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The *International Journal of Medical Students* (IJMS) is a peer-reviewed open-access journal, related to share the scientific production and experiences of medical students worldwide.

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International Journal of Medical Students

Year 2020 • Months May-Aug • Volume 8 • Issue 2

Int J Med Students. 2020 May-Aug;8(2)

Table of Contents

International Journal of Medical Students

Year 2020 • Months May-Aug • Volume 8 • Issue 2

Int J Med Students. 2020 May-Aug;8(2)

Case Reports

Experiences

International Journal of Medical Students

Year 2020 • Months May-Aug • Volume 8 • Issue 2

Int J Med Students. 2020 May-Aug;8(2)

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

To Stay at Port or to Go to Sea: Are Clinical Clerkships a Double-Edged Sword During the COVID-19 Pandemic? Where Do We Go From Here?

Mihnea-Alexandru Găman,[1] Paul MacDaragh Ryan,[2] Francisco Javier Bonilla-Escobar.[3]

The ongoing pandemic has changed the way medicine is taught and learned. The unexpected challenges of the spread of SARS-CoV-2 worldwide have forced our educators to rethink in a rather narrow window of time the organization of medical education all around the globe. In many countries, clinical clerkships have been cancelled and medical students' access to university hospitals has been restricted. Lectures have been replaced by online courses and, in many instances, case presentations have replaced classical rotations in the hospital. Although it is not difficult to understand why these measures were put into practice, one is still left wondering: are clinical clerkships dispensable in the training of a future physician? Also, to what extent has the SARS-CoV-2 pandemic affected the work of residents and young researchers? In the current and previous issue of the *International Journal of Medical Students*, many of these topics are tackled in the *Experience* articles that we decided to publish with perspectives from countries including Italy,[1,2] China/Zimbawe,[3] Spain,[4] the United States,[5-10] Mexico,[11,12] India,[13-18] Pakistan,[19] Vietnam,[20] Saudi Arabia,[21] Canada,[22,23] Thailand,[24] Ecuador,[25] Nigeria,[26] Democratic Republic of Congo,[27,28] Ireland,[29,30] the United Kingdom,[31,32] South Africa,[33] Jamaica,[34] and Greece.[35,36]

Sir William Osler's quote *"he who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all"* is the *theme* of the latest issues of the *International Journal of Medical Students*. As a rhetorical question has arisen in the minds of all students in medicine worldwide: can we actually learn medicine without direct interaction with real patients? When we were younger and progressing through medical school, we sometimes had the delusion that digesting as much medical information as possible could be comparable to the knowledge which we accumulated during our hospital rotations. We were both right and wrong simultaneously. In certain instances, our individual reading enabled us to better grasp a subject and perhaps to establish a correct diagnosis when faced with a patient. However, much of medicine remains an apprenticeship and the day-to-day practicalities of clinical work cannot be effectively taught or learned through the same modalities. The transition from medical student to resident physician is a rather complicated task. One quickly discovers that taking care of a patient does not only require you to establish a correct diagnosis and an appropriate treatment plan, but also that it involves a great deal of time-consuming paperwork: completing medical charts, spending hours in front of the computer or on the phone to request blood tests, scheduling the patient for imaging or verifying whether the medication you prescribed is available in the hospital pharmacy. With the restriction or cessation of clinical rotations, the outgoing classes of 2021 may feel short-changed on the in-between learning from which their predecessors unwittingly benefited.

Just a couple of days ago one of the Editors was asked by a colleague in the internal medicine ward to visit a patient with influenza pneumonia (unsurprisingly, flu-like symptoms in the summer can actually reflect a diagnosis of influenza and not necessarily COVID-19). The patient also has new thrombocytopenia and no signs of bleeding. What was the origin of the hematological finding? Could it be secondary to the viral infection? Could it be immune thrombocytopenia? Or does this sudden decrease of the platelet count hide a more severe diagnosis, i.e. cancer?[37-42] It is clear that the actual presentations of patients we see every day are far from the "textbook cases" we were versed on during our undergraduate training. Although the cancellation of clinical clerkships was decided in order to prevent the spread of SARS-CoV-2, as well as to reduce the unnecessary use of limited personal protective equipment, we wonder how our future colleagues will adapt to these changes and what will be the sequelae of these decisions. Medical educators are currently struggling between their duty to protect their students from unnecessary harms and their duty to educate the clinicians of tomorrow; to stay at port or to go to sea.

Medical academics will require rapid innovative thinking and continued determination to identify potential solutions to address unavoidable training deficiencies which are likely to arise as a result of these difficult times, since the lack of clinical clerkships will impact the education of medical students in a range of foreseeable and unforeseeable manners. In line with this, we believe that it has never been so important to provide a platform to present the unexpected ways in which the lives and training of medical students, residents, senior physicians, members of academia and researchers worldwide have all been affected by the SARS-CoV-2 pandemic.[43]

In this issue, we are sharing not only the experiences of colleagues from all over the world, but the results of a survey to identify perceptions of how the current lockdowns have affected students' learning process,[44] important reviews on COVID-19,[45] including the potential effects of probiotics in the disease,[46] and a case report of a patient with gastrointestinal symptoms as the main manifestation.[47] This last article kept us wondering about a public health problem that is yet to come if it is proven that the virus can spread in stools, especially for those regions of the world highly affected by disparities and low- and middle-income countries.[48] As always, we are also publishing about general medicine topics. You will find original articles about the effects of schoolbags weigh in children,[49] prognostic factors for mortality of rocky mountain spotted fever,[50] the association of acute liver failure with heat stroke,[51] gene variants in major depressive disorder in patients with childhood trauma,[52] novel biomarkers in Alzheimer's disease,[53] and the description of artifacts in electrocardiograms due to neurostimulators.[54]

Correspondence:

Mihnea-Alexandru Găman

Address: Bulevardul Eroii Sanitari 8, Bucureşti 050474, Romania

Email: mihneagaman@yahoo.com, scientific.editor@ijms.info

Affiliations:

1 MD, PhD student. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania. Scientific Editor, International Journal of Medical Students (IJMS)

2 MB BCh BAO PhD. Cork University Hospital, University College Cork, Cork, Ireland. Deputy Editor, IJMS.

3 MD, MSc, PhD(c). University of Pittsburgh, Pittsburgh, USA. Universidad del Valle, Cali, Colombia. Science to Serve the Community Foundation, SCISCO Foundation / Fundación SCISCO. Editor in Chief, IJMS.

Our missions of spreading science does not end with the publication of an issue.[43] Systemic racism continues to prevail in the face of the blinding spotlights which have been drawn upon it in the recent months. In an *Experience* article in this issue, Pak and colleagues explore the origins of SARS-CoV-2 and draw conclusions of the detrimental consequences intended by the use of xenophobic terms,[9] which are banned from the *International Journal of Medical Students*.

In these difficult times where science has been put on test by the general public and especially politicians, we close this *Editorial* with a call for decisions makers to listen to science. No vaccines should be administered without the proper research.[55] We cannot go back before the Nuremberg Code (1947). Even governors and people in power should follow ethical principles when dealing with human lives.

The *Journal* remains a global forum for medical trainees of all nations. As such, we will continue to play a central role in promoting accurate and respectful scientific dialogue, in an effort to combat misinformation and xenophobic rhetoric.

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Original Article

Effect of Schoolbag Weight on Musculoskeletal Pain among Primary School Children in Yaounde, Cameroon: A Cross-sectional Study

Wiliam Richard Guessogo,[1] Peguy Brice Assomo-Ndemba,[2] Edmond Ebal-Minye,[1] Jerson Mekoulou-Ndongo,[3] Claude Bryan Bika-Lélé,[3] William Mbang-Bian,[1] Eva Linda Djuine-Soh,[1] Jean Bertrand Ondoa,[1] Samuel Honoré Mandengue,[3] Abdou Temfemo.[4]

Abstract

Background: Heavy schoolbags are known to cause health problems for school children. The aim of this study was to determine the effects of carrying heavy schoolbags on the musculoskeletal pain among primary school children of the two subsystems in Yaounde, Cameroon. **Methods:** A cross-sectional study was carried out in primary schools in Yaounde. A total of 457 school children (8.2±2.2 years) were included, 202 from the French-speaking subsystem, and 255 from the English-speaking subsystem. Parameters studied included weight, height, and schoolbag weight. A questionnaire was used to collect socio-demographic information and potential musculoskeletal pain in three regions: back, shoulders, and neck. **Results:** The mean weight of children and their bags was 28.4±8.2 kg and 5.2±2.3 kg respectively. More than 50% of school children in the two subsystems carried a schoolbag weighing more than 15% of body weight. The back (38%) was the least affected area in comparison to the shoulders (58.6%) and neck (42.4%) ($p<0.001$). Carrying heavy bags and walking to school was associated with pain in the back, shoulders, and neck. School children in the French-speaking subsystem had lower risk (adjusted odds ratio 0.438, 95% confidence interval=0.295-0.651; $p<0.001$) to develop a sore neck compared to peers from the English-speaking subsystem. **Conclusion:** Carrying heavy schoolbags is associated with musculoskeletal pain in schoolchildren. The means moving to and from school is a main risk factor of developing musculoskeletal pain. French-speaking school children develop less neck pain than English-speaking school children.

Key Words: Weight-Bearing; Musculoskeletal Pain; Primary School; Cameroon (Source: MeSH-NLM).

Introduction

Excessive schoolbag weight is a health problem commonly reported in the pediatric age group.[1] Carrying heavy schoolbags is associated with a multitude of body biomechanical afflictions or disorders such as changes in the sagittal plane in posture and balance, spinal curvature, consistency of repositioning and musculoskeletal discomfort.[2-7] The particular situation of musculoskeletal pain is the basis of studies investigating the relative weight limit of schoolbags which has less impact on the imbalance of physiological and biomechanical functions.[2-7,8]

Previous studies showed that schoolbags should be within acceptable limits of 10-15% of a child's body weight to avoid musculoskeletal pain.[1,8-14] Secondary school children are a target group at risk for musculoskeletal pain because of the maximum development of the appendicular skeletal system that occurs especially during puberty.[15,16] Other studies conducted in the population of primary school pupils revealed negative effects on the musculoskeletal system associated to heavy schoolbag carriage.[6,17-22] In addition, considering the musculoskeletal development of school-age in children, the schoolbag weight and the negative consequences of heavy loads can lead to problems in the development of the spine.[23-26] Studies reported that the development of back pain in children can increase the risk of developing chronic back pains in adulthood.[27,28]

Items contributing to the weight of schoolbags include school manuals, and additional items such as afternoon tea, bottles of water, sports equipment, and jackets.[29]

Unfortunately, despite the negative consequences of carrying heavy schoolbags on the children's health,[2-7] to our opinion, this situation does not seem to worry parents and school officials. It is still accepted today that the weight of the backpack should be further reduced in order to limit the prevalence of back pains in children;[30] and with this regard many studies have been conducted in a variety of educational systems.[1,2,6,8,9,18,20,21,29,31-33]

In Cameroon, the educational system is bilingual, and is subdivided into two sub-systems: French-speaking and English-speaking. In November 2017, the Government recommended and prescribed one schoolbook per subject matter instead of the multiple books per subject as it was previously. Before this Government decision, the mean number of textbooks per student was 13 in Cameroon, whereas the average in Africa was 8.5.[34] One of the objectives of this prescription was to prevent health risks associated with increasing volume and weight of schoolbag.

Since this Government decision, no scientific investigation in our knowledge has been carried to evaluate the current impact of the weight of the schoolbag on musculoskeletal pain in Cameroon.

[1] National Institute of Youth and Sports, Yaoundé, Cameroon.
[2] Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, Cameroon.
[3] Exercise and Sport Physiology and Medicine Unit, Faculty of Science, University of Douala, Cameroon.
[4] Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Cameroon.

Degrees: [1]. PhD; [2]. MD, PhD; [3]. PhD; [4]. PhD; [5]. PhD; [6]. MSc; [7]. MSc; [8]. MSc; [9]. PhD; [10]. PhD.

About the Author: *Assomo-Ndemba is a MD of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde 1, Cameroon.*

Correspondence:
Abdou Temfemo
Address: Carrefour Ange Raphaël, Douala, Cameroon
Email: temfemo@hotmail.com

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The purpose of this study was to determine the effects of carrying a heavy schoolbag on the musculoskeletal pain among primary school children in the English-speaking and French-speaking educational systems of Cameroon.

Methods

Study design

A cross-sectional study was conducted in primary schools of the two subsystems in Yaounde, the Capital of Cameroon, during the first term 2017/2018 school year.

Sampling

In Cameroon, the two sub-systems (French-speaking and English-speaking) operate independently, particularly on the aspect of training programs, with specific books and schedules used in each sub-system. According to the authorization of the Regional Delegate of the Ministry of Basic Education, we used a non-probability sampling method of convenience to investigate. In each school, one class per level of study (6 levels) was chosen. In order to avoid any interference, the administration of each school randomly selected one class per level in the three classes that comprises each level, using the draw method from the list of classes. The school administration was not informed of the purpose of the study. All school children of both sexes attending the day of collection, able to walk and wear their schoolbag independently were included in the study. According to their medical information available in the administration, school children who were diagnosed by a medical doctor as having spinal and musculoskeletal problems such as leg length discrepancies were excluded.

Data collection

The body weight and schoolbag weight were measured using the same Tanita BC 532 electronic scale (Tokyo, Japan) placed on a flat and hard surface, calibrated before the start of data collection. The weight of each participant was first measured without schoolbag, then after, carrying his schoolbag, to obtain the total weight. The difference of the two weights was recorded as the schoolbag weight, and then, the schoolbag weight percentage compared to body weight was determined. The height was measured using a Graduated scale Mark Seca (Hamburg, Germany).

A questionnaire developed for the study and deriving from the Standardized Nordic Body Map Questionnaire was used to collect additional information. The questionnaire was administered and each student answered, if necessary, with the help of the investigator. This study tool consisted of a self-administered questionnaire translated in French and in English, the two official languages spoken in Cameroon. The tool was pre-tested in order to simplify the language of the questions. A diagram was introduced to indicate the body parts to report the pain. The questionnaire included: the mean of moving to and from school and the location of musculoskeletal pain.

Data analysis

Data were entered into an Excel spreadsheet (Microsoft Office 2016) before being exported to the statistical analysis software StatView 5.0 for windows (SAS Institute, Inc., IL, USA). Categorical variables were presented as frequency and percentage while continuous variables were presented as mean ± standard deviation (SD). The schoolbag weight as percentage of body weight (%BW) was classified into those with ≤10% BW, those with BW located from >10% to ≤15%, and those with >15% BW. The descriptive statistics were used to determine the anthropometric characteristics of the participants, the number of school children in each category of schoolbag weight as percentage of body weight, and the prevalence of pain symptoms in different regions of the body. The unpaired Student t-test was used to compare the mean schoolbag weight among school children in the two educational subsystems as well as the characteristics of the participants.

A Pearson chi square test ($\chi 2$) was used to compare percentages of participants in different categories of schoolbag weight to body weight. Multivariate logistic regression was used to identify factors associated with the presence/absence of pain on different body regions (back, shoulders and neck). The outcome variable was the presence of pain on the body region of interest and the independent variables (factors) included gender, age, educational system, means of transport and %BW. Adjusted values of odd ratio (aOR) along with their confidence interval at 95% (95% CI) and level of significance were computed. A log-transformed value of likelihood was used to appraise the goodness-of-fit of each logistic regression model. Statistical significance was set at p-value < 0.05.

Ethics Clearance

The current study received the approval of the National Committee of Ethics for Scientific Research and was conducted in conformity with the recommendations of the Declaration of Helsinki revised in 1989. Access into schools was authorized by the Regional Delegate of the Ministry of Basic Education. An informed written consent form including the description of the study and its importance was distributed to school children to obtain parental consent.

Results

Characteristics of participants

A total of 457 school children (50.6% boys) were included; 202 (44.2%) from the French-speaking subsystem and 255 (55.8%) from the English-speaking subsystem. The mean age, body height, body weight and body max index (BMI) of participants were 8.2 (± 2.2) years, 132.3 (±14.4) cm, 28.4 (±8.2) kg and 16.1 (± 2.9) kg/m² respectively.

No difference was found in the characteristics between boys and girls in both educational subsystems (***Table 1***).

Table 1. Sociodemographic and anthropometric characteristics of participants

Educational System	Gender	n	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m²)
French-speaking	Boys	100	8.1±2.3	132.4±16.4	30.2±9.9	17.1±3.9
	Girls	102	7.8±2.3^{NS}	131.0±15.6^{NS}	28.4±8.8^{NS}	16.3±3.3^{NS}
English-speaking	Boys	129	8.6±2.0	133.3±12.8	28.2±6.7	15.9±1.7
	Girls	126	8.3±2.1^{NS}	132.2±13.3^{NS}	27.3±7.6^{NS}	15.4±2.2^{NS}
Total		457	8.2±2.2	132.3±14.4	28.4±8.2	16.1±2.9

Legend: BMI = Body mass index; Educ. Syst. = Educational system. ^{NS}= Non significant difference between boys and girls.

Schoolbag weight to body weight

The mean schoolbag weight in the whole sample was 5.2 (±2.3) kg, ranging from 1.2 kg to 14.8 kg with no significant difference in the French-speaking subsystem (5.6 ± 2.2 kg, ranging from 1.2 kg to 11.0 kg) compared to the English-speaking subsystem (5.1 ± 2.4 kg, ranging from 1.6 kg to 14.8 kg). The majority of students (62.30%) belonged to the category >15%, both in the French-speaking (67.32%) and English-speaking subsystems (58.43%) (***Table 2***).

Musculoskeletal pain

A total of 174 (38.1%) participants reported pain at their back and 194 (42.4%) at the neck. But, 58.6% of them reported having pain at the shoulders. The prevalence of pains was significantly different in the back (p = 0.0091) and the neck (p = 0.0284) in the different category percentages of body weight. Self-reported pains at the back, shoulders and neck across schoolbag weight related to body weight are detailed in ***Table 3***.

