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Description: this document has been written up using official sources (where the sources are reported) and from the comparison of the experience gained in recent weeks by anesthesiologists and intensivists who deal with Covid-19 patients

EPIDEMIOLOGY

The severe acute respiratory syndrome coronavirus 2(SARS-CoV2) CoVs is caused by positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope. In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections. SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively) cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively. On February 11, 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, announced that the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019 [ref]. The whole-genome sequence identity of the SARS-CoV-2 virus is 96.2% similar to a bat SARS-related coronavirus (SARSr-CoV; RaTG13) collected in China, but less similar to the genomes of SARS-CoV1 (about 79%) or MERS-CoV (about 50%).[ref, ref]

The SARS-CoV-2 viruses have been categorized into two major types, with L being the major type (~70%) and S being the minor type (~30%).The S type is actually the ancestral version of SARS-CoV-2.Evidences are suggesting that the L type might be more aggressive than the S type due to the potentially higher transmission and/or replication rates.

It has been hypothesized that the two types of SARS-CoV-2 viruses might have experienced different selective pressures due to different epidemiological features.[ref]

This explains why initial reports from Wuhan described a higher mortality than some more recent case series.[ref,ref]

Main causes of overall death were respiratory failure(53%), respiratory failure with myocardial damage/ heart failure(33%), heart failure(7%) and least but not less important 7% showed unknown causes.[ref]

It has also been confirmed that the SARS-CoV-2 uses the same receptor of the SARS-CoV, the angiotensin converting enzyme II (ACE2).[ref]

Both SARS-CoV and SARS-CoV-2 bind to ACE2 through the RBD of spike protein, and in order 3D structural analysis indicated that the spike of SARS-CoV-2 has a higher binding affinity to ACE2 than SARS-CoV.[ref]

ACE2 mRNA is highly expressed in renal, cardiovascular, and gastrointestinal tissues [ref,ref,ref]

ACE2 is abundantly present in humans in the epithelia of the lung and small intestine, which might provide possible routes of entry for the SARS-CoV. This epithelial expression, together with the presence of ACE2 in vascular endothelium, also provides a first step in understanding the pathogenesis of the main SARS disease manifestations.[ref]

PATHOGENESIS

The main targets of SARS-CoV are the lungs, immune organs, and systemic small vessels, resulting in systemic vasculitis, decreased immune function, and respiratory distress caused by extensive pulmonary consolidation and diffuse alveolar damage with hyaline membrane formation [ref]. Early phase pneumonia changes, incidentally found in biopsies of patient underwent lobectomy for carcinoma and then resulted positive for COVID-19 (within 9 days from surgery) including: proteinaceous exudates in alveolar spaces, with granules; scattered large protein globules; intra-alveolar fibrin with early organization, mononuclear inflammatory cells, and multinucleated giant cells; hyperplastic pneumocytes, some with suspected viral inclusions [ref].

Marked ACE2 immunostaining was found in type I and type II alveolar epithelial cells in normal lungs. This finding was confirmed by ACE2 expression in the lung type II alveolar epithelial cell line A549 and in lungs with fibrotic changes which revealed abundant staining of type II epithelial cells. The cytoplasm of bronchial epithelial cells also showed weak positive ACE2 staining. this expression pattern provides a possible explanation for the pathological lung manifestations and their rapid progression. Initial viral entrance may cause cytopathological changes at the epithelial alveolo-capillary interface, initially resulting in induction of type II alveolar cells as a first attempt at repair. In SARS, the abundant expression of ACE2 in type II alveolar cells may cause a base for rapid viral expansion and a vicious circle of local alveolar wall destruction, resulting in rapidly progressive severe diffuse alveolar damage.[ref]

Acute respiratory distress syndrome (ARDS) developed in 17–29% of hospitalized patients, and secondary infection developed in 10%.[ref, ref]

ARDS characterized by diffuse alveolar damage (e.g. including hyaline membranes). Pneumocytes with viral cytopathic effect are seen, implying direct virus damage (rather than a purely hyper-inflammatory injury.[ref]

In nasal and oral mucosa and the nasopharynx, ACE2 expression in the basal layer of the non-keratinizing squamous epithelium was found. Tissues of the upper respiratory tract, such as oral and nasal mucosa and nasopharynx, did not show ACE2 expression on the surface of epithelial cells, suggesting that these tissues are not the primary site of entrance for SARS-CoV.[Ref]

The first remarkable finding was that ACE2 was present in endothelial cells from small and large arteries and veins in all the tissues studied. Moreover, arterial smooth muscle cells were consistently positive for ACE2. Positive staining for ACE2 was also noted in myofibroblasts and the membrane of fat cells in various organs[.ref]

In addition to ACE2 localization in the smooth muscle cells and endothelium of vessels from the stomach, small intestine, and colon, we found ACE2 in smooth muscle cells of the muscularis mucosae and the muscularis propria. ACE2 was abundantly present in the enterocytes of all parts of the small intestine including the duodenum, jejunum, and ileum, but not in enterocytes of the colon. The staining in enterocytes was confined to the brush border . ACE2 protein is abundantly expressed in the brush border of enterocytes of all parts of the small intestine, including the duodenum, jejunum, and ileum. Surprisingly, other organs of the digestive tract, such as the stomach and colon, did not show this brush border staining.

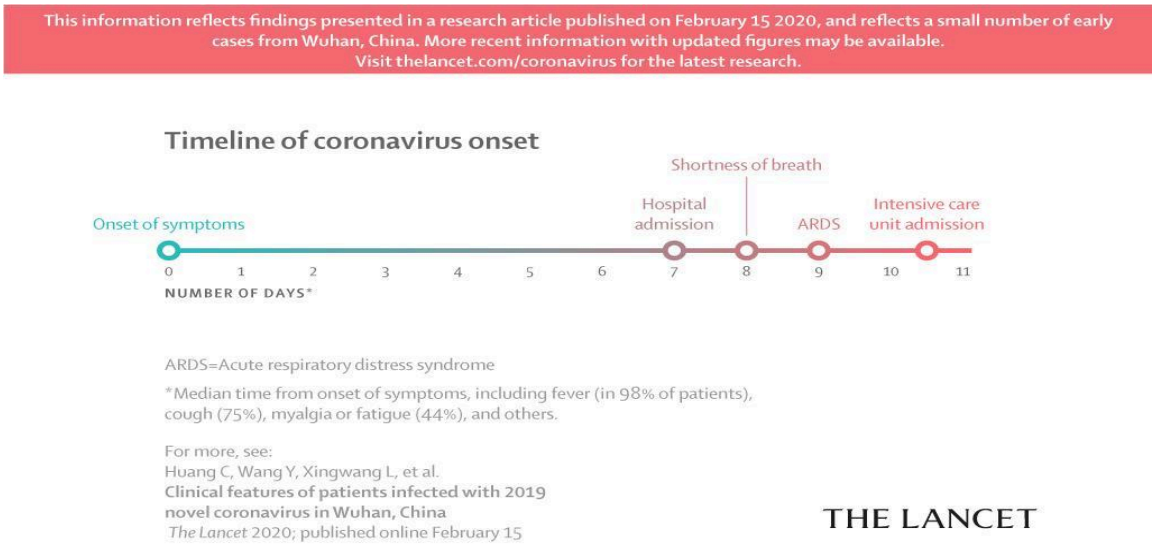
The presence of ACE2 and as a functional receptor for SARS-CoV and the presence of SARS-CoV in enterocytes of the small intestine, combined with the fact that virus is present in patients' stool samples, are consistent with the possibility of faeco-oral transmission. The epithelium modification and changes in permeability, due to the viral infection, may also justify gastrointestinal symptoms as diarrhea.[ref, ref, ref]
In the spleen, thymus, lymph nodes, and bone marrow, cells of the immune system such as B and T lymphocytes, and macrophages were consistently negative for ACE2. In some lymph nodes, we noted positive staining in sinus endothelial cells in a granular staining pattern.[ref]
SARS-CoV1 infection also causes massive necrosis of the spleen and lymph nodes. Furthermore, most patients develop lymphopenia. [ref] which, by analogy with respiratory syncytial virus disease, measles, and sepsis, has been ascribed to increased apoptosis of lymphocytes. [ref]
The consistent absence of ACE2 in immune cells in all hemato-lymphoid organs suggests that direct viral infection is unlikely to be the cause of these manifestations and that the pathological changes seen in these organs are probably related to the systemic effects of the abnormal immune reactions towards the virus.[ref]
Differentiation, activation and exhaustion of CD4+ or CD8+ T-cell subsets in patients with Covid-19.[ref]The first data on changes in lymphocyte populations in patients severely affected by Covid-19 indicate a low T cells count, an increase in naïve helper T cells and a decrease in memory helper T cells[ref] Confirming that, most recent data, related to the distribution of different subpopulations of peripheral blood CD4+ and CD8+ T cells from four aged patients in the symptomatic phase of the infection in an italian study [ref]
Despite the clear endothelial staining of many small vessels, the endothelial lining of the sinusoids in the liver was negative for ACE2.[ref]
In the kidney, weak glomerular visceral ACE2 staining was observed, whereas the parietal epithelial cells were moderately positive. Despite the clear endothelial staining of vessels, the mesangium and glomerular endothelium were negative for ACE2. Abundant staining was seen in the brush border of the proximal tubular cells, whereas the cytoplasm of these cells was weakly positive. Epithelial cells from the distal tubules and collecting ducts showed weak cytoplasmic staining.It is possible to observe the presence of 12 clusters among CD4+ and 13 among CD8+ T-cells and to see the high amount of naive cells in both T cell populations, and how the distribution of naive, memory, activated and exhausted lymphocytes is different among different types of CD4+ or CD8+ T lymphocytes. [ref]
While the 2019-nCoV is mainly distributed in the lung, the infection also involves the damages of heart, vessels, liver, kidney and other organs. Further studies are warranted to investigate the mechanism underlying pathological changes of this disease[ref].
SARS-CoV-2 may cause the liver function damage, and the emerging liver injury after admission has some connection with the application of lopinavir/ritonavir and the extend length of hospital stay[ref].
SARS-CoV-2 induces ARF in COVID-19 patients. Viruses directly infect human kidney tubules to induce acute tubular damage. The viruses not only have direct cytotoxicity, but also initiate CD68+ macrophage together with complement C5b-9 deposition to mediate tubular pathogenesis.[ref]
Human liver ductal organoids were permissive to SARS-CoV-2 infection and support robust replication. Notably, virus infection impaired the barrier and bile acid transporting functions of

