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9. Lie TA. Congenital malformations of the carotid and vertebral arterial systems, including the persistent anastomoses. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol. 12. North Holland: Amsterdam, 1972; pp 289–339.

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Editorial

BACK TO THE NORMALCY; IS IT POSSIBLE AFTER THE LATEST CORONAVIRUS DISEASE-COVID-19 ATTACK?

While writing these sentences I feel a sharp pain in my throat and even sharper is disturbing my heart- the fear of severe contagious disease. At the same time stressful radio news warn me how the infection could be dangerous: informing about the number of newly diagnosed, those who died yesterday, and those that are on ventilators.

On December 29, 2019 the first four cases of "pneumonia of unknown etiology" were identified by local hospitals, all linked to the Huanan (Southern China) Seafood Whole-Sale Market. Since then an increasing number of cases of novel coronavirus pneumonia have been identified in Wuhan, a large city of 11 million people in Central China [1]. Pneumonia of unknown etiology is defined as an illness without identified causative pathogen that fulfills following criteria: fever (≥38°C), radiographic evidence of pneumonia, low or normal white blood cell count or low lymphocyte count, and no symptomatic improvement after antimicrobial treatment for 3 to 5 days following the standard clinical guidelines. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), was quickly identified. On January 31, 2020, the WHO declared coronavirus a global health emergency. It abruptly generated a worldwide pandemic [1, 2]. The experience from Severe Acute Respiratory Syndrome (SARS) and the Middle East respiratory syndrome (MERS) case definitions as recommended by the WHO in 2003 and 2012 respectively were applied, but the new coronavirus unexpectedly showed its sneaky nature. It was different and it produced confusion and uncertainty among members of "The expert community". Whoever gave opinions and prognoses was deeply wrong.

Coronavirus outbreak forced us to interrupt our normal activities and to postpone our annual meetings and congresses. It seemed that it disrupted all activities on the planet except the bare essentials. The burden of the severe cases of SARS-CoV-2 overwhelmed health care capacities even in the developed western countries. Besides infectologists, pulmonologists, and anesthesiologists, many different specialists and subspecialists were engaged as first - line practitioners in the triage of suspected patients and even in the treatment of severely ill patients in need of vital support. The younger ones have been forced to work for months in so-called COVID - hospitals, changing their focus of clinical practice and scientific interest towards practical essentials in the treatment of COVID-19 infected patients. Virus gave us a lecture on how arrogant but helpless and minor we are at the same time. We are not permitted to go outside without masks, to shake hands with colleagues, nor to hug friends or family members-restrictions advised to patients with immunodeficiency. Just as COVID-19 causes physiological dysfunction in patients, so too, it caused systemic

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dysfunction in households, institutions, cities, and nations [2, 3]. In every evil, some benefit could lie: air pollution decreased, rivers became cleaner, terrorism stopped and wars halted. The flora and fauna are relieved.

Coronaviruses have been well known for decades as commonest pathogens, besides rhinoviruses and Respiratory Syncytial Virus (RSV) responsible for the upper respiratory tract infections in children and adults- the common cold (coryza) when patients and parents were advised that there is no need for specific curative treatment. The illness was mild and self-limiting. What changed this coronavirus from harmless to virus responsible for the high mortality rate among affected individuals? The virus obviously transformed its nature, but that is us who also changed. Our immune system is overreacting or stay in ignorant condition once the virus entered the body. Some individuals, mainly young people and children, in good condition as sportists, did not show any sign of disease, while others were producing strong infammation and even „cytokine storm".

Virus taught us what are fundamental human needs, besides essentials for life: food, water, shelter, sleep, physical and emotional connections and need for novelties. Novelty creates the opportunity to learn and the potential to fail. Without novelties, motivation wanes and a healthy sense of well-being is lost. Furthermore people need a place to gain and share knowledge, empowering to learn from others and better understand the world. Contentedness increases self-esteem, a sense of security, a sense of belonging... The virus jeopardized all above mentioned human needs.

What are the facts and controversies about the current pandemic?

In order to invade host cells SARS-CoV-2 (the virus responsible for the COVID-19 pandemic) and SARS-CoV-1 (responsible for the SARS epidemic in 2002) need to bind cell surface receptor angiotenzin-converting enzyme 2 (ACE2). They are expressed mainly in lungs, heart and kidneys. These receptors are sparse in children, explaining why children are less affected. This entry into host cells requires besides ACE2, the cleavage of S-spike protein of the corona virus surface by transmembrane protease serine 2 (TMPRSS2), which thus represents a critical host cell factor for the invasion and spread of the virus. The protease is upregulated by androgens, the fact that clarifies why male subjects are more frequently affected. Thus, it is also expected that hypertensive patients treated with the ACE inhibitors could have facilitated viral invasion [4, 5].

Captopril has recently been questioned for patients with diabetes in COVID-19 settings. Although ACE inhibitors and angiotensin receptor blockers (ARBs) are generally considered to have similar adverse event profiles, evaluation of postmarketing adverse events may shed light on minute differences that could have important clinical impacts during actual pandemic. Captopril appears to be associated with a higher rate of pulmonary adverse reactions in patients with diabetes than other ACE inhibitors or ARBs and therefore may not be the best choice for patients with diabetes and COVID-19, a new study suggests [5].

What was not curiosity for me as an endocrinologist is the new study's result that dexamethasone reduced mortality by one-third in ventilated patients and by one fifth in other patients receiving oxygen only.The study stoped because the survival benefit for a life-threatening disease was obvious. Continuing the study as originally designed is unethical — those randomized to receive "usual care" would be deprived of a potentially life-saving treatment [6,7]. Aside from those patients in whom corticosteroids are contraindicated, it is hard to imagine to not offer dexhametasone nowadays to a person

with COVID-19 who requires supplemental oxygen or ventilator support [6]. It is well known that adequate adrenocortical function is essential for survival in critical illness. Most critically ill patients display elevated plasma cortisol concentrations, which reflect activation of the hypothalamic-pituitary-adrenal axis and is considered to be a homeostatic adaptation. However, many critically ill patients have “relative” or “functional” adrenal insufficiency, which is characterized by an inadequate production of cortisol in relation to an increased demand during periods of severe stress. Not so recently, the term “critical illness-related corticosteroid insufficiency” (CIRCI) was introduced. CIRCI occurs as a result of a decrease in adrenal steroid production or tissue resistance to glucocorticoids [8]. Thus, It is reasonable to apply dexamethasone or methyprednisolone in severe COVID-19 or any other severe pneumonia as our pulmonologists have actually been doing for years.

There is another intriguing involvement of endocrine system with potential to produce long term consequences on growth and development in children, as well as on the well-being, healthy aging or even survival in adults.It is the potential of affecting the pituitary gland. Namely, hypocortisolism in survivors of SARS was reported in 2005. The authors speculated that the coronavirus infection could have caused a reversible hypophysitis [4,9]. Reversible or permanent - the time will show. So we must be prepared for a potential long-term endocrine impact of the disease that will reveal its real nature in the future.

Is a coagulation cascade crucial for the development of clinical presentation from the very beginning or its activation means final event? We consulted prof. Jovan Antović, PhD, an expert and Research Group Leader from Clinical Chemistry - Coagulation, Dept. Molecular Medicine Surgery and Medical head Coagulation Clinical Chemistry, Karolinska University Laboratory, and a member of our Editorial board to clarify the coagulation cascade activation in SARS-CoV-2. He opened many questions and offered solutions of critical importance for avoiding the fatal outcome. To find more on this topic read the Opinion Article that professor Antovic kindly accepted to write for Facta. He presented the first experiences in investigation and treatment of such patients in his institution [10].

Under pandemic circumstances and curfew, telemedicine finds its place in follow-up and surveillance of the older population with chronic diseases. Our Italian colleague Susanne Buechner and her team from the Department of Neurology/Stroke Unit, Bolzano Hospital, Bolzano/Bozen Italy shared their experience in applying telemedicine as an effective tool that replaces periodic medical examinations in patients suffering from Parkinson’s disease during COVID-19 pandemic when non urgent medical visits were impossible [11].

In the middle of this crisis we should behave like professionals and focus our energy on contribution to widen knowledge and share experiences; how to boost our immune system to resist the fatal infection or how to halt a “storm we have never seen before”, a cytokine storm adjacent by deleterious disseminated intravascular coagulation.Endocrine system as critical for survival should take a big part in investigation of hormonal differences between survivors and non-survivors during this pandemic.

I find appropriate to finish this Editorial by citing Juval Noa Harari, who said: “Forced physical distance and separation will create a new closeness and intimacy between people. The importance of the health system and health workers will be re-appreciated.The greatest danger is not the virus itself but our own inner demons, our hatred, greed and ignorance”.

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Opinion Article

HEMOSTATIC ABNORMALITIES IN COVID-19: UNDERLYING MECHANISMS AND CLUES TO TREATMENT
Do we Really See a "Storm" Never Seen Before?

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Abstract. *Despite relatively short time since Covid-19 infection has appeared in the world, enormous amount of literature data (more than 20 000 articles currently (mid-June)) is available on PubMed. Those data, together with our own experience at Karolinska University Hospital point towards hemostatic abnormalities in significant number of severe patients. Majority of those patients experience persistent hypercoagulation with massively increased D-dimer and fibrinogen. As a consequence, clinical thrombotic events, including venous thromboembolism (VTE) are common in Covid-19 patients and it seems that increased anticoagulant prophylaxis may be beneficial for severe (ICU/mechanical ventilation) patients. The lungs are most severely injured by the virus and that the potential underlying mechanism is a crosstalk between inflammation/complement and hemostasis. It is important to emphasize that the importance of hemostatic abnormalities in Covid-19 patients should not be overestimated since thromboembolic phenomena are, to a similar extent, present in other influenza and severely ill patients.*

Key words: *Covid-19, thrombosis, anticoagulant treatment, D-dimer.*

Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread from Wuhan in China around the world [1]. In February 2020, the WHO named the disease Covid-19. An infection with increasing mortality rates and burden on the health care system and particularly intensive care units (ICU) has been experienced around the world. Infected patients present with influenza symptoms of different severity and some suffer from severe respiratory problems [2-3].