Risk factors

In relation to risk factors, children whose schoolbag weight was >15% of their body weight were almost 4 times more likely to develop neck pain compared to those whose schoolbag weight was <10% of their body weight (aOR = 3.56, 95% CI = 1.38 - 9.21, p = 0.008) (***Table 4***).

Except from the mean of moving to and from school, the other variables (gender, age, educational system) were not significantly associated, with the risk of developing localized pain at the back, shoulders and neck. Children who moved using public car transport to school were less likely to develop musculoskeletal disorders at their back (aOR = 0.40, 95% CI: 0.27-0.60, p < 0. 001), shoulders (aOR = 0.48, 95% CI = 0.32-0.72, p = 0.0004) and neck (aOR = 0.56, 95% CI = 0.37-0.83, p = 0.0043) compared to those walking to school. Moreover, school children who were enrolled in the French-speaking subsystem were less likely (aOR = 0.44, 95% CI = 0.30-0.66, p < 0.001) to develop a sore neck compared to those in the English-speaking subsystem (***Table 4***).

Table 2. Distribution of school children by schoolbag weight as percentage of body weight

Characteristic	Total (n=457)	Educational system		p-value
		English-speaking (n=255)	French-speaking (n=202)	
SBW (kg)	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**	
	5.2 (±2.3)	5.1 (±2.4)	5.6 (±2.2)	0.0282
%BW	**n (%)**	**n (%)**	**n (%)**	
≤ 10%	29 (6.4)	17 (6.66)	12 (5.94)	0.8875
>10% to ≤15%	143 (31.3)	89 (34.90)	54 (26.73)	0.0769
> 15%	285 (62.3)	149 (58.43)	136 (67.32)	0.064

Legend: SBW = Schoolbag weight.

Table 3. Prevalence of pain symptoms in different regions of the body

Regions and symptoms	Total	Schoolbag weight (kg)			X^2	p-value
		≤ 10% n (%)	>10% to ≤ 15% n (%)	> 15% n (%)		
Back						
NO	283 (61.9)	18 (62.1)	105 (71.9)	160 (56.7)	9.40	0.0091
YES	174 (38.1)	11 (37.9)	41 (28.1)	122 (43.3)		
Shoulders						
NO	189 (41.4)	14 (48.3)	66 (45.2)	109 (38.7)	2.31	0.3144
YES	268 (58.6)	15 (51.7)	80 (54.8)	173 (61.3)		
Neck						
NO	263 (57.6)	23 (79.3)	87 (59.6)	153 (54.3)	7.12	0.0284
YES	194 (42.4)	06 (20.7)	59 (40.4)	129 (45.7)		

Table 4. Risk factors for musculoskeletal symptoms in the back, neck and shoulders.

Variables	Back		Shoulders		Neck	
	aOR (95% CI)	P-value	aOR (95% CI)	P-value	aOR (95% CI)	p-value
Gender						
Girls	1		1		1	
Boys	1.02 (0.69 - 1.51)	0.927	1.19 (0.81 - 1.74)	0.381	1.35 (0.92 - 2.00)	0.128
Age (years)	1.05 (0.95 - 1.15)	0.334	0.97 (0.89 - 1.07)	0.574	1,05 (0.96 - 1.15)	0.295
% Body Weight						
≤10	1		1		1	
>10 to ≤15	0.58 (0.24 - 1.37)	0.212	1.12 (0.49 - 2.53)	0.788	2.62 (0.98 - 6.95)	0.053
>15	1.19 (0.53 - 2.70)	0.670	1.48 (0.67 - 3.25)	0.327	3.56 (1.38 - 9.21)	0.008
Educational System						
English -speaking	1		1		1	
French-speaking	1.24 (0.83 - 1.84)	0.301	1.52 (1.03 - 2.25)	0.003	0.44 (0.30 - 0.66)	<0.001
Mean of transportation						
Feet	1		1		1	
Public car transport	0.40 (0.27 - 0.60)	<0.001	0.48 (0.32 - 0.72)	0.0004	0.56 (0.37 - 0.83)	0.0043

Legend: aOR = adjusted Odds Ratio; CI = Confidence Interval

Discussion

The objective of the current study was to investigate the association between schoolbag weight and musculoskeletal pain among Cameroonian school children.

We found that the average percentage of the schoolbag weight relative to the body weight of the school children was well above the recommended limits (10-15%)[12] in the two Cameroonian educational sub-systems. In addition, musculoskeletal pain was common in school children sample with a high prevalence of back pain compared to the neck pain and shoulders pain. Our study showed that the average of schoolbag weight in the whole population is close to what is reported by other authors.[9,27,35] Nevertheless, this value is higher than those found by Mwaka et al.[1], Dianat et al.[19], and Furjuoh et al.[36] On the other hand, the value obtained in school children in the present study is lower than that reported by Ibrahim[31] and Dorji et al.[37] This disparity in schoolbag weight in these different studies could be explained by differences in curricula in each country, by levels of development, and by behavioral and cultural differences between countries.

A possible reason for this increase in the average of schoolbag weight found in our study compared to the norms would be the particular context of the textbook policy in Cameroon. Indeed, the Government published in November 2017 a text fixing for each subject matter one textbook, but, to our observation of the educational environment, there is persistent violation and non-respect of this regulation, leading to an increase the weight of the schoolbag.

The percentage of the weight of the schoolbag relative to the body weight of school children was higher in the French-speaking subsystem compared to the English-speaking subsystem. Usman et al.[38] reported a slightly higher value among school children in Karachi, Pakistan. On the other hand, the percentage obtained in our study is higher than those obtained by some authors.[1,9,18,35] Some authors noted percentages close to the recommended standard, like Al-Hazzaa[33] and Grimmer et al.[39]

The results of our study revealed a higher proportion of school children (67.3%) in the category › 15% of body weight in the French-speaking subsystem. This observation justifies the fact that for a decade in Cameroon, there was a gradual loss of interest in the French-speaking subsystem in favor of the English-speaking subsystem. Indeed, the English-speaking subsystem is characterized with an earlier specialization of the studies, and leads to a reduction of the number of textbooks. This result is consistent with the one generally observed in many studies,[17,19,36] thus explaining the difference in educational systems and curricula. This result may also account for the low proportion of musculoskeletal symptoms in the participants of our study compared to some similar studies where the percentages was generally high i.e. more than 60%.[6,16,19,37]

The analysis of the adjusted odds ratio showed that the risk of developing musculoskeletal symptoms was higher for school children in categories ›10% to ≤15% and ›15% and this in the French-speaking subsystem compared to the English-speaking subsystem ($p < 0.001$). There was no significant difference in gender. This result justifies the governmental measures in the field of school policy that took place in November 2017 in Cameroon, which prescribed a single textbook per subject. The back was the least affected zone in comparison to the shoulders and neck ($p < 0.001$). This result joins the observations of Yamato et al.[40] who in their review did not find an objective link between the symptoms at the back and the weight of the schoolbag. According to these authors, the appearance of pain in this region is much more perceptive.

In the analysis of other factors determining the occurrence of musculoskeletal disorders, only the means moving to and from school was significantly associated with the risk of developing localized pain in the back, shoulders and neck ($p < 0.01$). School children who moved to school using public car transport were less likely to develop musculoskeletal symptoms.

Recommendations

Compliance with the Government circular on textbooks that prescribed one schoolbook per subject matter instead of the multiple books by subject as it was previously is recommended.

Limitations

First, the limited sample size cannot allow a generalization of the results at National level. On the other hand, the results obtained may be different if we take into account rural regions where access to the textbook is limited. Second, there is also the cross-sectional nature of the study which does not allow reliable conclusions on the causal link. Third, only few risk factors for musculoskeletal pain were studied. Future studies should highlight the long-term effects of schoolbag weight on musculoskeletal pain and many other risk factors should be investigated.

Conclusions

The schoolbag weight is high in the Cameroonian education system compared to international standards and is associated with common musculoskeletal pain. Carrying heavy schoolbag is associated to musculoskeletal pain in school children. The means moving to and from school is a main risk factor of developing musculoskeletal pain. French-speaking school children develop less neck pain than English-speaking school children.

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Author Contributions

Conceptualization: WRG & PBAN. Data Curation, Methodology, Resources & Validation: WRG, PBAN, EEM, JMN, CBBL, WMB, ELDS, JBO & AT. Formal Analysis, Project Administration, & Supervision: WRG, PBAN, SHM & AT. Investigation: WRG, PBAN, ELDS & JBO. Visualization: WRG, PBAN & CBBL. Writing – Original Draft Preparation: WRG, PBAN, EEM, SHM & AT. Writing – Review & Editing: WRG, PBAN, SHM & AT.

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Original Article

Survey Among Medical Students During COVID-19 Lockdown: The Online Class Dilemma

Andrew Thomas,[1] Mohan T. Shenoy,[2] Kotacherry T. Shenoy,[3] Sruthi Suresh Kumar,[1] Aboobakker Sidheeque,[1] C. Khovidh,[4] Jayakumar Parameshwaran Pillai,[5] Pramod Murukan Pillai,[6] Shana Sherin C. H,[7] Anna Mathew,[8] Twinkle Zakkir,[9] Sreelakshmi Dileep,[10] Victory Mekha,[11] Sony Raju,[12] Mohammed Junaid K.,[13] Sivendu P.[14]

Abstract

Background: In view of COVID-19 lockdown in India, many colleges started online classes. This study aimed to evaluate the attitudes of, and the factors affecting, medical students attending online classes during lockdown. **Methods:** We designed an online questionnaire with open-ended, close-ended, and Likert scale questions. Links to the questionnaires were shared with the medical students who have attended at least one online class during the COVID-19 lockdown period. Respondents were 1061 participants from 30 medical colleges from the states of Kerala and Tamil Nadu in India. **Results:** The majority of students – 94% (955/1016) – used smartphones to attend online classes. ZOOM/ Skype – by 57.1% (580/1016) – and Google platforms – by 54.4% (553/1016) – were commonly used. Learning at leisure – 44.5% (452/1016) – was the top reason why students liked online classes, whereas network problems – 85.8% (872/1016) – was the top reason why students disliked them. Lack of sufficient interaction – 61.1% (621/1016) was another reason why students disliked online learning. More than half the participants – 51.7% (526/1016) – did not want to continue online classes after COVID-19 lockdown. More students – 55% (558/1016) – favored regular classes than online classes. **Conclusion:** Students in our survey did not seem favorably disposed to online classes. Network problems experienced by students should be addressed. Furthermore, teachers should try to make the classes more interactive and educational institutions should address the problems pointed out by the students in order to make online classes more effective in the future.

Key Words: COVID-19; Lockdown; Cross-sectional survey; Undergraduate medical education; Medical students (Source: MeSH-NLM).

Introduction

Coronavirus disease (COVID-19) has been reported in 216 countries and has affected more than 5.4 million people[1]. The World Health Organization (WHO) on March 11, 2020 declared this disease to be a pandemic[2]. The first case of COVID-19 in India was confirmed on January 30, 2020[3]. In order to contain the spread of disease, India declared a national lockdown starting from 24 March, 2020[4]. Even with increased pathogen exposure, additional working hours, stigma and violence, health care workers still continue to be on the front line for preventing and treating COVID-19 disease. Educational institutions were shut down because of the lock-down; however, many medical students all around the world were involved in voluntary duties to control COVID-19. Colleges started online classes to ensure continuity of education. India is not new to online education. Study Webs of Active-Learning for Young Aspiring Minds (SWAYAM), an integrated web portal, conducts online education from the high school to the university level[5]. However, being a developing country, many areas of India lack reliable network and internet coverage. Many students cannot simply afford the extra cost and equipment needed to utilize online learning to its full potential.

Medical undergraduate education (MBBS) is a four and a half years program with one-year compulsory internship in hospitals. With 542 medical colleges and with a capacity of almost 79,000 medical students[6], updated competency-based curriculum requires students to acquire experience in various practical skills. Understanding complex pathologies and procedures demands more interaction and discussions with teachers. This is not possible without clinical rotations. The final year undergraduates spend most of their time on hospital wards, perfecting their history-taking and examination skills prior to university exams.

The use of technology in education is inevitable and online education seems to be the only logical solution during lockdown. From creating emails and connecting via WhatsApp groups, now communication is mainly by web-based live video conferencing platforms (WebEx, Skype, Zoom, Microsoft Teams), and teaching web platforms (Moodle, Google Classrooms). The success of online education depends on addressing the disparity across learning resources, use of technology, communication tools and the ability to understand information from sources like computers and mobile phones[7,8]. A systematic review and

[1] Medical student, Sree Gokulam Medical College and Research Foundation, Trivandrum, India
[2] MBBS, MD, DM. Department of Endocrinology, Sree Gokulam Medical College and Research Foundation, Trivandrum, India
[3] MBBS, MD, DM, FRCP. Head of Department of Gastroenterology, Chairman of Institutional Research Cell (IRC), Sree Gokulam Medical College and Research Foundation, Trivandrum, India
[4] Medical student, SRM Medical College Hospital and Research Centre, Chennai, India
[5] MSc. Department of Biochemistry, Government Medical College, Trivandrum, India
[6] Medical student, Sree Narayana Institute of Medical Sciences, Ernakulam, India
[7] Medical student, Believers' Church Medical College, Thiruvalla, India
[8] Medical student, Pushpagiri Medical College, Thiruvalla, India.
[9] Medical student, Travancore Medical College, Kollam, India
[10] Medical student, Government Medical College, Kannur, India
[11] Medical student, Malabar Medical College Hospital and Research Centre, Calicut, India
[12] Medical student, Government Medical College, Thrissur, India
[13] Medical student, Al Azhar Medical College & Super Specialty Hospital, Idukki, India
[14] Medical student, KMCT Medical College Hospital, Calicut, India

About the Author: *Andrew Thomas is currently a final year medical student of Sree Gokulam Medical College and Research Foundation, Trivandrum, India. He is also a recipient of Short-Term Studentship 2019 by ICMR (Indian Council of Medical Research), Best paper award at NATCON 2019, Government medical college, Trivandrum.*

Correspondence:
Andrew Thomas
Address: Aalamthara - Bhoothamadakki Rd, Venjarammoodu, Kerala 695607, India
Email: drandrewthomasj@gmail.com

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meta-analysis from China in 2019 that included 16 articles observed no significant differences between online and offline learning. Furthermore, post-test test scores even showed significant improvement among students who took online learning[9]. A survey of online class participants would give us an idea of which areas to concentrate upon. With this rationale, we collected the opinion of medical students who have attended the online classes and their perceptions on continuing online classes in the "new normal" era.

Methods

We conducted a cross-sectional survey using Google forms. A semi-structured questionnaire comprising 25 questions was pilot-tested for the content and structure. Undergraduate medical students who attended at least one online class were included in the study. This study was approved by the Institutional Research Cell (IRC) and the Institutional Ethical Committee (IEC) of Sree Gokulam Medical College and Research Foundation, Kerala.

Questionnaire

The questionnaires were self-administered in English using Google Forms (Google LLC, CA, and U.S.A.). It was distributed among WhatsApp groups (WhatsApp Inc, CA, U.S.A.) of students among medical colleges in the states of Kerala and Tamil Nadu. The questionnaire was available online for 48 hours (from May 03, 2020 to May 05, 2020). All the participants were informed about the aims, benefits and implication of the study and consent was obtained before starting the survey. A restriction on the number of responses from a single email-address was enforced to prevent duplicate responses from the participants. Completed data as obtained in Google forms with response rate was 100%.

The questionnaire comprised of four sections: the first section included socio-demographic details (gender, semester, government or private college, and pin code of the college). The second section included details on online classes they attended over the last 14 days (April 18, 2020 to May 02, 2020). These included types of devices, platforms used by students and duration of classes. The third section was on the students' perception of online classes. A five-point Likert scale[10] was used to determine the perception of audio, video quality, content, inter-activeness and discussion of doubts. The responses were categorized into five: very poor, poor, neutral, good and excellent. The fourth section was on students' like and dislike; suggestions and practice. We encouraged participants to select multiple answers for questions on likes and dislikes, devices, platforms, practice and suggestions. The data was extracted from the Google forms and analyzed using SPSS version 25 (Statistical Package for the Social Sciences, SPSS Inc, U.S.A) to compare the outcome of private institutions with that of government institutions.

Results

Self-declared information from 1016 students from 30 medical colleges from the states of Kerala and Tamil Nadu were included. All participants who entered the survey responded to each question. Answers on likes and dislikes, devices, platforms, practice and suggestions for online classes had considerable overlap. Gender and semester distributions are represented in ***Table 1***. The majority of responders – 443 (43.6%) – were from the sixth and the eighth semesters ***(Table 1)***.

Characteristics of Online Classes *(Figure 1)*

Most students – 955 (94%) – used smart phones. ZOOM/ Skype and Google platforms were used by 580 (57.1%) and 553 (54.4%) students respectively. The majority – 667 (65.6%) – of the students had one to four hours of online classes per day. A total of 945 (93%) attended classes lasting less than two hours.

Table 1. Distribution of participants by Gender, Semester in Government and Private Medical Colleges.