cholangiocytes through dysregulation of genes involved in tight junction formation and bile acid transportation, which could explain the bile acid accumulation and consequent liver damage in patients[ref].
Another study which uses the TWIRLS system, an automated process that can summarize the entities and genes specifically related to coronaviruses has found a possible mechanism involving ACE2/AT2R-RAS-Cytokine signaling, which becomes imbalanced under virus infection leading to cytokine storms.However, there is still a lack of histopathology-related data to support our preliminary findings generated by our machine approach.[ref]

TIMING

1.Viral replication occurs over a period of several days. An innate immune response occurs, but this response fails to contain the virus. Relatively mild symptoms may occur due to direct viral cytopathic effect and innate immune responses.

2.An adaptive immune response eventually kicks into gear. This leads to falling titers of virus. However, it may also increase levels of inflammatory cytokines and lead to tissue damage – causing clinical deterioration.[ref]



This progression may explain the clinical phenomenon wherein patients are relatively stable for several days, but then suddenly deteriorate when they enter the adaptive immunity stage. Some reports suggest the potential for clinical deterioration during the second week of illness.[ref]
In one report, among patients with confirmed COVID-19 and pneumonia, just over half of patients developed dyspnea a median of 8 days after illness onset (range: 5–13 days). [ref]
In another report, the mean time from illness onset to hospital admission with pneumonia was 9 days.[ref]
The median time from first symptom to dyspnea was 5.0 days, to hospital admission was 7.0 days, and to ARDS was 8.0 days.[ref]
Initial clinical symptoms aren't necessarily predictive of future deterioration.
Admission to the hospital occurs after ~8 days after the exposure while the ICU admission/intubation happens after ~10 days post exposure. However, this timing may be variable (some patients are stable for several days after admission, but subsequently deteriorate rapidly).
Antiviral therapies might need to be deployed early to work optimally (during the replicative stage) .[ref]

CLINICAL FEATURES

In a study the median age was 56 years (interquartile range, 42-68; range, 22-92 years), 54.3% were men. Hospital-associated transmission was suspected as the presumed mechanism of infection for affected health professionals in 29% of cases. Common symptoms included fever (98.6%), fatigue (69.6%), and dry cough (59.4%);and most of the patients had abnormal chest CT.[Ref, ref]
Patients treated in the ICU, compared with patients not treated in the ICU, were older (median age, 66 years vs 51 years), were more likely to have underlying comorbidities , and were more likely to have dyspnea, and anorexia.[ref]
Be aware of the differences between ARDS e PSEUDOARDS. [ref]
Between 23–32% of hospitalized patients with COVID-19 and pneumonia have required intensive care for respiratory support.[ref, ref, ref]
In one study, among critically ill patients admitted to an intensive care unit, 11% received high-flow oxygen therapy, 42% received noninvasive ventilation, and 47% received mechanical ventilation.[ref]
Some hospitalized patients have required advanced organ support with endotracheal intubation and mechanical ventilation (4–10%), and a small proportion have also been supported with extracorporeal membrane oxygenation (ECMO, 3–5%).[ref, ref]
Covid-19 ARDS are generally characterized by:
- good ventilation mechanics where the compliance occurs usually > 40 ml / cmH2O;
- a severe hypoxemia;
- good response to HIGH PEEP 16-18 cmH2O keeping Vt of 500-600 with normal driving pressure ;

To confirm what said before, it has been seen that patients with SARS-Cov-2 connected to Hamilton ventilators in ASV mode have a tendency to be ventilated with relatively low FR like 12-13 acts / min and with high Vt (similar to a postoperative patients) while patients with "classical" ARDS are generally always ventilated in ASV with higher and lower FR Vt)
Other SARS-CoV-related manifestations include systemic vasculitis, apoptosis, and swelling of endothelial cells and inflammation in various organs such as the heart, kidney, liver, and adrenal glands[ref]
It has been found that 7% of patients die of fulminant myocarditis, which may also be a contributing factor in 33% of deaths.[ref]
There is a spectrum of clinical features from mild to severe life threatening disease with major complications like (67%) ARDS, (29%) acute kidney injury, (23%) cardiac injury, (29%) liver dysfunction, and (2%) pneumothorax .[ref, ref]
Reported complications include arrhythmia, shock, and among hospitalized patients with pneumonia, the case fatality proportion has been reported as 4–15%.[ref.ref.ref]
Emerging evidence suggests that some patients may respond to COVID-19 with an exuberant “cytokine storm” reaction.[ref,ref]
The vascular abnormalities and inflammatory changes in various organs might therefore be related to systemic toxic effects of the immune reactions elicited by SARS-CoV infection.[ref]

- generally the first signs of respiratory improvement can be seen from the 3rd day, however real improvements occur in 6-7 days.

Among 36% and 30% of patients infected with SARS-CoV developed pulmonary fibrosis 3 and 6 months after infection [ref]
Compared with non-severe patients with COVID-19, severe patients commonly had neurologic symptoms manifested as acute cerebrovascular diseases, consciousness impairment and skeletal muscle symptoms.[ref]
Coronavirus disease 2019 can cause a viral pneumonia with additional extrapulmonary manifestations and complications. A large proportion of patients have underlying cardiovascular disease and/or cardiac risk factors. Factors associated with mortality include male sex, advanced age, and presence of comorbidities including hypertension, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases. Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality. Acute respiratory distress syndrome is also strongly associated with mortality.[ref]
Coronavirus disease 2019 is associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. Extensive efforts are underway to find specific vaccines and antivirals against SARS-CoV-2. Meanwhile, cardiovascular risk factors and conditions should be judiciously controlled per evidence-based guidelines. [ref]
Whether the data linking myocardial injury and high mortality risk in patients with COVID-19 from Chinese cohorts are generalizable to other countries is yet to be determined. [ref]
In an italian Case was reported that an otherwise healthy 53-year-old white woman presented to the emergency department with severe fatigue. She described fever(body temperature assessed was 36.6 °C and she remained afebrile during the subsequent clinical course.) and dry cough the week before. 12-lead electrocardiogram, Transthoracic echocardiography, Cardiac magnetic resonance imaging (MRI) were performed: findings were all consistent with acute myopericarditis. She was treated with dobutamine (the patient required inotropic support in the first 48 hours and the treatment was weaned on day 4), antiviral drugs (lopinavir/ritonavir), steroids, chloroquine, and medical treatment for heart failure, with progressive clinical and instrumental stabilization. Further evidence is needed to determine whether corticosteroids are useful in reducing the myocardial inflammatory response. At the time of submission, the patient was hospitalized with progressive clinical and hemodynamic improvement.[ref]
A case definition requiring fever and at least one respiratory symptom may lead to an underdiagnosis of a substantial proportion of patients with early Covid-19 and lead to increased transmission of the virus. [ref]

