COVID-19: the essential in three stages

La Colonia – Italian-German research group

Updated English version

When the first cases of COVID-19 infection started to be detected the profound difference between patients in terms of severity of disease quickly became evident. A vast majority of patients remained asymptomatic and eventually healed while some, despite lacking initial symptom, eventually worsen and a few fell ill quite rapidly. While facing a new disease, COVID-19 pneumonia was approached based on medical knowledge translated from the most similar illness but, a year later since the beginning of the outbreak in Northern Italy, knowledge has evolved. This text has the intent to offer a comprehensive view of COVID-19 pneumonia and its treatment options as a continuum of the same but complex disease, from the early to the late phase.

To give our contribution to the everyday care of these patients we released a first Italian version of this document in November, for knowledge has evolved since, we decided to release a second version, this time in English.

Contrary to our usual work, this has not been submitted to a journal and peer reviewed as we consider it more of a practical summary.

News, opinions, and statement about COVID-19 have dominated public discussion since the start of the pandemic. Unfortunately, public media communications are often reduced to a few words. Sentences are taken out of context and forced into catchy headlines. Experts from different medical fields have argued extensively and given different, often contrasting, point of view.

We believe that at least part of the disagreement comes from the fact that each physician is not necessarily referring to the same patient in the same phase of the disease: expertise in a specific field gives a really good view but with a narrow-angle.

When someone is infected with SARS-CoV-2 a wide spectrum of symptoms and manifestations may develop: from completely asymptomatic to severe respiratory impairment and multi-organ failure. So, being able to look at the whole picture, becomes more important than ever to understand the pathology and avoid drawing the wrong conclusions.

Thanks to the constant exchange of information with colleagues from different medical fields we conceptualized COVID-19 as a progressive disease with different stages. Depending on the virus-host interaction, the disease may progress to multi-organ failure, or may be self-limiting like the common cold. The reason why is yet not known. Consequently, the only weapon in our hands is to identify correctly each stage of the disease and treat each patient accordingly.

This is a summary of our view on the most severe manifestation of COVID-19: pneumonia. For educational purposes, we will divide the evolution of the disease into three stages or phases: early, intermediate, and late. It is important to remember that progression is a continuous process and features may merge and overlap.

Early phase

Of all patients that contract SARS-CoV-2 (i.e., patients with a positive test) a small fraction will develop symptoms that require medical attention. There is no explanation as to why, in general, the severity of a disease may depend on the load of infectious agent and the intensity of the host's reaction (1).

Most common early symptoms are fever, cough and fatigue (2). From the airway the virus enters into the lungs and through the bloodstream it can spread to other organs. However, the main target of the virus is the lung: Computer Tomography (CT) shows bilateral ground-glass density (3)(Figure 1).