Cytokines Disturbances in Covid-19

In severe cases, cytokine disturbances (e.g. increased interleukin (IL-1B), interferon (IFN-γ), and monocyte chemoattractant protein 1 (MCP-1)) have been detected in patients with Covid-19. The authors of that initial article [4] have used the term "cytokine storm" which is considered an excessive immune response to external stimuli. Readers have to be aware that the pathogenesis of the cytokine storm is complex, it progresses rapidly and is associated with high mortality. It has also been shown that the levels of IL-2R and IL-6 in patients with Covid-19 are positively correlated with the severity of the disease [5]. Due to such changes described in China among the first patients, in one of the very first articles it has been stated that "certain evidence shows that, during the coronavirus disease 2019 (COVID-19) epidemic, the severe deterioration of some patients has been closely related to the cytokine storm in their bodies" [6]. Although this may be potentially true, we advise that this term be carefully used for patients with Covid-19 without additional evidence.

Disseminated Intravascular Coagulation (DIC) in Covid-19: True or False?

Already in February 2020, first reports about coagulation abnormalities were available on the PubMed. In one of those studies it was reported (probably not completely correctly since it is not completely clear that ISTH DIC was fully properly calculated) that 71.4% of non-survivors with Covid-19 infection meet the criteria for disseminated intravascular coagulation (DIC) [7]. Based on the first papers, in one meta-analysis the conclusion that almost 3/4 of Covid-19 patients fulfilled laboratory criteria for disseminated intravascular coagulation (DIC) was drawn [8]. The first pivotal retrospective study has demonstrated that increased levels of IL-6 were found in non-survivors in comparison to survivors but D-dimer was considered to be an even better prognostic factor [9]. Substantially increased D-dimer and its importance for disease prognosis have been observed in other studies [10-12]. Our experience at Karolinska University Hospital is the same: massive increase of D-dimer (even values > 35 mg/L in some patients, compared to normal values of <0,5 mg/L). D-

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Table 1 ISTH DIC score [16]

	0	1	2
Platelet count	$>100 \times 10^9$/ml	$50\text{-}100 \times 10^9$/ml	$<50 \times 10^9$/ml
D-dimer*	No increase	Moderate increase (2)	Strong increase (3)
Prolonged PT	< 3s	3-6s	>6s
Fibrinogen	> 1g/L	< 1g/L	

>5 overt DIC; D-dimer 2 instead of 1 and 3 instead of 2 points for moderate and strong increase

dimer increases during the hospital stay in ICU, but not in non-intensive care patients. About 2-fold higher D-dimer in non-survivors was observed in comparison to survivors (manuscript in preparation).

However, DIC is commonly associated with bleeding, after initial microthrombosis in different organs, due to the consumption of coagulation factors, fibrinogen and platelets. Very soon, it was observed that the Covid-19 coagulation abnormalities pattern is different. In the majority of patients prothrombin time (PT) was normal, while fibrinogen was even increased [13]. In our laboratory, we have observed fibrinogen levels approximately 1.5-2 times above the limit of the reference range during intra-hospital course (longer than 2 weeks in the majority of cases), in both survivors and non-survivors. Although thrombocytopenia was described in some cohorts [14, 15] it does not seem to be a common finding. In our cohort initially normal platelet count was observed, with an increase later during the hospital stay both in ICU and in non-ICU patients (even more significantly in the survivors).

Clinical Manifestations of Coagulation Abnormalities

Clinical manifestations of coagulation abnormalities are very different. The majority of patients have acute respiratory distress (ARDS) or ARDS like conditions, but many patients experience deep vein thrombosis (DVT) and particularly pulmonary embolism (PE). Some patients have arterial thrombotic events. In one study, it has been observed that 31% of patients experienced some thrombotic events, primarily venous [17]. The impression of ICU doctors at Karolinska University Hospital is that this number may be even higher (up to 40%) (personal communication). However, some patients develop peripheral and acro-ischemic necrosis typical of thrombotic microangiopathies (TMA) (including antiphospholipid syndrome (APS) and DIC) [18].

Although an association between Covid-19 and antiphospholipid antibodies (syndrome) has been described [19, 20] there is no consensus and several debates have been raised about this issue [21].We at Karolinska University laboratory started to get more samples from patients suspected to have antiphospholipid syndrome (APS), heparin-induced thrombocytopenia (HIT) or thrombotic thrombocytopenic purpura (TTP) like syndromes. All those conditions belong to TMA and may indicate close association between coagulation and inflammation. But we cannot state that we have observed a significant increase of positive results which could indicate a clear association between Covid-19 positivity and the presence of those TMA syndromes. However, some unusual findings such as pseudothrombocytopenia have been described in Covid-19 [22]. This laboratory *in-vitro* phenomenon caused by platelet aggregation in the tube has been observed in one patient with Covid-19 in our laboratory. The author of this review has never seen HIT associated with platelet aggregation in the tube for 15 years of his laboratory career (some very seldom cases were described in the literature). Therefore, he was completely sure that there was no HIT in that patient. But both rapid (PaGIA) and ELISA tests were strongly positive and the functional platelet aggregation assay was also positive. Most importantly, after the cessation of heparin treatment and its replacement with Apixaban platelets increased. All those findings indicated clinically relevant HIT associated with (if not a consequence of) the Covid-19 infection (manuscript in preparation).

Anticoagulant Treatment in Covid-19

It has been shown that anticoagulant treatment decreases mortality from Covid-19 [22] and Karolinska University Hospital was among the first to introduce clear recommendations for anticoagulant treatment in these patients. Additionally, some specific recommendations as the double dose prophylaxis in hospitalized patients with, among other risk factors, D-dimer above 3 mg/L and/or fibrinogen over 8 g/L were given by Karolinska University Hospital coagulation experts very early (at the beginning of April 2020). This approach has not been widely accepted yet, and most consensus statement recommendations are based on more conventional standard dose prophylaxis [23]. Interestingly we have observed significant decrease of D-dimer after the introduction of an increased prophylactic LMWH dose (manuscript in preparation). It also seems that such an approach decreases mortality, but final evaluation is yet to be done.

Table 2 Karolinska University Hospital anticoagulant treatment recommendations

All adult patients hospitalized with (suspected) Covid 19*(Plt> 30×10^9/L, no bleeding)*
< 50 kg Fragmin® 2500E alt. Innohep® 3500 E × 1sc
50–90 kg Fragmin® 5000E alt. Innohep® 4 500 E × 1 sc
> 90 kg Fragmin® 75E/kg alt. Innohep® 75E/kg ×1 sc
All adult patients with Covid-19 hospitalized at ICU
and/or *D-D > 3 mg/L, fibrinogen> 8 g/L, cancer, previous thrombosis, thrombophilia*
< 50 kg Fragmin® 2500E alt. Innohep® 3500 E × 2 sc
50–90 kg Fragmin® 5000E alt. Innohep® 4 500 E × 2 sc
> 90 kg Fragmin® 75E/kg alt. Innohep® 75E/kg × 2sc
eGFR < 30ml / min: Consider 30% dose reduction.
High dose prophylaxis can be monitored with antiFXa after 3–5 doses due to accumulation risk, target through level antiFXa below 0.3 kIE/L.
All adult patients with Covid-19 hospitalized with VTE (or strong suspicion for VTE)
Alt. 1. Fragmin® 200E/kg x1 alt Innohep® 175E/kg x1
Bad clinical efficacy or extensive VTE: Fragmin® 120E / kg ×2 alt. Innohep® 100E / kg ×2. Higher doses lack evidence but increase the risk of bleeding!
eGFR < 30ml/min: Consider 30% dose reduction.
Full dose treatment can be monitored with antiFXa after 3–5 doses due to accumulation risk, target through level antiFXa below 0.6 kIE/L.
Alt. 2. Heparin infusion with monitoring of APTT
If it is difficult to achieve therapeutic APTT, control anti-FXa and antithrombin (AT);
Targeted antiFXa 0.3-0.7 kIE/L for heparin infusion.
If AT < 0.6 kIE/L, antithrombin substitution may be considered.

Potential Mechanisms of Thrombo-Inflammatory Conditions in Covid-19

It seems that the lungs are most severely injured by this virus and that the underlying mechanism is the release of pro-inflammatory cytokines and extravasation of blood cells, primarily neutrophils. At the same time, it is well known that the complement system is an important part of the innate immunity to viral infections. The link between complement and hemostasis has been intensively investigated in recent years [for a review see 24]. Additionally, both microparticles (MP), microvesicles (< 1 μm) released from different cells after activation and/or apoptosis[25] and neutrophil extracellular traps (NETs)[26] which represent part of the host defense are involved in the signaling process and communication between inflammation/complement and hemostasis. First pathohistological and autopsy reports are now available, and they demonstrate both the deposition of fibrin, neutrophils and C5b-9 and C4d in the lungs and peripheral tissues [27].

MPs, vesicles rich in phosphatidylserine (PS) that carry a subset of parent-cell proteins, are released primarily from platelet and endothelial cells but many other cells may also be the source of MPs and they can carry different proteins including complement, as it has been shown in patients with systemic disease such as vasculitis [28]. It has also been shown in another syndrome (APS), commonly associated with TMA, that thrombin activatable fibrinolysis inhibitor (TAFI), which is included in the stabilization of fibrin, may represent a link between coagulation and complement [29]. In one recent review, it has been discussed the association between brain injury (commonly associated with DIC or DIC-like coagulation abnormalities which have common features as some of Covid-19 coagulopathy), hemostasis and complement [30].