LABORATORY EVIDENCES

The most common laboratory abnormalities noted were hypoalbuminemia, lymphopenia, decreased percentage of lymphocytes (LYM) and neutrophils (NEU), elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH), and decreased CD8 count. [ref]
other common laboratory abnormalities observed were elevated alanine aminotransferase and aspartate aminotransferase levels (37%).[ref]
Among the eight blood biochemistry indexes distinguished in blood samples of 2019-nCoV infected patients, specifically ALB, creatinine (CRE), LYM, LYM (%), NEU (%), LDH, CRP, and CD8, we found ALB, LYM, LYM (%), NEU (%), LDH, and CRP were highly linked to lung injury Murray score. [ref]
Previous studies reported that hypoalbuminemia is a potent, dose-dependent predictor of poor outcome.[ref]
COVID-19 does commonly cause troponin elevations (which generally will not represent type-I myocardial infarctions). [ref]
Age, hypersensitive C-reactive protein(hs-CRP) and serum creatinine levels of the patients were higher in critical care cases than in mild cases(all P<0.05). Prevalence of male, elevated NT-proBNP and cTnI, hypertension and coronary heart disease were significantly higher in critical cases care patients than in the mild cases. Univariate logistic regression analysis showed that age, male, elevated NT-proBNP, elevated cTnI, elevated hs-CRP, elevated serum creatinine, hypertension, and CHD were significantly correlated with critical disease status. Multivariate logistic regression analysis showed that elevated cTnI and CHD) were the independent risk factors of critical disease status[.ref]
We measured the plasma level of Angiotensin II from 2019-nCoV infected patients and healthy individuals, the plasma levels of Angiotensin II from 2019-nCoV infected patients were significantly higher than that of healthy individuals. The level of Angiotensin II in 2019-nCoV patients was strongly associated with viral load and lung injury.[ref]
Most patients had normal serum levels of procalcitonin on admission.[ref, ref, ref,ref,ref,ref,ref]
Serum IL-2R and IL-6 levels were significantly different in the general, severe and critically ill groups (all P <0.05), critically ill group> severe group> ordinary group; There were no significant differences in the levels of IL-1β, IL-8, IL-10, TNF-α, hs-CRP, lymphocytes and LDH (all P > 0.05)[ref]
The duration of SARS-CoV-2 RNA detection in the upper and lower respiratory tracts and in extrapulmonary specimens is not yet known. It is possible that RNA could detected for weeks, which has occurred in some cases of MERS-CoV or SARS-CoV infection.[ref, ref]
Viable SARS-CoV has been isolated from respiratory, blood, urine, and stool specimens.

- higher serum creatinine may be due to cellular lysis and not to acute renal failure. it may be useful to test the renal functional reserve with lasix 1 mg/kg.
- Patients seems to develop a capillary leak syndrome that remains localized mainly in the lungs causing hypoalbuminemia

IMAGING

X-RAY

Chest X-ray evaluation included:
(A) presence of interstitial involvement (reticular, nodular o mixed pattern),
(B) presence of lung opacities,
(C) presence of pleural effusion,
(D) presence of pleural calcification,
(E) hilar enlargement,
(F) mediastinal lines,
(G) cardiac silhouette
but chest X-Ray was performed two days after symptom onset and it was not consistent with lung alterations ; in the second patient chest X-Ray was performed 2 days after symptom onset with evidence of interstitial lung alterations [ref]

Chest **CT** images have shown bilateral involvement in most patients. Multiple areas of consolidation and ground glass opacities are typical findings reported to date.[ref, ref, ref,ref,ref,ref,ref]
Uncommon elements such as pleural effusions, a tubular and enlarged appearance of pulmonary vessels with a sudden caliber reduction and mediastinal lymphadenopathy were noted during the follow-up.[ref]
Emergence of CT abnormality before symptoms could be consistent with the existence of an asymptomatic carrier state
Shi et al performed CT scanning in 15 healthcare workers who were exposed to COVID-19 before they became symptomatic. Ground glass opacification on CT scan was seen in 14/15 patients. 9/15 patients had peripheral lung involvement (some bilateral, some unilateral). The vessels appearance during the follow up, resembling a “feeding vessel sign”, could be an early alert radiological sign to predict initial lung deterioration.[ref]

ULTRASOUND

Lung ultrasonography appears to correlate very well with the findings on chest CT scan[ref]
With increasing disease severity, the following evolution may be seen(ref)
(A) Least severe: Mild ground-glass opacity on CT scan correlates to scattered B-lines.
(B) More confluent ground-glass opacity on CT scan correlates to coalescent B-lines (“waterfall sign”).
(C) With more severe disease, small peripheral consolidations are seen on CT scan and ultrasound.
(D) In the most severe form, the volume of consolidated lung increases.

Other features described are :

- Peripheral lung abnormalities can cause disruption and thickening of the pleural line.
- Areas of normal lung (with an A-line pattern) can be seen early in disease, or during recovery.
- Tiny pleural effusions may be seen, but substantial pleural effusions are uncommon (ref).
- As with CT scans, abnormalities are most common in the posterior & inferior lungs.

Lung US sensitivity will depend on several factors and specificity is extremely low[ref]

BRONCHOSCOPY

Bronchoscopy might be considered in situations where it would otherwise be performed. Bronchoscopy should not be done for the purpose of ruling COVID-19 in or out (as this entails risk with no definite benefits)(ref).
High risk of transmission to providers. May cause some deterioration in patient's clinical condition (due to instillation of saline and sedation)[ref]

Bronchoalveolar lavage (BAL)

Four groups of lung macrophages were identified which can be classified by FCN1, SPP1 and FABP4 markers according to recent reports [ref,ref].
Group 1 & 2 macrophages are FCN1+ and highly inflammatory. They express higher levels of interferon stimulated genes and multiple chemokines, CCL2, CCL3, CCL5, IL-8, CXCL9, CXCL10 and CXCL11, thus identifying the FCN1+ macrophages as the culprit for the deranged hyper-inflammation. We identified the group 3, SPP1+ macrophages likely represented a repaired but also a pro-fibrotic subset [ref,ref]. They may counteract the FCN1+ macrophages to dampen the inflammation. Their roles and associations with patient outcomes should be further investigated.[ref]
The group 4 macrophages are FABP4+ alveolar macrophage (AMs) showing higher PPARγ activity which play important physiological roles in metabolizing lipid surfactant[ref,ref]
AMs consisted the principle lung macrophages in both controls and mildly infected patients, but was almost completely lost in severely infected lungs. The loss of AMs likely contributed to the failed lung functions.[ref]
In a study, the presence of a larger population of CD8+ T effectors in mild group, but also showed that these CD8+ T cells contain highly expanded clones, indicating their SARS-CoV-2 specificity. Thus, CD8+ T cell response likely holds the key for successful viral control in COVID-19 patients[ref]
Declared limits of this study were that only 6 samples are able to be investigated and the endpoint study may not determine the triggering factors leading to different clinical outcomes.[ref]

PROGNOSTIC FACTORS

There are factors relating to a severe course of the pathology, which has a higher risk of morality, with a GFR of 49%[Ref.].
Patients are defined as severe when one of these criteria is met[Ref.]:

- Respiratory Distress with RR >= 30/min
- Pulse oximeter oxygen saturation ≤93% at rest
- oxygenation index
- (artery partial pressure of oxygen/inspired oxygen fraction, PaO_2/FiO_2) ≤ 300 mm Hg

General conditions of the patients need to be evaluated for the prognosis: APACHE II, SOFA and CURB-65 are associated with a higher mortality rate. [Ref., ref.]
Age plays a major role in the definition of the prognosis-[Ref., ref., ref., ref., ref., ref., ref.]
Comorbidities also define the prognosis: hypertension, diabetes, cardiovascular and cerebrovascular diseases being the most important. Smoking habit, COPD and respiratory diseases have also determine a worse prognosis [Ref., ref., ref., ref., ref., ref.].
A respiratory frequency >24/min and a heart rate >124 bpm have an independent influence on patients' mortality rate[Ref.]. Creatinine and CKD also determine a more severe course and a higher risk of mortality[Ref.].
Symptoms like cough, nausea and vomiting are associated with a more severe disease [Ref.].
ARDS, sepsis, shock and the need of mechanical ventilation are related to a higher risk of mortality[Ref., ref., ref.].
Laboratory test which are associated to a higher risk of severity and death are:

- Leukocytosis, which is higher in non survivors [Ref., ref., ref.]
- Increased neutrophils, which is higher in non survivors [Ref., ref.]
- Severe lymphopenia [Ref., ref., ref.]
- Thrombocytopenia [Ref.]
- Increased eosinophils [Ref.]
- D-Dimer is higher in survivors, considering that several deaths are related to DIC[Ref., ref., ref.]
- Increased CK-MB. Consider SARS-CoV-2 has a cardiac tropism, with reported cases of primary heart failure [Ref., ref.]
- Increased troponin [Ref.]
- LDH relates to a more severe condition and fatality [Ref., ref.]
- Increased AST [Ref.]
- Increased ALT [Ref.]
- Bilirubin levels are not clearly defined, it seems increased in some studies [Ref.]
- Prolonged PT (>16") [Ref.]
- Increased BUN in non survivors [Ref.]
- Increased creatinine relates to higher mortality [Ref., ref., ref.]
- CRP is more increased in non survivors than in survivors [Ref., ref.]
- Serum ferritin is increased in non survivors [Ref.]
- Pro-CT is higher in severe conditions and non survivors, considering it is related to bacterial superinfection [Ref., ref., ref.]