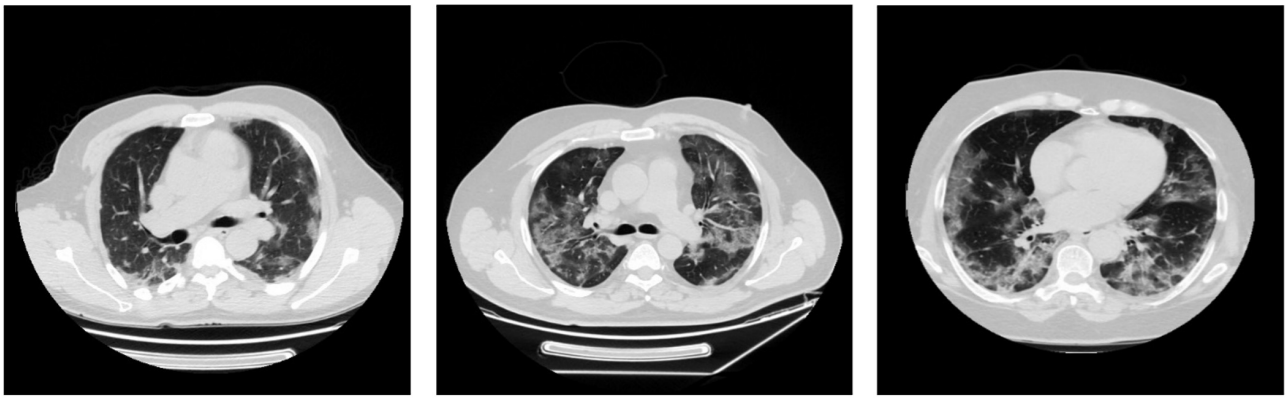


Figure 1. Three examples of COVID-19 pneumonia on Computer Tomography in the early phase.

What is distinctively peculiar of COVID-19 pneumonia is hypoxemia - which, in the early phase, is accompanied with only minor radiological signs. CT scan often indicates interstitial alterations that are out of proportion with the severity of the observed hypoxemia (4). Many patients present deeply hypoxemic but without any other respiratory symptoms such as dyspnea. What was defined as *silent hypoxia* (5).

Gas exchange, so oxygenation and CO2 removal, is determined with mathematical precision by the ratio between ventilation and perfusion: if the lung has nearly normal gas content (as observed in COVID-19 patients) and oxygenation is profoundly reduced, the only possible explanation is a altered perfusion (6)(7). This was repeatedly confirmed in COVID-19 patients by direct measures (8)(9). In other words, the distinctive trait of this disease is that the first target of the virus is not so much the alveolar side of the lung parenchyma but its vascular component – and therefore its perfusion (10). Hypercoagulability (11) and alterations of endothelium (12) and pericytes were also observed (13).
In physiological conditions, the ratio between ventilation and perfusion (VA/Q) is close to 1 and this allows for adequate gas exchange. In COVID-19, due to both an altered perfusion and microembolization of pulmonary vessels (14)(15), in some alveoli ventilation exceeds perfusion, altering CO2 elimination. In other perfusion exceed ventilation, the blood is only partially oxygenated, and, considering the extreme case of absence of ventilation, blood may leave the pulmonary capillary with the same oxygen content of the mixed venous blood.

So, in the early phase of COVID-19 pneumonia we can observe the following phenomena:

- The patient is deeply hypoxic
- Lungs present with ground glass opacities
- Patients are not necessarily dyspneic

It is mandatory to remember that dyspnea is – by definition - a subjective sensation. The patient is dyspneic when the tidal volume which follows an inspiratory effort does not match the tidal volume desired by the brain. This unbalance between expected and effective tidal volume generates dyspnea. Silent hypoxemia is then explained by the fact that, if the lung has nearly normal compliance, the patient receives an adequate tidal volume in relationship to its inspiratory effort.
With progression of the disease the lung parenchyma becomes more altered. Radiologic opacities, including both collapsed alveoli and units filled with fluid, cells, and products of inflammation, occupy a place normally full of aerated tissue hence lowering the gas content and the lungs become heavier. The decrease of gas content causes the lung to become less compliant. Consequently, a certain inspiratory effort does not match with the expected tidal volume and generates dyspnea.

Treatment

In general, the treatment of every disease can be broken down to three principles.

- Etiological: treating the cause of the disease, the virus.
- Pathophysiological: intervening in the process, that, from the cause of the disease, leads to the anatomical and physiological damage of the target organ. It means modulation of the inflammatory response and the enhanced coagulability associated with COVID-19.
- Symptomatic: treating the symptoms such as reversing hypoxemia.

When SARS-CoV-2 started to spread, many attempts were made to find etiological and pathophysiological treatment. Leading to the use of various drugs and their combination. Most of these were, at best useless (16)(17)(18)(19).

Etiological treatment

No drug proved to be effective concerning etiological treatment: Remdesivir showed a slight decrease in hospital length of stay but results on the benefits on mortality are conflicting (20)(21). Monoclonal antibodies, theoretically able to neutralize the virus, are still undergoing evaluation (22).