Neutrophil extracellular traps (NETs) were first described in 2004 as a means for neutrophils to trap and kill bacteria and are released as a result of a programmed cell death mechanism referred to as NETosis. The most recent study revealed high levels of NETs in many patients with Covid-19, where they may have contributed to cytokine release and respiratory failure [31].

Are Hemostatic Disturbances in Covid-19 Unique – Implications for Treatment?

Despite dramatical clinical and laboratory findings and massive overload of "scientific" information (at the moment of writing this article (mid-June 2020) more than 20,000 articles including the term Covid are available on PubMed) based mostly on case-reports and small series of patients (published without a thorough peer-review process) medical practitioners dealing with thrombosis and hemostasis have to keep the ability for logical decision making based on scientific evidences. Therefore, we should carefully think about the fact that increased D-dimer is common in hospitalized and criti-

cally ill patients [32-34] but is not routinely measured on a daily basis in other patients as is currently being done in patients with COVID-19 [35]. Increased incidence of VTE is not exclusively present in Covid-19. Even in other viral influenza (H1N1) it was observed that severe patients with ARDS who were positive to H1N1 had 20-fold higher risk to develop VTE, and anticoagulation dramatically decreased that risk [36].

Nevertheless, it seems that apart from ARDS or ARDS like syndromes some kind of thromboembolic complications (mostly VTE) are present in about one third of severe (mostly ICU) patients with Covid-19. However, one should be reminded that venous thromboembolism was present in approximately the same (or even higher, up to 40%) percentage on routine autopsies and that the number was the same within several decades [37, 38]. The same number of VTE (40%) was found in the very first larger series of autopsies of patients who died after Covid-19 [39]. Interestingly enough**,** although now there is a definite consensus that coagulation abnormalities in Covid-19 are not similar to those in DIC, mortality in overt DIC is also described to be about 40% [40]. So almost a philosophical question should be raised: are hemostatic abnormalities something that happens at the end of life in severely ill patients irrespectively of whether they have Covid-19, another influenza or some other severe terminal disease? It also seems that the proinflammatory response is also a part of those pathophysiological conditions.

Taking into account the preliminary results that the use of anticoagulation not only decreases the incidence of VTE but also seems to improve the outcome of severe patients with Covid-19, a question may be posed the other way round: Should (all) severely ill patients may experience the benefit of increased anticoagulation prophylaxis?

Table 3 Karolinska University Hospital coagulation findings in patients with severe Covid-19

Analysis	Change	Kinetics during hospitalization
PT-INR	N	→
Fibrinogen	↑↑	→
Platelet count	N/↑	↑*
D-dimer	↑	↑↑

N-normal, ↑ increase, ↑↑ major increase, → preserve on initial level.

*Non-survivors had slight platelet count decrease (within reference range between day 5 and 10).

Instead of Conclusions

To summarize what is known about thrombo-inflammatory abnormalities in Covid-19 (both from the literature and from Karolinska University Hospital experience):

1. High levels of inflammatory markers, particularly IL-6, neutrophils, fibrinogen and D-dimer are present and are associated with prognosis;
2. Almost 40% of severe patients apart from ARDS-like phenomena develop thrombosis, predominantly VTE/PE but also arterial thrombosis and TMA type changes in peripheral organs including acro-necrosis;
3. Pathophysiologically, complement-neutrophils-fibrin deposition is present in affected tissues (primarily the lungs);
4. Increase of the prophylactic dose of heparin/LMWH seems to be justified in the prevention of thrombosis.

What is not certainly known:

1. Is thrombocytopenia or thrombocytosis more common in Covid-19 patients?
2. Is the mechanism behind large vessel thrombosis and TMA the same?
3. How to diagnose thrombosis?
4. How to manage thrombosis (primarily VTE/PE) not responding to the standard treatment?
5. Is there a place for antiplatelet treatment in addition to anticoagulation treatment?
6. Does the level of complement activation correlate with the development of thrombosis propensity and severe pulmonary engagement?
7. Are there changes in additional modulators of hypercoagulability, such as microparticles and neutrophil extracellular traps, which contribute to the complex interplay of hemostasis, inflammation and the SARS-Cov2 infection?

Hemostatic abnormalities including VTE are common in Covid-19 and it seems that increased anticoagulant prophylaxis may be beneficial for severe (ICU/mechanical ventilation) patients. However, the importance of those changes should not be overestimated since it seems that thromboembolic phenomena are, to a similar extent, present in other influenza and severely ill patients.

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Short Communication

BILATERAL ABSENCE OF THE INTERNAL CAROTID ARTERY VERSUS BILATERAL ABSENCE OF THE VERTEBRAL ARTERY

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Abstract. *Despite the rare appearance of the bilateral absence of paired cerebral arteries - internal carotid or vertebral one, the purpose of this paper is the comparison of such cases. Described differences (or similarities) are mostly related to the general data, morphophysiology, and (selected) pathological conditions.*

Key words: *Internal carotid artery, vertebral artery, bilateral absence, comparison*

What is the significance of internal carotid (ICA) or vertebral (VA) arteries in the vascularization of the brain (two thirds in relation to one third), as well as other cranial or vertebral structures has already been very well known. However, what is little known is that there is a possibility of the bilateral absence of ICA or VA. The purpose of this paper is to compare some substantial facts about the general, morphological, and pathological status of these cases.

The comparison of 68 and 31 cases of the bilateral ICA and VA absence, respectively is presented according to the content in the reviews about them [1, 2] and the newly discovered cases of ICAs absence [3−10]; the new cases of the bilateral VA absence (older or more recent date) were not found (Table 1).

The main differences between the cases of the bilateral ICA and VA absences were as follows: Generally, the cases of bilateral ICA absence were more commonly described in the literature than the cases of the bilateral VA absence (G2, Table 1). From an anatomical point of view, the proposed literature types of the bilateral ICA absence according to the absence (or presence) of carotid canals in the petrous part of temporal bone could be disputable due to the presence of ICA vascular source in almost of described cases (G6 and M1, Table 1). The presence of terminal ICA branches in almost all of these cases could prove a hypothesis about possible bilateral obliteration of the 3rd primitive aortic arches (PAAs) and a part of dorsal aortae between the PAA1 and PAA3 in a human embryo, probably with the crown-rump length of 5 to 6 mm, i.e. after a division of the primitive ICA in the anterior and posterior branches; on another side, the constant presence of the BA with the help of some of the CVBAs leads us to suppose that the longitudinal neural arteries (precursors of the BA) on the hindbrain are decisive for their persistence than the absence of anastomoses of six cervical intersegmental arteries (precursors of future VA) (M4, Table 1).

Although the embryonic precursors of both ICA and VA are different [1, 2], their morphofunctional relationships in the postnatal life are to be expressed; a crucial role of the VBS in a case of bilateral ICA absence or some CVBA (common branch of ICA) in a case of the bilateral VA absence are the arguments for further discussion. Morphologically, there were more common variations of the VA in a case of the bilateral ICA absence, than ICA variations in a case of the bilateral VA absence (M6, Table 1). Regarding the pathology of these cases, it should be underlined that discovered cerebral aneurysms were more associated with the bilateral VA absence thus with the bilateral ICA absence; however, only 2/6 cerebral aneurysms were located on the ICA and persistent primitive hypoglossal artery in the cases of the bilateral VA absence, while all diagnosed cerebral aneurysms were located on the VBS branches in the cases of the bilateral ICA absence (P1, Table 1). The next specificity was that there were more frequent cases of the ICA stenosis associated with the bilateral VA absence than the contrary (P2, Table 1).

Although in almost half of the cases of both groups of abnormalities no accompanying pathology was recorded (N1, Table 1), for the time being these cases cannot be compared.

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Table 1 Comparison of cases of the bilateral absence of internal carotid (ICA) and vertebral (VA) arteries