Variables		Government Medical college		Private Medical college		Total		p-value
		N	%	N	%	N	%	
Gender	Male	74	41.1	269	32.2	343	33.8	0.021
	Female	106	58.9	567	67.8	673	66.2	
Semester	First and Second (1st year)	85	47.2	154	18.4	239	23.5	
	Third semester	3	1.7	60	7.2	63	6.2	
	Fourth semester	4	2.2	89	10.6	93	9.2	
	Fifth semester	2	1.1	51	6.1	53	5.2	<0.001
	Sixth semester	13	7.2	172	20.6	185	18.2	
	Seventh semester	5	2.8	46	5.5	51	5	
	Eighth semester	65	36.1	193	23.1	258	25.4	
	Ninth semester	3	1.7	71	8.5	74	7.3	

Figure 1. Comparison of Private Medical College vs. Government Medical College in Terms of: A. Devices; B. Platforms; C. Duration of Classes per Day; D. Duration of Average Class

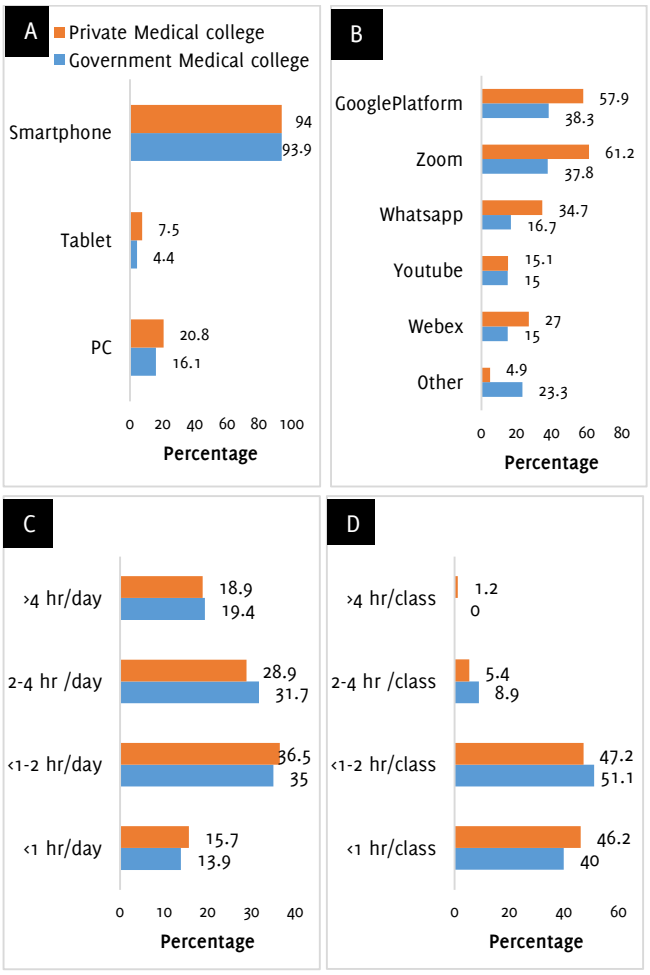


Figure 2. Participants' Perception: A. Rating B. Preference C. Whether to Continue Online Class after Lockdown.

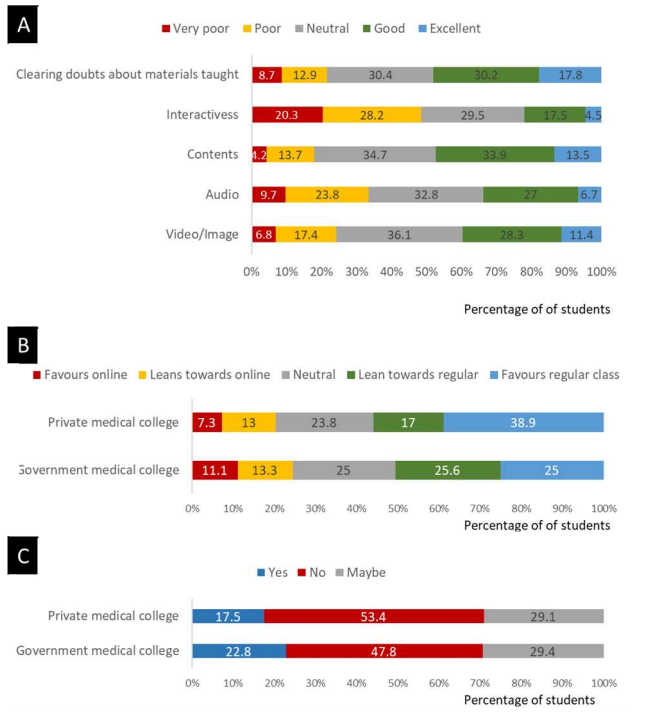
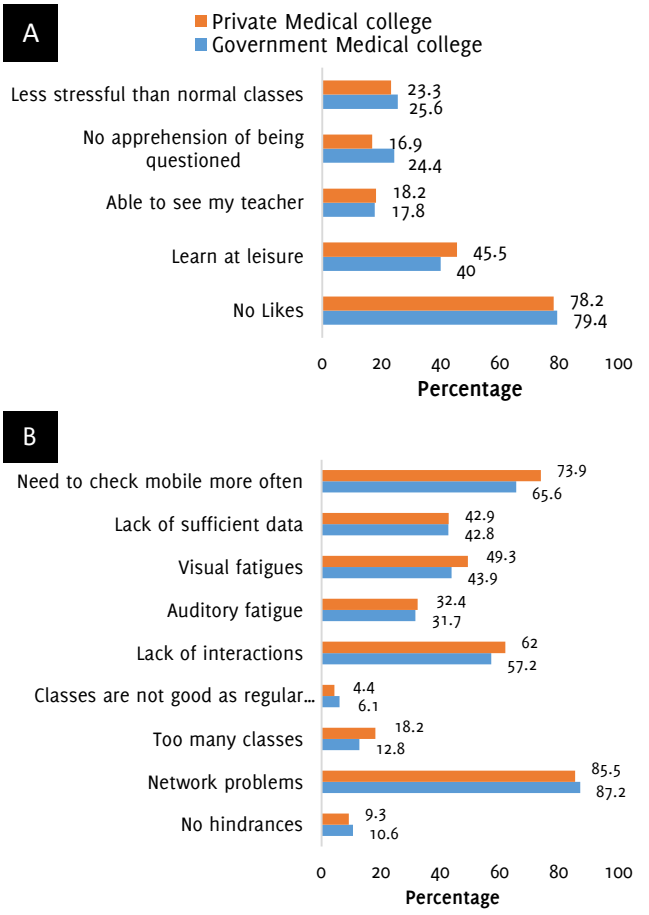


Figure 3. Participants' attitude (A) Likes (B) Dislikes regarding Online Classes.



Students' Perception of Online Classes

Participants were asked to rate five components of online class using a five-point Likert scale, which included clearing doubts, interactiveness, contents of the class, audio quality and video/image/slide quality. This is summarized in ***Figure 2.***

Students' attitude towards Online Classes: Likes and Dislikes (*Figure 3*)

Learning at leisure – 452 (44.5%) – was the top reason for liking online classes, although over three-fourths – 797 (78.4%) – of the participants disliked online classes. Network problems 872 (85.8%), the need to check their mobiles more often 736 (72.4%) and the lack of interaction 621 (61.1%) were the top factors that the participants disliked about online classes. Almost half the participants – 491 (48.3%) experienced visual fatigue after attending online classes. Only 97 (9.5%) of the participants experienced no hindrance while attending online classes.

Students' Practice of and Suggestions about Online Classes

One-third of the participants – ***Figure 4 A***, 328 (32.3%) – did not do anything while attending online classes. However, 688 (67.7%) and 179 (17.6%) students took down notes and recorded the classes, respectively. We asked the students for factors that would increase their ability to participate in the class. The responses were summarised in ***Figure 4 B.***

Discussion

To the best of our knowledge, there have been no studies on the students' perspectives of online classes during COVID-19 lockdown in India. Our survey included 1016 students from 30 medical colleges – 836 (82.3%) from the private and 180 (17.7%) from the government sector. This was because many government colleges have not started online classes yet. Among the participants, 673 (66.2%) and 343 (33.8%) were females and males, respectively. This is on par with the institutional structure. Due to temporary shutdown of schools and colleges, COVID-19 had seriously affected the education of over a billion students' world-wide. This is almost 68% of total enrolled students globally[11].

Online education is challenging in developing countries like India, because of poor network coverage in remote areas. India is second only to China in terms of internet users with the internet user penetration rate of 50%. This implies that nearly half of the country's population has no access to Internet[12]. In our study, the mobile phone was the predominant medium used for online learning 955 (94 %). Many students still use smart phones which are not optimized for attending online classes. Now, medical students have access to a wide range of learning materials during lockdown. Students can look at complex procedures and diseases that cannot be seen in remote or smaller institutions. Khurana et. al. reviewed the pros and cons of various mediums that can be used by medical students[13]. Craddock et. al. observed that pediatric residents who used an online module for learning atopic dermatitis showed statistically significant improvement in disease-specific knowledge when compared to controls[14]. Shah et. al. initiated a satellite school in India in 2006 which evoked tremendous response because of its ability to teach techniques in remote places via telemedicine[15].

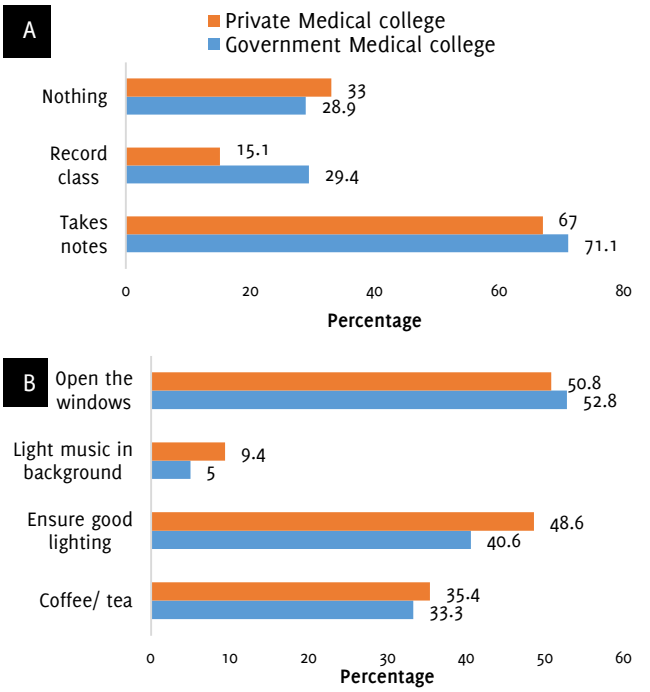
In our study, ZOOM/ Skype platform was utilized by 580 (57.1%) and Google platforms by 553 (54.4%) with overlap in use of applications. On the whole, the participants rated 'average' to 'good' for factors like video, audio, content and clearing of doubts on content covered during the lectures. Online classes lack insufficient interaction. The general frustration of COVID-19 lockdown made 526 students (51.7 %) feel that they did not want to continue online classes. Regular classes were favored by 370 (36.4 %) whereas online classes were preferred by 81 (8 %) of the participants. Students are likely to perform better when the components of online and offline classes are mixed judiciously. This is called "blended education". E-learning modules in higher education will be successful, if teachers and students integrate online classes into the

current curriculum[17,18,19]. There is practically very little experience of online classes within the existing medical curriculum. In order to observe social distancing norms, educational institutions with limited resources have to struggle to support their students. This puts an additional burden on medical teachers, who are working during COVID-19 crisis, as they have to tackle pedagogical and clinical responsibilities simultaneously. Additionally, students face many hassles while attending online classes. They are unanimous in stating that teachers must explore ways to make their classes more interactive to improve the students' attention span.

One limitations of this study was that we included the viewpoint of only students. The teachers' opinion was a part of the study; however, due to anticipated delay in data collection, we could not include their data in present study. Secondly, we included students from medical colleges in south India as they were relatively easy to access and Kerala was one of first to start conducting online classes. Thirdly, comparison between government and private college was analyzed by descriptive statistics (Chi square) as we did not have a priori hypothesis.

The concept of online classes is still evolving. Network problems experienced by the students should be addressed. Scheduling classes in advance, trying to minimize the duration of classes and giving short breaks would minimize fatigue and improve interactions. It is appropriate that educational institutions adhere to the "new normal "-blended learning approach after the lockdown period.

Figure 4. Students' (A) Practice and (B) Suggestions about Online Classes comparing Private Medical College vs. Government Medical College



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Author Contributions

Conceptualization: AT, SKT. Data Curation: AT, MTS, SKT, SSK, CK, JPP, PMP, SSCH, AM, TZ, SD, VM, SR, MJK, SP. Formal Analysis: AT, MTS, SKT, AS. Funding Acquisition: AT. Methodology: AT, SKT. Investigation, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, & Writing – Review & Editing: AT, MTS, SKT.

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Original Article

Prognostic factors in patients with Rocky Mountain Spotted Fever

Hiram J. Jaramillo-Ramírez,[1] Jeremy J. Hernández-Ríos,[2] Fátima M. Martínez-González,[2] Luz A. Gutiérrez-Bañales,[2] Eliot R. García-Valenzuela,[2] J. Andrés Beltrán-López,[2] Jorge L. Peterson,[3] Flor M. Yocupicio,[3] Rodolfo Ruíz-Luján.[4]

Abstract

Background: Rocky Mountain Spotted Fever (RMSF) is a disease with a high mortality rate, caused by Rickettsia rickettsii, a bacteria transmitted to humans by infected ticks. In 2008 there was a Rocky Mountain Spotted Fever (RMSF) outbreak in the city of Mexicali, México, resulting in an increased mortality rate amongst the area population. **Methods:** Case-series study of patients admitted to the General Hospital of Mexicali between 2014 and 2019 with a confirmed diagnosis of RMSF. Mortality was compared dividing the population on those ≤20 and younger than >21 years of age. **Results:** A total of 129 patients' records during a 5-year period whose diagnosis was RMSF confirmed with PCR were included. Mortality was compared among patients admitted who were younger than ,20 years of age with that among patients who were older than >20 years of age (61 versus 68 respectively), the latter being higher with an OR 4.2 (p<0.0001). **Conclusion:** RMSF in hospitalized patients has a high mortality rate in spite of early treatment in all age groups, without showing any predominance in gender. However, patients older than 20 years of age had a higher mortality rate than those younger than 20 years, without any predominance in gender.

Key Words: Rocky Mountain Spotted Fever; Rickettsia rickettsii; Mortality; Acute kidney injury; Necrosis (Source: MeSH-NLM).

Introduction

There are various disease-causing agents from the Rickettsia group, in North America and México some species prevail like R. rickettsii, R. akari, R. prowazekii, R. typhi y R. parkeri, the last one being a common infectious agent in the state of Arizona, United States of America (USA). and has been identified in ticks located in a city of México, however, there aren't reports of infected patients.[1-2]

Rocky Mountain Spotted Fever (RMSF) is a disease with a high mortality rate, caused by Rickettsia rickettsii, a bacteria transmitted to humans by infected ticks.[1, 4-5] This disease can be found in North and Central America, with a higher prevalence in México, Canada and United States of America.[6] Ticks are the natural reservoirs of Rickettsia rickettsii, their life cycle lasts approximately two to three years. In the fall, adult females drop off the host to lay eggs which hatch into larvae and later attach to their first host. Then in the summer, larvae abandon the host and molt into nymphs.[3] During the following spring, nymphs attach to the second host, they feed on it and drop off later in the summer. Nymphs molt into adults and attach to a third host to feed and mate on it. Lastly, females drop off the host in the fall to continue the cycle.[14]

RMSF was first described in early 1899 by Edward E. Maxey, he demonstrated an interest for the disease while reading an article called "Some observation on the so-called spotted fever of Idaho", and described it as "A febrile disease, clinically characterized by continuous moderately high fever, severe arthritic and muscular pains and petechial or purpuric eruption in the skin, appearing first on ankles, wrist and forehead".[11, 15] Variation in clinical presentation interferes with diagnosis and with it the start of specific treatment, which increases mortality. Fever rose up to 38.9° C in 63% of patients during the first 3 days, and in 90% of patients during the first week.[8] In 49% of patients skin lesions appeared during the first 3 days after fever developed, rising to 88-90% of patients during the 3rd and 5th day, these are representative signs of the disease. In severe cases, gangrene may appear in upper and lower extremities, as well as ears and scrotum.[4, 10] The combination of skin lesions by bacteria and vasculitis can result in skin necrosis and gangrene that may require amputation.[7-8, 12]

Diagnosis is usually achieved with indirect immunofluorescence, or with high antibody levels.[13] Other techniques like DNA amplification with polymerase chain reaction (PCR) have very sensitive and specific results, however, these techniques aren't always available in the country of México.[13]

The aim of the study is to demonstrate the benefit of an early treatment (initiation of treatment ≤5 days after the beginning of symptoms), to identify risk factors that increase mortality rate amongst the population of the city of Mexicali, México, and the importance of an accurate diagnosis as a prognostic factor.

Methods

Case series of patients admitted to the General Hospital of Mexicali, a city located in northwestern México, between 2014 and 2019 with a confirmed diagnosis of Rocky Mountain Spotted Fever. The diagnosis was confirmed by polymerase chain reaction (PCR), which was processed by the Thermocycler Applied Biosystems 7500 Real-Time PCR System with llustraTM puRe Taq Ready-To-GoTM PCR Beads, according

1 MD. Internal Medicine, Chief Professor of the Internal Medicine academic course at the General Hospital of Mexicali, México
2 Medical Student. General Hospital of Mexicali. Faculty of Medicine UABC Mexicali, México.
3 MD. Internal Medicine resident General Hospital of Mexicali, México
4 MD. Internal Medicine and Infectious Diseases, General Hospital of Mexicali, México

About the Author: *Fátima M. Martínez-González is currently a 7th year medical student of the Faculty of Medicine, Mexicali Campus, México, of a seven-year program. She is also part of a student fellowship program dedicated to community scientific research at the General Hospital of Mexicali.*

Correspondence:
Hiram J. Jaramillo-Ramírez
Address: Calle del Hospital SN, Centro Cívico. Mexicali B.C. México.
Email: hiramjaramillo@yahoo.com.mx

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to the policies of the Institute of Diagnosis and Epidemiological reference.

We searched the patients' charts for the following variables: Date of admission, age, gender, multimorbidities, time between symptom onset and the initiation of treatment, animal contact, previous tick bites, signs, symptoms, and laboratory tests (***Table 1***). Delayed treatment was defined as the initiation of treatment .5 days after the beginning of symptoms.

