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Review Article

Covid-19 Public Health Emergency: Mini Review and Impact on Maxillofacial Practice in Serbia- What we have Learnt during Our Wireless Journal Club between 10th and 30th March

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Abstract

From the global outbreak of SARSCoV-2 caused infection disease in 2019, the state of emergency was declared on the territory of the republic of Serbia with serious consequences on the entire population and the National Health Service. The mini review and the description of the reorganization of the Clinic for maxillofacial surgery School of Dental Medicine, University of Belgrade, provided in this paper is not a recommendation but a background to help practitioners to better understand this novel coronavirus pandemic and its impact on maxillofacial practice in Serbia during challenging conditions.

Keywords: *Covid-19; Maxillofacial Practice; Serbia*

Background

After the outbreak of 2019 novel coronavirus disease (COVID-19) in the end of December in Wuhan, Hubei Province, in China, it has spread quickly worldwide. On March 10th, 2020 the State of the Republic of Serbia decided that the Covid-19 caused by the virus Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-Cov-2) represent an infectious disease according to the art. 16. al. 1. of the Law for Citizens Protection against Infectious Diseases and put it on the list of diseases according the art. 5 of this Law [1].

According to the Hippocratic Oath and in order to improve our practice in treating maxillofacial patients (urgent new ambulatory and hospitalized patients) in a safe manner, to protect them and to protect all the medical staff during the novel coronavirus pandemic we organize a Covid-19 journal club from March 14 up to March 30, 2020. The purpose of this article is not to give recommandations but to share the results of our work in challenging conditions with everyone who is not usually dealing with the emerging infectious disease. Of course like the other medical practitioners we follow the official recommandations of the World Health Organization (WHO) [2] and the Ministry of the Health of the Rebublic of Serbia [3].

Methods

Because of the reorganisation at our Clinic and our behaviour changes (social distancing, confinement) as a consequences of novel coronavirus pandemic we organized our journal club between 10th and 30th of March and exchange of informations by wireless devices. Data were commonly colected from internet and official tv broadcasting. Because the number of articles about Covid-19 is increasing rap-

idly on daily basis the cut off date of our overview is finnished on the March 30th, 2020.The following scientific sources have beenused: Covid-19 resource center, Pubmed and preprints servers (MedRxiv, websites of health institutions).

Covid-19

Etiology

The sourse of infection are the COVID 19 patients. The asymptomatic infected people can also be a sourse of infection which represent big problem regarding fast spreading worldwide.

Epidemiology

Symptomatic or asymptomatic patients with Covid-19 can spread the infection by respiratory droplets and close contact (main routes of transmission) and rarely by , aerosol, stools and urine contamination of the environnement. All the age group are generally susceptible by the Covid-19, mostly the elderly patients and those with chronic underlying diseases because they to the group at risk. These patients with severe or critical clinical state have a poor prognosis [4,5]. The incubation period is usually between 3 and 5 days, rarely 1 to 14 days [4,5]. Some authors reported in their study that the detectable RNA of the novel coronavirus SARS-Cov-2 persisted for 20 days (median value) in patients who survive [6]. Among confirmed positive patients in Hubei Province, China, 86,6% were aged 30 - 79 years and 80,9% have a mild form od the disease. An overall case fatality rate of 2.3% is observed in this region [7]. Overestimation of the case fatality rate reported from Wuhan, Hubei Province, China may be possible. The case fatality rates may differ country to country because of differences in the preparedness and availability of health care, control and mitigation policies implemented [8]. Some authors estimate the fatality ratio of COVID-19 in China at 1.38%, that is lower than estimates for other coronaviruses, including SARS and Middle East respiratory syndrome (MERS), but higher than estimates concern the 2009 H1N1 influenza pandemic. On the basis of PCR testing of international Wuhan residents returning on repatriation flights the same authors reported an infection fatality ratio of 0.66% in China. In comparaison the fatality ratio observed in passengers on the Diamond Princess cruise ship up to March 5, 2020 are approximately similar [9].