	Comparison	Absence of both ICAs	Absence of both VAs
		General data*	
G1	First (available) description	In 1913	In 1970
G2	Number of cases + additional cases (gender)	60 (31 male, 23 female, 6 of unknown gender)** + 8 (3 male, 3 female, 2 of unknown gender)***	31 (19 male, 11 female, 1 of unknown gender)**
G3	Age of cases	Newborn−80s	Neonate−80s
G4	Ethnicity predisposition	Expressed doubt	No data
G5	Familiar predisposition	No data	No data
G6	Literature types	Agenesis Aplasia	No data Aplasia
		Morphophysiology*	
M1	Presence of common vascular sources	There was bilateral absence of the common carotid a. (CCA) only in one case and unilaterallyalso in one case.	Both subclavian arteries (SAs) were always presented.
M2	Status of constant vascular osseous canals or grooves	Carotid canals in the petrous part of temporal bones were bilaterally absented in 37/60 (known) cases and unilaterally in 2/60 cases; cited 8 cases did not included. There were no data for the presence of the carotid sulcus on the side of the body of the sphenoid bone.	Bilaterally, the foramen transversarium of the cervical vertebra was always presented; an exception was one cited case for which there were no available data. There were no data for the presence or absence of the groove for the VA on the posterior arch of atlas.
M3	Status of side-branches of (absented) ICA or VA	There were several descriptions of the origin of the ophthalmic or posterior communicating a.	There were several descriptions about the origin of some cerebellar arteries.
M4	Status of terminal branches of (absented) ICA or VA	The anterior cerebral artery was bilaterally described (or showed) in 56/60 (known) cases, except in two cases on the right side, while the middle cerebral artery was described (or showed) in all cases; cited cases did not included.	The basilar artery (BA) was mostly in a continuation of the persistent primitive carotid-vertebrobasilar anastomosis (CVBA) —proatlantal intersegmental (15 times) or hypoglossal artery (11 times). It was a continuation of the occipital a. in 2 cases and the ascending pharyngeal or paired primitive trigeminal arteries each in one case.
M5	Collateral circulation	The anterior cerebral circulation was supplied mostly via the vertebrobasilar system (VBS), while it was supplied via the CVBA(s) in 5 patients or via the branches of the external carotid arteries (ECAs) in 2 patients, although some branches of ECA were the supplements to the CVBA.	Idem
M6	Additional vascular variations of the VA and/or BA or ICA, respectively	Left VA originated from the aorta (2) or the left-sided arterial duct (1); hypoplasia of the right VA (2); duplication of the left VA in the intracranial part (1); tortuosity of VBS arteries (4); leftward deviation of the BA (1); ectasia of the BA (4) or VA (2); bridging fenestration into the BA lumen (1).	Irregular caliber of the ICA (1), tortuous course of the persistent primitive hypoglossal artery (PPHA) (1)).
M7	Association of the bilateral ICA and VA absences	There were only single (published) cases of an association of the segmental aplasia ICA and VA	
		Reasons of discovery*	
R1		Unspecified	
		Selected pathology*	
P1	Aneurysms --- Aneurysmatic VA (or other VBS branches), or ICA (branches)	13.33% or 8/60 (known) cases --- 8 cases (VA (1), left posterior cerebral artery (1), BA (6))	20% or 6/30 (known) cases --- 2 cases (ICA (1), PPHA (1))
P2	Additional specific disorders of the VA or ICA	2 cases (VA dissection (1), VA stenosis (1))	9 cases (ICA stenosis)
		No explored pathology*	
N1	Σ (un)known cases	28 (10+18 cases)	15 (1+14 cases)

*Summarized data from all cited articles (1−10)
**Data according to the contents in the corresponding review (1 and 2, respectively)
***Data according to the new discovered cases (3−10)

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Mini-Review

THE NEW ADDRESSING PROBLEM IN INTESTINAL CANDIDOSIS

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Abstract. *Herein, we discussed a new problem concerning diagnosis, treatment, and monitoring of patients with intestinal candidosis. The lack of official attitude about the significance of Candida overgrowth on intestinal mucosa as well as the absence of guidelines regarding its treatment and required diet, significantly complicate this problem in medical practice. Possible overgrowth of species Saccharomyces cerevisiae-bulardi from probiotics in intestines is a newly recognized problem in diagnostic procedures.*

Key words: *intestinal candidosis, Candida overgrowth, Saccharomyces cerevisiae-bulardi.*

Introduction

The role of *Candida* spp. in the etiology of gastrointestinal disturbances, infection, and diseases hasn't been clarified yet. Gastrointestinal candidosis is still a subject of controversy in scientific circles without a unique opinion about pathogenic potential of this yeast, interpretation of mycological analysis result, and, most importantly, without referral guidelines for its treatment. Lack of official recommendations regarding this problem, alongside a huge number of unreliable theories and misbeliefs in referent literature, electronic media and newspapers, have confused both scientists and laymen since the 1980s [1-3].

Valid Postulates

We can point out following facts:

- It is well known that *Candida* spp. represent the part of gut microbiota (normal gastrointestinal flora) in healthy people, but in certain cases, these commensal fungi can convert from non-pathogenic to pathogenic ones [4].
- The most important *Candida* infections of the gastrointestinal tract are esophageal and gastrointestinal candidosis in severely immunocompromised. Esophageal candidosis is usually seen in AIDS patients or those receiving long-term chemotherapy. In addition, patients with leukemia and other hematologic malignancies are at increased risk for the development of multiple ulcers on the intestinal mucosa due to fungal infection. Thus, gastrointestinal perforation and complications such as peritonitis or hematogenous spread of fungi to the liver, spleen, and lungs are common in these patients [5].
- A big portion of healthy, immunocompetent, people having *Candida* spp. in their digestive system as part of microbiota, therefore have positive laboratory findings (positive *Candida*-isolates from the stool samples). For this reason, the discrimination between *Candida*-colonization and *Candida*-infection is difficult [6].
- Unlike obligate pathogens, whose detection implies disease, differential diagnosis between *Candida*-infection and *Candida*-colonization is more complex. In order to make a distinction, it is necessary to perform endoscopic biopsy and subsequent histopathological examination. This is the reason why there is still no unique approach regarding the treatment of patients with gastrointestinal candidosis and there are a lot of questionable viewpoints regarding the pathogenic effect of *Candida* on the intestinal mucosa.
- Regardless of many controversial postulates about pathogenic potential of *Candida*, current opinion in medical theory and praxis is that *Candida* spp. has a role in the occurrence of diarrhea after antibiotic consumption. Consequently, nystatin prophylaxis is recommended during the antibacterial treatment [7].
- The theory that immune dysregulation in intestinal mucosa, specifically IgE-mediated reaction to *Candida* antigens, actually leads to local and systemic damage of tissues is under investigation [8].
- There is still no official recommendation for antifungal "intestinal decontamination". However the use of nystatin showed satisfactory anti-*Candida* effect with reduction and even complete withdrawal of symptoms in patients with diarrhea [7, 9].

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Current Consideration and Observation

The presence of *Candida* yeast as a member of microbiota on intestinal mucosa is mainly benign. However, the results of the newest research concerning *Candida* spp. impact on the digestive tract, demonstrated that, if present, these yeasts may contribute to the destruction of already damaged mucosa. Studies that included patients with gastrointestinal diseases and the ones done on animal models, without a doubt revealed that presence of *Candida* may lead to an even bigger defect and massive inflammation [10-13].

Investigation of Crohn's disease and the presence of *Candida* on intestinal mucosa established the relationship between this inflammatory bowel disease and intestinal *Candida* colonization [10]. Furthermore, it was demonstrated that antifungal treatment to reduce *Candida*-colonization lessens the severity of ulcerative colitis [11]. Moreover, analysis of the animal model suggested that *Candida* colonization may create a vicious cycle where yeasts slow down the healing of inflammatory lesions while inflammation promotes fungal colonization [12]. There is also an assumption that if *Candida* can cause infection and inflammation of the skin, severe damage of nail, inflammation of vulvovaginal mucosa, pseudomembranous and erythematous oral candidosis, as well as perianal eczema, then it can as well have a pathogenic effect at the level of the intestinal mucosa.

Problems

In addition to these still unresolved issues, in practice, there are also problems of diagnosis and patients treatment. *Candida* spp. can, under the influence of various factors, multiply rapidly and overgrow the rest of gut microbiota, leading to dysbiosis. Based on this simplified, long-standing, concept and on our experience in routine work with patients who have *Candida* infection/colonization of digestive tract, we can point out that physicians usually prescribe local antimycotic, with or without a diet, but recommendation of probiotics is practically mandatory. The role of microorganisms contained inside a probiotic supplement is to successfully colonize intestinal mucosa, stay resistant to the influence of other microorganisms, and persist in intestines. The use of these supplement products increases the possibility of gut colonization with non-pathogenic microbes and preservation of normal balance among usual members of physiologic flora [14].In the best-case scenario, this treatment will improve condition in a certain number of patients with dysbiosis. However, some of them, despite antifungal treatment, will have recurrent episodes, and will require repeated mycological examination of the stool.

Our Experience and New Problem

Our previous study [2] as well as the records of approximately 80,000 patients examined in our mycological laboratory, showed that in over 60% of cases there are positive findings of *Candida* in the stool samples. Nevertheless, the percentage of patients with *Candida* overgrowth (>10^6 CFU/g of faeces) is significantly lower (8-10%). Interestingly, in a ten-year period, 2% of examined patients had positive findings of yeast overgrowth with causative species being *Saccharomyces (S.) cerevisiae*. This is a ubiquitous ascomycetous yeast that colonizes the respiratory, urinary and gastrointestinal tract of humans and is traditionally considered non-pathogenic. Recently, however, it has started to be considered as a potential pathogen and cause of superficial and invasive fungal infection. Accordingly, *S. cerevisiae* overgrowth on intestinal mucosa could be as problematic as *Candida* -overgrowth. On the other hand, *S. cerevisiae-bulardi* strain is a component of many probiotics and can quickly proliferate during prolonged treatment. In order to correctly interpret the findings of *S. cerevisiae*, we decided to have an interview with 100 patients. All of them, except one, stated that, according to physician recommendation, they have used probiotics that contain *S. cerevisiae-bulardi* strain for more than 20 days.

Besides previously stated problems that there is no general opinion about *Candida*-overgrowth on the intestinal mucosa and official guidelines regarding treatment and diet for this condition are lacking, additional problems are being recognized:

- Mycological analyses of the stool can suggest yeast overgrowth, yet it can be overgrowth of yeast from probiotics.
- In Serbia there are only a few microbiological laboratories equipped for mycological analysis and even fewer for differentiation of yeast strains.
- During the mycological analysis of the stool, overgrowth of *Saccharomyces* yeasts from probiotics can be easily mistaken for high counts of *Candida* spp. Therefore, only in case of macroscopic and microscopic examination,, misinterpretation of result as *Candida* overgrowth may occur.
- Errors in result interpretation, as well as the fact that most physicians are neither familiar with the latest trends in mycology, nor with the risk that yeasts from probiotics can lead to *Saccharomyces* overgrowth on the intestinal mucosa, may subsequently mislead the doctor to start „treating the treatment"[15,16].