- IL-6 and IL-2R are increased and may be predictive of a development in a severe conditions[Ref., ref.]
- IL-10, IL-1, TNF-alfa, IL-8 levels do not show a statical significant difference between severe and not severe conditions. [Ref.]
- Serum AT2 seems to be increased [Ref.]
- PaO_2/FiO_2 ratio is lower in non survivors [Ref.]

CRP, ESR and LDH relate to the radiological severity[Ref.].
Radiologically, lymphadenomegaly, pericardial essudation and pleuric essudation relate to a more severe condition [Ref.].
It seems that revelable virus-RNA in blood relates to a worse course of COVID-19, if compared to patients with negative blood samples. The same seems to happen for patients with positive anal swabs. [ref.]

CARE TO CARE

IPC strategies to prevent or limit transmission in healthcare settings include the following:
1. ensuring triage, early recognition, and source control (isolating patients with suspected nCoV infection);
2. applying standard precautions for all patients;
3. implementing empiric additional precautions (droplet and contact and, whenever applicable, airborne precautions) for suspected cases of nCoV infection;
4. implementing administrative controls;
5. using environmental and engineering controls.[ref]
Human coronaviruses can remain infectious on inanimate surfaces for up to 9 days.Contamination of frequent touch surfaces in healthcare settings are therefore a potential source of viral transmission. Data on the transmissibility of coronaviruses from contaminated surfaces to hands were not found.[ref]

MECHANISM OF TRANSMISSION

As already mentioned, the principal ways of transmission of SARS-CoV-2 go through the upper airways.
Saliva has been suggested as a specimen for the search of viral load and showed a good relation to pharyngeal swabs [ref.]
The conjunctiva has been discussed as another way of transmission [ref., ref.]. A pre-review study on Rhesus macaques has shown that SARS-CoV-2 inoculated via conjunctiva was to find in several tissues on 0,1,3,5 and 7 dpi. The virus code was to find in all the proved tissues, even though in different times and in conjunctiva, nose, pharyngeal and anal swabs. Sera were also collected on days 0, 7, 14, 21 and examined for IgM and IgG, which proved positive, with IgG spike at day 14. [ref.] Interestingly, another pre-review study on patients showed that conjunctiva swabs were negative in patients with positive pharyngeal swabs. [ref.]
As mentioned before, gastrointestinal symptoms have been reported in several studies, suggesting the possibility of an orofecal transmission [ref.]. Virus copies have been found in the stool of infected patients. [ref.]. Anal swabs have proved positive even in patients with a negative pharyngeal swab, which remained negative also in a further control, the first remaining positive. Interestingly, pharyngeal swabs were negative also in patients with a positive viremia. These data make multiple ways of transmission possible, including the orofecal one. [ref.].
These findings arise in importance, if we consider that virus copies are to be found on surfaces even after 72h both on plastic and stainless steel, even though with a very important reduction of viral copies. It was not possible to find copies after 4h on copper and after 24h on cardboard. All these data are similar to the ones we have about SARS-CoV-1. Consider SARS-Cov-2 was to find in aerosol in rooms for at least 3h, again similarly to SARS-CoV-1. [ref.]
Interestingly, median length of virus duration was longer for stool samples than for respiratory and blood samples. Virus duration in samples related to disease severity, which was also associated to the overall viral load. In mild patients, the viral load was greater during early stages of the disease, reaching a peak during the second week and then became lower, whereas it remained high in patients with a severe condition. [ref.]

MANAGING THE PATIENT WITH COVID 19

First approach:

- HIGH PEEP (16-18 cmH2O): C-PAP with high PEEP
- EARLY PRONATION EVEN IN awake patients with C-PAP: if compliant, also the non-sedated C-PAP patient can benefit from pronation !!

PAY ATTENTION TO DO NOT DELAY THE USE OF IOT: especially young people may initially be able to maintain discrete oxygenation with SatO2 94-96% with C-PAP and then worsen suddenly after about 24-36 h. This could lead to "later" intubations and a greater compromise of respiratory exchanges (worse prognosis?)
once intubated, patients with more severe respiratory compromise and poor adaptation to the ventilator despite sedation can be curarized for 48-72h.
Usually set high PEEP 14-18 cmH2O (generally those are patients that at first do not show hemodynamic instability [max 0.1-0.2 mcg / kg / min of vasopressor to counteract deep sedation]) and a Vt necessary to maintain an acceptable oxygenation (maintaining an acceptable driving pressure not exceeding 15 cmH2O),

- Start with high FiO2 even at 100% for the first 24 h. Then with improvement of the exchanges are achieved lower it progressively. when the FiO2 is about 50% start dropping the PEEP
- EXTUBATION: effective extubations were carried out with PEEP even at 12 cmH2O and subsequent maintenance of high PEEPS with helmet in young patients, and when a place is needed

NONINVASIVE RESPIRATORY SUPPORT

WHO guidelines on COVID-19 state that “Recent publications suggest that newer HFNC and NIV systems with good interface fitting do not create widespread dispersion of exhaled air and therefore should be associated with low risk of airborne transmission.”[ref]

HIGH-FLOW NASAL CANNULA (HFNC)

HFNC is generally a rational front-line approach to noninvasive support in patients with ARDS (based partially on the FLORALI trial).
One case series from China suggested that HFNC was associated with higher rates of survival than either noninvasive or invasive ventilation (of course, this could reflect its use in less sick patients).[ref]
A management strategy for COVID-19 by a French group used HFNC preferentially, instead of BiPAP[ref]
The potential weakness of HFNC is concern that it could increase transmission to healthcare workers remains unknown.[ref]

BiPAP

BiPAP vs. HFNC, (https://emcrit.org/ibcc/support/)

A helmet interface has been proposed to reduce environmental contamination (ref).Placement of a viral filter in-line with the exhalation tubing could also potentially reduce contamination [ref]
In a multicenter cohort of 302 patients with MERS coronavirus, 92% of patients treated with BiPAP failed this modality and required intubation (ref).
In the FLORALI trial of ARDS patients (with mostly pneumonia of various etiologies), patients randomized to BiPAP did worse compared to patients randomized to HFNC.[ref]
BiPAP could have a role in patients with combined syndromes (e.g. COPD plus COVID-19).[ref]

AWAKE PRONE POSITION

This involves a non-intubated patient on nasal cannula who prone themselves by lying on their belly. There is relatively little evidence to support this and it is useful only for highly selected patients (ref).
Awake-prone ventilation could be a useful option if the availability of mechanical ventilators is exhausted. Typically awake prone ventilation is paired with high-flow nasal cannula, but it could also be used with a standard nasal cannula (e.g. running at ~6 L/min or a bit higher if tolerated). Consider securing the nasal cannula to the patient's face using tape or tegaderm, to prevent dislodgement when the patient moves.[ref]

INTUBATION PROCEDURE

high risk for transmission to healthcare workers: 1)endotracheal tube confirmation with a stethoscope could pose a risk of transferring virus to the practitioner [ref] and 2)airborne precautions are indicated (check for properties of protection devices COVID-19 [ref] Attach a viral filter to the bag-valve mask before the procedure, if possible. This should reduce the spread of viral particles out of the endotracheal tube following intubation (or during bag-mask ventilation if that is required)(ref).

INVASIVE MECHANICAL VENTILATION

ventilator settings [ref]

Tidal volumes should be targeted to a lung-protective range (6 cc/kg ideal body weight). Informal reports coming out of Italy and Singapore suggest that:

- Driving pressures required aren't very high.
- Patients require lots of PEEP and also respond well to prone ventilation.