Pathophysiological treatment

Concerning pathophysiological treatments, steroids, in particular, dexamethasone 6 mg/day for 10 days was able to significantly lower the mortality in patients hospitalized for COVID-19 (23) and a higher dose of 20 mg for 5 days followed by 10 mg for another 5 day reduced ventilation requirement

in moderate/severe ARDS patients (24). Low-molecular weight heparin in anticoagulant dose has allowed for a reduction in thrombosis (25) and there are anecdotal reports of its use as an aerosol (26). It was recently announced by the ATTACC/ACTIV4/REMAP-CAP network that interim analysis of their data seams to show that full blood thinners in hospitalized moderately ill COVID-19 patients reduced requirements for vital organ support whereas anticoagulation was stopped in severe COVID-19 patients for futility. In order to correctly interpret these data, it will be necessary to wait for publication, one possible explanation, however, is that the start of anticoagulation when the patient is already critically ill may present little advantage for the damage to pulmonary perfusion has already occurred.

Tocilizumab, used to counteract ILs storm, did not showed survival benefit in early phases (27) but a recent analysis by REMAP-CAP show its efficacy in the most severe patients treated in the ICU (28).

Symptomatic treatment

Symptomatic treatment consists of correcting hypoxia: low oxygen delivery, especially if associated with other organ dysfunction, may lead to multi-organ dysfunction and death. Interventions of increasing complexity at the worsening of the condition are therefore necessary.

In general, there are two possible reasons for hypoxemia to develop in a patient: VA/Q mismatch and right to left shunt. In the first case the blood runs through alveoli that have a low VA/Q ratio and therefore is not sufficiently oxygenated. In the second case, the blood runs through a region of the lung that is not aerated and remains venous. In COVID-19 the first mechanism is predominant in the early phase. This type of hypoxemia is responsive to a higher inspired fraction of oxygen. Right to left shunt, on the other hand, requires closed pulmonary units to be reopened via recruitment (29).

In the early phase, the amount of atelectasis is small, and therefore the potential recruitment is limited. The most effective symptomatic treatment is to increase oxygen available by increasing FiO2. If atelectasis becomes quantitively important it becomes useful to reopen those pulmonary units with a positive pressure ventilation such as the application of Continuous Positive Airway Pressure (CPAP). Another possibility to improve oxygenation is prone positioning. This technique, usually applied to intubated patients, during the current pandemic has also been used in non-intubated patients, with oxygen masks or helmet CPAP or non-invasive ventilation (30).

During this phase is mandatory to check the inspiratory effort of patients: for reasons that are still not clear some have an altered respiratory drive despite correction of hypoxemia. When the lung is inflamed, a large tidal volume may lead to the damaging of lung tissue. This is what we referred to when talking about p-SILI (patient Self Induced Lung Injury). The stretching due to increased tidal volumes, worsen inflammation and worsens the edema. It is hence probable that in some patients, the natural evolution of the disease is worsened by this mechanism (31). The esophageal pressure swings, the pressure swinges of CVP, the ultrasound displacement of the diaphragm and the close observation of inspiratory muscle action are all possible means to measure or estimate the inspiratory effort.

Intermediate phase

In this phase the lung starts to lose its elasticity, gas content is reduced, and atelectasis expand (6). Densities are especially enhanced in the dependent region of the lung (Figure 2). Edema and lung weight increase, consequently dependent regions are pressed and gas content decreases. In this phase hypoxia is determined by two factors: on top of ventilation/perfusion mismatch, due to the developed atelectasis, right to left shunt starts to play a significant role. It is noteworthy that in prone position, closed pulmonary units that are no longer suffering the weight of the whole lung, open up again improving lung compliance and hypoxia (32).

