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HYPOTHESIS

Antibiotics against COVID-19 and mitochondria? Urgent thinking out of the box

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Abstract

Italian, Spanish, French vs German, Austrian or Norwegian COVID-19 tracks? Antibiotics might have a partial impact on COVID-19 death rates in various countries. Our working hypotheses based on recent publications is that that antibiotics may be a major factor that negatively affects patients' immune system during viral infections. We are all aware that there is no specific and effective medical treatment for COVID-19 so far. However, we know that our immune system is the only efficient weapon that fights against this syndrome right now. In fact, antibiotics are very often prescribed to prevent secondary infections following an antiviral immune response. Various antibiotic therapies have also been commonly applied to support COVID-19 treatments in China and Italy. Unfortunately, the frequent antibiotic off-site targets include mitochondria that are genetically and evolutionary closely linked to bacteria. Mitochondria are multifunctional organelles responsible for bioenergetics in nearly all our cells, acting as signaling hubs in antiviral and antibacterial immune responses. Several studies have demonstrated that mitochondria are vulnerable to antibacterial treatments, interrupting their physiology. Inhibition of these processes by antibiotics might render the immune system less capable of fighting acute COVID-19 viral infections. Some antibiotics, including those prescribed for COVID-19 in Wuhan, have been shown to inhibit the synthesis of mitochondrial DNA. The question is whether antibiotics support such a treatment or weaken patient immune responses in this case. This hypothesis should be evaluated based on comparative clinical data that seem to be unavailable at the moment. Possibly the COVID-19 risk group should be extended to all patients being treated with antibiotics, including those who finished antibiotic therapies days up to several months before SARS-CoV-2 infection. We therefore urge health service response groups to evaluate the impact of antibiotics on COVID-19 recovery vs death retrospective data. We would like to motivate international, national and local health authorities to share available clinical treatment data, discuss and optimize treatment strategies.

Keywords: COVID-19, SARS-CoV-2, pandemic, antibiotics, immune response, mitochondria, epidemiology, health policy

Introduction

We live in the global village and our village has got infected. Most mass media focus on the progress of total numbers of infected people either worldwide or country by country. Unfortunately, we are pretty sure that these number will grow in the upcoming weeks or even

months. The strategy to separate infected from those uninfected absolutely makes sense. Nevertheless, this is not enough!

Scary numbers

We know that we have to look for efficient therapies to avoid increasing severity and death rates. Most SARS-CoV-2 infections might be asymptomatic or cause mild health perturbations. However, if we compare outbreak records around the world, we see very different patterns. Total numbers of infected people in every country are relatively easy to understand, even if they are still highly underestimated due to shortage of tests. What we do not understand are differences on death rates caused by COVID-19 (total infected/total deaths expressed in %) in particular countries. Why does Italy experience a 12.47% death rate that is several times higher than in Germany that is 1.87%? (https://www.worldometers.info/coronavirus/ - retrieved on 2020-04-07). The total death rate in Germany is relatively stable for the last few weeks. In contrast, the death rate in Italy grew for 0.3-0.6% nearly every day.

There are other countries that show similar trends to Italy such as Iran, Spain, France, UK, Belgium, the Netherlands, and Indonesia. The German scenario is followed by Austria, Norway, Czech Republic, Israel and a few other countries. Such a high death rate in Italy, compared to other countries, can be explained by the age structure of its population. Indeed, Italy has the 2nd oldest population in the world with about 23% of residents being at least 65 years old (Rettner, 2020). Japanese population is the only older one. In fact German population ranks third oldest in the world, so it can't account for such a big discrepancy.

Italy may not be catching many of the mild cases of COVID-19 that could cause underestimations of the overall death rate. This might be correct, but this rate is much too high when compared to countries following German scenario. According to public media around March 20-22, Italy tested c. 1005 cases per million citizens, and Germany twice as many, i.e. 2080 tests per million. There is an estimate that undetected SARS-CoV-2-positive individuals might be 4 times the number of confirmed cases (Pedersen & Meneghini, 2020). Our conclusion is that even, if we normalize death rates by numbers of tests in Italy and Germany, we still cannot explain great difference in these values. In fact, the number of tests per million in Italy, Germany, and Austria is comparable, therefore, it should not bias death rates (see (https://www.worldometers.info/coronavirus/)

Recognizing that SARS-CoV-2 keeps mutating like all viruses (Lu et al., 2020), there is also a great risk that Italy imported a more virulent strain of the virus. In fact, recent investigations confirm some genomic differences between strains in Germany and Italy (Zehender, et al., 2020). According to the European Centre for Disease Prevention and Control (ECDC, 2020), geographic regional differences in viral structure "could contribute to differences in infectivity, transmissibility and possibly to severity of COVID-19 disease". Variability of receptor-binding domain of SARS-CoV-2 (Wrapp et al., 2020) may presumably have impact on virulence of certain strains (ECDC 2020). Whereas this is difficult to test at the moment, one must ask why there is such high variability in SARS-CoV-2 virulence among adjacent countries?