Pathology

Covid-19 mainly cause pulmonary lesions. It makes varyning degrees of lungs solid changes. The presence of fibro myxoid exudation (monocytes and macrophages) and hyaline membrane in the damaged pulmonary alveoli is reported. Vascular congestion and hyalin thrombi, edema, infiltration of monocytes and lymphocytes are found in the alveolar interstitial space. Hemorrhagic and hemorrhagic infarction with necrotic foci are observed in the lungs with mucus and mucus plugs in the bronchi. Using electronic microscopy cyto-plasmatic virions in the type II alveolar and bronchial epithelium were found [4,5]. The spleen is shrunk with lymphocytopenia and focal hemorrhage and necrosis, and macrophage proliferation and phagocitosis. Lymph nodes could show sparse lymhocytes and occasional necrosis [4,5].

Pathophysiology

For the entry into the pulmonary epithelial cells Severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 need to bind angiotensin-converting enzyme 2 receptor (ACE2) and the serine protease TMPRSS2 for S protein priming [10]. Target cells are also epithelial cells of intestine, kidney and blood vessels. Some authors make the hypothesis that upregulation of ACE2 increase the risk of developing severe and fatal Covid-19. Patients who presented Type 1 or type 2 diabetes, hypertension treated by ACE inhibitors, angiotensin II type-I receptor blockers and treated by ACE2-stimulating drugs (Ibuprofen, thiazolidinediones) are at risk according this hypothesis [11,12]. Some authors describe immunological changes in blood before symptomatic recovery (increased antibody-secreting cells, follicular helper T cells, activated CD4+ T cells and CD8+ T cells and immunoglobulin M and Ig G antibodies) in a case of a patient positive to coronavirus SARS-Cov-2 with non-severe form of disease. The immunological reaction to the Covid-19 causing agent persist for at least seven days following full resolution of symptoms. Elderly and people with underlying diseases can present a progression of

the disease in to a serious condition, which may be associated with acute respiratory distress syndrome (ARDS) characterized by diffuse alveolar lesions and "cytokine storm" (response with an exuberant immunological reaction) [14].

Signs and symptoms

Fatigue, fever and dry cough as main performance followed by, asthenia, headache, diarrhoea, conjunctivitis, anosmia and ageusia. Dyspnoea or hypoxemia could be seen one week after the onset of the disease in severe cases. The severe or critical cases may have low fever, even no fever. The signs and symptoms vary between viral phase and host immune response [4,5,15,16].

Virological and serological tests

Viral RNA can be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, stools using RT-PCR. Viral specific IgM antibody are detectable 3 - 5 days after the onset of the disease. Viral specific IgG antibody titration is at least 4-times higher during convalescence compared with the acute phase [4,5].

Radiological investigations

On the RX thorax infiltration shadows is found in the lungs initially close to the pleura and gradually spread to the centre. On CT scan initially we can find subpleural distribution infiltration in a ground-glass shadows manner that develops to the centre with the presence of consolidation [4,5].

General management

It is important to instore rest and symptomatic support therapy with sufficient caloric nutrition, fluids and electrolytes with monitoring vital signs, oxygen saturation and laboratory tests including blood and urine routine tests, C-reactive protein, procalcitonin, biochemical indicators (liver and myocardial enzyme, renal function), arterial blood gas analysis, chest imaging and cytokines detection if necessary, early oxygen therapy and airway drainage. For severe clinical case prevention of complications, treatment of underlying diseases, prevention of secondary infections and timely organ function support are critically [4,5]. The recommendation of the University Hospital Centre Vaud in Lausanne, Switzerland is to treat the fever if necessary, only with Paracetamol and to avoid anti-inflammatory drugs (ibuprofen, ketoprofen, naproxen, diclofenac, etc.) [17].

Origin of the Covid-19-causing SARS-Cov-2

Applying E.U. regulations aimed at preventing the proliferation of weapons of mass destruction and so-called "dual use" technology, the Dutch government win a legal battle with the Dutch virologist over the publication of his controversial H5N1 influenza research. In public opinion people might share the fears of Dutch government [18-20]. According to this case law governments have the right to require researchers to formally ask official permission before they "export" papers of their research for publishing. The logic behind viral engineering collectively called gain-of-function (GOF) research that could allow an animal virus to jump to unprepared humans is exactly to prepare scientific defences against such a human treat. Virologist Simon Wain-Hobson questioned the need for GOF influenza virus research in his article: "Increased risk per se should not be frowned on if there are substantial benefits to be had. So, what are the purported benefits of influenza A GOF research?" (citation) [21]. Hopefully the US researchers confirm from comparative analysis of genomic data that the Covid-19-causing SARS-Cov-2 "is not a laboratory construct or a purposefully manipulated virus" (citation) [22].

