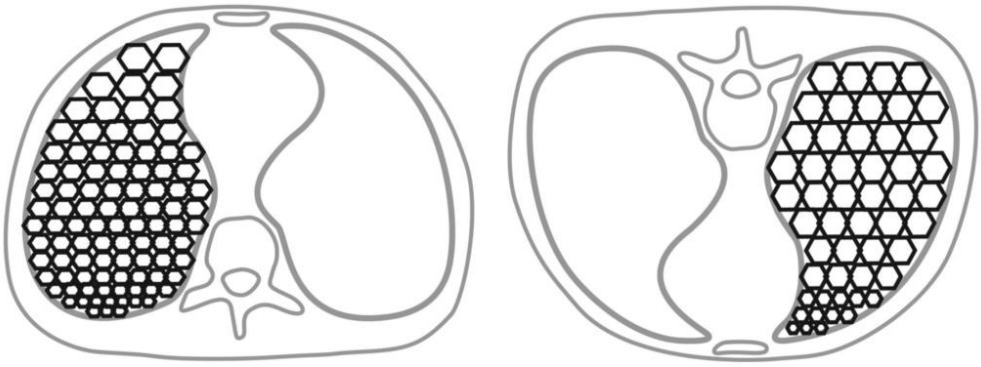
How to awake prone:

- Help patient lie on their belly in a prone position. For patients with difficulty maintaining this position, other positions may be used (e.g. rotating between lying on alternate sides).
- Make sure support devices are well secured to the patient (e.g. it could be helpful to use tegaderm to anchor a nasal cannula).
- Encourage proning as much as is tolerated (ideally ~12-18 hours/day, but this may be difficult for some patients).
- Follow oxygenation and FiO2 requirement. Ideally an improvement in oxygenation should be seen within a few hours. If no change in oxygenation is observed, ongoing pronation may have less merit

Patients can remain in the prone position for at least 30 minutes and if well tolerated potentially even longer (Up to 6hours). In one study this was performed at least two times a day for the first 3 days. No sedation was required, and patients could be monitored at the bedside to ensure their comfort and tolerance was successful.

Awake proning seems to have the most benefit in patients with the L-phenotype, and minimal impact on patients with the H-phenotype.

In some centres, awake repositioning is being used in lieu of awake proning. This means that the patients are being repositioned every 60 minutes from left side, to right side, to sitting up, to proning. The prone position seems the most beneficial but this is not achievable in all patients. At each stage the patient needs to be assessed to ensure that the patient feels better, not worse.



Physiological Effects of Proning

In the prone position:

- Optimisation of V/Q matching (increased blood flow in the dependent lung)
- Increased in functional residual capacity (FRC)
- Reduced atelectasis
- Facilitates secretion drainage

- Increased homogeneity in lung tissue due to decreased lung deformity resulting in increased ventilation
- Less abdominal distention (aids in increased FRC)
- Heart does not compress lung as it sits against the sternum rather than the lung
- Decreased transpleural pressure gradient between dependent and non-dependent lung
- Plateau pressure more uniformly distributed
- Lungs are able to inflate at lower pressures

Potential Complications of Awake Proning

- Increased intraabdominal pressure
- Increased intracranial pressure
- Difficulty monitoring (e.g. ECG leads)
- Can be labour intensive
- Difficult to perform procedures
- Pressure trauma if position not regularly changed

Proning of intubated patients should only occur in ICU where staff have trained extensively for this difficult procedure

Intubation in COVID-19 Respiratory Failure

Covid-19 is not a homogenous disease. As discussed above, there are multiple stages of disease, and multiple pathophysiological processes going on.

The silent hypoxaemic patients (profound hypoxaemia without significant respiratory distress and without many compensatory mechanisms occurring) with SaO2 <80% should not prompt a knee-jerk response of intubation, when the underlying pathophysiology is not one that responds well to mechanical ventilation in the first instance. Theoretically this applies to early application of PPV in awake patients, when these patients still fit the L-phenotype. These patients do not have standard lung injury, and by increasing PEEP early will potentially result in iatrogenic acute lung injury.

Intubation seems to be necessary when the patient displays:

- Altered level of consciousness/change in mental status
- Increased work of breathing
    - Clinical distress with:
        - Paradoxical chest movement
        - Increasing use of accessory muscles
    - Increasing $PaCO_2$

    - Not necessarily just increased RR alone, as isolated tachypnea may not indicate increased WOB per se
- High absolute oxygen requirement

Be aware that patients will drop their saturations precipitously during the peri-intubation period, no matter what stage of the illness they are in. Haemodynamic decline is also a possibility so prepare with inotropes prior to intubation.

The process of intubation for COVID-19 patients is covered in a different education package.

Ventilation in COVID-19 Respiratory Failure

There has been some debate over how best to assess whether a patient is in the COVID-L or the COVID-H subgroup. If the patient is intubated set the tidal volume to 8mL/kg and observe their plateau and driving pressures.

COVID-L will respond like normal lungs, and COVID-H will respond with high pressures indicating poor lung compliance.

However, prior to intubation there has been no system developed to differentiate the two phenotypes.

There remains a degree of controversy around the most appropriate ventilator settings for these patients, complicated by the proposed L- and H-phenotype model. In particular, the use of PEEP and how much is hotly debated. The ANZICs guidelines (V2) make no PEEP recommendations at all.

Anecdotally, patients that are in the L-phenotype stage of the disease do very poorly on the standard ARDSnet management protocol with use of high PEEP. There is a degree of iatrogenic lung injury when high PEEP is used for lungs with normal compliance.

It is important to note, however, that avoiding high PEEP does not equate with providing low, or no, PEEP. Instead, the traditional ARDSnet *high*-PEEP strategy can be replaced with a *standard*-PEEP setting to mitigate the theoretical risk of lung damage from higher pressures.

Use of an intermediate TV (8mL/kg), a high FiO2, and enough PEEP to maintain SaO_2 >90% appears to be an effective initial strategy.