To conclude, it would be best to establish laboratory capacity for differentiation between *Candida* and *Saccharomyces* yeast; to implement purposeful education for both medical personnel and laymen which would enable regular patient follow-ups; and before mycological analysis of intestinal microbiota to obtained anamnestic data of each patient regarding disturbance of gastrointestinal tract and consummation of probiotics, as well as the duration of this kind of treatment. Finally, the most correct interpretation of mycological examination can be provided only by a multidisciplinary team and patient participation.

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Original Article

KNOWLEDGE, BELIEFS AND HABITS OF SERBIAN UNIVERSITY STUDENTS REGARDING USAGE OF ANTIBIOTICS – A CROSS-SECTIONAL STUDY OF BIOMEDICAL AND NON-BIOMEDICAL STUDENTS

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Abstract. *Proper usage of antibiotics is an often-overlooked subject, leading to a high level of ignorance among youth towards this important topic. The aim of this study was to examine the knowledge, beliefs, and habits of students at Nis University regarding the usage of antibiotics and discover whether an anticipated difference existed between knowledge and habits of biomedical students and that of non-biomedical students. The data were acquired through an online questionnaire that addressed knowledge, beliefs, and habits regarding antibiotics. The study adhered to the principles of the Helsinki declaration. Data were separated into two groups and tested for statistical significance using the Chi-squared test. The questionnaire showed that the majority of students (76.86%) were able to correctly identify bacteria as the main target of antibiotics. More students from non-biomedical faculties thought viral infections could be treated with antibiotics (37.35% vs. 7.06% of medical, $p<0.05$), and identified incorrectly Paracetamol as an antibiotic (42.17% vs. 8.15% of medical, $p<0.05$). However, a similar percentage in both groups (49.14%) claimed they interrupted their regimen before the prescribed time, and as much as 67.39% of biomedical students acquired antibiotics with no prescription. Biomedical students demonstrated much better knowledge and beliefs on antibiotics, however, students from both groups were found to have similar habits regarding the usage. The results are similar to available studies from the developing world. A large percentage of students tampers with antibiotics on their own. Campaigns are necessary to inform students better on the subject.*

Key words: *antibiotics, antibiotic resistance, appropriate use of antibiotics, knowledge, public health, university students.*

Introduction

Proper usage of antibiotics is an important topic often overlooked in high school education, therefore leading to a high level of ignorance among youth. Misuse of antibiotics (regime altering, self-medication, and abuse, missed purpose) can lead to a lowered effect of treatment, ultimately leading to antibiotic resistance [1]. Increased usage of antibiotics has been reported throughout the world, with a growing rate of self-medication [2, 3]. Antibiotics' misuse most commonly leads to antibiotic resistance, which has been estimated to cause 700 000 deaths per year; by 2050 this number may rise to 10 000 000 deaths per year [4].

In relation to this, literature data report that public unawareness level regarding the ineffectiveness of antibiotics in viral diseases was as high as 60% in the European population in 2001 [5, 6]. Ochoa et al [6] have reported that overuse of antibiotics has been reported in upper respiratory tract infections, regardless of the fact that these infections are mostly viral in origin. Furthermore, a study conducted across Europe showed large rates of self-medication using antibiotics, even in the immediate proximity of Serbia. These numbers include 28% in Slovenia and 20.5% in Croatia [7], as well as high levels in other South European countries like Malta, Spain, and Italy [7, 8].

The most worrying statistics is related to the level of knowledge of antibiotics and antibiotic resistance among university students, who are expected to make up the most educated part of the future world's population. Physician's error and antibiotics over-prescription are among the main causes of the development of antibiotic resistance [4]. Therefore, a special emphasis is put on the students of the biomedical profession, as young researchers and clinicians are in a crucial phase of their education where their opinion on the issue should be formed. It has been found difficult to alter their perception once they adopt wrong habits [9].

The objective of this study is to examine the knowledge, beliefs, and habits of students regarding usage of antibiotics and to investigate whether students of medical and similar faculties have a better understanding of the matter in comparison to less relative study courses.

Based on the previous studies [10] and taking into account the curriculum of biomedical faculties, the hypothesis of the study is that biomedical students will demonstrate a better knowledge of the subject and that their habits will be more in compliance with the principles of the rational use of antibiotics.

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According to available research, this study was among the first to investigate and compare the knowledge, habits, and beliefs of medical/pharmaceutical students to students of other branches at the same university. The importance of such a study, besides being one of the pioneers in the field, is to provide a good insight into students' knowledge and attitude on the subject. This can be further used to assess whether campaigns on knowledge improvement are needed and what specific points are to be addressed. Considering that the study focuses on the future academic population of the City of Nis and its broader region, students make up the most important population group whose awareness should be assessed.

Materials and Methods

Data gathering was performed in collaboration with student representatives from each of the surveyed faculty (cited in *Acknowledgements*). The main data gathering method was an online survey, in addition to printed questionnaires used in conditions where an online survey could not be implemented.

Prior to completing the online survey, participants gave their informed consent for processing their answers and basic personal details for research purposes. The study was conducted in accordance with the principles of the Helsinki declaration. The questionnaire was completed fully anonymously, and only personal data asked from the participants included age, sex, and faculty affiliation. There was no compensation nor reward offered to participants.

In compliance with the three main domains of the study, the questionnaire was divided into three parts that assessed participants' knowledge, beliefs, and habits, respectively. The questions were designed in compliance with some previous studies conducted in Norway [11], Italy [12], Indonesia [2] and the United Arab Emirates [10].

The survey encompassed a total of 19 questions. The questions were laid out in a manner so that the survey does not resemble a knowledge test, as this could press students to do better and bias the results. Most of the questions asked for a simple Yes/No answer (or Agree/Disagree), however, several questions asked students to choose among given answers (where more answers were possible), and several others asked students to put in an answer on their own (such as the question that asked for an example of an antibiotic). The diverse questions aimed to cover most of the topics related to the consumption of antibiotics.

The questions are enumerated in the following Table 1, along with the correct (expected, rational) answer highlighted in **bold.**

Table 1 Questions and possible answers. Correct answers are shaded in bold.

No.	Question	Answer(s)
	K N O W L E D G E	
1.	Antibiotics are effectively used against (more responses possible):	***bacteria***, *viruses, fungus*
2.	What of the following drugs are antibiotics (more responses possible)? *Paracetamol* (acetaminophen) / Brufen* (ibuprofen) / Probiotic / Sinacillin* (**Amoxicillin**) / Bromazepam / **Penicillin***	
3.	Antibiotics need not be taken in regular intervals, if the daily dosage is respected.	Yes/**No**
4.	Antibiotics help after all types of cough, throat pain, and common cold.	Yes/**No**
5.	Antibiotics can be kept for further usage, if the illness reappears.	Yes/**No**
6.	Taking antibiotics out of dosing regime is not dangerous.	Yes/**No**
	B E L I E F S	
1.	I believe that antibiotics can help with most diseases.	Agree/**Disagree**
2.	I believe that taking antibiotics preventively can immunise us against the common flu.	Agree/**Disagree**
3.	I believe that the therapy may be interrupted when the symptoms fade out.	Agree/**Disagree**
4.	I believe that antibiotics have no side-effects.	Agree/**Disagree**
	H A B I T S	
1.	Have you ever acquired antibiotics with no prescription?	Yes/**No**
2.	Have you ever acquired antibiotics preventively?	Yes/**No**
3.	Have you ever consumed alcohol during your therapy with antibiotics?	Yes/**No**
4.	Do you carry an antibiotic when you travel, in case someone falls ill?	Yes/**No**
5.	Have you ever interrupted your regime before the time prescribed?	Yes/**No**
6.	Do you always consult your doctor prior to taking antibiotics?	**Yes**/No
7.	Do you always inspect the instruction manual and check the expiry date prior to taking an antibiotic?	**Yes**/No
8.	Have you ever skipped a dose that you went on to make up for?	Yes/**No**
9.	If you take antibiotics on your own, the reasons that you do it for are… *a) You have the antibiotics at home* *b) You study medicine (or a relevant faculty, so you are informed* *c) someone from you household works in healthcare* *d) you've had a good experience with that medicine* ***e) You do not take them on your own***	

*: throughout the survey, the common (commercial) name of the antibiotic in Serbia was used, however, in the report, scientific (INN) name is also reported for better understanding of the questions.

For interpretation, the results have been quantified and represented both in the number of students and in percentile (from the given group – medical or non-medical students). For the questions where multiple answers were possible, a mode was determined, showing the most frequent option. In order to determine the statistical importance of data obtained and its connection to the studied factor, a common χ^2-test for independence (Chi-squared test) was used, where value $p<0.05$ was considered significant.

Results

A total of 350 students from Nis University participated in the survey. The students were divided into two main groups. The first group encompasses students of biomedical sciences. This included the Medical Faculty, which includes study programmes *Medicine (MD)* and *Pharmacology*, as well as students from the *Faculty of Natural Sciences (Biology).*

The second group includes students of other faculties, whose study programmes do not have any common points with the topic of antibiotics. These included *Faculty of Electronic Engineering, Faculty of Law, Faculty of Economics, Faculty of Philosophy, Faculty of General Engineering, Faculty of Architecture, Faculty of Art and Faculty of Natural Sciences (informatics).*

The results have been quantified and divided into three subgroups (knowledge, beliefs, habits), for easier interpretation. There were 184 students from the Medical Faculty and related sciences (52.57%), and 166 students from other faculties (47.43%). Among the whole number of interrogated students, 123 identified as male (35.14%) and 227 as female (64.86%). In tables, questions that allowed the participants to give more than one response are denoted with an asterisk (*), to indicate that the overall number of answers is higher than 350. The group of biomedical students will be referred to as Group A, and the group of students from other faculties will be known as group B.

Knowledge on antibiotics

Table 2 enumerates answers to the questions regarding students' knowledge on antibiotics. The numbers are given along with percentage in the respective group of data.