Comments on laboratory tests

Some authors reported that procalcitonin levels were < 0.5 in 94.5% of patients with Covid-19. There is probably no correlation between elevation of procalcitonin and Covid-19 [23]. Procalcitonin elevation may suggest a bacterial superinfection in Covid-19 positive patients or pure bacterial lung infection in Covid-19 negative patients.

Protein C reactive (CRP) and troponin increase in Covid-19. Some authors reported that 7% of patients hospitalized for Covid-19 die of fulminant myocarditis, 57% of respiratory failure and 33% of cardiorespiratory failure [24]. Patient with severe respiratory failure without elevation of CRP may have a non-Covid disease (heart failure). Elevated ferritin and IL-6 seems to be predictors of fatality from a retrospective multicentre study of 150 patients Covid-19 positive in Wuhan, China [24].

Searching for effective treatment

There is no antiviral drugs and vaccines with clinical proven efficacy against SARS-Cov-2 although there are several candidates that might be effective in prevention and treatment. The rapidly evolving Covid-19 pandemic is placing overwhelming burden on health systems, national authorities and stakeholders (the media) to respond with effective and appropriate interventions, policies and messages. Rapid and widespread behavioural change (personal hygiene, social distancing, confinement) is critical to reduce transmission of the virus. The research community respond also vigorously with recruiting patients in clinical trials that should be large and well designed to generate evidence. Among the candidate drugs to treat Covid-19, repositioning old drugs for use is an interesting strategy, because knowledge about these drugs' characteristics (posology, side effects, drug interactions and safety profile) are already well known and they are currently available. Hydroxychloroquine generally used for treatment of malaria and amebiasis and as malaria prophylaxis appears to work via impairment of acidification of endosomes, which interferes with virus trafficking within cells [25-27]. Lopinavir/Ritonavir (HIV antiretrovirals) are protease inhibitors which block viral replication. The Chinese Clinical Trial (ChiCTR20000029308) shows no benefit in hospitalized patients with severe Covid-19 treated with these virally targeted agents (Lopinavir/Ritonavir*)* [28]. Probably when the pulmonary involvement (ARDS) occurs an additional treatment of the hyperinflammation is mandatory [29-31]. For this reason, early diagnosis and treatment is critical to avoid progression to a serious and irreversible condition. French microbiologist Professor Didier Raoult and colleagues at the Mediterranean Infection University Hospital Institute in Marseille, France reported in their study of 20 confirmed Covid-19 patients treated by Hydroxychloroquine that this host targeted agent had reduced viral load in nasal swabs in 75% of cases and in 100% of cases in combination with the antibiotic Azithromycin [32]. This low-cost antiviral therapy could be probably the most cost-effective response to the nationwide urgent need for an effective treatment but also to decrease the duration of virus carriage and thus limit transmission in the community. Remdesivir, another virally targeted agent developed to combat Ebola and related viruses, shuts down viral replication by inhibiting a key viral enzyme, the RNA polymerase. Some researchers showed *in vitro* and animal studies that the drug can inhibit the SARS and MERS viruses. The drug has been used in hundreds of COVID-19 patients in the United States and Europe under what's known as compassionate use [33,34]. Some researchers have high hopes in the antiviral treatment by Camostat mesylate, a drug licensed in Japan for chronic pancreatitis, which inhibits a human serine protease TMPRSS2 involved in the entry of the virus into the cells [10]. In clinical study "Coviplasm" French researchers try to boost immunity with plasma from recovered COVID-19 patients or monoclonal antibodies directed at SARS-CoV-2 [35]. Other combination of virally targeted agents will also be used in clinical trials, including the influenza drug Favipiravir and additional HIV antiretrovirals [36].