This suggests that a primary problem may be small airway closure and atelectasis manageable, as follows:

- If conventional ventilation is used, high PEEPs should be utilized.This table may be useful as a general guide

High & Low PEEP tables from ARDSnet

FiO2	Low PEEP	High PEEP
0.3	5	5-14
0.4	5-8	14-16
0.5	8-10	16-20
0.6	10	20
0.7	10-14	20
0.8	14	20-22
0.9	14-18	22
1.0	18-24	22-24

PEEP tables don't need to be followed precisely, but can be useful as a general guide. The WHO recommends using a high-PEEP strategy, which seems consistent with available experience thus far with COVID-19. If high PEEPs are used, make sure to keep tidal volumes low to prevent excessively high plateau pressures. APRV is an alternative strategy which would likewise provide high mean airway pressures.

-The Internet Book of Critical Care, @PulmCrit

.

- Early APRV could be very useful for these patients (i.e. used as an initial ventilator mode, rather than a salvage mode). A practical guide to using APRV can be found here. APRV is essentially an aggressive recruitment strategy which can help sort out how much recruitable lung the patient has. however, true failure to respond to APRV within 12-24 hours (e.g. with PaO2/FiO2 <100-150) would be a stronger argument to move towards prone ventilation (discussed here).

Hypercapnia is preferred over lung-injurious ventilation. Therefore permissive hypercapnia will likely be extremely important when ventilating these patients in a safe fashion. The safe extent of permissive hypercapnia is unknown, but as long as hemodynamics are adequate a pH of >7.1 or >7.15 may be tolerable .

- Slow administration of IV bicarbonate is an acceptable strategy to improve pH while simultaneously continuing lung-protective ventilation (discussed here). Targeting a mildly elevated serum bicarbonate (e.g. 28-30 mEq/L) can facilitate safe ventilation with low tidal volumes (more on different forms of IV bicarbonate here).

Ventilation and pathophysiology of lung damage in COVID-19

Since COVID-19 (Coronavirus Disease 2019) affects primarily the lung, ventilation should have been one of the topics in which literature research spread the most. Unfortunately, lack of pathophysiological evidence for this specific phenotype of Acute Respiratory Distress Syndrome (ARDS) required to rent the practical approach to ventilation from guidelines of standard ARDS guidelines [ref].
Literature and data regarding ventilation expect also the adequate time to proceed to oral intubation and invasive mechanical ventilation (MV).

INTUBATION PROCEDURES

Studies from China, the first involved country , report detailed algorithms about endotracheal intubation [ref]. According to the Chinese recommendation, intubation has to be performed in severe patients with no relief of respiratory symptoms (persisting respiratory distress and/or hypoxemia) after standard oxygen therapy; or in patients with symptoms (respiratory distress, respiratory rate > 30 / min, oxygenation index <150 mmHg) that persist or exacerbate after high-flow nasal oxygenation (HFNO) or non-invasive mechanical ventilation (NIMV) for 2 hours [ref]. Early intubation has also been proposed from Italian Society of Analgesia Anesthesia and Intensive Care (SIAARTI) in which it has been recommended after a single attempt of 1 hour trial of NIMV in Continuous Positive Airway Pressure (CPAP) with 10 cmH2O and FiO2 60% or Positive Support Ventilation (PSV) with Pressure Support of 10-12 cmH2O, Positive End Expiratory Pressure 10 cmH2O and FiO2 60%. Consider alternatively a trial with HFNO with flow of at least 50 l/min and FiO2 at least of 60%. [ref].
Literature suggests also to be prepared for a rapid and adequate procedure of intubation since it is considered a high-risk manoeuvre for operators.

- Video laryngoscope with disposable blades.
- Disposable seeing optical stylet or disposable video endotracheal tube.
- Disposable second-generation intubating laryngeal mask.
- Prepare devices for needle or scalpel cricothyroidotomy.
- If available, prepare supraglottic & subglottic injectable ETT.

Some authors suggest the acronym OH-MS-MAID to remember all the passages:

- Oxygen
- Helper
- Monitor
- Suction
- Machine (ICU or Anesthesia ventilator set up and ready to plug)
- Airway supplies (videolaryngoscopy and difficult airway cart ready)
- Intravenous access
- Drugs (included vasoactive to support secondary hemodynamic instability)

A careful airways assessment before proceeding is crucial, including the evaluation of reliable position for cricothyroidotomy.
Pre-oxygenation with Face Mask (FM) should be avoided if possible; if necessary, two layers of wet gauze should be placed between the mask and the mount of the patient. Prefer pre-oxygenation through 3min tidal volume with FiO2 100% or 1 min OR 8 breath at Forced Vital Capacity (FVC) OR through NIV with FiO2 100% or PSV/CPAP 10cmH20 + 5cmH2O, FiO2 100%, to prevent production of aerosol. To prevent desaturation during apneic phase of intubation, HFNO may be useful, but it can generate aerosol, othehewise nasal cannula 3l/min O2 could be applied.

Videolaryngoscopy should be preferred over direct laryngoscopy and the procedure has to be performed by the most expert operator to minimize the attempt of intubation. In absence of predicted difficult airway, awake intubation should be avoided in order to minimize the risk of aerosol production by cough. If needed, prefer topical liquid anesthetics (no aerosol or vaporization).
Rapid Sequence Intubation (RSI) should be preferred in every patient to minimize FM ventilation. Some authors suggest the injection of opioids after the induction and muscle relaxation, because of their possibility to give cough [ref]
HEPA filters have to be installed between the FM and the respiratory bags and at the end of the breathing circuit.
If intubation is impossible, proceed to positioning an II generation laryngeal mask with guidance for fiberoptic bronchoscope to provide intubation.
If intubation as well as oxygenation(CICO) using the laryngeal mask is precluded, proceed with cricothyroidotomy

MECHANICAL VENTILATION

As mentioned before , strategies for MV were mainly and primary inferred from ARDS.
Concerning the setting for MV, clinics from Wuhan region reported poor tolerance to high PEEP and suggest starting from PEEP 20cmH2O and titrate down by 2 cmH2O until reach the goal of oxygenation, plateau pressure (pP) and compliance [ref] (intubation and ventilation amid…). The goal for driving pressure (dP = plateau pressure – PEEP) was below 12-15 cmH2O. Commonly used PEEP in this patient population was 10 cmH2O. They also summarized their respiratory goals and strategies [ref]

- PaO2: 55-80 mmHg
- SpO2: 88-95%
- pH: 7.30-7.45
- PaCO2: permissive hypercapnia for patient without intrathoracic hypertension and adjusted for pH goal
- Ventilatory mode: no recommendation for preferred mode
- Tidal volume (Vt): ≤ 6ml/kg of predicted body weight (PBW) adjusted for pH and pressure goals
- Respiratory rate (RR): ≤ 35 breaths/min adjusted for pH and pressure goals
- Airways pressure: pP ≤ 30 cmH2O maintain ≥ 25 cmH2O to open alveoli
- PEEP: higher PEEP over lower PEEP adjusted for pH and SpO2 goals
- FiO2: 0.3 – 1 adjusted for pH and SpO2 goals
- Prone position: recommended
- Semi recumbent position: recommended
- Sedation and analgesia: recommended
- Muscle relaxation: no recommendation
- Recruitment maneuver: recommended

SIAARTI suggested Volume Controlled Ventilation (VCV), Vt 4-8 ml/kg of PBW, RR 18-26/min (if pH < 7.23 and PaCO2 > 55 mmHg DO not increase RR > 35/min), targeting as follow: SpO2 88-95%, PaO2 55-80 mmHg, pP ≤ 28 cmH2O or ≤ 32 cmH2O in patient with BMI > 30 and dP ≤ 12-14 cmH2O or ≤ 15 cmH2O in patient with BMI > 30 [ref doc SIIARTI]. If PaO2/FiO2 ratio < 150 prone position was recommended within 72h from endotracheal intubation (ETI) lasting 12-16h; neuromuscular block was also recommended within 24h from ETI.

Prone positioning is recommended in conscious patients too[ref]. Recruitment maneuvers were recommended either in the staircase methods and sustained inflation limiting the increasing in airway pressure to a maximum of 40-45 cmH2O for 30-40 sec [ref].

From a pathophysiological point of view there were proposed two different clinical patterns: type L (Low elastance, Low Ventilation to Perfusion (VA/Q) ratio, Low lung weight and Low recruitability) and type H (High elastance, High right-to-left shunt, High lung weight, High recruitability). They depend on 1) the severity of the infection, the host response, physiological reserve and comorbidities; 2) the ventilatory responsiveness of the patient to hypoxemia; 3) the time elapsed between the onset of the disease and the observation in the hospital. The natural history of the disease is meant to start with phenotype L and, if conditions get worse, there could be a shift into the H one. Also, therapeutic approach is different: H phenotypes should be treated as classic ARDS (high PEEP, responding to prone position…), while L phenotypes could be treated with higher Vt, lower PEEP and with less response to prone position because of a better compliance [ref][ref]
Adequate MV is crucial to avoid either Ventilator Induced Lung Injury (VILI) [ref][ref] and Self-Induced Lung Injury (SILI) [ref] especially because some reports from China showed very high mortality between both NIV and IMV patients [ref] outcome.