Information was analyzed with MiniTab statistical package version 19.2.0 and with the aid of Microsoft Office Excel (2018). Spearman's correlation coefficient was used to interpret all data. The study was approved by the Institutional Review Board of the General Hospital of Mexicali.

Results

A total of 129 hospitalized patients' records were included, all diagnosed with Rocky Mountain Spotted Fever confirmed by PCR (***Table 1***). There were 71 males (55%) and 58 women (45%) with age ranging between 1-67 years old, with a mean of 25 years From the patient total, 58% were diagnosed during summer (April-September), and 42% during winter (October-March). Forty-one patients died, from which 51% were females, not showing a statistical difference between genders. We compared mortality among patients admitted who were ≤ 20 years of age with that among patients >21 years of age, the latter being higher with an Odds Ratio (OR) of 4.2 (95% Confidence Interval [95% CI]: 1.86-9.78, p=0.0001). One hundred five patients were tested for serum electrolytes, 71% developed hyponatremia (<135 mEq/L). Mortality rate in patients with hyponatremia was 34%, compared to those who did not have hyponatremia for an OR of 1.7 (95% CI 0.6-4.6; p=0.13) not statistically significant.

From the 51 patients with delayed treatment, 17 cases were fatal (33%) (OR 1.37, 95% CI 0.6-3.11; p=0.2). When comparing the group of patients who received delayed treatment against those who received early treatment (≤5 days after the onset of symptoms), mortality rate for patients who received delayed treatment was 33%, with an OR of 1.37 (95% CI 0.6-3.11)

We gathered platelet levels from 111 patients, where 99 patients (76%) presented with thrombocytopenia below 150,000 cells (OR 6.01, 95% CI 0.7-48, p=0.02), in comparison to those who did not develop thrombocytopenia.

A total of 100 patients presented exanthema, from which 31 died, with an OR 0.8 (95% CI, 0.3-2.04; p=0.3) without representing a risk factor for mortality. Skin necrosis of the limbs is a known complication, which was present in 9 patients from our sample (7%). Six of them died (67%) OR 4.6 (95% CI 1.1-20, p<0.02).

Acute kidney injury (considered as a creatinine value > 1.5 mg/dL based on the KDIGO criteria for Acute Kidney Injury) is a risk factor associated with higher mortality rate (OR 9, 95% CI 3.4-23.5, p <0.001). Neurological dysfunction was present in 68 patients (53%), from which 26 (38%) died (OR 1.8, 95% CI, 0.88-4; p=0.05).

A higher incidence was recorded during the months of July and September, with a total of 42 patients (33%), and a fatal outcome in 12 of them (28%), in comparison to the rest of the months where the incidence was 19-23%.

Discussion

RMSF has a rising incidence in northwestern regions of México, where the weather mainly consists of two seasons, summer (April-September) and winter (October-March). Those who did not receive treatment had a 30% mortality, which could be reduced to 15% with treatment. [7-8] In this study there were 129 patients, all diagnosed with a confirmatory test by PCR.

Table 1. Characteristics of patients with RMSF † admitted to the General Hospital of Mexicali (n=129)

Demographic	**Total (%)**	**Fatal**	**Non-fatal**	**% Lethal**	**OR (95%CI)**	**p-value**
Male	71 (55)	20	51	28	Ref	
Female	58 (44.9)	21	37	36	0.69 (0.3-1.4)	
Age	**Total**	**Fatal**	**Non-fatal**	**% Lethal**	**OR**	
<20 years	61 (47.2)	10	51	16	Ref	
>20 years	68 (52.7)	31	37	45	4.27 (1.86-9.78)	<0.0001
Hyponatremia	68 (71.4)	23	45	34	1.7 (0.6-4.6)	
Thrombocytopenia	99 (76.7)	35	64	35	6.01 (0.7-48)	
Delayed treatment (>5 days)	51 (39.5)	17	34	33	1.37 (0.6-3.11)	
Rash	100 (77.5)	31	69	31	1.1 (0.35-2.04)	
Necrosis	9 (6.97)	6	3	66	4.8 (1.1-20)	<0.02
Neurological dysfunction	68 (52.7)	26	42	38	1.8 (0.88-4)	
Elevated creatinine	52 (40.3)	29	23	55	9 (3.4-23.5)	<0.001
Cases per month	**Total**	**Fatal**	**Non-fatal**	**% Lethal**		
Jan-Mar	30 (23.2)	9	21	30		
Apr-Jun	33 (25.5)	12	21	36		
Jul-Sep	42 (32.5)	12	30	28		
Oct-Dic	24 (18.6)	8	16	33		

Legend: † Rocky Mountain Spotted Fever.

There was a 32% mortality rate, twice as much as those reported by previous studies in México.[3, 8] This high mortality rate in treated patients can be explained because patients that were hospitalized were more severe than those who received ambulatory treatment. Treatment initiation delay is not related with a high mortality rate, unlike the 2016 study. [3] Mortality is also related to the presence of skin necrosis of the limbs with an OR 4.6, a variant not considered in the previous study. [3] RMSF in hospitalized patients has a high mortality rate in spite of early treatment in all age groups, without showing any predominance in gender [9]. However, patients older than 20 years of age had a higher mortality rate than those younger than 20 years, without any predominance in gender. Acute kidney injury, skin necrosis of the limbs, and age older than 20 years were predictors of mortality. Thrombocytopenia was also a risk factor for higher mortality rate, yet, only one patient without thrombocytopenia died. Such a small sample makes it almost impossible to define its risk accurately.

Regarding treatment, tetracyclines have been the only accepted treatment for RMSF for many years, however, the medical community is in need of alternative solutions just as effective as doxycycline, but these may require future research.[7]

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Author Contributions

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Short Communication

Acute Liver Failure in Patients with Classic Heat Stroke

Jeremy J. Hernández-Ríos,[1] Fátima María Martínez-González,[1] Luz A. Gutiérrez-Bañales,[1] J. Andrés Beltrán-López,[1] Hiram Jaramillo-Ramírez.[2]

Abstract

Background: Classic heat stroke is defined by a core temperature greater than 40° C, severe dehydration and neurological alterations. Patients with liver disease due to heat stroke have been described, mostly by exercise. Hepatic failure is defined as the presence of a coagulopathy accompanied by any degree of hepatic encephalopathy. The primary objective of the study lies in the fact that patients who developed acute liver failure during their hospital stay had a higher risk of mortality. **Methods:** A retrospective, analytical study of patients admitted to the General Hospital of Mexicali who suffered from classic heat stroke from March 2006 through August 2010, and a second period from June 2018 to August 2019. **Results:** A sample of fifty patients were recruited, the group included 48 (96%) male, with a total of 10 fatalities, representing 20%. It was observed that parameters such as INR greater than 1.5, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were not associated to an increased mortality rate. **Conclusion:** Neither transaminase levels, nor liver failure, were related to a higher mortality rate in this cohort of patients with classic heat stroke.

Key Words: Heat Stroke; Liver Failure; Mortality (Source: MeSH-NLM).

Introduction

Heat stroke is a severe condition that is commonly seen in countries with a warm climate. [1] There are two types: classic and exercise-induced heat stroke. The classic type occurs in individuals who are exposed to high environmental temperatures without any physical activity involved. The exercise type occurs in people who are physically active in warm climates or when the ambient temperature is higher than they are adapted to or acclimatized.[2] In several case reports, liver disease secondary to heat stroke have been described, mostly by exercise, with multiple outcomes like successful liver transplant, or no signs of liver function impairment.[3] These patients have a core body temperature greater than 40° C, severe dehydration and neurological disorders such as delirium, seizures or coma.[4-5]

Acute liver failure (ALF) is defined as the presence of coagulopathy (INR≥1.5) that is accompanied by any degree of hepatic encephalopathy, clinically defined by the West Haven criteria.[6]

The mechanism of coagulopathy development due to acute liver failure is multifactorial, consisting of decreased synthesis of procoagulant factors, anticoagulant and fibrinolytic system imbalance (mainly factors V and VII) and platelet dysfunction, all of this as a result of liver cell injury. [7-8]

Acute liver failure compromises brain metabolism by increasing cerebral flow, reducing oxygen metabolism and impairing the cerebrovascular autoregulatory mechanism. This generates neuroinflammation, which activates the microglia to produce interlukines and tumor necrosis factor-alpha (TNF-α), these cause hepatic encephalopathy. [9]

We aim to evaluate whether patients who developed acute liver failure during their hospital stay had a higher mortality rate than those who did not present liver function impairment.

Methods

We conducted a retrospective, analytical study of patients admitted to a secondary university Hospital in the city of Mexicali (México), who suffered from classic heat stroke from March 2006 through to August 2010, and a second period from June 2018 to August 2019. The reason there is an 8-year gap between the first and second cohort is that many patient's records were lost in a fire, the hospital only began implementing electronic files until 2015, hence the gap. The records that remained were preserved thanks to a database collected by a fellow medical resident during those years. Patients admitted to the emergency department with a diagnosis of heat stroke were included. A case of heat stroke was defined as central body temperature greater than 40ć C, changes in alertness, and previous exposure to high environmental temperature.[4] Information as sex, age, admission date, laboratory studies (blood cytometry and chemistry, liver function panel, coagulation tests), morbidities, and mortality, was collected. The highest ambient temperature according to *The Weather Channel* was recorded the day they were hospitalized.

Quantitative variables were expressed as mean and standard deviation (SD) or as median and interval. Student's t-test was used to compare continuous variables. The association between quantitative variables was analyzed using Spearman's correlation coefficient test.

The categorical variables were expressed as frequencies and percentages. For the comparison of proportions, the x^2 test was applied. A value of $p < 0.05$ was considered statistically significant. This study was approved by Mexicali's General Hospital Institutional Review Board.

Results

The study group included 48 (96%) male. The mean age was not obtained due to a lack of information; most of the patients were homeless and usually arrived with an altered mental status that did not allow them to respond for themselves during hospitalization, many of them passed away (20%) before being identified by a relative. Of all

[2] Medical Student, Faculty of Medicine, Autonomous University of Baja California, Mexicali, B.C., México. General Hospital of Mexicali, Mexicali, B.C., México.
[1] MD. Internal Medicine, Chief Professor of the Internal Medicine academic course at the General Hospital of Mexicali, México.

About the Author: *Jeremy Hernández-Ríos is currently a 7th year medical student at the State University, Faculty of Medicine. This is his last year of a seven-year program. He is also part of a student fellowship program dedicated to community scientific research at the General Hospital of Mexicali.*

Correspondence:
Fatima Maria Martínez-González
Address: Dr. Humberto Torres Sanginés S/N, Centro Cívico, 21000 Mexicali, B.C., Mexico.
Email: fatima.martinez@uabc.edu.mx

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patients, 19 had an INR > 1.5, with a total of 5 fatalities (OR 1.8, 95%CI 0.45-7.52, *p=0.2*) (***Table 1***). INR values ranged from 0.65 to 4.34 with a mean of 1.30. Spearman's correlation coefficient for INR levels and mortality was moderately positive (0.408). Eleven patients had AST levels five times greater than the normal value with a mean of 575 U/L (*p*=0.175).

Spearman's correlation coefficient for AST levels and mortality was very low (-0.017). Nine patients had ALT five times greater than the normal value (values ranged from 16 - 19,136 U/L) with a mean of 559 U/L (*p*=0.26). Spearman's correlation coefficient for ALT levels and mortality was very low (-0.057) **(*Table 1*)**. The body core temperature recorded in patients ranged from 40 °C-42.5 °C with a mean of 42 °C. Finally, Spearman's correlation coefficient for body temperature and mortality was also low (-0.252). There was a 20% mortality rate.

Table 1. Relation of variables and mortality

Variable	n (%)	Mortality [n (%)]	OR (IC 95%)	p-value
INR >1.5	19 (38)	5 (26)	1.85 (0.45-7.52)	0.205
AST/TGO (>5 times its normal value)	11 (22)	1 (9)	0.33 (0.03-2.96)	0.175
ALT/TGP (>5 times its normal value)	9 (18)	1 (11)	0.44 (0.48-4.03)	0.26

Discussion

Several studies have reported the relationship between acute liver failure and heat stroke induced by exercise.[1-6, 10] Numerous case reports about exercise-induced heat stroke were analyzed, and most of them presented an increase in liver function enzymes and INR during hospitalization, meeting criteria for ALF. Giercksky et al. reported a biopsy obtained on the fifth day of hospitalization with hemorrhagic centrilobular necrosis with diffuse ballooning of the hepatocytes and moderate mixed portal and lobular inflammatory infiltrate.[1] Figiel et al. analyzed five patients with ALF who met criteria for liver transplant, three of them underwent surgery and survived, maintaining close follow-up during the consecutive year without complications. One of the non-transplanted patients developed intracerebral hemorrhage, while the other patient recovered spontaneously on the fourth day.[3] This is a retrospective study within a specific period, March 2006 thru August 2010, and a second period from June 2018 to August 2019, including patients with ALF due to classic heat stroke. However, the definition of acute liver failure (INR≥1.5 and encephalopathy) can be ambiguous in these patients, [6] because encephalopathy is a common manifestation in patients with heat stroke.

Heat stroke is characterized as a multi-organ dysfunction; previous studies have stated that it mostly occurs in patients with multimorbidities and severe hemodynamic instability.[11] In this cohort of patients, we did not find that liver dysfunction contributes to increased mortality. Davis et al. reported a case of liver failure in a patient with heat stroke induced by exercise, they considered that hypophosphatemia was a risk factor for liver damage, [6] Our study could not study this particular variable due to limitations in the design.

Other authors have previously established acute liver failure's incidence at 5% in patients with heat stroke due to exercise.[3] In contrast, our study demonstrated double the incidence without an increase in mortality. There is a great difference between exertional and classic heat stroke, the pre-existent physical condition of a patient who suffers from exercise induced heat stroke is not the same as the one seen at the General Hospital of Mexicali. The hospital receives a great amount of cases of classic heat stroke during summertime, therefore the staff has developed expertise on the matter, although there are not any written guidelines for management. The main strength of this study is the sample size obtained for such an uncommon disease. Nonetheless, compared to patients who suffered exertional heat stroke, our group is conformed of homeless people with an unknown history of comorbidities or previous liver damage. Classic heat stroke has a high incidence during summer in our community, further studies are necessary to evaluate the association between ALF and classic heat stroke.

There are multiple weaknesses in our work, such as including two cohorts separated in time, the absence of further workup for multi-organ failure or other causes of hepatic liver failure. However, we are at an advantage seeing that heat stroke is an uncommon disease worldwide, yet fairly common in our city, which allowed us to report its impact to liver function.

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Author Contributions

Conceptualization: HJJR. Data Curation: LAGB. Formal Analysis: JJHR, FMMG, LAGB, JABL, HJJR. Investigation: JJHR. Methodology, Project Administration & Supervision: HJJR. Resources: JJHR, FMMG, LAGB, JABL. Visualization: FMMG. Writing – Original Draft Preparation: JJHR, FMMG, LAGB. Writing – Review & Editing: JJHR & FMMG.

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ULS

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Review

Pathology and Therapeutics of COVID-19: A Review

Haleema Anwar,[1] Qudsia Umaira Khan.[2]

Abstract

COVID-19 pandemic has taken over the world. Spreading from its epicenter in a seafood market in Wuhan, China to more than 200 countries, it has caused alarming situations. The viral infection is caused by an RNA virus called SARS-CoV-2. Its genome resembles the SARS-CoV-1 and MERS-CoV genome. COVID-19 cases were first reported in December 2019 in China, with infection causing a mild to severe respiratory disease. No antiviral drug for the infection has been shown to be effective, however many drugs are approved in the context of clinical trials. The review article will first present the structure of the SARS-CoV-2 and compare it to SARS-CoV-1 and MERS-CoV. The article will then highlight its effect on different organs. Finally, it will highlight the therapeutics which are in consideration and those which are being used.

Key Words: Pandemic; Phylogenetic Analysis; Differential Diagnosis; Incubation Period; Viral Genome (Source: MeSH-NLM).

Introduction

In December 2019, several cases of unexplained pneumonia appeared in Wuhan, China. The symptoms were like those caused by SARS-CoV (Severe Acute Respiratory Syndrome-Coronavirus) in 2003 which included cough, fever and fatigue. The infectious virus responsible for this was identified as SARS-CoV-2 and the infection was called COVID-19. Starting from its epicenter in China, COVID-19 has affected more than 200 countries. The virus mostly causes mild cases. The status of COVID-19 for the world at present is: total deaths 310,003, total people recovered 1,780,118, and total cases 4,670,224 as on 16th May 2020, 4:00 pm GMT.[1]

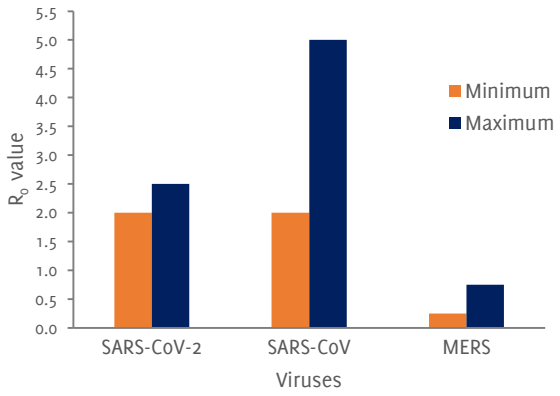
COVID-19 was declared a 'global pandemic' on March 11, 2020 by the director general of the World Health Organization (WHO).[2] This study aims to present the structure of the SARS-CoV-2 and compare it to SARS-CoV-1 and MERS-CoV, highlight its effect on different organs, and the therapeutics which are in consideration and those which are being used. Information was extracted from PubMed and Google Scholar searches using keywords as: "COVID-19", "SARS-CoV-2", and "Pandemic".

Previous pandemics

COVID-19 is not the only pandemic that has been experienced by the world. Coronaviruses have previously caused infectious outbreaks. These include SARS-CoV and MERS-CoV (Middle East respiratory syndrome-coronavirus). SARS-CoV was identified in 2003. It began in China causing approximately 8000 cases. MERS-CoV began in Saudi Arabia in 2012 and led to 2500 cases.[3] Each virus caused an estimated 800 fatalities.