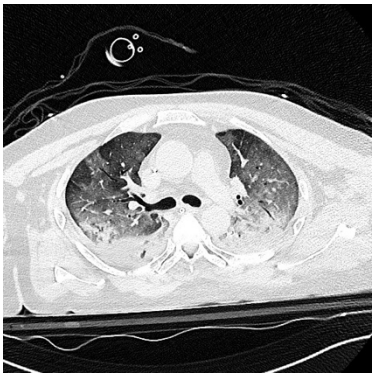


Figure 2. One example of COVID-19 pneumonia on Computer Tomography in the intermediate phase.

Respiratory management requires increasing interventions. Mechanical ventilation is needed to sustain muscles that are no longer able to move a heavy lung while positive pressure keeps pulmonary units open. In this phase most patients become dependent on mechanical ventilation, eighter invasive, or non-invasive.

Late phase

This phase concerns a small portion of patients and is characterized by a profound alteration of the structure of the lung. There is a considerable increase in fibrotic tissue (33) that is longer recruitable and alters deeply the anatomy and function of the lung. Based on its extension it may determine the irreversibility of the disease.

To summarize, depending on the observed phase of the disease, patients may present with a condition ranging from nearly normal lung compliance and hypoxemia (mainly due to ventilation/perfusion mismatch) to severely decreased compliance, increased lung weight, and relevant right to left shunt (Figure 3).

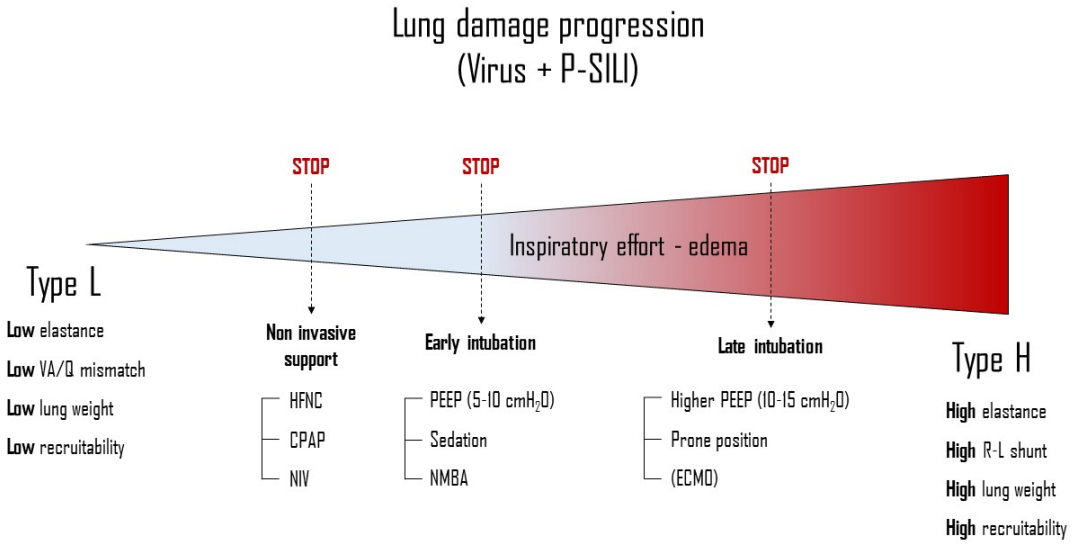


Figure 3. Time course of COVID-19 ARDS.