Extubation

D'Silva et al. proposed a method to manage extubation in COVID-19 patients [ref].

"Mask Over Tube" extubation

- Position the patient 30° head up.

- Anaesthetist and assistant positioned behind the patient's head, attempting to avoid exposure to any coughing.

- Optimise anaesthetic facemask seal (prior to induction of general anaesthesia the anaesthetist will have ensured correct facemask size, adjusted inflation of mask cuff, shaved any facial hair).

- Attach a second airway filter to the facemask. The CO2 sampling port should be capped.

- Position the tracheal tube (TT) to one side of the mouth, closest to the anaesthetic assistant's position for extubation.

- Position the facemask with second airway filter, using a two-handed technique to ensure a seal over the mouth and nose with the TT exiting under the facemask.

- No positive airway pressure during extubation: ventilator off with no or low fresh gas flow. Consider attempting to extubate at end-expiration.

- Deflate TT cuff and extubate while maintaining facemask seal.

- Discard TT and connect circuit to the second airway filter facemask to the anaesthetic circuit (in the operating theatre) or the non-rebreather valve of a self-expanding bag (in the intensive care unit).

- Maintain a two-handed mask seal until regular breathing via the circuit and any immediate post-extubation coughing has subsided.

Post-extubation

- Place a surgical mask on the patient once the anaesthetic facemask is no longer required. Supplemental oxygen can be delivered under a surgical mask via nasal prongs.

- Staff members should confirm that PPE integrity has been maintained.

- Doffing should only occur once the patient has been handed over to another staff member. The room requires airborne precautions for at least 30 min after an aerosol generating procedure such as extubation.

proning [ref]

Prone ventilation does seem to be a useful intervention for profound or refractory hypoxemia. However before taking in consideration proning , optimization on the ventilator for 12-24 is generally preferable however For those who fail to respond to initial ventilator optimization (e.g. with persistent PaO2/FiO2 below 150 mm), prone ventilation may be considered.
There are some reasons that prone ventilation might not be desirable here:

Prone ventilation demonstrated mortality benefit in the PROSEVA trial in France, in the context of centers which were highly experienced at prone ventilation. It's controversial whether these benefits would be replicated in another RCT in a country less experienced with prone ventilation.

Prone ventilation would require exposing numerous healthcare providers to the patient, multiple times per day.

ECMO

Despite of the covid-19, in patients during ECMO is frequently observed a reduction in the number and normal function of circulating neutrophils and lymphocytes, which may further increase the susceptibility to infection. (ref). Moreover during ECMO, IL-6

concentrations are consistently elevated and inversely correlated with survival in children and adults.(ref]It has been reported by Risnes et al. that while survivors showed a marked decrease within 2 days in IL-6, the non- survivors were characterized by persistently high IL-6 levels. IL-6 and CRP were significantly correlated at baseline and at the end of the observation period in non-survivors(when they died), this pattern was not seen in survivors. Interleukin (IL)-1β, IL-8 and IL-10 were also analyzed: the non-survivors expressed increased levels of IL-8 and IL-10, as compared to survivors, although the standard deviation was large and the differences did not reach statistical significance IL-1β, IL-8 and IL-10 levels showed no significant differences between the two groups of patients during follow-up.(ref). As it might be hypothesized the levels of lymphocytes could be key to recovery from COVID-19. (ref).Clinicians should consider tracking both lymphocyte count and IL-6 during ECMO to monitor patient status and prognosis.(ref

HEMODYNAMIC SUPPORT

Avoid fluid resuscitation (Fluid properties ref)
Patients rarely are shocked on admission (even among critically ill patients, admission blood pressure is generally normal and lactate elevations are mild-moderate)((ref)).
The cause of death from COVID-19 is nearly always ARDS – which may be exacerbated by fluid administration.
Gentle fluid administration could be considered for patients with evidence of hypoperfusion and a history suggestive of total body hypovolemia (e.g. prolonged nausea/vomiting and diarrhea).

EVIDENCES ABOUT DRUG THERAPY

(https://www.genengnews.com/a-lists/how-to-conquer-coronavirus-top-35-treatments-in-development/)

ANTIVIRALS

Various antivirals are being trialled in patients with COVID-19 (e.g., oseltamivir, lopinavir/ritonavir, ganciclovir, favipiravir, baloxavir marboxil, umifenovir, interferon alfa); however, there are no data to support their use.[ref]
Binding energies and modes of interactions of Anti-HIV protease inhibitors with SARS-COV-2 protease depend on the pH and increase at acidic pH. [ref]
Some of the target candidates may be the following.
The Antiviral activity of ribavirin is due to the block of an RNA-dependent RNA polymerase for replicating viral genome and its target is RNA-dependent RNA polymerase(RdRp) [ref; ref; ref] Camostat mesylate activity is due to the block of a host cell-produced protease that primes S protein to facilitate its binding to ACE2 which is transmembrane protease, serine 2(TMPRSS2).[ref]
Another Antiviral agent is Arbidol. Its effectiveness is due to the block of a viral surface protein for binding to host cell receptor ACE2 and a viral receptor protein on the host cells which binds to viral S protein the targets are, respectively, viral spike glycoprotein(Protein S)(ref; ref) and angiotensin-converting enzyme 2(ACE-2)(ref; ref), but Its direct action on S protein and ACE2 is yet to be confirmed(ref)
WHO has identified the following for immediate evaluation[ref]:

- Remdesivir based on the broad antiviral spectrum, the in vitro and in vivo data available including against coronaviruses and the extensive clinical safety database
- Lopinavir/ritonavir, either alone or in combination with Interferon β

Remdesivir

the Antiviral activity of remdesivir is due to the block of an RNA-dependent RNA polymerase for replicating viral genome and its target is RNA-dependent RNA polymerase(RdRp)(ref; ref; ref;)
Remdesivir, an investigational antiviral drug, was reported to have in-vitro activity against SARS-CoV-2[ref]
Remdesivir might be an excellent antiviral, based on a study involving in vitro and animal data with MERS (e.g. Sheahan 2020).[ref]
Remdesivir is being used in one trial in the United States being sponsored by NIAID. [ref]
Data suggests that timing of antiviral initiation may be important, as administration of remdesivir with high viral loads seen after peak viral titer failed to reduce lung damage despite reducing viral loads. [ref]

Lopinavir / ritonavir

(Kaletra® also marketed as Aluvia; lopinavir/ritonavir)
[in alternativa al Remdesivir per i pz che non rientrano nei criteri per l'uso del Remdesivir]
the Antiviral activity of lopinavir is due to the block of protease for the proteolysis of viral polyprotein into functional units that are coronavirus main protease(3CLpro) and papain-like protease (PLpro).[ref; ref]
Lopinavir showed in vitro antiviral activity against SARS at concentration of 4 ug/ml. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 ug/mL [ref]
the peak and trough serum concentrations of lopinavir are 10 and 5.5 ug/ml [ref].
Lopinavir/ritonavir was effective against MERS-CoV in a primate animal model [ref].
Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study
Evidence of lower quality:

- Lopinavir/ritonavir has been used to treat one patient with COVID-19 [ref].
- Lopinavir/ritonavir is currently under investigation within multiple RCTs in China (but none in the United States[ref]

In Chu et al. 2004, 41 patients with SARS tolerated lopinavir/ritonavir reasonably well (one patient needed to discontinue due to doubling of transaminase levels). [ref]
In Chan 2003, 75 patients with SARS were treated with lopinavir/ritonavir without reports of severe adverse effects.[ref]
South Korean guidelines suggest lopinavir 400mg/ritonavir 100mg (Kaletra two tablets, twice a day) or chloroquine 500mg orally per day. There is no evidence that using lopinavir/ritonavir with chloroquine is more effective than monotherapies. Combining lopinavir/ritonavir with chloroquine or hydroxychloroquine could cause side effects and should be administered cautiously.[ref]
There was no statistical difference in prehospital medications between normal and abnormal liver function groups, while the utilization rate of lopinavir/ritonavir after admission was significantly higher in patients with emerging liver injury than that in patients with normal liver functions[ref]

RIBAVIRIN

South Korean physician guidelines state to only consider using ribavirin and interferon only if lopinavir/ritonavir or chloroquine or hydroxychloroquine does not work, or the administration is impossible. This is due to the side effects.
[http://www.koreabiomed.com/news/articleView.html?idxno=7428]