The measure of the infectiousness of the disease is of significance. It is depicted by a value called R_0 which is the number of secondary cases per case in a totally susceptible population. R_0 greater than 1 means that the case numbers will increase. A comparison of maximum and minimum R_0 for SARS-CoV-2 with other coronaviruses is shown in ***Figure 1***; however, this value might change at the end of the pandemic. SARS-CoV-1 has the highest Ro value. The seriousness and severity of the disease is measured by the case fatality. At present the case fatality of SARS-CoV-2 is 2% (i.e. 1 in 50 people with the disease will die). For MERS-CoV it was thought to be 37% and for SARS-CoV it was 10%.[4] There may be discrepancies in the data because most of the COVID-19 patients are asymptomatic and therefore many patients may have not been tested.

Figure 1. Maximum and minimum R_0 value of the viruses.



Structure of SARS-CoV-2

SARS-CoV-2, a member of the coronavirus family, is the name given to the causative agent of COVID-19 infection by International Virus Classification Commission. Coronaviruses have four known genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Seven CoVs have been identified so far that may infect humans (HCoVs): two of which are alphacoronavirus (229E and NL63) and the other are Betacoronavirus, or β-CoV, (such as OC43, HKU1, SARS-CoV-2).[3] SARS-CoV-2 has been classified as β-CoV. Corona is a Latin word which means 'crown', a name which was associated with the family because the surface projection on the viral envelope gives it such an appearance.

[1] Medical student, CMH Lahore Medical College & IOL, Lahore, Pakistan.
[2] MBBS, M.Phil., FCPS II, CMH Lahore Medical College & IOL, Lahore, Pakistan.

About the Author: *Haleema Anwar is currently a 2nd year medical student of MBBS at CMH Lahore Medical and Dental College, Lahore, Pakistan of a 5-years medical program. She is enthusiastically involved in medical research to keep herself abreast with the current techniques and technologies being used in the field of medicine. She is very energetic in social work, presently selected as a Head of a team in a blood donating society of the college 'Cmh LMC lifeline'.*

Correspondence:
Haleema Anwar
Address: Infantry Road, Abdul Rehman Rd, Sarwar Colony, Lahore, Punjab, Pakistan.
Email: haleemaa670@gmail.com

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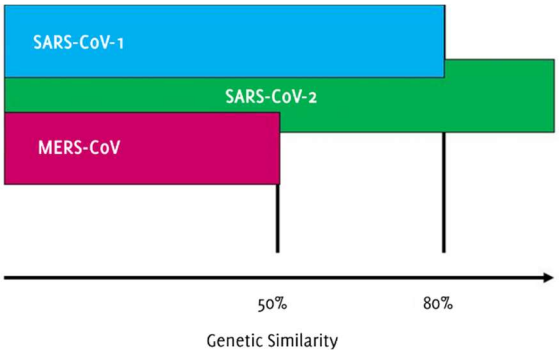
CoVs are RNA enveloped viruses with nucleocapsid proteins and have a genome of around 30 kb in length, making them the largest known RNA viruses, with a diameter of approximately 60–140 nm. The SARS-CoV-2 has ten Open Reading Frames (ORFs).[4]

The genomic structure has a 5′-cap structure and a 3′-poly-A tail and encodes for structural and non-structural proteins. The structure has mainly four structural proteins: spike (a glycoproteins composed of two subunits S1 and S2) which helps the virus to attach to the host, membrane which help shape the virion particle, envelop which is involved in assembly and release of particle, and nucleocapsid which aids the binding of the genome to a replication transcription complex for the replication of its genetic material.[5]

Phylogenetic analysis revealed that SARS-CoV-2 is 80% and 50% identical to SARS-CoV and MERS-CoV, respectively (***Figure 2***). Similarly, both viruses were of bat origin. A single intact ORF was found on gene 8. This evidence points out that the possible origin of SARS-CoV-2 virus is from bats.

Figure 2. Genetic similarity of SARS-CoV-2 with other viruses.



MERS-CoV uses dipeptidyl peptidase (DPP4) as a receptor whereas SARS-CoV and SARS-CoV-2 utilize ACE-2 (Angiotensin-Converting Enzyme-2) as their receptors, which is a membrane bound aminopeptidase. SARS-CoV-2 entry is dependent on protease, the most important of which being the employment of protease Transmembrane Serine Protease 2 (TMPRSS2) for priming of the viral S protein. This is of significance as TMPRSS2 activity is important for viral spread and pathogenesis.[4] These receptors are under pharmacological considerations.

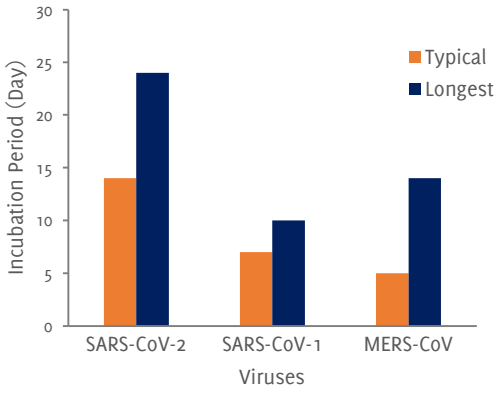
The incubation period of COVID-19 is calculated to have a median of 6.4 days.[6] This gives information about how long it takes for a patient infected with SARS-CoV-2 to develop symptoms and forms the basis for a quarantine period. A longer incubation period signifies a higher rate of asymptomatic and subclinical infection in individuals who are immunologically competent. A comparison of three related viruses is shown in ***Figure 3***, wherein we have chosen the maximum value of the period i.e. 2 – 7 duration of SARS-CoV we selected 7. The virus is very infectious, and a study on familial group of five patients has revealed that asymptomatic carriers can transmit the infection to others even when the virus is in the incubation period.[7]

Diagnosis and Pathology

Various methods for the diagnosis of the infection are used. These include Real-Time quantitative Polymerase Chain Reaction (RT-qPCR), high-throughput sequencing, CT scan and immunological detection kits. These methods are shown in ***Table 1***.

After the onset of the infection, the clinical manifestation ranged from asymptomatic patients to patients with septic shock. As the disease progresses, it may be categorized as mild, moderate, severe, or critical. 81% of the cases were mild. Cases critical in severity were reported to be 5%.[8] The case fatality rates of patients with chronic illnesses and patients of critical severity were high.

Figure 3. Incubation periods of the viruses.



The following findings are laboratory features for early stage ICU patients and critical patients were the following. CD4 and CD8 lymphocytes were reduced in patients of early stage. Interleukin level (IL-2, IL-7, IL-10), granulocyte colony stimulating factor and tumor necrosis factor-α (TNF-α) were high in intensive care unit patients. Amylase levels were high in critical patients. C-reactive protein (CRP) levels are directly proportional to disease severity and its progress.[8] From pieces of evidence, it has been suggested that there is a subgroup of severe COVID-19 patients that might have cytokine storm syndrome. In this condition, there is an urgent need to reduce rising mortality by using approved, existing therapies and treatments of hyper-inflammation with safety profiles and measures. The current method of managing and curing COVID-19 patients is supportive and protective. It has been investigated that the prime cause of death in COVID-19 patients is the respiratory failure that is due to acute respiratory distress syndrome (ARDS). Another syndrome that is characterized by sudden and severe fatal hypercytokinemia with the probability of multi-organ failure is secondary haemophagocytic lymphohistiocytosis (sHLH). It is a hyperinflammatory syndrome that is generally triggered by viral infections in adults and responsible for 3.7–4.3% of sepsis cases. Major features of sHLH are fever, hyperferritinanemia, cytopenia, and involves pulmonary system (ARDS) in 50% cases. Severe COVID-19 disease has a cytokine profile resembling sHLH. It is characterized by an increased number of interleukins, monocytes, interferons, macrophages, inflammatory proteins, and TNF-α. The study of 150 COVID-19 cases shows mortality from a recent retrospective study.[9,10]

SARS-CoV-2 stands for Severe Acute Respiratory Syndrome- Coronavirus 2. It is found to damage the lungs, but its effects are not limited to the lung tissue. Its influence on liver, central nervous system (CNS) and cardiovascular system (CVS) are under consideration. SARS-CoV-2 infects ciliated bronchial epithelial cells and type II pneumatocytes of lung tissue.[11] In a study, biopsy samples were taken from the lung tissue. It showed desquamation of the pneumatocytes, hyaline membrane formation and pulmonary edema. All these findings are suggested of ARDS. In the intersitium, mononuclear inflammatory infiltrates were seen with lymphocyte predominance. The intra-alveolar space showed viral cytoplasmic-like changes, which included multinuclear syncytial cells with atypically enlarged pneumatocytes that had prominent nucleoli, large nuclei, and amphophilic granular cytoplasm.[12] SARS-CoV, SARS-CoV-2 and MERS-CoV infect a common cell, which is the type II pneumatocytes. MERS-CoV differed from the others in that it damaged the unciliated bronchial epithelial cells as compared the ciliated bronchial epithelial cell infected by SARS-CoV and SARS-CoV-2.

SARS-CoV-2 can directly bind to ACE 2 receptors on cholangiocytes leading to problems with the biliary system and secondary causing injury to the liver. This finding was in congruence with a study in which patients in the subclinical phase (that is before the onset of the symptoms) had lower aspartate aminotransferase (AST) level abnormalities than the patients who were diagnosed after the onset of

Table 1. The various diagnostic methods used for detection of COVID-19.

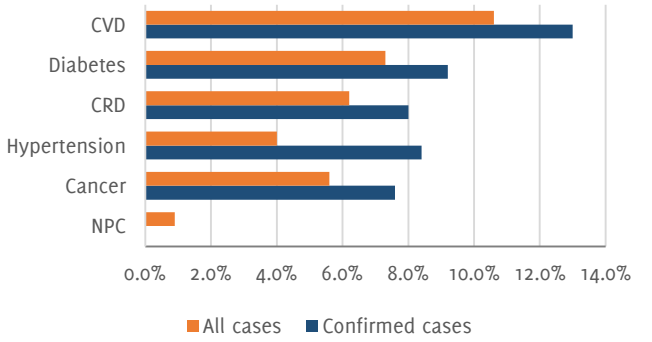
Diagnostic method	Efficiency and Limitations
RT-qPCR (Real-Time quantitative Polymerase Chain Reaction)	High sensitivity and specificity Limitations: • Long waiting time for result • Can show false-negative result
High-throughput sequencing	Authoritative identification method Limitations: • High cost • Equipment dependency
CT scan	Has higher clinical diagnostic value for COVID-19 Limitations: • Cannot distinguish between pneumonia caused by COVID-19or another pathogen • Hysteresis of abnormal CT imaging
Immunological detection kits	ELISA kits have been developed and pretested by some companies SARS-CoV-2 N-based Ig G ELISA has higher sensitivity than S- based Ig G ELISA.

the symptoms.[8] Inflammation caused by immune activation (i.e. cytokine storm) can cause liver damage. Hypoxia due to respiratory syndrome causes lack of oxygen to the liver tissue contributing to liver dysfunction. In MERS-CoV, no viral particle was detected in liver tissue.[13] There is an association of extreme severity of COVID-19 disease to a cytokine profile that resembles secondary haemophagocytic lymphohistiocytosis (sHLH). This is distinguished by increased IL-2, IL-7, granulocyte colony-stimulating factor (GCSF), IFN (interferon)-γ inducible protein 10, monocyte chemoattractant protein (MCP) 1, macrophage inflammatory protein (MIP) 1-α, and TNF-α.[14] A multi-center study (clinical research of multi-labs and clinics) of 150 confirm COVID-19 cases predicted fatality from some recent retrospective study. Hyper-inflammatory screening should be done, with the help of recent clinical-lab inventions, for the patients who suffer severe SARS-CoV-2 infection. The clinical techniques should keep a check on ferritin increase, decrease in platelet count, or erythrocyte sedimentation rate. Along with the screening, HScore11 (patient's performance record table) should be used to distinguish the patients who can show transient improvement through immuno-suppression. Ingestion or intake of steroids, intravenous immunoglobulin, selective cytokine blockade, and JAK inhibition are some considerable curative options.[15]

The functional receptor of SARS-CoV-2 is ACE2. This receptor is present on different human tissue which include nervous tissue, skeletal muscle, cardiac tissue and liver tissue. In a study of 214 COVID-19 patients, it was revealed that these patients had neurological symptoms with PNS and CNS involvement.[16] The symptoms were more pronounced in patients with severe infection of COVID-19. The symptoms were acute cerebrovascular disease and conscious disturbance. CNS symptoms included dizziness and headache. In comparison to other coronaviruses, neurological injury was confirmed in SARS-CoV and MERS-CoV. SARS-CoV nucleic acid was detected in CSF and brain tissue biopsy of the patients. A case study supports the possibility of the COVID-19 causing neurological dysfunctions. A COVID-19 infected 61-year-old women presented with acute weakness and severe fatigue of lower limbs. There was a decrease in sensation of light touch and pinprick. Laboratory findings revealed demyelinating neuropathy. She was diagnosed Guillain-Barré syndrome. This might suggest an association between SARS-COV-2 and Guillain-Barré syndrome because the starting point of Guillain-Barré syndrome overlapped with the duration of COVID-19 infection.[16]

ACE2 is highly expressed in lung and heart tissue.[17] SARS-COV-2 enters the lung tissue via type II pneumatocytes. This viral entry causes down-regulation of the ACE2 receptor which leads to accumulation of angiotensin II (Ang II) and reduced angiotensin-(1–7). Ang II-induced cardiac hypertrophy, fibrosis and infarction are the consequences of increased level of circulating Ang II.[13] Acute myocarditis and heart failure can also be caused by MERS-CoV. There is some mechanism by which heart injury is caused which includes hypoxemia complications, ACE2 related signaling pathways and an unbalanced response of two helper cells (type 1 and type 2) leading to cytokine storm.[4] ***Figure 4*** shows COVID-19 fatality rate by comorbidity.

Figure 4. COVID-19 Fatality Rate by Comorbidity.[51]



Legend: CVD, Cardiovascular disease; CRD, Chronic respiratory disease; NPC, No pre-existing conditions.

In patients who had COVID-19 and sepsis various signs and symptoms were observed. Such symptoms include severe dyspnea and hypoxemia due to the damage to lungs, renal impairment and decreased urine output because of kidney damage, and tachycardia.[3] There are certain cardiovascular complications due to viral infections that include myocarditis, heart failure, myocardial infarction of type 1 and 2, arrhythmias, pericarditis, and myocardial ischemia. COVID-19 is impacting many populations in the world. According to the current published data, many patients who are suffering from COVID-19 develop some cardiovascular complications. Almost 7% develop acute cardiac injuries, while 16% of the patients develop arrhythmia. Heart failure is caused in 23 % of the COVID-19 patients. The reasons for heart failure are stress cardiomyopathy, new cardiomyopathy, and myocarditis. The new cardiomyopathy is related to the strong cytokine storm. Procoagulant activity, as well as systematic inflammatory response along with COVID-19, can increase the risk of acute myocardial infarction and cardiac injury. There may be a chance of myopericarditis, but it's rare. Some complications are associated with women only e.g. stress and cardiomyopathy. These are preceded by physical triggers or emotional triggers. Stress cardiomyopathy is usually associated with decreased left ventricular function as compared to the coronary syndrome.[18,19]

A cohort study of 41 patient confirmed with SARS-CoV-2 infection and admitted to a hospital in Wuhan, China reported clinical features of the infection. Certain features of the infection were like SARS-CoV and MERS-CoV which were fever, dry cough and dyspnea.[4] Other similarities included: pneumonia, nonproductive cough, myalgia and fatigue.[5] However, COVID-19 differed in that it showed apparent signs and symptoms of upper respiratory tract (e.g., rhinorrhea, sneezing or sore throat) and did not show intestinal signs and symptoms. MERS-CoV induced increased concentration of proinflammatory cytokines (IFNγ, TNFα, IL15, and IL17).[20] Patients infected with COVID-19 also had high amounts of IL1β, IFNγ, IP10, and MCP1. COVID-19 differed from SARS-CoV as COVID-19 caused an increase in secretion of T-helper-2 cytokines (e.g. IL4 and IL10).[4]

There are some complications due to COVID-19 that must be brought to light. These complications are ARDS, cytokine storm complicated with

hemophagocytic syndrome, myocardial injury and coagulopathy. There is a high risk of venous thromboembolism. D-dimer might be helpful in early recognition of patients with high risk of such coagulations.[21] In a study of 449 patients with severe COVID-19 who had sepsis-induced coagulopathy or elevated levels of D-dimer, anticoagulant therapy was given and the result showed a lowered mortality. They were treated with low molecular weight heparin (LMWH).[22]

Differential diagnosis is very important to give appropriate and timely treatment to the patient. It includes the possibility of an infectious or non-infectious respiratory disease.[3] These disorders include common cold caused by rhinovirus, upper and lower respiratory disease by human metapneumovirus (hMPV) and pneumonia caused by influenza and parainfluenza. Investigations such as detection of antigens must be carried out to rule out the possibility of such diseases.

Therapeutics

There is no antiviral treatment that has been approved for COVID-19, however, certain approaches for the cure are under consideration.

The base-line treatment for the patient infected with SARS-CoV-2 is symptomatic. Isolation of the individual is most effective and oxygen therapy is recommended. The measure taken to contain the epidemic is quarantine because the virus is transmitted by human to human contact and physical contact with surfaces (i.e. cardboard, copper, stainless steel, plastic). Zoonotic transmission has also been stated. Drug intervention includes antiviral, antibacterial and antimalarial drugs.

