

Note 3. The bacteria are very frequently taking advantage of viral infections. Treating at the community level may avoid infected patients flooding the ICU's?

For the majority (more than 80%) of Covid19 infected persons, their flu-like symptoms will be mild, and they will recover in a few days. For some the symptoms will be more painful. It is estimated that 10-30% of the infected will develop a secondary bacterial infection. Half of those (which means 5-15% of the total infected) will die from a bacteria if not treated well (see Reference 1 from Antibiotic Research below).

Unless a person is in severe bad health, nearly no one dies DIRECTLY from the virus, but many may die from its complications. The major complication is a bacterial infection on top of the virus. This was ALREADY reported in Wuhan (Zhou et al. Lancet). 50% of the patients who died, died of a secondary infection. [Quote] *Sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, heart failure, and septic shock (table 2). Half of non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in ten (31%) of 32 patients requiring invasive mechanical ventilation. The frequency of complications were higher in non-survivors than survivors (table 2).* A lot of those are related to bacterial pneumonia and sepsis (bacterial septicemia ie. blood invasion by bacteria) – Once the situation reaches ICU level, then further complications like cardiac or kidney damages and further lung tissue damage (Destruction of pulmonary alveolae) may happen. We have early reports that increased levels of Troponin 1 could indicate the patients at risk of cardiac worsening.

Numerous studies report frequent co-infections or secondary infections with this virus:

- A French paper by Bleibtreu in 2018, analyzing a cohort of 93 patients (74 were pilgrims from Mecca) that were supposed to be infected with MERS-CoV (Middle East Corona Virus) showed that 24% had a bacterial infection (Streptococcus pneumonia, Legionella pneumonia). EARLY and EMPIRICAL treatment with 1 or 2 antibiotics saved everyone except 2 persons! (Empirical means : blind, without antibiogram).
- A Canadian study (by Zahariadis et al.) evidenced that during SARS (SARS-CoV1) epidemic, co-infection with bacteria like Chlamydomypha pneumoniae and/or Mycoplasma pneumoniae was present in half the cases (40%). Patients were positive for those infections even when the genetic test for those bacteria were negative. [Fully expected as those bacteria remains mostly **inside** cells and barely reach the blood].
- Same rates are found (30%) in Community acquired pneumonia, infections with multiple germs. (Libermann et al., as 1 example, many reports exist). 30% multiple infections in children, etc...
- In another study, such co-infections can also be triggered by the corticotherapy used to treat the respiratory distress – 3 cases out of 20 in a case-controlled study in Toronto (Hwang et al.).
- In a more general study about SARS-CoV, Gu et al. reported again that one finds various bacteria in the lungs (Aspergillus, Pseudomonas, Streptococcus, Staphylococcus...)

The situation was the same in the different mortal Flu pandemics of 1918, 1957, and 1968, where it was shown that MOST deaths were caused by the bacterial secondary infections. During the pandemic of 2009 (caused by H1N1), between 4 and 20% of the cases had secondary bacterial infections, and this was the main cause for the severe cases (deaths and ICU's). It was calculated that between 30% and 55% of the deaths were caused by secondary bacterial pneumonia (Morris et al. - See also 5 refs about the Flu below).

Treating early – and blindly – with antibiotics could really make a difference (20-30 % of the cases). Choosing NOT to treat empirically to avoid bacterial resistances, waiting that bacteria is confirmed misses the 'intracellular' not traceable bacteria, and is a bit like trying to read the license plate of the truck that comes running you over. We could treat ALL or use some criteria (see additional note at the bottom of the references below). Such strategy was successfully implemented in some places like the HUG (Hôpital Universitaire de Genève) in Switzerland (see additional note and ref)

Using OLD molecules (like Penicillin, Amoxycillin, Vibramycin, Bactrim,...) can save lives while at the same time avoids increasing antibiotic resistance risks (see again Ref. 1 below). An added advantage

would be to catch and treat patients when they are still in relative good shape, instead of seeing them at the complicated stage in the ICU (better outcomes, less costs, no panic).

References:

- Ref 1 - <https://www.antibioticresearch.org.uk/our-charity-coronavirus-covid-19-bacterial-infection-and-antibiotic-resistance/>
- **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.** Zhou et al. *The Lancet*, March 1, 2020. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
- **Clinical management of respiratory syndrome in patients hospitalized for suspected Middle East respiratory syndrome coronavirus infection in the Paris area from 2013 to 2016.** Bleibtreu et al. *BMC Infect Dis.* 2018; 18: 331. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6048819/>
- **Risk of ruling out severe acute respiratory syndrome by ruling in another diagnosis: Variable incidence of atypical bacteria coinfection based on diagnostic assays.** Zahariadis et al. *Can Respir J.* 2006 Jan-Feb; 13(1): 17–22. <https://www.hindawi.com/journals/crj/2006/862797/>
- **Multiple co-infections in CAP.** Libermann et al. *Thorax*, 1996 Feb; 51(2):179-184. <https://doi.org/10.1136/thx.51.2.179>
- **Toronto Pathological study.** Hwang et al. 2005; 18(1): 1–10. Online in 2004 Jul 23. <https://www.nature.com/articles/3800247>
- **Pathology and Pathogenesis of Severe Acute Respiratory Syndrome.** Gu et al. *Am J Pathol.* 2007 Apr; 170(4): 1136–1147. Online 2010 Dec 16. [https://ajp.amjpathol.org/article/S0002-9440\(10\)61329-6/fulltext](https://ajp.amjpathol.org/article/S0002-9440(10)61329-6/fulltext)
- **FLU - Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness.** Morens et al. *J. Infect Dis.* 198 (2008), pp. 962-970, <http://dx.doi.org/10.1086/591708>
- **FLU - Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza** Bautista et al. *N Engl J Med*, 362 (2010), pp. 1708-1719, <http://dx.doi.org/10.1056/NEJMra1000449>
- **FLU - J.K. Louie, M. Acosta, K. Winter, C. Jean, S. Gavali, R. Schechter, for the California Pandemic (H1N1) Working Group** <https://pubmed.ncbi.nlm.nih.gov/21041595/>
- **FLU - Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California.** Louie et al. *JAMA*, 302 (2009), pp. 1896-1902, <http://dx.doi.org/10.1001/jama.2009.1583>
- **FLU - Secondary Bacterial Infections Associated with Influenza Pandemics.** Morris et al. *Front Microbiol.* 2017; 8: 1041. Online 2017 Jun 23. <https://www.frontiersin.org/articles/10.3389/fmicb.2017.01041/full>

Additional Information for the specialists – Who to treat? :

1. There is a huge misconception about the clinical definition of the virus, as written earlier, the SARS-2 virus can easily and quickly cause pneumonia. So in the early stage, it is a bit like the flu, and very quickly it goes deeper in the lungs [See Note 4].
 2. This difference between early and late stages - the early stage with symptoms similar to a flu, and the florid phase of pneumonia - is one of the reasons that the group of Dr. Raoult in Marseille developed the low-dosage lung CT scan method to detect the pneumonia signs even if the symptoms were scanty, for a differential diagnosis with the seasonal flu. In other words this would allow to make the difference between those patients who may be receiving early and empirical antibiotics and those for whom one could wait. Maybe some lung sonography would have its place here.
 3. As of mid-March 20, the Infectious Diseases unit of the HUG Geneva had issued regular guidelines for broad antibiotic use, and even Remdesivir (which back then was not fully approved) 2 notes « **Prise en charge d'un patient infecté par le SARS-CoV-2** » et « **Stratégies Thérapeutiques SARS-Cov2** » by Dr Vetter et al. (see next page – fig in French).
 4. It is also worth noting that 4 coronaviruses show a well-known seasonal pattern in humans, (see Monto et al in April 2020 here below). So it will be most likely a seasonal recurrence and it is too early to know.
- **Coronavirus Occurrence and Transmission Over 8 Years in the HIVE Cohort of Households in Michigan.** Monto et al. *The Journal of Infectious Diseases*, jiaa161, <https://doi.org/10.1093/infdis/jiaa161>

Examples of guidelines in HUG (CH).

First line, severe pneumonia is mentioned. [Translated Quote] *The new coronavirus SARS-CoV2 may give rise to severe pneumonia* [End quote]. This is the core of the situation as these pneumonia are either very rapidly leading to bacterial deep lung infections or sepsis, or even worse to a generalized viral infection termed viral sepsis. Second exhibit shows a clear flow chart for EARLY treatment.

 Hôpitaux Universitaires Genève SERVICE DES MALADIES INFECTIEUSES	Date création V 1.0: 05.02.2020 Date version actuelle: 26.03.2020	Version 2.5
	Rédacteurs : P Vetter, DL Vu, A Calmy, C Samer, T Agoritsas	Approuvé par : L Kaiser, M Schibler, MC Zanella Terrier Groupe Guidelines COVID
Stratégies thérapeutiques SARS-CoV-2		

1. Introduction

Le nouveau coronavirus SARS-CoV-2 peut entraîner des pneumonies sévères.

Il n'existe pas de traitement spécifique qui soit validé, et la prise en charge repose sur les soins symptomatiques et les soins de support (mesures de réanimation), avec administration d'oxygène, traitement des surinfections bactériennes, des complications parfois graves telles que myocardites ou ARDS, avec prise en charge dans une unité de soins intensifs au besoin.

Certains traitements expérimentaux actifs sur les coronavirus pourraient avoir une activité sur le SARS-CoV-2, mais très peu de données cliniques sont actuellement disponibles. Plus de 80 essais cliniques randomisés sont en cours, la plupart en Chine, dont les résultats à cette date ne sont pas encore publics. Ce document a pour but de le revoir et de fournir des recommandations basées sur les évidences cliniques.

 Hôpitaux Universitaires Genève SERVICE DES MALADIES INFECTIEUSES	Date création V 1.0: 05.02.2020 Date version actuelle: 26.03.2020	Version 2.5
	Rédacteurs : P Vetter, DL Vu, A Calmy, C Samer, T Agoritsas	Approuvé par : L Kaiser, M Schibler, MC Zanella Terrier Groupe Guidelines COVID
Stratégies thérapeutiques SARS-CoV-2		