Favipiravir

Favipiravir is being explored as a possible treatment.[ref,ref,ref,ref] According to China National Center Favilavir is demonstrating encouraging profile with mild adverse reactions in COVID-19 patients in trials (findings of the trial are yet to be published)(ref). In one clinical trial is also being studied in association with Tocilizumab[ref]. Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor.[ref, ref]
On February 14, a clinical trial on favipiravir for the treatment of COVID-19 initiated by the Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen achieved promising results. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir. No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group. [ref]

ANTIMALARIAN

Chloroquine(Chloroquine phosphate-hydroxychloroquine)

(marketed by Bayer as Resochin®)
The anti-viral and anti-inflammatory activities of chloroquine may account for its potent efficacy in treating patients with COVID-19 pneumonia.[ref]
Chloroquine exerts a pleiotropic effect in eukaryotic cells, including an elevation of vacuolar pH when trapped in acidic organelles, such as lysosomes. This increase in pH disrupts lysosomal acidification leading to the impairment of autophagosome fusion and autophagic degradation.[ref, ref]
At the molecular level, chloroquine data show that the Akt inhibitor synergizes with the lysosomotropic inhibitor of autophagy chloroquine to induce apoptosis [ref]
Chloroquine is effective in preventing the spread of SARS CoV in cell culture. Favorable inhibition of virus spread was observed when the cells were either treated with chloroquine prior to or after SARS CoV infection.[ref]
A number of subsequent clinical trials have been quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19 associated pneumonia in more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo. Some of those RTC investigated also chloroquine phosphate compared to those before mentioned as well as chloroquine therapy for the treatment of different illness severity [Chinese Clinical Trial Registry: ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref, ref]. Chloroquine is a cheap and safe drug that has been used for more than 70 years [ref].
Bmj assumed that Chloroquine shows in vitro activity against SARS-CoV-2 and is likely to be added to the updated version of the Chinese management guidelines.[ref]
The outcomes of some current clinical trials of chloroquine in China have been announced, without access to the data. Peer review of the results and an independent assessment of the[ref]

potential benefit for patients are essential. recommended chloroquine phosphate tablet, 500mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine.[ref] China published an expert consensus that However, this suggest that studies were not blinded.
South Korean guidelines suggest lopinavir /ritonavir or chloroquine orally per day. As chloroquine is not available in Korea, hydroxychloroquine 400mg orally per day is being considered. There is no evidence that using lopinavir/ritonavir with chloroquine is more effective than monotherapies. Combining lopinavir/ritonavir with chloroquine or hydroxychloroquine could cause serious arrhythmias and drug interactions due to the increased QT interval. The combination should be administered cautiously, in a very limited case.[ref]

Azithromycin

Macrolides influence a broad range of immunological mechanisms resulting in immunomodulatory effects. Immunomodulatory effects were investigated for four types of macrolides, including Clarithromycin, Azithromycin, Erythromycin, and Roxithromycin.[Ref]
The most frequently reported macrolide-induced changes were a decrease in interleukin (IL)-8 concentration, neutrophil count, tumor necrosis factor-alpha (TNF-alpha) , neutrophil elastase, IL-1beta , eosinophilic cationic protein, IL-6, matrix metalloproteinase 9 (MMP-9), and oxidative burst activity. Inhibition of neutrophil function was reported more frequently than eosinophil function. A decrease in T helper (Th) 2 cells cytokines (IL-4, IL-5, IL-6) was reported more frequently than a decrease in Th1 cytokines (IL-2, INF-gamma).[ref]
Azithromycin was more frequently associated with no influence on the immunological markers investigated compared to any of the other macrolides.[ref]
However, most of these studies were either in healthy volunteers or Azithromycin was administered for only a few days [ref,ref, ref]. By contrast, clinical studies in patients with cystic fibrosis suggest that Azithromycin leads to an improvement in respiratory function and reduction in pulmonary exacerbations.[ref, ref]
It has been shown that Azithromycin, but not Clarithromycin or Roxithromycin, inhibits IL-1alpha and IL-1beta production [ref, ref]
Drug accumulation in immune cells may result in immunomodulatory effects occurring at lower doses and lasting longer compared to the antimicrobial effects [ref]
a Azithromycin has direct activity on airway epithelial cells to maintain their function and reduce mucus secretion.[ref]
Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination. Hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin. Twenty cases were treated with oral hydroxychloroquine sulfate 200 mg, three times per day, for ten days, in a study. This showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature.[Ref]

In a study was evaluated the effect of Azithromycin on the production of proinflammatory mediators by alveolar macrophages up to 4 weeks after a 3-day course of Azithromycin (500 mg, once a day). No significant differences between groups for blood or BAL proinflammatory cytokines levels (TNF-α, IL-1β, IL-6), and for superoxide generation by alveolar macrophages was detected. Data showed that a 3-day course of Azithromycin 500 mg/day in healthy subjects does not alter the proinflammatory cytokine profile in blood and in alveolar macrophages despite the prolonged tissue impregnation by this drug. [Ref]

ACE2-mediated COVID-19 - Potential approaches to address

There are several potential therapeutic approaches :

Spike protein-based vaccine.

Development of a spike1 subunit protein-based vaccine may rely on the fact that ACE2 is the SARSCoV-2 receptor. Cell lines that facilitate viral replication in the presence of ACE2 may be most efcient in large-scale vaccine production. [ref]

Inhibition of transmembrane protease serine 2 (TMPRSS2) activity.

Hofman et al.[ref.]recently demonstrated that initial spike protein priming by transmembrane protease serine 2 (TMPRSS2) is essential for entry and viral spread of SARS-CoV-2 through interaction with the ACE2 receptor. [ref, ref] Te serine protease inhibitor camostat mesylate, approved in Japan to treat unrelated diseases, has been shown to block TMPRSS2 activity[ref,ref] and is thus an interesting candidate.

Blocking ACE2 receptor.

The interaction sites between ACE2 and SARS-CoV have been identified at the atomic level and from studies to date should also hold true for interactions between ACE2 and SARS-CoV-2. Tus, one could target this interaction site with antibodies or small molecules.[ref]
Angiotensin-II receptor antagonists such as losartan are being investigated as a potential treatment because it is thought that the angiotensin-converting enzyme-2 (ACE2) receptor is the main binding site for the [ref, ref]

Delivering excessive soluble form of ACE2.

Kuba et al [ref]demonstrated in mice that SARS CoV downregulates ACE2 protein (but not ACE) by binding its spike protein, contributing to severe lung injury. Tis suggests that

excessive ACE2 may competitively bind with SARS-CoV-2 not only to neutralize the virus but also rescue cellular ACE2 activity which negatively regulates the renin-angiotensin system (RAS) to protect the lung from injury.[ref,ref]Indeed, enhanced ACE activity and decreased ACE2 availability contribute to lung injury during acid- and ventilator-induced lung injury.[ref,ref, ref] Tus, treatment with a soluble form of ACE2 itself may exert dual functions: (1) slow viral entry into cells and hence viral spread [ref, ref] and (2) protect the lung from injury [ref, ref, ref, ref]

Recombinant human ACE2

(rhACE2; APN01, GSK2586881) has been found to be safe, with no negative hemodynamic effects in healthy volunteers and in a small cohort of patients with ARDS[ref, ref, ref] Te administration of APN01 rapidly decreased levels of its proteolytic target peptide angiotensin II, with a trend to lower plasma IL-6 concentrations. The availability of recombinant ACE2 was the impetus to assemble a multinational team of intensivists, scientists, and biotech to rapidly initiate a pilot trial of rhACE2 in patients with severe COVID-19. [ref, ref]

IMMUNOSUPPRESSIVE DRUGS

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome.ref

TOCILIZUMAB

(Humanized mAb targeting interleukin-6)

In a chinese study on 21 patients tocilizumab is reported to have effectively improved clinical symptoms and repressed the deterioration of severe COVID-19 patients(ref). Here are reported the baseline lab tests of the patients compared to the the lab tests of the patients after the first, third and fifth doses of tocilizumab.(Tab reference here)

Cancelled by the investigator Combination of Tocilizumab, IVIG and CRRT in severe patients with novel coronavirus pneumonia (COVID-19) (last refreshment on 2020-03-14, not approved by the ethic committee)(ref).
Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS) People are being recruited since March 13th in this retrospective study to evaluate safety and efficacy of Tocilizumab compared to continuous renal replacement

therapy in controlling CRS triggered by COVID-19. Among the inclusion criteria there are a laboratory-confirmed novel coronavirus infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in oropharyngeal or anal specimen within 72 hours prior to hospitalization and Serum IL-6 ≥3 times the upper limit of norma. The exclusion criteria include ALT/AST > 5 times the upper limit of normal, Stage 4 severe chronic kidney disease or requiring dialysis, hemoglobin<80 g/L, Leukocytes<2.0×10^9; Platelets<50×10^9;Expected life span does not exceed 7 days. The first Primary Outcome Measure addressed is the normalization of Fever(< 36.6 °C armpit, < 37.2 °C oral sustained for at least 72 hours) ref