The border between northern Italy and Austria was open long enough to spread the Italian strain across the Alps. Therefore, Austria was most likely infected from China via Italy, as well as via Germany. Surprisingly, there is no evidence that the strain imported from Italy behaves differently from strains arriving from Germany because the death rates in both countries on March 27 are still much lower than in Italy and Spain (see Fig. 1). These observations suggest an alternative explanation for differences in geographic mortality rates in Europe (Fig. 1).

One possible factor could be that the German health system is more modern and better equipped than the Italian health system. In fact, the health system in Lombardy, the most

infected Italian region, is well known for its excellent health care. The health system in Italy is overwhelmed now and this might have a high impact on the death rate. However, if we compare all these features, we should consider that there must be another reason for such a huge and alarming difference in patient mortality between countries. There is also a reasonable risk that some countries do not test fatal cases, nor attribute deaths due to other reasons (like sepsis, heart attacks etc.) which are often associated with COVID-19. A sociological explanation for these differences could be that southern European countries experience much closer social contact between all family generations. This might be on average quite different from Germanic and Scandinavian countries. Such contacts may have accelerated Italian and Spanish spread of virus to the older generation at initial epidemic stages, before significant testing was in place and social isolation/quarantine rules were applied.

If we take all quite specific national features, including culture, social behaviors, political decisions, health conditions into account, it is still hard to explain the multiple difference between death rates in Italy vs Germany.

A novel hypothesis that “national differences in COVID-19 impact could be partially explained by the different national policies respect to Bacillus Calmette-Guerin (BCG) childhood vaccination” should also be taken into account (Miller et al. 2020). Although differences between Spain and Portugal seem to be well correlated, the differences between Italy and Germany, as well as between France and Austria are less straightforward (see http://www.bcgatlas.org/index.php). Further multidimensional epidemiological studies and randomized controlled trials using BCG are required to confirm this hypothesis, as well as to determine how fast an immune response develops that protects against COVID-19 (Miller et al. 2020). Nevertheless, if even partly correct, this approach may support our immune system that seems to be a reasonable strategy.

Retrospective analysis of treatment strategies

Figure 1 presents the average pattern of antibiotic usage in the past. The best would be to compare COVID-19 retrospective analysis of treatment data from both contrasting groups of countries. Unfortunately, such data are still highly limited, nevertheless, there is an increasing number of retrospective studies available from China. Let’s have a brief look at these essential records.

In general, the severe version of COVID-19 syndrome is expressed in a rapidly progressing lung failure caused by the novel pneumonia that kills infected patients. Chen et al. (2020) report 11% death rate (11 patients) of 99 patients with 2019-nCoV pneumonia in Wuhan. Most of the patients (70 patients, i.e. 71%) were treated with antibiotics, however only one (1%) patient had a coinfection with bacteria and four others with fungus. Patients died of multiple organ failure. In order to reduce complications and death rate, for patients with compromised immune system, authors suggest prompt administration of antibiotics to prevent infection and strengthening of immune support treatment.

Another report (Huang et al., 2020) from Wuhan describes specific clinical characteristics of 36 non-survivors infected with SARS-CoV-2. Antibiotic treatment was administrated to all patients, 38.9% with a single antibiotic and 61.1% with combination therapy. Antibiotic treatment was applied to prevent secondary infections in critically ill patients.

In December 2019 Chinese health authorities in the Hubei province, identified a cluster of pneumonia cases of unknown etiology. Among other features, failure to resolve over 3 to 5 days of antibiotic treatment was mentioned (Lake, 2020).

Zhou et al. (2020) report a retrospective study of 191 patients from two hospitals in Wuhan, China, of whom 137 were discharged and 54 died in hospital. 181 (95%) patients, including 53

(98%) non-survivors and 128 (93%) survivors, were treated with antibiotics. However, no bacterial pathogens were detected in these patients on admission. All non-survivors experienced sepsis before death.

This is not surprising that there are still not so much data available from Italy. However, the latest report of the *Istituto Superiore di Sanità* (Italian National Institute of Health) present pharmacologic therapies applied to patients who passed away. During hospitalization, 84% of COVID-19 positive deceased patients received antibiotic therapy, less used was antiviral therapy (54%) and steroid therapy (31%). The common use of antibiotic therapy is explained by the presence of superinfections or the beginning of empirical therapy in patients with pneumonia (ISS 2020a).