Most of the questions have yielded a statistically important difference between the two groups. It is shown that students of both groups have identified bacteria as the main pathogen killed by antibiotics (78.80% in Group A vs. 74.7% in group B). However, a significantly larger portion of the group B considered antibiotics useful against viruses (37.35% vs.7.06%, $p<0.00001$) and fungi (18.67% vs. 7.61%, $p=0.002$).

Similar important differences were found as far as classifying medicines is concerned. A similarly low

Table 2 Results: Knowledge on antibiotics: biomedical students against students of other faculties

Question	Answers		All students (350)	Group A (184)	Group B (166)	p-value
Antibiotics are effective against…	Bacteria	**Y**	269 (76.86%)	145 (78.80%)	124 (74.7%)	0.363
		N	81 (23.14%)	39 (21.19%)	42 (25.3%)	
	Viruses	**Y**	75 (21.43%)	13 (7.06%)	62 (37.35%)	<0.001
		N	275 (78.57%)	171 (92.94%)	104 (62.65%)	
	Fungus	**Y**	45 (12.86%)	14 (7.61%)	31 (18.67%)	0.002
		N	305 (87.14%)	170 (92.39%)	135 (81.33%)	
Of the following drugs, antibiotics are…	*Brufen*	**Y**	33 (9.43%)	5 (2.72%)	28 (16.87%)	<0.001
		N	317 (90.57%)	179 (97.28%)	138 (83.13%)	
	Paracetamol	**Y**	85 (24.29%)	15 (8.15%)	70 (42.17%)	<0.001
		N	265 (75.71%)	169 (91.85%)	96 (57.83%)	
	Probiotic	**Y**	29 (8.29%)	10 (5.43%)	19 (11.45%)	0.042
		N	321 (91.17%)	174 (94.57%)	147 (88.55%)	
	Sinacillin	**Y**	279 (79.71%)	163 (88.59%)	116 (69.88%)	<0.001
		N	71 (20.29%)	21 (11.41%)	50 (30.12%)	
	Bromazepam	**Y**	9 (2.57%)	1 (0.54%)	8 (4.82%)	0.012
		N	341 (97.43%)	183 (99.46%)	158 (95.18%)	
	Penicillin	**Y**	282 (80.57%)	166 (90.22%)	116 (69.88%)	<0.001
		N	68 (19.43%)	18 (9.78%)	50 (30.12%)	
Antibiotics need not be taken in regular intervals, as long as the daily dosage is respected.		**Y**	48 (13.71%)	10 (5.43%)	38 (22.89%)	<0.001
		N	301 (86.00%)	174 (94.46%)	127 (76.51%)	
Antibiotics help after all types of cough, throat pain, and common cold.		**Y**	62 (17.71%)	12 (6.52%)	50 (30.12%)	<0.001
		N	278 (79.43%)	163 (88.59%)	115 (69.28%)	
Antibiotics can be kept for further usage, if the illness reappears.		**Y**	116 (33.14%)	58 (31.52%)	58 (34.94%)	0.399
		N	230 (65.71%)	126 (68.48%)	104 (62.65%)	
Taking antibiotics out of dosing regimen is not dangerous.		**Y**	16 (4.57%)	8 (4.35%)	8 (4.82%)	0.882
		N	331 (94.57%)	175 (95.11%)	156 (93.98%)	

Abbreviations: Y: yes, N: no, Group A: biomedical students, Group B: non-biomedical students

number of students identified *Probiotic* as an antibiotic in both groups (5.43% vs. 11.45%). However, all other medicines have been better identified (with a significant difference) by students of the biomedical sciences (group A). *Ibuprofen* was correctly identified as a non-steroid anti-inflammatory drug [NSAID] by 97.28% of participants from group A, whereas 16.87% of group B identified it as an antibiotic (p<0.00001). The largest difference was found when it came to identifying *Paracetamol (acetaminophen).* This drug was classified as an antibiotic by as much as 42.17% of students from group B, whereas this number drops to 8.15% among group A (p<0.00001).

Yes-no questions were answered with less discrepancy between the groups. Similar percentages (31.52% students from A, and 34.94% of students from B) considered that antibiotics can be kept for future use, and similar percentages (4.35% of group A vs. 4.82% of group B) considered that taking antibiotics out of dosing regime is not harmful. However, differences were found in the question regarding the regularity of the dosing regimen. A large portion of group A (94.46%) considered that antibiotics must be taken in regular intervals only, whereas this number drops to 76.51% in group B, p<0.00001. Another large gap is seen in the question about the effectiveness of antibiotics. They were found useful against all types of common cold and cough by 30.12% of the group B, whereas as little as 6.52% of students from the group A considered this statement true, p<0.00001.

Beliefs on antibiotics

Table 3 enumerates answers to questions about beliefs on antibiotics and their effectiveness. The same notation is kept as in Table 2.

Statistical significance was noted in all four questions related to beliefs about antibiotics. Fewer students from group A believed that antibiotics are helpful with most diseases than in group B (24.46% vs. 39.16%, p<0.00001). A slightly larger number of students from group B thought that antibiotics can be taken to prevent disease (8.43% vs. 2.17%, p=0.007), similarly to the belief in relation to side-effects. Only two students from group A (1.08%) stated that antibiotics had no side effects, whereas 7.83% of students from group B have reported such a belief (p=0.002). However, a significantly larger portion of students from group B believed that the therapy may be interrupted when the symptoms fade out (20.48% vs. 7.61%, p=0.001).

Habits about taking the antibiotics

Table 4 summarises the results from last nine questions that are related to students' habits when it comes to consuming antibiotics. The notations remain the same as in previous tables.

The two groups have more in common as far as habits of antibiotics' usage is concerned. There was no statistical difference in answers on questions about preventive usage of antibiotics, alcohol consumption during therapy, carrying antibiotics on travels, regime interruption, and consulting a doctor prior to therapy, with the percentages being similar across the range. However, the statistical difference (p=0.001) was observed when it comes to acquiring antibiotics without a prescription. Students from group A have reported this in a larger percentage (67.39% vs. 48.19%). Also, a statistical difference was observed in answers to the question that addresses expiry date verification and the instruction manual. Again, a much larger percentage of students from group A reported reading the manual and verifying the date (80.43% vs. 62.05%, p=0.001).

The final question, which asks about the reasons for which students take antibiotics on their own, has statistically significant results at p<0.00001. More students from group A listed that it was hard to reach a doctor (24.46% vs. 6.63%) and that they took advice from a family member working in healthcare (25.00% vs. 21.69%). However, students from group B opted in a larger percent for "I have it at home" and "I had a good experience with the medicine", 30.72% vs. 25.54% and 20.48% vs. 15.22%, respectively, so there was a clear distinction between the answers of the two groups. Note that the percentages account for the part of the students' answer in the whole group of students, not just those who answered this question.

Table 3 Beliefs on antibiotics.

Question		All students (350)		Group A (184)		Group B (166)		p value
I believe antibiotics can help me with most diseases.	A	101	(28.86%)	45	(24.46%)	65	(39.16%)	<0.001
	D	236	(67.43%)	139	(75.54%)	97	(58.43%)	
I believe that taking antibiotics preventively can immunise us against the common flu.	A	18	(5.14%)	4	(2.17%)	14	(8.43%)	0.007
	D	329	(91.39%)	180	(97.83%)	149	(89.76%)	
I believe that the therapy may be interrupted when the symptoms fade out.	A	48	(13.71%)	14	(7.61%)	34	(20.48%)	0.001
	D	298	(82.78%)	168	(91.39%)	130	(78.31%)	
I believe that antibiotics have no side-effects.	A	15	(4.29%)	2	(1.08%)	13	(7.83%)	0.002
	D	331	(94.57%)	181	(98.37%)	150	(90.36%)	

Abbreviations. A: agree, D: disagree, Group A: biomedical students, Group B: non-biomedical students. NB. Not all the participants have answered the questions.

Table 4 Results on questions about habits on antibiotics.

Question		All students (350)	group A (184)	group B (166)	p value
Have you ever acquired antibiotics with no prescription?	Y	204 (56.67%)	124 (67.39%)	80 (48.19%)	0.001
	N	145 (41.43%)	60 (32.61%)	85 (51.21%)	
Have you ever acquired antibiotics preventively?	Y	15 (4.17%)	10 (5.43%)	5 (3.01%)	0.261
	N	324 (92.57%)	168 (91.30%)	156 (93.98%)	
Have you ever consumed alcohol during your therapy with antibiotics?	Y	74 (20.56%)	36 (19.57%)	38 (22.89%)	0.412
	N	274 (78.29%)	148 (80.43%)	126 (75.91%)	
Do you carry an antibiotic when you travel, in case someone falls ill?	Y	197 (56.29%)	101 (54.89%)	96 (57.83%)	0.536
	N	152 (43.43%)	83 (45.11%)	69 (41.57%)	
Have you ever interrupted your regime before the time prescribed?	Y	172 (49.14%)	87 (47.28%)	85 (51.20%)	0.485
	N	173 (49.43%)	94 (51.09%)	79 (47.59%)	
Do you always consult your doctor prior to taking antibiotics?	Y	211 (60.29%)	111 (60.33%)	100 (60.24%)	0.987
	N	139 (39.71%)	73 (39.67%)	66 (39.76%)	
Do you always inspect the instruction manual and check the expiry date prior to taking an antibiotic?	Y	251 (71.71%)	148 (80.43%)	103 (62.05%)	0.001
	N	94 (26.86%)	36 (19.57%)	58 (34.94%)	
Have you ever skipped a dose that you went on to make up for?	Y	125 (35.71%)	64 (34.78%)	61 (36.75%)	0.831
	N	229 (63.61%)	120 (65.22%)	109 (65.66%)	
If you take antibiotics on your own, the reasons that you do it for are… (multiple responses)	I have it at home	98 (28.00%)	47 (25.54%)	51 (30.72%)	<0.00001
	I study medicine (or relevant faculty), so I am informed	65 (18.57%)	63 (34.24%)	2 (1.20%)	
	Someone from my household works in healthcare	82 (23.43%)	46 (25.00%)	36 (21.69%)	
	it's hard to reach a doctor	56 (16.00%)	45 (24.46%)	11 (6.63%)	
	I had a good experience with that medicine	62 (17.71%)	28 (15.22%)	34 (20.48%)	

Abbreviations: Y: yes, N: no, Group A: biomedical students, Group B: non-biomedical students

Discussion

As mentioned in *Introduction*, this study is one of the rare few to approach comparatively the subject. The study has found statistically significant differences between the two groups in the sections on knowledge and beliefs. Similar results were reported in the United Arab Emirates [10] where the two groups have been compared, and the hypotheses of the two surveys coincide.