A multicenter, single arm, open label trial for the efficacy and safety of CMAB806 in the treatment of cytokine release syndrome of novel coronavirus pneumonia (COVID-19) Intervention：conventional therapy+tocilizumab are not recruiting.(ref)

A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19)

A 94-patient trial assessing Tocilizumab has been registered where the primary outcome is the cure rate. Secondary outcomes include mortality, days on ventilation, hospitalization days.ref. However in a preprint about outcome reporting from protocols of clinical trials , the tocilizumab clinical trial was defined as course of treatment unclear (ref)

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin is being trialled in some patients with COVID-19; however, there are no data to support this [ref,ref]

A neutralizing antibody targeting the S protein on the surface of 2019-nCoV is likely the first therapy contemplated by biomedical researchers in academia and industry, providing passive immunity to disease[ref, ref]

Both 2019-nCoV-HR2P and EK1, the pan-CoV fusion inhibitor, exhibited potent inhibitory activity against S-mediated cell–cell fusion and 2019-nCoV pseudovirus infection, suggesting potential development of either 2019-nCoV-HR2P or EK1 peptide in nasal spray and inhalation formulations, respectively, to prevent and treat 2019-nCoV infection.SARS-CoV spike (S) protein S2 subunit plays a key role in mediating virus fusion with and entry into the host cell, in which the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) can interact to form six-helical bundle (6-HB), thereby bringing viral and cellular membranes in close proximity for fusion.Using S-HR1 as a target, we have previously designed and developed several potent fusion inhibitors against SARS-CoV (e.g., SARS-HR2P)[ref,] and Middle East respiratory syndrome (MERS)-CoV (e.g., MERS-HR2P).[ref,ref]

this strategy may be viable for a short-term, but would not easily scale in the 2019-nCoV outbreak, which is already rapidly multiplying.[ref]

CONVALESCENT PLASMA

Convalescent plasma from patients who have recovered from viral infections has been used as a treatment in previous virus outbreaks including SARS, avian influenza, and Ebola virus infection [ref]. A clinical trial to determine the safety and efficacy of convalescent plasma in patients with COVID-19 has started in China; however, there is no data on its use as yet.[ref, ref]

EMPIRIC ANTIBIOTICS

Among patients who died from COVID-19, one series found that 11/68 (16%) had secondary infections (ref). In case of concerns regarding the possibility of a superimposed bacterial pneumonia. Based on culture and procalcitonin results, antibiotics might be discontinued in <48 hours if there isn't evidence of a bacterial infection (this is exactly the same as management of influenza pneumonia).This may be investigated and treated similarly to other ventilator-associated pneumonias, or hospital-acquired pneumonias (ref).

Teicoplanin, a glycopeptide antibiotic that inhibits bacterial cell wall synthesis, was recently found to have actions against MERS-CoV and Ebola virus in cell culture.[ref]

Further search of the publications is needed in this area.

GLUCOCORTICOIDS (GCS)

Metilprednisolone - In this study, critically ill patients with 2019-nConV were enrolled and randomized to receive ether standard care or standard care in combination with methylprednisolone therapy. The primary outcome is the difference of Murray lung injury score between two groups [ref].

A combination of antiviral therapy, methylprednisolone, and an immune modulator was used in severe acute respiratory syndrome coronavirus (MERS) patients with varying success.

The use of corticosteroids in viral pneumonia and ARDS is controversial. Their usage are left to the discretion of the treating physicians [ref].

Methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay.[ref]

it has been observed in a study that expression levels for IL-10, IFN-gamma and CXCL10 consistently peaked within 4 days of peak viral load. IL-12p70, IL-4 and tumour necrosis factor-alpha concentrations were consistently highest within 5 days of peak viral load. These results suggest that elevated levels of inflammatory cytokines are sensitive correlates of

disease severity, including lung abnormalities and viral load in serum, and may provide a tool for monitoring disease progression in affected individuals. [ref]
In another study, Plasma SARS-CoV RNA concentrations in the second and third week of illness were significantly higher in patients who received initial hydrocortisone treatments compared to those who received placebo. The median time for SARS-CoV to become undetectable in plasma was 12 days (11-20 days) versus 8 days (8-15 days), respectively. "Early" corticosteroid treatment was associated with a higher subsequent plasma viral load. [ref]
The use of high dose of hydrocortisone or methylprednisolone for an extended duration in MERS patients was shown to be a significant risk factor for osteonecrosis. Its prevalence in this cohort is comparable to those reported in the literature for SARS patients with high-dose corticosteroid therapy. [ref]
Hyperglycemia and hypokalemia were seen to be correlated with GCS dosage and duration. Administration with GCS influences SBP, DBP, and duration of hypocalcemia. Appropriate low dosage of GCS causes few changes of blood glucose, serum potassium, and blood calcium. It is important to monitor laboratory findings during the treatment with GCS.[ref]
The timing and dosage regimens of steroid in the treatment of SARS are controversial. Pulse methylprednisolone 250 to 500 mg/day for 3 to 6 days has been reported to have some efficacy in a subset of patients with "critical SARS"(critically ill SARS patients with deteriorating radiographic consolidation, increasing oxygen requirement with PaO2 <10 kPa or SpO2 <90% on air, and respiratory distress (rate of 30/min)). Prolonged therapy with high-dose steroids, in the absence of an effective antimicrobial agent, could predispose patients to complications such as disseminated fungal infection, and avascular necrosis.[ref]
Small dose of steroid seemed to have protective effect, but it did not reach significant level, COX regression revealed that steroid was not related to instant mortality rate, Length of stay in hospital of patients steroid usage in medium dosage seemed to be 0.619 time less risky than in patients without steroid usage, Incidence of infections in patients with steroid was 3.095 times higher than in patients without steroid.[ref]
Immunosuppressive therapy (e.g. low-dose steroid) might be best initiated during the adaptive immune stage (with a goal of blunting this immunopathologic response slightly, in the sickest patients). But this is purely speculative.[ref]

ASCORBIC ACID

Ascorbic acid did appear to improve survival in the multicenter CITRIS-ALI trial. However, interpretation of this trial remains hopelessly contentious due to nearly unsolvable issues with survival-ship bias.(ref).
Extremely limited evidence suggests that ascorbic acid could be beneficial in animal models of coronavirus.[ref]
Administration of a moderate dose of IV vitamin C could be considered (e.g. 1.5 grams IV q6 ascorbic acid plus 200 mg thiamine IV q12). This dose seems to be safe. However, there is no high-quality evidence to support ascorbic acid in viral pneumonia.

OTHERS

TMPRSS2 inhibitor (Camostat Mesylate)

SARS-CoV-2 infection depends on the host cell factors ACE2 (explained above) and TMPRSS2. TMPRSS2 stands for “Transmembrane Protease Serine 2”, and is a transmembrane protease of the serine protease family that is involved in many physiological and pathological processes. TMPRSS2 can be blocked by a clinically proven protease inhibitor Camostat Mesylate. This drug is known to inhibit TMPRSS2, and therefore could theoretically prevent viral infection of the host cell via this transmembrane protease. This therefore could be a potential therapeutic agent for COVID-19 infection. Camostat Mesylate has been approved in Japan for the treatment of pancreatic inflammation. When tested on SARS-CoV-2 isolated from a patient, Camostat managed to prevent the entry of the virus into lung cells.[ref,ref]

Zinc

In vitro study has found that increasing the intracellular Zn2+ concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of coronaviruses.[ref]
In vitro, chloroquine was found to be a zinc ionophore. [ref]

Human Umbilical Cord Mesenchymal Stem Cells

Clinical trials are being undertaken.
This study aims to investigate whether MSC transplantation improves the outcome of 7 enrolled patients with COVID-19 pneumonia in Beijing YouAn Hospital, China, from Jan 23, 2020 to Feb 16, 2020. In this study after treatment, the peripheral lymphocytes were increased, the C-reactive protein decreased, and the overactivated cytokine secreting immune cells CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells disappeared in 3-6 days. In addition, a group of CD14+CD11c+CD11b mid regulatory DC cell population dramatically increased. Meanwhile, the level of TNF-α was significantly decreased, while IL-10 increased in MSC treatment group compared to the placebo control group. Furthermore, the gene expression profile showed MSCs were ACE2- and TMPRSS2- which indicated MSCs are free from COVID-19 infection. Thus, the intravenous transplantation of MSCs was safe and effective for treatment in patients with COVID-19 pneumonia, especially for the patients in critically severe condition.[ref]