Various official mass media, as well as social media, report a growing number of cases of younger than 60 years old patients who die after an early diagnosis of “bacterial infection” followed by dedicated antibacterial treatments carried out at home, then in a local hospital, and at the end in a dedicated infectious hospital, where SARS-Cov-2 tests are eventually done.

In contrast, there are some more optimistic cases shared by scientists around the world. Thevarajan et al. (2020) “provide novel contributions to the understanding of the breadth and kinetics of immune responses during a non-severe case of COVID-19”. Authors report a mild case of the 47 years old female patient arrived from Wuhan, consistent with non-severe but symptomatic disease, hospitalized in Melbourne. No antibiotics (!), steroids or any antiviral agents were administered. This patient recovered and was discharged from hospital after a week (Thevarajan et al., 2020).

Why use antibiotics?

We are all aware that there is no specific and effective medical treatment for the coronavirus (SARS-Cov-2) so far. Thousands of researchers around the world are working on vaccines or dedicated drugs that might be available by the end of 2020 or next year.

On the other hand, we are convinced that our immune system is the only efficient weapon that fights against this syndrome right now. The problem is that certain treatments may disturb our immune system to fulfil the task by learning a new virus and defending itself. Our working hypotheses is that that antibiotics may be a major factor that negatively affects our immune systems in this case. In fact , antibiotics are often prescribed to prevent secondary infections following an antiviral immune response. Figure 1 shows a relationship between COVID-19 death rates and an average dose of antibiotics reported in selected and comparable well developed European countries that have at least 1000 SARS-Cov-2 infected citizens. Italy, Spain, UK and France representing the alarming scenario, show the highest death rates correlated with highest averaged usage of antibiotics recorded in 2017 by EU. In contrast, Germany, Austria, Norway, Denmark, and Switzerland, following more optimistic scenario, show the lowest death rates and lowest usage of antibiotics on average. This is just an estimate of treatments applied in these countries during the COVID-19 pandemia. It is worthwhile to mention that in the northern hemisphere we experience the coldest seasons, thus, period when antibiotics are most likely regularly applied. We can be sure that the countries following Italian scenario take much more antibiotics than the countries following the German scenario during winter and spring.

Antibiotics also target mitochondria

We all know that antibiotics primarily target bacteria. Unfortunately, the frequent off-target includes mitochondria that are genetically and evolutionary linked to bacteria (Sagan, 1967). The point is that the prokaryotic origin of mitochondria also makes them vulnerable to

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antibiotics (Wang et al., 2015) which target prokaryotic bacteria (the human cell is eukaryotic which is not affected by antibiotics). Mitochondria are multifunctional organelles responsible for bioenergetics in nearly all our cells. It is responsible for highly dissipative processes like massive cell divisions during rapid generation of leukocytes, differentiation into required progenitor cells and acting as signaling hubs in antiviral and antibacterial immune responses (Albert et al., 2014; Mistry et al., 2019).