Knowledge on antibiotics

Students from both groups have correctly identified bacteria as the main pathogen for which antibiotics are used. They have done so with a lower percentage than students from Nepal [13] and Malaysia [14], where almost all participants denoted bacteria correctly. By contrast, students in Serbia have done considerably better than their counterparts in Jordan, where the percent of correct answers was 70.4% and 29.9% of medical and nonmedical students, respectively [15].

However, non-biomedical students have identified viruses in a much larger percentage than the ones from the biomedical domain (37.35% vs. 7.06%). These numbers are somewhat better than ones reported in South Jordan [15], where the ratio of medical vs. non-medical stood at 28.1% vs. 67.2%. The rate was similar in the United Arab Emirates [10], where the percentages were 34.2% and 69.8%, of medical and non-medical students, respectively. These percentages indicate that students from the Serbian university have a somewhat better knowledge of the ineffectiveness of antibiotics in viral infections. This is supported by studies from Malaysia [14, 16] and Italy [17], where 20% of medical students considered antibiotics effective against viruses.

Similarly, students of biomedical sciences are more aware that time of the dosage regiment needs to be respected to prevent the development of antibiotic resistance, with as low as 5.43% reporting that antibiotics need not be taken at regular intervals. This percentage is more reassuring than the one reported by a study on medical students from Sudan [18], where 46.1% reported making-up dosages as frequent.

Students from non-biomedical faculties were found more likely to consider antibiotics helpful against all types of cough and common cold (30.12% vs. 6.52%). A completely opposed ratio of the two groups was found in the only similar study in the United Arab Emirates [10], where more medical students were likely to employ antibiotics against cold cough (34.2%) than non-medical students (25.2%). Comparing answers of biomedical students from Nis to the immediate region, one sees that numbers reported in Poland were slightly better, where only 6.6% of medical students stated having employed antibiotics against the common cold [19]. However, much more worrying data was found in Trinidad and Tobago (35.2%) [20], South India (22.7%) [9], and United Arab Emirates (34.12%) [10]. Besides, a

multitude of studies conducted in Asia has reported much larger percentages of students of medicine or pharmacology employing antibiotics in this fashion. These include Saudi Arabia (64.2%) [21], Qatar (62%) [22], and Sri Lanka (57%) [23]. This shows that biomedical students from Nis University have a better perception of the subject.

Differently to most questions, a similar number of students from both groups (between 30% and 35%) have reported that they keep antibiotics for future usage. Similar numbers have been reported in Sudan [18], and Malaysia [14], without distinction between study courses. Nevertheless, the number of students from Nis who keep antibiotics for future use is lower than the one in Nigeria [24], where 51% of the general population of university students have admitted doing so.

Finally, when asked to identify antibiotics, biomedical students in Nis were far more successful than their peers from other faculties. Large differences in percentages were reported when it comes to Amoxicillin (marketed as *Sinacillin*), *Bromazepam*, *Paracetamol*, *Probioti,c* and *Ibuprofen* (marketed as *Brufen*). These differences can undoubtedly be explained by the fact that students of biomedical sciences have much more theoretical knowledge on the subject than ones from the other faculties. Compared to a study done in Saudi Arabia [21], students from Serbia from both groups have been more successful in identifying drugs. In Saudi Arabia, as much as 74% have not been sure about the nature of *Paracetamol.* In Nis, *Paracetamol* was incorrectly identified by 42.17% of non-biomedical and 8.15% of biomedical students. The largest number of students have identified correctly *Bromazepam* and *Sinacillin* (amoxicillin), as the two are among more famous drugs in Serbia. Similar findings were reported in China [25]. Amoxicillin was identified correctly in both groups (88.59% vs. 69.88%), with a better percentage than the one reported in the United Arab Emirates [10], where the percentages were 69% vs. 50.5% for medical and non-medical students, respectively. Therefore, students from the Serbian university have distinguished better between the commonly used medicines.

In a nutshell, biomedical students have demonstrated a better knowledge of antibiotics than their counterparts from other study courses. This confirms the hypothesis of this survey. When compared with similar studies conducted elsewhere, one concludes that students of Nis University have demonstrated average or slightly better results. This applies also to the studies conducted in the near region, like in Italy and Portugal [17, 26]. Yet, they need to be educated as far as keeping antibiotics for future use is concerned.

Beliefs

In all questions regarding students' beliefs on antibiotics, biomedical students have scored better with a statistical significance. This is in compliance with the hypothesis of this research, as the biomedical students should be more aware of the correct usage of antibiotics. In addition, they have done somewhat better than some studies in the proximate region of Southern Europe, such as the one in Italy [17]. In this study, 15% of students from a biomedical school reported approval of premature interruption of treatment, compared to 7.61% from Nis. Furthermore, a much lower number of biomedical students from Nis reported that antibiotics had no side-effects (1.08%) than in South India, whereby as much as 15.5% considered antibiotics to be universally safe drugs [9].

Nevertheless, in the group of non-biomedical students, relatively satisfactory answers have been reported. However, it is worrying that as much as 20.48% consider that therapy may be interrupted as soon as the symptoms fade out, neglecting possible surviving pathogens. Therefore, they appear unaware that, in order to obtain the complete effect of the prescribed medication, the full dose must be taken. This can be explained by the fact that antibiotics often display the desired result before the entire treatment is complete [3, 4]. Similar numbers were reported by studies in developing countries, such as Sudan [18].

Habits

Despite the fact that the biomedical students were better informed about antibiotics, as seen in the *Knowledge* section, and that they have demonstrated results that are as good as or even better than those of their peers in comparable countries, the habits seem to be more or less same in both groups.

Statistical difference was found in answers to the question regarding the acquisition of antibiotics with no prescription, where as much as 67.39% of biomedical students reported doing so, compared to 48.1% of non-biomedical students. This can be linked to the fact that the biomedical students may consider themselves informed enough to take the matter in their own hands. Similar numbers were reported in Qatar [22]. However, a much more promising result was noted in Malaysia [16], where only 11.3% of students from non-biomedical faculties have reported acquisition without a prescription.

Another statistical significance was found in answers to the question on the instruction manual and expiry date. A larger percentage of biomedical students reported that they check them regularly (80.43%) in comparison to non-biomedical students (62.05%). The rational behaviour is in compliance with a study from Sudan [18].

The reasons that students take the antibiotics on their own are also different between the groups. A part of biomedical students considers themselves informed enough to decide on the usage of antibiotics (34.24%). Also, a larger percentage of biomedical students have reported it hard to reach a doctor. The numbers show that students from non-biomedical faculties tend to put more faith in their previous experience with the drug. A larger

percentage (30.72%) keeps the antibiotic at home and one- fifth of participants return to the medicine they have had a good experience with. These numbers are more acceptable than those reported in China [25], where as much as 63% of students kept antibiotics at home. Also, in South Jordan [27], almost a third of interrogated parties reported that they would use antibiotics they already have.

Other questions have yielded no statistical significance. This is different than studies from Jordan [15], and the United Arab Emirates [10], where biomedical students have demonstrated better habits than their counterparts from other faculties. In any case, the general correct response rate moves between 50% and 60%. Around 60% report consulting their physician before using the medicines. Similar numbers were found in studies on the general public in Italy and Norway [11, 12], and drastically different to a study from Turkey, where as much as 89% reported using antibiotics on their own [28], as well as to a study from China [29], where just over a quarter stated they would consult their doctor. Around 55% of students have reported carrying antibiotics on holidays, implying they might reach out to them without consulting their doctor should they assess the situation as dangerous.

Around 21% have admitted to using alcohol during the treatment. This demonstrates their awareness of the side effects of alcohol usage during antibiotic therapy which includes inhibition of the drug's effect or even violent physical reactions when combined with certain antibiotics [30]. Numbers from Nis are better than ones reported in a study in Tamil Nadu, where 61.54% were aware of the fact [31]. Percentages of students who have made up for lost doses is similar (around 35%), and considerably better than the Sudanese study, where nearly half of the interrogated students reported constant making up for the missed doses [18]. Therefore, it is conclusive that students from this Serbian university tend to have similar habits regarding the usage of antibiotics.

Abovementioned numbers show that students from the University of Nis generally have better knowledge than some comparable groups when antibiotics come to question. Still, their practices are not satisfactory, despite their overall acceptable knowledge. A large percentage of the students take antibiotics on their own. Similarly, they seem to decide for themselves when to stop the dosage, with around half of interrogated students from both groups doing so. This means that the overall habits of the students should be improved.