As the virus affects the lungs, the major therapy for the infection is oxygen therapy. One of the preferred strategies is the endotracheal tube. It is recommended in patients with critical respiratory conditions. A waveform capnograph monitoring device should be used. This gives information about correct placement of endotracheal tubes and gives an idea about the extent of seal adequacy. High-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) improve oxygenation and lower the work of breathing but are not recommended for the treatment as they produce aerosol and the virus can be aerosolized. Their use is discouraged universally unless an airborne infection isolation room is accessible, or the patient has viral clearance.[23]

Studies have revealed that chloroquine has antiviral activity against RNA viruses in vitro. Several mechanisms by which this drug works is proposed. It might be due to interference of chloroquine with ACE 2 receptor glycosylation which prevents its attachment to the host cell. Chloroquine can work indirectly by reducing pro-inflammatory cytokines. A preliminary study indicated that the drug interferes with SARS-CoV-2 attempt to acidify lysosome, thus it works by increasing endosomal pH.[24]

Remdesivir is an antiviral prodrug. It has been tested in animal model (i.e. mice), the test revealed that the drug reduced viral load in SARS-CoV-2 infected mice. Remdesivir was used in three patients with severe disease. In one patient it was discontinued after 5 days because of ALT elevation. There was no confirmation whether this elevation was due to Remdesivir. A patient of renal replacement therapy was given only one dose and then Remdesivir was discontinued because it contained cyclodextrin (which is nephrotoxic).[25] According to a placebo-controlled, multicenter trial for Remdesivir in ten hospitals in China, the drug did not show significant reduction in mortality or time to clearance of virus in seriously ill patients as compared with placebo group. A reduction in time of recovery was observed in patients who were treated earlier.[26] Although there is inadequate knowledge about the safety and effectiveness of Remdesivir, the drug has been shown to shorten the time of recovery in some COVID-19 patients. It has been authorized for emergency use by FDA.

Many biopharmaceutical companies are aiming to develop prophylactic vaccines for the virus. These attempts are being made using DNA, mRNA and adenovirus vectors as platforms. The most advanced platform is DNA. Due to technological improvement, mRNA vaccines are more stable and have high efficiency for protein translation. These properties induce a strong immune response.[27] ***Table 2*** shows a list of recommended drugs for the COVID-19.

Table 2. A list of recommended drugs with their properties and possible mechanism of action.

Drug	Type	Properties and mechanism of action
Chloroquine	Antimalarial	Pharmacokinetics: • Reaches maximum plasma level in 3 hours • Principally excreted by kidney with initial half-life of 3-5 days and terminal half-life of 1-2 months Mechanism: • Halts pH-dependent entry of virus by altering pH of endosome. Therefore, viral genome is not released in the cytosol because the viral and endosomal membrane fail to fuse. • It interferes with sialic acid biosynthesis. Sialic acid forms a complex with protein capsid of virus that interact with cell surface receptor of human cell
Kaletra (Lopinavir and ritonavir)	Antiviral	Inhibitor of cytochrome P450 3A.
Ivermectin	Anti-parasitic	Single dose controls viral replication in 24-48 hours A hypnotised mechanism of action is by inhibition of nuclear import of viral protein by the drug.
Remdesivir	Antiviral	It inhibits viral RNA polymerase, thus prevents viral multiplication
Teicoplanin	Antibiotic	Used for treatment of gram-positive bacteria Inhibits cleavage of viral spike protein at low pH by Cathepsin L.

An expert consensus recommended chloroquine phosphate tablets (500 mg twice per day for 10 days) for mild to severely infected patients.[24] Certain precautions were also highlighted. These were blood testing, routine electrocardiography, administration of antiarrhythmic, antidepressant and antipsychotic drugs. Their precautions were recommended to exclude the possibility of anemia, thrombocytopenia or leukopenia, electrolyte disturbances, QT interval prolongation or bradycardia.

Dutch Center of Disease control suggested the need to stop treatment with chloroquine (CQ) at day five as the drug has a long half-life and can cause side effects. It also highlighted the need to differentiate between regimens based on chloroquine phosphate and chloroquine base. Italian scientists have recommended the utilization of Chloroquine or Hydroxychloroquine (HCQ) for patients with mild to severe respiratory symptoms.[24] The use of CQ and HCQ is still controversial due to low clinical study at present.

CQ is largely being considered for the treatment for COVID-19. A study was carried out in Manaus, Brazilian Amazon to test the dosage of the drug. CQ was given orally or by nasogastric tube. High dose was given

to one group (i.e. a total dose of 12g over a period of 10 days) and low dosage was given to another group (i.e. a total dose of 2.7g for 5 days). The results were against the use of high dose because it raised safety concerns.[8]

To determine the efficiency of HCQ, a study was conducted in Renim Hospital of Wuhan on 62 patients. The result showed a decrease in time to clinical recovery and cough remission time. Resolution of consolidation in pneumonia was also noted. This favors the use of HCQ under managed circumstances. A large-scale research study is still required for absolute support of the use of HCQ on a large scale.[28]

Two lead compounds have been designed 11a and 11b. These lead compounds bind to Cys145 of M^{pro} (a protease used by the virus for entry into cells) via the aldehyde group. Trials were conducted in mice which revealed that 11b has shorter half-life and faster clearance than 11a. 11a showed lower toxicity. Thus, the pharmacokinetic (PK) properties indicate that these are good candidates for treatment of SARS-COV-2.[29] As TMPRSS2 (Transmembrane Serine Protease 2), an enzyme, is used for viral entry, an inhibitor to TMPRSS2 (such as camostat mesylate) can block the infection. Interferons inhibit replication of SARS-CoV-2 in vitro. The effectiveness of interferon β, interferon α and interferon γ was studied. The result showed that interferon β was most potent amongst all of them. Thus, interferon β could be a drug used for treating the COVID-19.[30]

Some promising therapies are Remdesivir, vaccine, plasma therapy and stem-cell transfusion. Convalescent plasma has been used to treat previous outbreak like Ebola and MERS-CoV. This immunoglobulin treatment is understudy for COVID-19 because it blocks infection and suppresses viremia.[31]

Trial for vaccine development are accelerating. The aim is to device a vaccine which will be suitable for stocking for future use, suitable for adult health care workers and adults with underlining hypertension and diabetes. The major vaccines that have been established are whole virus vaccine, subunit vaccines and nucleic acid vaccine.[32]

Various companies and universities around the globe are working to develop the vaccine for COVID-19. At present, more than 90 vaccines have been designed.[33] The vaccine presents antigen to the body to induce immunity to combat the infection when a person is infected. The type of vaccines being used are virus vaccine, viral vector vaccine, nucleic acid vaccine and protein-based vaccine, as shown in ***Table 3***.

Convalescent plasma (CP) therapy is also being considered as a treatment because it has shown to decrease serum cytokine response. This is of great importance as viremia reaches its peak in the first week after infection and in the second week after onset of symptoms there is a cytokine storm which could prove to be life threatening.[34] SARS-CoV-2 induces a cytokine storm in the patients and CP therapy might be the gate way to improve this condition. CP has its limitations as it causes adverse results like chills, fever, anaphylactic reactions, transfusion-related acute lung injury, circulatory overload and hemolysis.[35]

For the limitation of onward spread of the virus between individuals to contain the epidemic and slow its progression, WHO and other organizations have given some recommendation for the prevention of spread of the infection. These recommendations include staying away from subjects who have acute respiratory infections, washing hands regularly, covering coughs or sneezes. Public gathering must be avoided especially by subjects with a compromised immune system.

Discussion

This article has led to the finding that coronavirus outbreaks have occurred before. This outbreak is unique due to the extent of emergency situations it has caused around the world. SARS-CoV- 2 does hold certain similarities with MERS-CoV and SARS-CoV in terms of genetics, receptor (i.e. ACE2 receptor used by SARS-CoV and SARS-CoV- 2) and some symptoms. R_0, case fatality and incubation periods are distinctive for SARS-CoV- 2. This information is of importance because it serves as a pioneer for the establishment of treatment.

Table 3. Current state of COVID-19 vaccines.

Vaccine	Type	Trials
Virus Vaccine	1.Weakened virus: Mutations are introduced in the virus by passing it through animal and human cells to decrease its infectiousness	Codagenix in Farmingdale, New York, and Serum Institute of India are working in collaboration to weaken the virus by changing the genetic code.
	2.Inactivated virus: Chemicals or heat is used to make the virus infectious	Sinovac Biotech in Beijing has started to test an inactivated version of SARS-CoV-2 in humans
Viral vector Vaccine	1.Replicating viral vector: A virus is genetically modified so that it does not cause disease. This type replicates in the cells.	Around 25 groups are working on viral-vector vaccines.
	2.Non-replicating viral vector: These are also genetically engineered but do not replicate because the key gene has been disabled	US-based drug giant Johnson & Johnson is working on Non-replicating viral vaccine
Protein based Vaccine	1.Protein subunits: Coronavirus proteins are directly injected into the body. This includes the use of the virus spike protein or other key part.	At present 28 teams are working on vaccines with viral protein subunits.
	2.Virus-like particles: These are empty virus without the genetic material and thus are not infectious.	5 teams are working on 'virus-like particle' (VLP) vaccines.
Nucleic acid vaccine	1.DNA-based vaccine: Genetic code for coronavirus protein is injected in form of DNA.	20 teams are aiming to use this technique
	2.RNA-based vaccine: RNA is used as genetic instruction for coronavirus protein. Typically, the spike protein is encoded.	

The study has limitations in terms of the time it has been done in because the pandemic has not been contained yet. Thus, some conclusions drawn from clinical trials and tests may change in future due to a better understanding on the grounds of the latest research.

The pandemic has posed obstacles in many aspects including economic, environmental, and psychological aspects. The most significant obstacle, at present, is its treatment because it is a certain tool to eradicate the COVID-19 infection and subsequently all problems that are arising due to it will settle down (especially the issue of economic crisis). Studies support that the best treatment is quarantine. The absolute treatment for the infection will take time and a great deal of future research.

The review has emphasized the virology, pathology and therapeutics of the most recent pandemic COVID-19. The pandemic is still escalating. It

is evident from the literature that the effect of this viral infection is not only bound to the lungs but is also harming other systems of the body. The exact mechanism about how COVID-19 is associated with certain disorders (such as neurological and cardiac) still require further research. This explains the complexity of the disease itself and difficulty for the search for its cure. At this point of the pandemic, there are an appreciable number of drugs and other therapeutic methods that have been researched but the absolute treatment is still to be achieved. Continuous development and research are underway to form a promising medication. Especially work is being done to design a vaccine for the infection and the latest research is pointing towards a promising result.

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Review

Probiotics as Promising Immunomodulatory Agents to Prevent COVID-19 Infection: A Narrative Review

Muhammad Luthfi Adnan,[1] Miranti Dewi Pramaningtyas.[2]

Abstract

After the outbreak in December 2019, Coronavirus Disease (COVID-19) has become a global health problem because of its rapid spread throughout the world. To date, there are no effective therapies to treat or prevent COVID-19 infection. Probiotic bacteria are widely used to prevent gastrointestinal infections by modulating intestinal microbiota. Therefore, this literature review focuses on the potential possessed by probiotic bacteria for the prevention of future COVID-19 infections. Information was extracted from PubMed and Google Scholar using the keywords: "COVID-19", "immunomodulator", "inflammation", and "probiotic" and synthesized into this narrative review. The results showed that probiotic bacteria have immunomodulatory activity that can increase immunity against pathogens by regulating the immune system through modulation of intestinal microbiota and interactions with the lymphatic system in the digestive tract. The ability of the immune system regulation by probiotic bacteria has the effect of increasing the body's defense mechanisms against pathogens that infect the respiratory tract. However, further evidence is still needed regarding the effect of probiotic immunomodulators in combating future COVID-19 infections.

Key Words: COVID-19; Immune system; Inflammation; Probiotics (Source: MeSH-NLM).

Introduction

Since its appearance in December 2019 in Wuhan, China, Coronavirus Disease (COVID-19) has become a worldwide pandemic by infecting more than 43,000 people in 28 countries as of February 11, 2020 and becoming a health problem in many countries. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and can be transmitted through patient droplets or direct contact with COVID-19 patients.[1] The SARS-CoV-2 virus is a type of virus of the genus β-coronavirus that is enveloped in a non-segmented positive-sense RNA virus.[2] The SARS-CoV-2 virus has the same genus as SARS-CoV, known for the SARS outbreak in 2003, and the Middle East respiratory syndrome coronavirus (MERS-CoV) which can cause deadly respiratory infections.[2]

Symptoms of COVID-19 patients include symptoms similar to influenza infections such as fever, coughing, muscle aches and dyspnea.[3] Treatment for COVID-19 patients is still limited to giving symptomatic therapy to patients. Providing care to patients is done to prevent complications that arise. Some of the treatments that are often used include the use of invasive mechanical ventilation, systemic corticosteroids and antiviral therapy. The most common complications that arise are acute respiratory distress syndrome (ARDS), anemia, acute heart injury and secondary infection.[3] However, some of the uses of the treatment are still unclear as to their effectiveness and there are currently no effective drugs for treating COVID-19.[3]

Treatment through immune system modulation has attracted much attention because it initiates the body's immune response to fight bacterial and viral infections.[4] The use of many immunomodulating agents was developed to initiate the body's immune system against infection and reduce the risk of damage to the host due to the activity of the immune response from proinflammatory cytokines. With research on vaccines to prevent COVID-19 still in development stages, the use of immunomodulators in modulating the immune system may be useful for pathology related to viral infections.[4]

Recent studies have shown the immunomodulatory effects of probiotic bacteria.[5] Probiotics are defined as being "living microorganisms which, when consumed in sufficient quantities, provide health benefits to the host".[5] Probiotics are widely used in the fermented food processing industry such as cheese, yoghurt or as supplements. Many studies show the health benefits of probiotics, one of which is to modulate the immune system to prevent viral infections through modulation of probiotic bacteria with the immune system in the intestinal mucosa.[5]

The purpose of this literature review is to discuss the immunomodulatory effects and the potential of probiotics to prevent COVID-19 infection.

Methods

Literature Search Strategy

A comprehensive electronic literature search was carried out using search tools from Medline (PubMed) and Google Scholar to identify relevant publications regarding COVID-19, immunomodulators, and probiotics. Database parameters performed using keywords include "COVID-19", "immunomodulator", "inflammation", and "probiotic". The literature used is full-text written in English and published within the last 10 years. The literature used consists of keywords that include "COVID-19", "immunomodulator", "inflammation", and "probiotic".

Eligibility Criteria

Excluded articles did not have a full-text publication or were not written in English. Inclusion criteria parameters include full-text in English,

[1] Medical Student, Universitas Islam Indonesia, Sleman, Indonesia.
[2] Master of Science, Department of Physiology, Universitas Islam Indonesia, Sleman, Indonesia

About the Author: *Muhammad Luthfi Adnan is currently a 4th year medical student of Faculty of Medicine, The Universitas Islam Indonesia of a 6-years medical program. His several research studies have been published at the 7th International Congress on Lipid Metabolism & Atherosclerosis (ICoLA 2018) in Seoul, South Korea, the Indonesia International (Bio)Medical Students' Congress (INAMSC) 2019 in Jakarta, Indonesia and the 30th European Student Conference (ESC) 2019 in Berlin, Germany.*

Correspondence:
Muhammad Luthfi Adnan
Address: Kaliurang St No.Km. 14,5, Krawitan, Umbulmartani, Ngemplak, Sleman Regency, Indonesia.
Email: 16711133@students.uii.ac.id

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published less than 10 years ago, articles have the keywords "COVID-19", "immunomodulator", "inflammation", and "probiotic", articles studying COVID-19, probiotics, probiotic activity as an immunomodulator, and probiotic immunomodulatory activity in the respiratory tract.