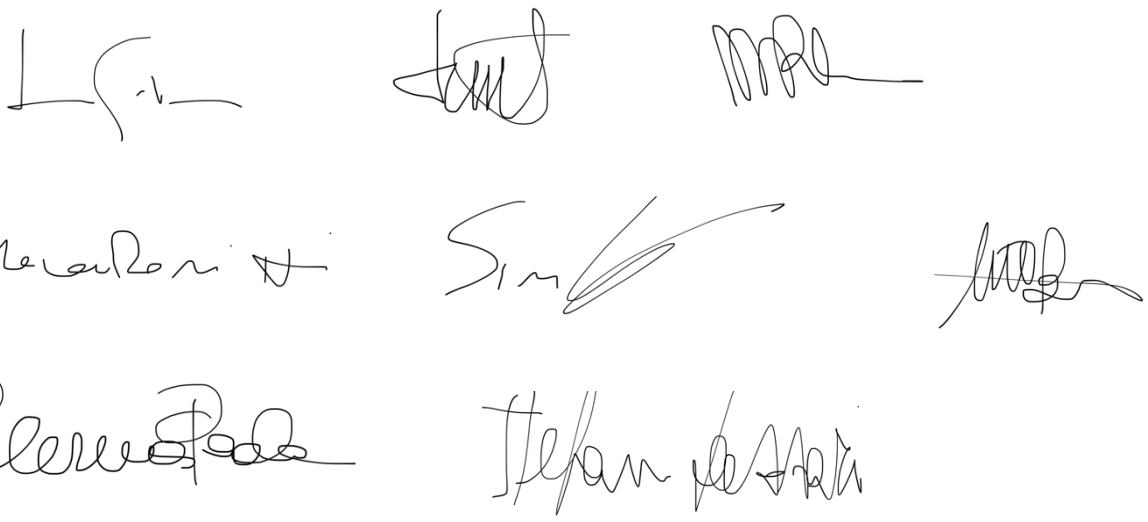
With the surge of the pandemic, intensivists have been arguing about treatment options. To understand this phenomenon, it should be remembered that Intensive Care was born addressing respiratory conditions and intensivists have been discussing over the best treatment approach for ARDS (Acute Respiratory Distress Syndrome) for the last 30 years. The reason is probably surprisingly simple, ARDS is a term that was born to facilitate communication, but the undelaying conditions may be profoundly different. The common denominators are hypoxemia and bilateral infiltration at X-ray or CT. COVID-19 pneumonia falls under this wide umbrella, nevertheless, since at least in the early

phase, despite the deep hypoxemia, we cannot see reduced compliance and increased lung weight, it is sort of an atypical ARDS.

This matter is not without direct consequence on clinical approach and consequently has fueled a heated debate (6)(34)(35)(36). In typical ARDS intensivist use high end-expiratory pressure to correct atelectasis, together with low tidal volumes to minimize VILI. Whereas in COVID-19, at least in the early phase, this approach could, in our opinion, be devastating: low tidal volume in a patient that does not need it leads to hypoventilation and high end-expiratory pressure, when there is no atelectasis to reopen, only impairs cardiovascular function.

Consequently, we firmly believe that the correct recognition of the stage of the disease may provide a framework upon which optimal delivery of individualized treatment can be achieved for patients with COVID-19.

Göttingen, 02/03/2021



Bibliography

1. Mazzoni A, Maggi L, Capone M, Spinicci M, Salvati L, Colao MG, et al. Cell-mediated and humoral adaptive immune responses to SARS-CoV-2 are lower in asymptomatic than symptomatic COVID-19 patients. Eur J Immunol. 2020 Dec;50(12):2013–24.
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–20.
3. Zhou S, Wang Y, Zhu T, Xia L. CT Features of Coronavirus Disease 2019 (COVID-19) Pneumonia in 62 Patients in Wuhan, China. Am J Roentgenol. 2020 Jun;214(6):1287–94.
4. Chiumello D, Busana M, Coppola S, Romitti F, Formenti P, Bonifazi M, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. Intensive Care Med [Internet]. 2020 Oct 21 [cited 2020 Nov 16]; Available from: http://link.springer.com/10.1007/s00134-020-06281-2
5. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020 Dec;21(1):198.
6. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020 May 15;201(10):1299–300.
7. Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S, et al. Potential for Lung Recruitment and Ventilation-Perfusion Mismatch in Patients With the Acute Respiratory Distress Syndrome From Coronavirus Disease 2019*. Crit Care Med. 2020 Aug;48(8):1129–34.
8. Si-Mohamed S, Chebib N, Sigovan M, Zumbihl L, Turquier S, Boccalini S, et al. *In vivo* demonstration of pulmonary microvascular involvement in COVID-19 using dual-energy computed tomography. Eur Respir J. 2020 Oct;56(4):2002608.
9. Santamarina MG, Boisier Riscal D, Beddings I, Contreras R, Baque M, Volpacchio M, et al. COVID-19: What Iodine Maps From Perfusion CT can reveal—A Prospective Cohort Study. Crit Care. 2020 Dec;24(1):619.
10. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020 Aug;S2213260020303702.
11. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb Haemost. 2020 Jun;120(06):998–1000.
12. Goshua G, Pine AB, Meizlish ML, Chang C-H, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020 Aug;7(8):e575–82.
13. Cardot-Leccia N, Hubiche T, Dellamonica J, Burel-Vandenbos F, Passeron T. Pericyte alteration sheds light on micro-vasculopathy in COVID-19 infection. Intensive Care Med. 2020 Sep;46(9):1777–8.
14. Grillet F, Busse-Coté A, Calame P, Behr J, Delabrousse E, Aubry S. COVID-19 pneumonia: microvascular disease revealed on pulmonary dual-energy computed tomography angiography. Quant Imaging Med Surg. 2020 Sep;10(9):1852–62.
15. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 09;383(2):120–8.
16. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A