Current impact on maxillofacial practice in Serbia

The outbreak of the SARS-COV2 virus is rapidly changing our habits and surrounding. Many hospitals are directing more and more energy to those departments who are directly facing the emergency. The department of Maxillofacial Surgery, School of Dental Medicine, University of Belgrade, covers following fields: traumatology, orthognathic surgery, Maxillofacial Tumour surgery and reconstructive microsurgery, and head and Neck Infections. The department is still open for surgery, but with serious restrictions. Only the emergencies have been treated so far: cancer patients, severe infections and trauma cases. All elective cases are postponed. After the onset of COVID-19 in Serbia and implementation of prevention measures, regarding the transmission of the infections, patients with maxillofacial cancer cannot be offered by free flap reconstruction as these procedures are long-lasting (average time 9 hours). In order to minimise the risk of infection the work is organised in shifts with shortlisting the number of staff on daily basis. The department is currently active less than 30%. These measures are the part of official hospital guidelines to face the outbreak. So far, all staff are protected by surgical masks, disposable suits, protection glasses and gloves according to national recommendations. Before clinical judgment on viral infections patients

are required to fulfil particularly designed questionnaire for possible risk factors (interpersonal contact and travel) regarding the current pandemic.

The hospital stay is shortlisted as much as possible depending on cases individually.

1	Have you got any symptoms: dry cough, fever, fatigue, headache, diarrhoea.
2	Have you been in contact with COVID 19 positive person in the last 14 days
3	Have you travelled in the risk countries in the last 14 days
4	Have you got any contact with person who were in the risky countries in the last 14 days

We tend to do COVID 19 test prior to admission in hospital (patients have been referred to do COVID 19 PCR test). So far, we have not collected human specimens for SARS-COV2 screening or diagnosis. Since far our Department has not faced patient positive for SARS-COV2 virus. Our Department is traditionally very well organised regarding the prevention of intrahospital infections as we are the one of the leaders in region regarding the maxillofacial microvascular transplants. As the staff and department is highly equipped, alerted and prepared for infection prevention, due to surgeries, it was very convenient to adjust already existed preventive measures versus novel SARS-COV2 virus. The hygiene and preventive measures have been raised at the highest level in relation to pandemic. Nobody in department have been tested for SARS-COV2 so far. It is important to stress out that based on the one of the latest study, it seems that infected patients may just present olfactory and gustatory dysfunctions without other significant complaints. It should not be overlooked by maxillofacial surgeon. The sudden anosmia or ageusia must be recognized by the international head and neck scientific community as important symptoms of the COVID-19 infection [36].

What we can expect after the Covid-19 public health emergency?

Vaccines would be probably available in 2021. In democratic high-income countries, the recommendations of WHO for collective immunisation by vaccine against coronavirus will be the purpose of vigorous discussions between pro- and antivaxxers. Encouragingly Zhilin Ren and colleagues have reported in 2012 that the emerged SARS-Like coronavirus, the human betacoronavirus 2c EMC/2012 (HCoV-EMC) also has an "Achilles' heel": a 3C-like protease and concluded: "If this "Achilles' heel" hypothesis proves to be correct, CoVs (coronavirus) will not be a threat to human health" (citation) [37]. Virologist Christian Drosten at Charité University Hospital in Berlin, Rolf Hilgenfeld (Rolf Hilgenfeld is studying coronavirus since 1998) at the German Center for Infection Research (DZIF) and colleagues reported that improved α-ketoamide inhibitor (compound 13b) inhibits SARS-CoV-2 replication in human Calu3 lung cells targeting the main protease of the virus (Mpro also called 3CLpro or 3C-like pro). They also conclude that inhalation was well tolerated by mice without any adverse effects. Direct administration of the compound 13b to the lungs would be possible. The optimized inhibitor would be suitable for administration by inhalation [38].

Conclusion

There is no drug with clinical proven efficacy and no vaccine against SARS-Cov-2.

Early diagnosis and treatment of the patients with Covid-19 is critical to impair contagiousness and to avoid progression to a serious and irreversible condition. Repositioning old drugs seems to be a good cost-effective strategy in such a public health emergency. Optimized α-ketoamide inhibitor would be a good therapeutic option for remerging or new emerging coronavirus. The coronavirus "Achilles' heel" hypothesis is being proven.

According to the cancelation of elective surgeries, treatment modality changing due to COVID-19 pandemic, the impact on the final treatment outcome of maxillofacial patients could not be calculated so far. It cannot be precisely estimated in this tough time, but we should be aware of that. Multicentre studies regarding the consequences on treatment outcome should be initiated in order to answer

this question. It should be concluded after pandemic as the more evidence-based data are collected. The researchers must address unanswered questions. Collaboration at the local, national, international and global lever should be encouraged. The most important topics should be patient survival, impact on patient survival, quality of life as well as that were the most important emergencies in maxillofacial practice during COVID 19 pandemic.

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