Results & Discussion

Pathogenesis of COVID-19

The SARS-CoV-2 virus, is closely related to the SARS-CoV-1 virus that targets angiotensin-converting enzyme 2 (ACE2) cells as receptor cells in host targeting.[6] The virus has an incubation period of 2-14 days during which the host is infectious.[6] The greatest burden of the virus is contained in the lung organs, causing symptoms similar to pneumonia with characteristic changes in lung opacity on CT imaging. Other symptoms of COVID-19 that are similar to that of pneumonia include fever, cough, shortness of breath and sore throat.[6] Some other symptoms of COVID-19 include gastrointestinal symptoms such as diarrhea, nausea and vomiting. This may be due to ACE2 receptors also found in intestinal epithelial cells. The finding of SARS-CoV-2 nucleic acid in a patient stool reveals a potential route for viral infection through feces.[7]

COVID-19 also impacts the body's immune system during the infection stage. For example, an increase in the ratio of neutrophils to lymphocytes (NLR) and T lymphopenia and a decrease in CD4 + T cells are found in patients with COVID-19. These findings indicate the presence of immune system dysregulation induced by viral activity targeting T lymphocytes. NLR, which is a systemic infection marker, was also found as part of a proinflammatory cytokine storm (TNF-α, IL-1, IL-6) and chemokine (IL-8) which correlated with the severity of COVID-19 patients.[8] The cytopathic effect of proinflammatory cytokine activity results in systemic inflammation which has the potential to cause death.[8]

The emergence of cytokine storms is in this case an overzealous immune response against viral infections. Cytokine storms are a form of immune homeostasis disorder and self-tolerance through interference with regulatory T cells that play a role in the control of systemic and tissue-specific autoimmunity. The high level of proinflammatory signals in cytokine storms results in collateral host tissue damage.[8] Uncontrolled cytokine storm activity in the immune system's reaction to a viral infection affects the process of remodeling airway tissue which risks increasing the severity of infection and damage to important organs causing a risk of death.[9,10]

Potential Health Effects of Probiotics

Probiotics are types of bacteria that can provide health benefits to the host. Some characteristics possessed by probiotic bacteria are (1) having the ability of probiotic bacteria to survive and reproduce in the intestine; (2) having benefits for the host through growth in the host body; (3) being non-pathogenic or toxic; (4) protect against pathogens (*i.e.*, bacteria, viruses or fungi); and (5) are resistant to transfer of antibiotic resistance. Probiotic bacteria of different strains can provide different benefits to the health of the host.[11]

Bacteria from the genus *Lactobacillus* and *Bifidobacterium* are widely used probiotics known as probiotic lactic acid bacteria (LAB). Probiotics work in part by binding to the intestinal mucosa and producing antimicrobial compounds, increasing the defense function of the intestinal barrier, and modulating immunity against intestinal pathogen infections.[12] Probiotics have an important role to play in fighting diarrhea, antibiotic-related diarrhea, prevention of colorectal cancer, and treatment agents for gastroenteric infections caused by various pathogens such as *Escherichia coli*, *Bacillus*, *Salmonella*, *Shigella*, *Vibrio cholera*, *Klebsiella* and *Pseudomonas*.[12]

Lactobacillus and *Bifidobacterium* bacteria have the structure of lipoteichoic acid (LTA), surface layer associated proteins (SLAPs) and mucin binding proteins (Mubs) that bind to glycocalyx in the intestinal epithelial layer.[13] Glycocalyx contains glycolipids and glycoproteins that interact with the structure layers of LTA, SLAPs and Mubs from probiotic bacteria. The composition between the structure of probiotic bacteria and intestinal mucosa has hydrophobic and adhesion properties that can synthesize the extracellular matrix components of fibronectin, collagen, and laminin.[13,14] Through the mechanism of adhesion on the surface of the intestinal epithelium, probiotic bacteria exert an increased effect on the integrity of the intestinal barrier and result in maintenance of immune tolerance, decreases the translocation of pathogenic bacteria across the intestinal mucosa, and prevent phenotypic changes due to diseases such as gastrointestinal infections, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).[15] The immune tolerance response from the interaction between the intestinal mucosa and the probiotic bacteria induces a balance in the microflora in the intestinal environment.[16]

In probiotic bacteria, antitoxins can produce a serine protease and phosphatase that degrades toxins from *E. coli* and *Clostridioides difficile,* as well as displaying the ability to destroy intersections between pathogenic bacteria with epithelium and viruses with enterocytes.[17] Probiotic bacteria also can interact with other microbiota in the intestinal environment and can rehabilitate intestinal microbiota balance in diarrheal infection conditions.[17]

Beyond the microbiome homeostasis effects of probiotics, their ability to fermentation non-digestible polysaccharides is an important attribute which is thought to affect host metabolism in a meaningful manner. Disorders caused by intestinal microbiota dysbiosis correlate with the onset of hypertension, obesity, and metabolic syndrome.[18] With this interaction activity between intestinal microbiota and host metabolism, probiotic bacteria may have potential as antihypertensive and hypocholesterolemic interventions in metabolic syndrome.[18,19]

Probiotic Immunomodulatory Activity

Some probiotic bacteria display an immunomodulatory function, regulating the production of two types of cytokines namely anti-inflammatory cytokines such as interleukin-10 (IL-10) and proinflammatory cytokines such as interleukin-6 (IL-6). In addition, the immunomodulatory activity of probiotics also works by balancing the T-helper (T_h)1 / T_h2 immune response through interactions on antigen-presenting cells (APC) in lymphocyte-dense Peyer's patches on part of the intestinal epithelium.[20,21] The ability to initiate immune system modulation from probiotics may minimize epithelial injury resulting from the inflammatory response. [22]

The immunobiotic ability of *Lactobacillus* and *Bifidobacterium* bacteria through the production of lactic acid can modulate the immune response in the intestinal mucosa by interacting with Toll-like Receptor 2 (TLR2).[21] Probiotic interactions in the intestinal environment induce a T_h1 immune response that results in the production of interferon cytokines (IFN)-β and activate the bactericidal activity of macrophages.[23] The host of intestinal probiotic interactions triggers lymphatic maturation, epithelial repair through endotoxin signaling and promotes intestinal microbial mucosal tolerance.[24]

The ability of probiotic bacteria to modulate the host immune system through activation of natural killer cells, dendritic cells, intraepithelial lymphocyte cells and macrophages that have an important role in the innate immune system. Probiotic bacteria work by binding to aryl hydrocarbon receptors and activating macrophages and dendritic cells so that there is a stimulus to release TNF-α proinflammatory cytokines from epithelial cells and enhance the immune system. Research conducted by Villena *et al.* (2014) showed the defense mechanism of intestinal cells through the administration of probiotic bacteria through immunoregulators with the production of proinflammatory cytokines

such as IL-6 and TNF-α in response to pathogens and the production of anti-inflammatory cytokines IL-10.[21]

Besides their immunomodulator role in the immune system, probiotics have anti-inflammatory potential through bioactive peptide compounds.[25] The compounds produced from these probiotic bacteria can restore intestinal permeabilities. Also, the probiotic activity suppresses the activity of T_h2 cells to produce IgE, interleukin-4 (IL-4) and IL-13 preventing asthma and allergic reactions.[25,26] Anti-inflammatory activity in the lungs plays a role in decreasing lung inflammation such as decreasing the levels of proinflammatory cytokines and C-reactive protein (CRP).[27]

Probiotic bacteria produce metabolites in the form of short-chain fatty acids (SCFA) consisting of acetate, propionate, and butyrate which are widely present in the colon epithelium. Parts of the butyrate are used as energy by the colonocytes while the rest of the other SCFA are absorbed into the portal circulation through the intestine.[28] The SCFA metabolite binds specifically to the G-protein-coupled receptor 43 / free fatty acid receptor 2 (GPR43 / FFAR2), GPR41 / FFAR3 and GPR109A. Interactions on these receptors result in the development of macrophages and increase the differentiation of dendritic cell precursors that can migrate to the lungs and change the regulator T cells with T_h2 cells.[29]

Interaction between the intestinal relationship with the lungs is mediated by the lymphatic system through the TLR4 dependency mechanism and produces IgA associated with gut-associated lymphoid tissue (GALT).[30] These probiotic bacteria will induce regulatory T cells and initiate T helper 17 (T_h17) production and T_h1 immune memory response.[30] The circulation of the lymphatic system from the gut-lung axis enables T_h17 cells to be transferred from the intestinal mucosa to the bronchial epithelial mucosa in lymph nodes in the airways. Besides suppressing the activity of pathogens that attack the respiratory system, the activity of probiotic interactions in the intestine with the airways prevents damage to the airway tissue by controlling the defense of the host immune system in the lungs.[30]

Immunomodulatory Effect from Probiotic Against Covid-19

COVID-19 infection attacks the lung tissue and activates inflammation in the airways.[31] The results from serum sampling of COVID-19 patients has shown an increase in the number of proinflammatory cytokines such as IL-1B, IL-6, IL-15, IL-15, IL-17 IFN-γ and TNF-α.[31] This leads to the emergence of cytokine storms and correlates with the severity of the disease.[31] The emergence of cytokine storms can lead to pulmonary fibrosis and damage to respiratory organs.[32] This inflammatory stimulus-response may be due to the activation of the T_h1 cell response.[33]

The potential effect of probiotics in influencing the activity of cytokine storms due to COVID-19 infection may be through interactions in the gut microbiota with the immune system.[34] Disruption to the intestinal microbiota environment results in an imbalance of T_h1 / T_h2 cells, which results in the production of proinflammatory cytokine storms in the lungs.[34] Through modulation of intestinal microbiota, there is a shift in the balance between T_h1 / T_h2 cells which could theoretically reduce the inflammatory response in the respiratory tract, thereby reducing the severity of disease.[34]

The activity of modulating intestinal microbiota through administration of probiotic bacteria has an impact on controlling the lung immune system response to viral infections. Probiotic bacteria can reduce the excessive inflammatory response in the face of viral infections by influencing T cells to produce IFN-γ.[35] The activity of probiotic bacteria in regulating the immune system is carried out through interactions with regulatory T cells in Peyer's patches on the intestinal surface thereby preventing excessive cytokine storm activity in fighting viral infections.[36]

In addition to stimulating the regulation of T_h1 / T_h2 cell balance, the activity of probiotic bacteria can initiate a defense system in the airway mucosa.[37] As a result of the response of proinflammatory cytokines in the airway mucosal epithelium, airway remodeling activity causes narrowing of the airways. Airway remodeling arising from pro-inflammatory cytokines can lead to breathing difficulties and a worsening of patient condition.[38] Prevention of airway remodeling due to viral infection creates therapeutic targets for probiotic bacteria to potentially prevent worsening the condition of patients in COVID-19.[39,40]

Conclusion

With the development of therapies and vaccines for the prevention of COVID-19 infection still ongoing, the immunomodulatory effects of probiotic bacteria may have the potential to help with COVID-19 infection. The ability of probiotic bacteria to regulate the gut microbiota may in turn modulate immune system in a manner which could be useful in COVID-19. The findings from previous studies still need further research on broader subject matter to ensure the safety of therapy, so that the immunomodulatory potential of the probiotic bacteria can be maximized in the fight against COVID-19 infection in the future.

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Review

FKBP5 Gene Variants as Predictors for Antidepressant Response in Individuals with Major Depressive Disorder Who Have Experienced Childhood Trauma. A Systematic Review

Natalie Wietfeldt,[1] Andrew J. Boileau.[2]

Abstract

FKBP5 gene variants may predict antidepressant treatment response in individuals with Major Depressive Disorder. PubMed and Web of Science were searched systematically for articles studying individuals who had received a diagnosis of Major Depressive Disorder (MDD) and were given antidepressant treatment. Inclusion criteria were studies that researched FKBP5 and its variants and focused on antidepressant treatment response. Previous studies support a potential underlying epigenetic mechanism, demethylation at FKBP5 polymorphisms (rs1360780, rs3800373, rs9470080, and rs4713916) after experiencing childhood trauma, leading to increased hypothalamic-pituitary-adrenal (HPA) axis sensitivity and a propensity for the development of MDD. These polymorphisms informed the review, but additional polymorphisms (rs9380514, rs352428) were also considered. Studies conducted prior to 2008, reviews, meta-analyses, editorials, and non-research-based articles were excluded. Studies examined in this article suggest FKBP5 polymorphism rs4713916 and FKBP5 RNA levels may be associated with antidepressant response. Variants rs1360780, rs3800373, and rs9470080 were associated with both positive response and non-response or lack of remission. Variants rs9380514, rs352428, and rs936882 were associated with poor response to antidepressant treatment or non-remission. Further insights into the role FKBP5 plays in development and antidepressant treatment response may be aided by future studies focused on individuals who previously experienced childhood trauma and later developed MDD.

Key Words: Pharmacogenetics; Depressive Disorder, Major; Adult Survivors of Child Adverse Events (Source: MeSH-NLM).

Introduction

In 2018, approximately 17.7 million adults in the United States had suffered at least one major depressive episode,[1] and a survey conducted by the Centers for Disease Control and Prevention (CDC) estimated 12.7 percent of Americans aged 12 and over took antidepressant medication within the past month.[2] Antidepressants used to treat Major Depressive Disorder (MDD) have historically varied in efficacy for different individuals. Prescription of these medications is often on a trial-and-error basis, potentially delaying effective treatment for patients.

In an effort to improve the selection of an effective treatment, antidepressant pharmacotherapy has become one of the first ventures into pharmacogenetics, a field that aims to identify ideal therapies based on the patient's genetic data. Companies including Myriad Genetics have developed genetic testing (GeneSight) to identify genetic polymorphisms that can be used to clinically predict antidepressant efficacy, and are currently being used in practice today. However, the research linking genetic polymorphisms to MDD and antidepressant efficacy have not yielded consistent results.[3-5] Support from professional organizations including the American Psychiatric Association is lacking,[6] suggesting further study in defined subpopulations may be necessary. Traditionally, studies have used race and ethnicity. Recent studies indicate that there may be several origins and subtypes of MDD, suggesting that a more appropriate subpopulation for genetic studies may be identified by a shared experience or other factors contributing to MDD development.[7,8]

Increased hypothalamic-pituitary-adrenal (HPA) axis activity has been linked to depression in several studies.[9,10] The glucocorticoid receptor plays a critical role in preventing a continued stress response mediated by the HPA axis after a threat has ended.[11] FK506 binding protein 5 (FKBP5) is a gene for a glucocorticoid receptor binding protein that regulates glucocorticoid receptor sensitivity within the HPA axis. It has been identified as a probable predictor of antidepressant response and has a potential defined subpopulation for study, individuals who have experienced childhood trauma. FKBP5 variants located in regions of transcriptional regulation including rs1360780 undergo epigenetic alterations (demethylation) as a result of childhood trauma, and have been associated with MDD.[11-14] In the proposed mechanism, decreased methylation of FKBP5 at transcriptional regions leads to upregulation of FKBP5, which decreases glucocorticoid receptor sensitivity by binding to its complex and preventing its translocation to the nucleus. This molecular interaction results in increased resistance and ultimately dysregulation of the HPA axis, predisposing individuals to developing MDD.[11,15-20] Additionally, early studies in mice show that loss of FKBP5 reduces expression of excitatory glutamate receptors and increases the expression of GABA in the hippocampus, ultimately affecting long term potentiation and neuroplasticity.[21] FKBP5 rs1360780 polymorphisms in individuals with MDD who experienced childhood trauma have also been associated with structural and functional differences within the brain, including reduced activity in the insula following emotional stimuli, and lower FKBP5 methylation levels have been linked with reduced gray matter concentration in the inferior frontal orbital gyrus bilaterally, an area associated with depressive symptoms.[22-24] Other studied variants include the rs9296158, rs3800373, and rs9470080 alleles.[3,11,12, 25-28]

[1] BS, Saba University School of Medicine, The Bottom, Caribbean Netherlands.
[2] PhD, Full Professor, Saba University School of Medicine, The Bottom, Caribbean Netherlands.

About the Author: *Natalie Wietfeldt is currently a medical student of Saba University School of Medicine, Saba, Dutch Caribbean, Class of 2021. She was inducted into the Alpha Omega Phi honor society in September 2018.*

Correspondence:
Natalie Wietfeldt
Address: The Bottom, Caribbean Netherlands.
Email: n.wietfeldt@saba.edu

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This review will examine the epigenetically-modified FKBP5 variants associated with previously experienced childhood trauma and their potential to predict antidepressant response. Searching the literature for genetic variants associated with a pathophysiologic mechanism may yield insights into future research directions to identify targeted treatments for specific subpopulations.

Methods

Search Strategy and Selection Criteria

PubMed and Web of Science were searched for relevant articles. Titles and abstracts were analyzed manually for direct relevance to the hypothesis. Required inclusions were 1) focus on individuals diagnosed with unipolar MDD and 2) associations between FKBP5 variants and response to antidepressant treatment. FKBP5 polymorphisms associated with childhood trauma and development of MDD were of particular interest, but polymorphisms that did not meet these criteria were also included. Other inclusion criteria were human-based studies that specifically researched the FKBP5 gene and its variants and antidepressant treatment response.

Studies that were published prior to 2008, meta-analyses, literature reviews, consensus papers, editorials, and updates were excluded. Additionally, articles that were considered out-of-scope of this review included studies that used non-human models with a focus on neuronal differentiation, studies that focused on the interaction between FKBP5 and other genes, and those that focused on FKBP5 variants and their impact on conditions other than MDD (e.g., anxiety disorders and bipolar disorder, high stress reactivity and stress hormone regulations). Studies that did not differentiate between unipolar and bipolar depression in their patient sample and those that examined FKBP5 and MDD in older adults without a history of childhood maltreatment were also excluded.

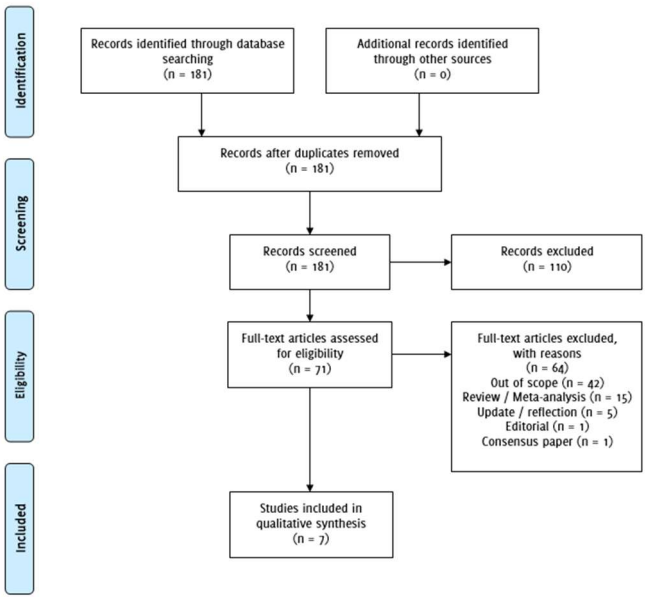
An initial search in PubMed for articles published between 2008-2018 with the search string "fkbp5" AND "major depression" yielded 32 results. Of these articles, 31 were excluded: 23 were out of scope as determined by the criteria above, 3 were review articles, 2 were meta-analyses, 2 were updates or reflections, and 1 was an editorial. The search string "fkbp5" AND "depression" AND "pharmacogenetics" yielded 10 results; 7 articles were excluded as 4 were determined to be out of scope, 2 were updates or reflections, and 1 was a meta-analysis. The search string "antidepressant response" AND "fkbp5" yielded 13 results. Nine of these articles were excluded, with 4 out of scope, 2 reviews, 1 meta-analysis, 1 consensus paper, and 1 update. Due to the specificity of the search for the FKBP5 gene and its variants, utilizing MESH terms did not yield results within the inclusion criteria.

Repeating the searches with Web of Science using "fkbp5" AND "major depression" published between 2008-2018 yielded 112 findings, and one additional article for analysis. Using the search terms "fkbp5" AND "depression" AND "pharmacogenetics" yielded 14 results, and included 3 repeated findings. "Antidepressant response" AND "fkbp5" did not yield additional articles for analysis. In total, 7 articles were selected for inclusion in analysis. ***Figure 1*** describes the PRISMA flow diagram.