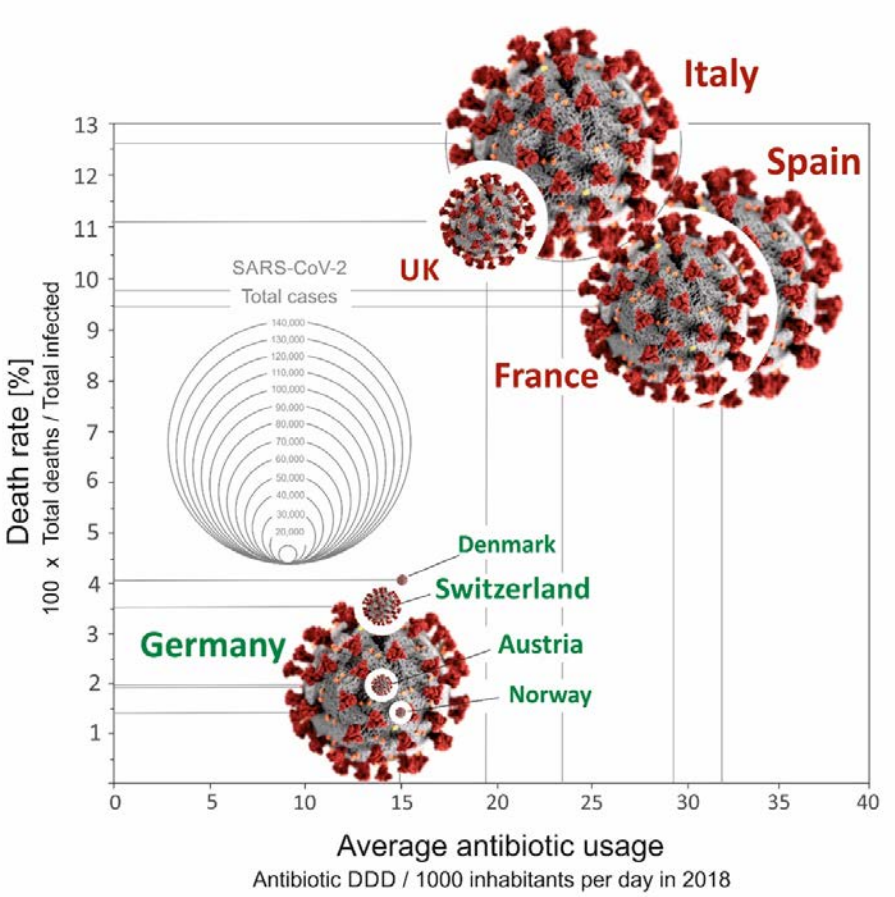

Figure 1. Relationship between COVID-19 death rates, average antibiotic usage in selected EU countries in 2018 (ECDC 2019) and SARS-Cov-1 total cases. DDD - average maintenance dose per day for a drug (antibiotics) used for its main indication in adults according to WHO. Death rates calculated based on data on April 7, 2020, downloaded from https://www.worldometers.info/coronavirus/ SARS-CoV-2 graphic model credit to Alissa Credit to Eckert, MS, Dan Higgins, MAMS for sharing SARS-CoV-2 graphic model downloaded from https://phil.cdc.gov/Details.aspx?pid=23312

Several studies have demonstrated that most intensively used antibiotics interrupt mitochondrial proteostasis and physiology in animal and human cell lines (Wang et al., 2015). Inhibition of those processes by antibiotics might render the immune system less capable of fighting acute COVID-19 viral infections. Antibiotics induce mitochondrial damage, inhibition of mitochondrial activity and biogenesis (Surbatovic et al., 2013) that affect generation of ATP with adverse metabolic consequences on bioenergetics of cell/organ/body, leading to activation of cell death pathways (Singer, 2014). Some antibiotics, including those prescribed

for COVID-19 in Wuhan (Fan et al., 2020), have been shown to inhibit the synthesis of mitochondrial DNA (e.g., Castora et al., 1983). Moullan et al. (2015) urged that tetracyclines disturb mitochondrial functions by promoting mitonuclear protein imbalance that effects mitochondrial translation, as well as alters mitochondrial dynamics and function.

It might not be coincidental that severe and fatal cases of COVID-12 mainly develop in older patients (e.g., Huang et al., 2020; ISS 2020a; WHO data; Zhou et al., 2020). Age is associated with decreased bioenergetic capacity related to decreased mitochondrial biogenesis and increased mutations in the mitochondrial DNA (mtDNA), as well as increased levels of mitochondrial ROS (Wallace, 2010; Mora et al., 2017a). Therefore therapies that target improved mitochondrial activity (Mora et al., 2017b) combined with a reduction in antibiotic usage, might be especially beneficial in treating COVID-19 in the highest risk group (> 65 years).

Sensitivity to side-effects of antibiotic treatments might differ per individual. Patients with diagnosed specific mitochondrial disorders are acutely sensitive to certain antibiotics (e.g., Stoker et al., 2019). Antibiotic side effects might be more or less enhanced in certain organs, like heart, brain, kidney, the auditory system etc. Age of patients might enhance side effects due to the cumulative load of mitochondrial mutations (e.g., see Wallace, 2010).

Recommendations and future research prospect

WHO recommendations say (1) antibiotics do not work against viruses, only bacteria; (2) The new coronavirus (2019-nCoV) is a virus and, therefore, antibiotics should not be used as a means of prevention or treatment; (3) However, if you are hospitalized for the 2019-nCoV, you may receive antibiotics because bacterial co-infection is possible (WHO 2020a) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters).

Supportive treatment of COVID-19 include oxygen, hydration, antibiotics and fever/pain relief to reduce death rate (WHO 2020b, c). The question is whether antibiotics truly reduce death rate or weaken patient immune responses in this case. This hypothesis should be evaluated based on comparative clinical data that seem to be unavailable at the moment.