Randomized Clinical Trial. JAMA. 2020 Aug 4;324(5):460.
17. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020 Dec 1;324(21):2165.
18. Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. The Lancet. 2020 Oct;396(10256):959–67.
19. The RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Nov 19;383(21):2030–40.
20. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020 Sep 15;324(11):1048.
21. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 Nov 5;383(19):1813–26.
22. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2021 Jan 21 [cited 2021 Jan 27]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2775647
23. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med. 2020 Jul 17;NEJMoa2021436.
24. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020 Oct 6;324(13):1307.
25. Chistolini A, Ruberto F, Alessandri F, Santoro C, Barone F, Cristina Puzzolo M, et al. Effect of low or high doses of low-molecular-weight heparin on thrombin generation and other haemostasis parameters in critically ill patients with COVID-19. Br J Haematol [Internet]. 2020 Aug [cited 2020 Dec 26];190(4). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.17003
26. van Haren FMP, Page C, Laffey JG, Artigas A, Camprubi-Rimblas M, Nunes Q, et al. Nebulised heparin as a treatment for COVID-19: scientific rationale and a call for randomised evidence. Crit Care. 2020 Dec;24(1):454.
27. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Dec 10;383(24):2333–44.
28. The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Feb 25;NEJMoa2100433.
29. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020 Jun;46(6):1099–102.
30. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med. 2020 Aug;8(8):765–74.
31. Esnault P, Cardinale M, Hraiech S, Goutorbe P, Baumstrack K, Prud'homme E, et al. High Respiratory Drive and Excessive Respiratory Efforts Predict Relapse of Respiratory Failure in Critically Ill Patients with COVID-19. Am J Respir Crit Care Med. 2020 Oct 15;202(8):1173–8.
32. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. Am J Respir

Crit Care Med. 2020 Jun 15;201(12):1560–4.
33. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol. 2020 Nov;33(11):2128–38.
34. Camporota L, Chiumello D, Busana M, Gattinoni L, Marini JJ. Pathophysiology of COVID-19-associated acute respiratory distress syndrome. Lancet Respir Med. 2020 Nov;S2213260020305051.
35. Grasselli G, Tonetti T, Filippini C, Slutsky AS, Pesenti A, Ranieri VM. Pathophysiology of COVID-19-associated acute respiratory distress syndrome – Authors' reply. Lancet Respir Med. 2020 Nov;S2213260020305257.
36. Tsolaki V, Zakynthinos GE, Mantzarlis K, Vazgiourakis V, Makris D. Pathophysiology of COVID-19-associated acute respiratory distress syndrome. Lancet Respir Med. 2020 Nov;S2213260020305063.