Conclusion

The study has found that students of biomedical sciences possess better theoretical knowledge on the subject of antibiotics and their usage and effectiveness. In addition, their beliefs seem to be more rational. This is generally similar to studies conducted around the world. However, habits of the students are mostly the same across the range, without extensive linkages to their study course (with the exception of the acquisition of antibiotics without a prescription and checking the instruction manual of the drug). In general, percentages regarding their habits can be worrying in relation to the length of the treatment course and should be ameliorated with a campaign to better inform the students.

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Letter to the Editor

TELEMEDICINE DURING THE COVID-19 PANDEMIC: EXPERIENCE FROM AN ITALIAN OUTPATIENT CLINIC FOR MOVEMENT DISORDERS

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Abstract. *Patients with chronic diseases such as Parkinson's disease need periodic medical examinations. During the COVID-19 pandemic non-emergent medical visits were impossible. To ensure continuity of health care, telemedicine has been demonstrated to be a potential and useful tool.*

Key words: *COVID-19, Movement Disorders, Parkinson's Disease, Telemedicine.*

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly become a world pandemic [1]. The fear of coronavirus contagion has led to self-isolation and social distancing. In Italy, a hotspot of the pandemic, the COVID-19 infection spread within a few weeks from the initial foci (i.e. Codogno, a small town close to Milan, Lombardy) to the rest of the country [2]. In order to slow down the wave of infections, drastic governmental measures for containment of transmission were enacted. On March 8, 2020 a legal decree was issued, asking people of 16 North Italian provinces to stay indoors unless they need to buy food or medicine. These severe limitations to mobility were subsequently widened to the whole of Italy. Non-emergent surgical procedures and medical outpatient visits were also cancelled. However, patients with chronic diseases, such as Parkinson's disease (PD), need routine examinations for physical assessment and medication adjustments.

In this setting of COVID-19, telemedicine (TM) has been promoted and used to triage or monitor COVID-19 patients, reducing the risk of transmission, especially in the United Kingdom and the United States of America [3]. TM has already been suggested as a response to public health emergencies [4]. The functional definition of TM is medicine delivered over distance, whereby the communication can be in real-time (i.e. synchronous) or not (i.e. asynchronous) [5]. TM has been around in some form for many centuries and some authors relate the first use of TM to be when ancient civilizations sent smoke signals to warn other clans of a contagious illness outbreak [6]. Of course, TM has changed during the centuries, especially in the last decades due to significant and rapid improvement in the underlying enabling digital technologies. There are many different types of TM, and phone calls or video conferencing replacing in-person outpatient visits are only one kind of TM [5]. TM has been already used successfully for many different fields, for example in asthma care over distance [7] or for diabetic retinopathy screening [8]; the validity of TM to assess PD patients has been also well documented [9].

Our Movement Disorders Outpatient Clinic is located in the Hospital of Bolzano, which belongs to the Autonomous Province of South Tyrol in Northern Italy. Our clinic provides, for more than 1000 patients, access to three neurologists specialized in diagnosing and treating movement disorders for assessment and follow-up. Our team includes three nurses, one of which is a PD nurse specialist. Our clinic also provides opportunities for patients to participate in research studies related to movement disorders, characterized mainly by collaborative projects with other movement disorder outpatient clinics.

In order to guarantee continuity of medical care for our established patients during the COVID-19 pandemic, our ambulatory in-person appointments were immediately converted to phone calls. All patients who had scheduled an in-person visit for March or April 2020 were called by one of the three neurologists of our Movement Disorders Outpatient Clinic. In fact, no preselection of patients' suitability for TM had been performed; in case of patients with cognitive impairment or reduced ability to use technology, we directly contacted their caregivers.

We have made some interesting observations using TM. From March 10 until April 27, 2020 we called 150 patients from our Movement Disorders Outpatient Clinic. No phone call was refused, and all patients wished for a telemedical contact rather than a face-to-face consultation in order to avoid contact with potentially infected persons. In total, 165 telephone-calls were made, as some patients had to be called two (11 patients) or three times (2 patients). The mean age of the patients was 74 years (range: 45-96); 70 were females, 80 were males. Most patients (115) had the diagnosis of

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idiopathic PD or Parkinsonism, 18 patients suffered from essential tremor or other kinds of tremor, 14 patients had restless-legs syndrome, while the remaining 3 patients were affected with rare movement disorders (2 patients with Huntington disease, 1 patient with stiff person syndrome) (Table 1).

In nearly two thirds of the patients, clinical-therapeutic problems could be resolved during the telephone-call, and therefore the following out-patient visit could be scheduled for autumn. In 58 patients the phone call was not conclusive, and therefore an in-person visit was necessary as soon as possible (Figure1). The mean age of these 58 patients was 72 years and most of them, namely 52 patients, suffered from PD or Parkinsonism, 34 of which for more than 5 years. In 24 patients from this group, the current therapy was modified during the telephone-call; 35 patients were on medication with two or more Anti-Parkinson drugs. Thus, these aspects (severe movement disorder disease, polymedication, advanced age) associated to other comorbidities (e.g. arterial hypertension or diabetes mellitus) influenced the need for an in-person encounter.

In summary, despite one third of the 150 contacted patients of our Movement Disorders Outpatient Clinic needing an in-person visit, for the majority the phone calls were successful and could substitute the scheduled appointments. Of course, a phone-conversation is not the same as an in-person encounter and cannot replace an outpatient clinic, however, many of our patients seemed quite satisfied with the contact by telephone. This TM experience was also associated with satisfaction among our staff, permitting uninterrupted care of our patients, reducing the risk of SARS-CoV-2 transmission to other patients and ourselves and saving personal protective equipment. Finally, phone consultation worked without particular difficulties, and all patients were able to respond more or less immediately to the phone calls due to the lockdown introduced by the Italian government.

Certainly, we have identified the need to improve our telehealth technology in the near future, using video-conferencing instead of "simple" telephone-calls according to the practical guidance offered by the International Parkinson and Movement Disorder Society [10] and recommended by other movement disorders specialists [11], as video consultations would give us also the possibility to see the patient and to assess clinical features. However, for this pandemic there was no time for adoption of video conferencing solutions, mainly due to technical issues, such as installing a dedicated video software or web cameras on our and patients' computers. Unfortunately, we were also unprepared for video consultations because Italy does not include TM in the essential levels of care granted to all citizens within the National Health Service [3].

However, we should think about integration of TM within our health care system, guaranteeing, of course, a

Table 1 Demographic and clinical characteristics of the contacted patients

Total number and sex of pts.	Mean age of pts. (years)	Diagnosis with disease duration (>5 years) and PD polymedication (≥ 2 drugs) (number of pts.)
150	74 (range 45-96)	PD/Parkinsonism: 115; > 5 years: 76; ≥ 2 drugs: 67
70 females	75 (range 45-96)	ET/tremor: 18; > 5 years: 11
80 males	73 (range 45-93)	RLS: 14; > 5 years: 9
		HD: 2; > 5 years: 1
		SPS: 1; > 5 years: 1

Abbreviations: pts.: patients; PD: Parkinson's disease; ET: essential tremor; RLS: restless-legs syndrome; HD: Huntington disease; SPS: stiff person syndrome

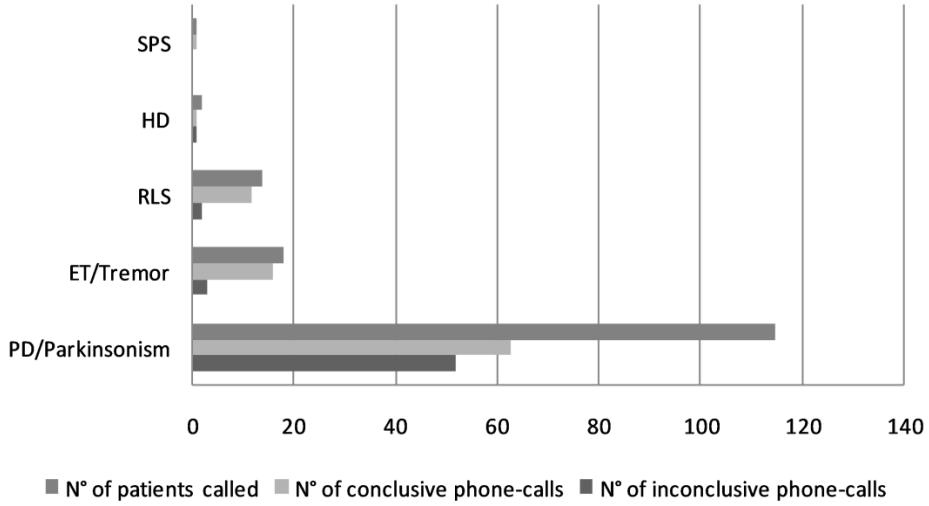

Fig. 1 Outcome of phone-calls during COVID-19 pandemic
Abbreviations: SPS: stiff person syndrome, HD: Huntington disease, RLS: restless-legs syndrome, ET: essential tremor, PD: Parkinson's disease

high-quality standard. Furthermore, after the current COVID-19 pandemic emergency TM might be considered a useful supplementary tool for our outpatient clinic, especially for established patients who are fragile, who have significant difficulties of moving around and who need to be accompanied by a caregiver. In these cases, the utilization of TM would save travel-costs and caregiver work-days, providing a positive effect also on the economy and on the environment. Of course, implementing TM takes time and does not happen overnight. TM is highly complex and full of challenges, and its integration requires precise guidelines. Adequate technical equipment, including modern devices and a secure, high-speed Internet connection, is needed, which must be available for everybody, and easy to use also by elderly patients, unless relatives are on hand to help. Other challenges of TM include legal aspects, payment, credentialing, ethical considerations and staff training. In conclusion, although the presence of the COVID-19 pandemic is a dramatic event, it is also an opportunity for us to implement TM and to change something in long established processes and routines in our medical health care system.

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