There are several treatment recommendations that follow reports and advice from Wuhan that include antibiotics prescribed for secondary bacterial infections in patients with COVID-19. (Matthay et al., 2020 after Huang C. et al., 2020). If antibiotics are used for bacterial prevention, they might reduce antiviral immune response and overall bioenergetics (see citations above).

A clinical strategy based on trade-offs between secondary infection control and standard medical principles was developed in Wuhan during the early outbreak period (Zhang et al., 2020). In most cases, either confirmed or unconfirmed cases of SARS-CoV-2 infections various antibiotics are recommended. This algorithm advises empirical therapies that consist of various quinolones and other antibiotics. However, we have to be aware that these recommended bactericidal antibiotics are known to induce mitochondrial dysfunction and oxidative damage in mammalian cells (Kalghatgi et al., 2013).

Searching for promising alternative strategies, we would like to mention the COVID-19 triage strategy adopted for low-income settings (Ayebare et al., 2020). This strategy partly follows Zhang et al. (2020), nevertheless, it does not mention antibiotics during the whole COVID-19 triage algorithm that is in opposition to the four measures presented in the original algorithm (Zhang et al., 2020).

Possibly strategies, trying to avoid application of antibiotics, might be more optimal for treating COVID-19. We should therefore mention Du et al. (2020) who concluded in their pharmacological therapeutic review that “inappropriate application of antibiotics should be avoided, especially the combination of broad-spectrum antibiotics, for the new coronavirus pneumonia is not often complicated with bacterial infection..

Scientists may select and/or design antibiotics that do not target components of organelles, such as mitochondria (Wang et al., 2015). However, it might not be easy, because even Azithromycin that has been used to treat mild case patients with typical symptoms under home care in Wuhan (Zhang et al., 2020) causes mitochondrial toxicity, ROS overproduction, DNA oxidative damage, and other negative side effects (Jiang et al., 2019). Recently, French scientists have just tested on the small sample size (6 patients, 20-60 years old) the hydroxychloroquine treatment combined with Azithromycin that significantly reduced/eliminated viral load in COVID-19 patients (Gautret et al., in press). These examples show that cautious application of selected, dedicated antibiotics may be promising, however, evaluation of risk is necessary.

Possibly the COVID-19 risk group should be extended to all patients being treated with antibiotics, including those who finished antibiotic therapies days up to weeks or even months before. Such people might still have impaired bioenergetics and efficient immune response.

Our motivation and concluding remarks

We are aware that we do not have data to advise the health care system about this hypothesis. This paper is only a meta-analysis based on available data and peer-reviewed publications. We are a group of scientists with decades of experience in the Life and Earth Sciences who are trying to combine our knowledge of basic cell biology and physiology to help find an explanation for the variable global mortality patterns we have analyzed.

We hope this thought paper provokes dedicated scientists, health authorities and physicians to gather and share antibiotic vs. COVID-19 treatment data. We recommend a careful examination of all infected symptomatic patients and focus on records of antibiotic treatments 1-2 months prior infection, as well as during COVID-19 treatments. It is essential to compare these data between countries that have a moderate and high number of coronavirus infections. Therefore, it is critical to compare data from China, Italy, Spain, Iran, South Korea, Germany, Denmark, Belgium, Norway and so on to compare treatments in countries that show contrasting death rates.

In conclusion:

(1) We urge health service response groups to evaluate the impact of antibiotics on COVID-19 recovery vs death retrospective data. We further recommend the sharing and publishing of available clinical treatment data, including quantitative and qualitative data on antibiotics;

(2) We would like to motivate international, national and local health authorities to discuss and optimize treatment strategies, including recommendations on general and selected antibiotic treatments;

(3) WHO networks of researchers (WHO 2020d), as well as independent mathematicians, statisticians, epidemiologists, natural scientists and other researchers are encouraged to analyze available data and recommend best solutions to help Italy, Spain, Iran, and all other countries around the world. We all need your knowledge, data, advice, and help;

(4) Caution with antibiotics in respect to of COVID-19 and influenza might decrease death rates and side effects of treatments. This is the last but not least conclusion from our meta-analysis.

One highly inspiring statistic might be the latest COVID-19 update from the Czech Republic that on April 7, 2020 report 4828 total SARS-Cov-2 cases and 80 fatalities. These translates to a 1.66% death rate that is 7 times lower than in Italy (12.63%). The Health Ministry of Czech Republic states "Antibiotics are not effective against viral diseases. On the contrary, their excessive consumption can harm human body" (MZCzR 2020). This recommendation follows WHO Advise for Public, however skips recommendation on application of antibiotics against virus-bacterial co-infections. We hope that shifting to the Czech COVID-19 scenario is still real.

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