Data Extraction

For the articles included in the analysis, the study characteristics and methods were extracted. The number of participants, methods used to assess depression symptoms, specific antidepressant treatments or algorithms, and methods used to assess treatment response were noted for each study. Articles were examined for associations between antidepressant response and FKBP5 polymorphisms or mRNA levels. These findings were grouped by FKBP5 expression levels, polymorphisms previously found to be associated with childhood trauma and development of MDD, and polymorphisms that did not have previous evidence of association with childhood trauma and development of MDD.

Figure 1. PRISMA Flow Diagram.



Results

Antidepressant treatment and FKBP5 expression levels

Cattaneo *et al.*[29] and Banach *et al.*[30] examined FKBP5 expression levels following antidepressant treatment with conflicting results (Table 1). Cattaneo *et al.*[29] selected participants from the GENDEP trial for analysis. Leukocyte mRNA levels of FKBP5 and other candidate genes were measured using quantitative PCR. FKBP5 expression levels were normalized to the mean expression of reference genes including glyceraldehyde 3-phosphate dehydrogenase, beta actin, and beta-2 microglobulin. The Pfaffl method, which accounts for differences in primer efficiencies, was used to compare FKBP5 expression with controls. Additionally, changes in FKBP5 mRNA levels were compared before treatment and after 8 weeks.

FKBP5 mRNA levels in depressed patients were found to be higher than in controls (controls (mean±SEM): 0.99±0.02; patients: 1.26±0.02; +27% change, $p<0.0001$). 51 patients responded to antidepressants, with 26 responding to escitalopram and 25 responding to nortriptyline. 23 patients did not respond to antidepressants, with 12 not responding to escitalopram and 11 not responding to nortriptyline. For all 74 patients, FKBP5 mRNA levels were 1.26±0.02 prior to treatment, and 1.17±0.02 after 8 weeks of treatment. Successful antidepressant treatment, irrespective of drug class, reduced FKBP5 mRNA levels in depressed patients (no errors reported; -11% change, $p<0.0001$). There was no effect on FKBP5 levels in patients who did not respond to treatment (no errors reported; -2% change, $p=0.45$; response x time interaction: $F=4.4$, $p=0.04$; drug x time interaction: $F=0.05$, $p=0.8$).

Banach *et al.*[30] collected peripheral blood for isolation of RNA from leukocytes and a dexamethasone suppression test prior to the start of antidepressant treatment. Eight weeks after receiving treatment, a second blood sample was collected. FKBP5 gene expression was quantified using qPCR with 18S rRNA used as a reference gene. Differences in gene expression before and after treatment were compared using the non-parametric Wilcoxon signed-rank test.

Three patients were observed to have HPA axis dysregulation at the beginning of the study, and two had normal function following 8 weeks of treatment. No statistically significant difference in mean cortisol levels before and after 8 weeks of treatment was found ($p=0.944$). Following 8 weeks of antidepressant treatment, all participants experienced improvement in depressive symptoms and all but one, were in remission. The mean HAM-D score value was 3.4±3.1 for

Table 1. Studies that Examined Antidepressant Response and FKBP5 Gene Expression/Polymorphisms

Author	Genetic variant or gene expression	Population	MDD criteria	Antidepressant	Assessment of response
Banach *et al.* (2017)[30]	Leukocyte FKBP5 gene expression	30 female patients age 18-60 from the Department of Adult Psychiatry at Poznan University of Medical Sciences	DSM-IV and HAM-D Moderate severity	Participants were drug free at least 6 months prior to entering study Sertraline (50-150 mg) or Venlafaxine (75-225 mg)	Improvement in depressive symptoms, as determined by >50% reduction in HAM-D Remission determined by HAM-D <8
Cattaneo *et al.* (2013)[29]	Leukocyte FKBP5 mRNA levels	31 males and 43 females from the GENDEP trial (811 adult outpatients; 296 men and 514 women from 9 psychiatric center in 8 European countries) age 19-72	DSM-IV Moderate severity	Selected subset did not take medication for at least 2 weeks prior to entering the trial Nortriptyline (50-150mg daily) or Escitalopram (10-30 mg daily) for 12 weeks	Assessed weekly for depression symptom severity and antidepressant response using MADRS, HAM-D, and BDI Successful response: >50% reduction in MADRS score from baseline through week 12
Lekman *et al.* (2008)[31]	rs4713916	1,809 patient samples age 18-75 from STAR*D study that were determined to have MDD Patients were compared to 739 controls that were obtained from the Rutgers Cell Repository and were determined not to have a mental health condition	DSM-IV	Citalopram as a first-line antidepressant; data up until 14 weeks was used for analysis to account for patients that were resistant and required a second treatment	QIDS-C to measure antidepressant response at each visit and at 14 weeks; patients were determined to have responded to treatment if they had at least a 50% reduction in their QIDS-C score and patients determined to be in remission had a QIDS-C score ≤5
Zobel *et al.* (2010)[32]	rs3800373, rs755658, rs1360780, rs1334894, rs4713916	110 German patients age 18-60 with recurrent unipolar depression, as determined by DSM-IV, after accounting for drop-outs and 284 controls	DSM-IV	Tapered off previous antidepressants prior to start of study Citalopram (20-40 mg) with or without Lorazepam	HAM-D at baseline (Day 8) and Day 36 Antidepressant response assessed using dexamethasone-suppressed corticotropin-releasing hormone test
Stamm *et al.* (2016)[33]	rs1360780	298 patients age 18-70 with MDD who were recruited from hospitals and were participating in the German Algorithm Project (GAP3) or the Zurich Algorithm Project	DSM-IV and HAM-D score ≥15	Patients in both studies received a stepwise treatment regimen guided by an algorithm (n=171) or standard treatment (n=127). Participants first received one of four antidepressant classes (venlafaxine, sertraline, amitriptyline, or reboxetine) and maintained the same dosage for at least 4 weeks. Patients who did not respond (HAM-D score reduction <30%), received lithium, an increased dose of the same medication, or change to a different antidepressant class. Patients who did not respond to the escalated step continued with other options until receiving electroconvulsive therapy.	Assessed for antidepressant response at the start of the study and every two weeks throughout the treatment period using HAM-D Patients with a HAM-D score less than 10 were determined to be in remission

Author	Genetic variant or gene expression	Population	MDD criteria	Antidepressant	Assessment of response
				For the standard treatment group, physicians were allowed to choose the appropriate treatment	
Fabbri *et al.* (2018)[34]	rs3800373 rs1360780 rs9470080	Three original populations: 1) First European sample consisted of 357 patients diagnosed with MDD and received antidepressants 2) Second European sample contained 218 patients with moderate or severe MDD 3) Italian sample (ITAS) consisting of 96 patients with MDD STAR*D sample was used for replication	1) DSM-IV 2) DSM IV and MADRS score >22 Moderate or severe MDD 3) DSM IV and a HAM-D score ≥13	First European Sample: Unspecified antidepressants Second European Sample: Venlafaxine then Escitalopram (if no response after 6 weeks) Italian Sample: Unspecified antidepressants	First European Sample: HAM-D after 4 weeks of treatment Second European Sample: MADRS was used to evaluate each patient's symptoms of depression biweekly from the start of the study through week 12 Italian Sample: HAM-D; evaluated weekly from beginning of the study through week 8 For the three original patient populations, response to antidepressant treatment or remission was evaluated at week 4 or 6; response was determined by a decrease of 50% or greater in the HAM-D or MADRS and remission was a score of less than or equal to 7 on the HAM-D or less than 10 on the MADRS
Ellsworth *et al.* (2013)[35]	rs9380514 SNP 35758265 (no rs number available) rs352428	512 patients in the Mayo Clinic Pharmacogenomics Research Network-Antidepressant Medication Pharmacogenomic Study (Mayo PGRN-AMPS) and a replication study of 950 patients from the STAR*D study	HAM-D score ≥14	Citalopram or escitalopram	Treatment response was assessed at 4 and 8 weeks using the QIDS-C, and patients with ≥50% reduction in QIDS-C score were determined to have responded. Patients with a QIDS-C score less than 5 were determined to be in remission

Legend: Major Depressive Disorder (MDD); (DSM-IV) Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Depression Rating Scale (HAM-D); Beck Depression Inventory (BDI); Sequenced Treatment Alternatives to Relieve Depression (STAR*D); Quick Inventory of Depressive Symptomatology-Clinician rating scores (QIDS-C)

patients taking sertraline and 5.0±2.4 for patients taking venlafaxine. There was no difference in gene expression of FKBP5 before and after antidepressant treatment (pre-treatment: max=16, upper quartile=15, median=13.2, lower quartile=11.2, min=11; post-treatment: max=16.8, upper quartile=14.4, median=13.1, lower quartile=11.8, min=9.9; p=0.813).

FKBP5 variants linked to childhood trauma in prior studies: rs1360780, rs3800373, rs9470080, and rs4713916

Lekman *et al.*,[31] Zobel *et al.*,[32] Stamm *et al.*,[33] and Fabbri *et al.*,[34] found correlations between rs1360780, rs3800373, rs9470080, and rs4713916 and antidepressant response/non-response and remission.

Lekman *et al.*[31] determined FKBP5 genotype using Illumina Next Generation Sequencing. In the genotype association test to identify associations with antidepressant response, FKBP5 rs4713916 was shown to be significantly associated with remission (AA/GG genotype: OR=1.60, 95% CI: 1.04-2.43; AG/GG genotype: OR=1.47, CI: 1.15-1.88; p=0.049) but not treatment response (p>0.05) when studied in all ethnicities and corrected for multiple testing. Studying linkage disequilibrium patterns reveals that rs4713916 single nucleotide polymorphisms (SNP) may serve as the functional region of FKBP5.

Zobel *et al.*[32] examined five FKBP5 polymorphisms located in the same haplotype block including rs3800373, rs755658, rs1360780, rs1334894, and rs4713916. DNA samples were collected from whole blood and fluorescence-based allelic discrimination techniques were used for analysis. Comparison of FKBP5 genetic variants between the treatment group and controls and mean values of treatment response were compared using t-tests.

FKBP5 variants rs3800373 (AA allele) and rs4713916 (GG allele), also associated with MDD diagnosis, demonstrated a decreased reduction in cortisol secretion after 4 weeks of treatment (rs3800373: pre-treatment mean=2211, errors not given; post-treatment mean=-426, errors not given; p=0.08; rs4713916: pre-treatment mean=1932, errors not given; post-treatment mean=-338, errors not given; p=0.04). These associations were insignificant with multiple testing. No significant changes were found in HAM-D scores.

Stamm *et al.*[33] determined FKBP5 rs1360780 genotypes. Cox regression analysis was used to analyze the interaction between genotype and antidepressant treatment. The FKBP5 rs1360780 C allele carriers were found to benefit from the standardized antidepressant treatment algorithm. Approximately 64.4% of patients undergoing the algorithm treatment reached remission compared to 38.8% of those in the usual treatment group (p<0.001). Patients who were rs1360780 TT allele carriers showed better treatment response with the first treatment step than CT/CC allele carriers (TT: 60.9%, CT/CC: 38.2%, p=0.03), but there was not a significant difference at the end of the treatment sequence (TT: 69.6%, CT/CC: 53.5%, p>0.05). After six weeks of treatment with one antidepressant, rs1360780 TT allele carriers were found to have significant improvement (HR=1.89, p<0.03). Additionally, rs1360780 TT allele carriers were more likely than CC/CT allele carriers to achieve remission (HR=0.52; p=0.01).

Fabbri *et al.*[34] analyzed genetic data from three original patient populations and the patients from the STAR*D sample to study the association of various candidate genes, including FKBP5, with remission, antidepressant response, and treatment resistance. The STAR*D sample, as described previously, was used for replication. Effects of selected SNPs on antidepressant response, remission, and treatment resistance were tested using logistic regression models.

Fabbri *et al.*[34] examined FKBP5 polymorphisms and their association with four phenotypes: response to the treatment provided to the associated population, remission to the provided treatment, lack of response to escitalopram, and lack of remission when taking escitalopram. In the first European sample, FKBP5 rs3800373 CC genotype and C allele were associated with a higher risk of non-response (genotype: p=0.046, OR=0.11, 95% CI: 0.005-0.68). Additionally, the rs3800373 CC genotype corresponded with treatment resistance, including lack of response (p=0.01 OR=5.15, CI: 1.47-18.87) and lack of remission (p=0.02, OR=6.44, CI: 1.51-35.34) when taking escitalopram. The rs3800373 CA genotype was only correlated with lack of remission when taking escitalopram in the second European sample (p=0.04, OR=2.93, CI: 1.07-8.55), and was associated with a higher risk for lack of response (p=0.01 OR=0.28, CI: 0.09- 0.73) and remission (p=0.03, OR=0.27, CI: 0.07-0.83) in the ITAS sample. The rs3800373 C allele was linked with higher risk of non-response in the first European sample (p=0.03, OR=0.50, CI: 0.26-0.93) and the second European sample (p=0.02, OR=0.52, CI: 0.29-0.91). The rs3800373 C allele was also associated with lack of response to escitalopram (p=0.005, OR=2.35, CI: 1.29-4.27) and lack of remission when taking escitalopram in the second European sample (p=0.002, OR=3.07, CI: 1.52-6.42).

The rs1360780 TT genotype was associated with a higher risk of non-response to venlafaxine (p=0.02, OR=0.24, CI: 0.065-0.71), lack of response to escitalopram (p=0.01, OR=4.27, CI: 1.40-13.04), and lack of remission when taking escitalopram (p=0.02, OR=4.76, CI: 1.36-19.77) in the second European sample. In the ITAS sample, the rs1360780 CT genotype correlated with a higher risk of non-response to antidepressants (p=0.002, OR=0.22, CI: 0.08-0.55) and non-remission (p=0.003, OR=0.17, (CI: 0.05-0.52). The rs1360780 T allele corresponded with lack of response to venlafaxine in the second European sample (p=0.02, OR=0.60, CI: 0.38-0.93) and treatment in the ITAS sample (p=0.009, OR=0.40, CI: 0.20-0.78). Additionally, in the second European sample, the T allele was associated with lack of response (p=0.01, OR=1.95, CI: 1.16-3.26) and lack of remission (p=0.01, OR=2.05, CI: 1.17-3.60) when taking escitalopram. In the ITAS sample, the T allele was linked with a higher risk of non-remission (p=0.04, OR=0.45, CI: 0.20-0.95).

In the second European sample, the rs9470080 TT genotype was associated with lack of remission when taking escitalopram (p=0.0469, OR=3.96, CI: 1.06-16.65). The rs9368882 TT SNP, found to be in high linkage disequilibrium with rs9470080 (R2=0.67), was correlated with a higher risk of non-remission in patients taking citalopram in the STAR*D replication study (p=0.035, OR=0.82, CI: 0.69-0.98).

Fabbri *et al.*[34] also provided another perspective of their results, as described within this paragraph. All findings showed consistent effects in two or more of the groups that responded to antidepressant treatment, were in remission, or did not respond or achieve remission while taking escitalopram. In the second European sample, rs3800373 AA genotype/A allele showed some evidence of response and remission (no OR or CI reported; p=0.03 for the allelic repeated-time analysis). The rs1360780 CC genotype/C alelle were linked with response to venlafaxine and remission, and confirmed using repeated time analysis (allele: no OR or CI reported, p=0.01 and gen..otype: no OR or CI reported, p=0.0059). In the ITAS population, the rs1360780 CC genotype/C alelle, rs3800373 AA allele, and rs9470080 CC genotype were associated with antidepressant response and remission (rs1360780 genotype: p=0.014, no OR or CI reported and allele: p=0.001; rs3800373 AA allele: p=0.003, no OR or CI reported; significance for rs9470080 not given).

FKBP5 variants not linked to childhood trauma in prior studies: rs9380514, rs352428

Ellsworth *et al.*[35] found additional single nucleotide polymorphisms that may play a role in functional regulation of FKBP5. Ellsworth *et al.*[35] utilized Sanger and Illumina Next Generation genetic sequencing to sequence FKBP5 in lymphoblastoid cells. FKBP5 variants were identified using Next Generation sequencing, and 340 SNPs met criteria for analysis including having a minor alley frequency of 1% or higher, passing the Illumina Golden Gate genotyping quality control criteria, and absence of significant deviation from Hardy-Weinberg equilibrium. The effect of different SNPs on response and remission were analyzed using logistic regression models and were adjusted for potential population stratification. Electrophoresis mobility shift and reporter gene assays were performed on nuclear extracts from two glioblastoma cell lines and lymphoblastoid cells.

Association analysis for the Mayo PGRN-AMPS patients found that FKBP5 rs9380514 (A allele) corresponded to poor antidepressant response at the last visit (P=0.0249, OR=0.65 (95% CI: 0.44-0.95)) and after 8 weeks (P=0.0175, OR=0.59 (CI: 0.38-0.91)). SNP 35758265 (no rs number available) corresponded with a percentage change in QIDS-C after the last visit (no mean or SEM provided; Spearman: 0.09, P=0.042). Twenty-two SNPs were affiliated with remission after 8 weeks at the last visit, 15 trans FKBP5 expression quantitative trait loci (eQTL) SNPs corresponded to antidepressant response after 8 weeks or at the last visit, and 6 FKBP5 eQTL SNPs were associated with remission after 8 weeks of treatment or at the last visit; however, none of these associations were found to be significant after correcting for multiple testing. Association analysis replicating 6 SNPs from the STAR*D study found FKBP5 eQTL SNP rs352428 to be associated with poor antidepressant response after 6 to 8 weeks (P=0.05, OR=0.74, CI: 0.54–1.00). There were no associations found between rs1360780, rs3800373, and rs4713916 and antidepressant response (no statistical information provided). Electrophoresis mobility shift and reporter gene assays confirmed that rs352428 (A/G alleles) may play a potential role in regulation of transcription.

Discussion

This review examined studies that evaluated FKBP5 polymorphisms and expression levels and their association with antidepressant response. Studies that included polymorphisms previously linked to a potential underlying epigenetic mechanism of development of MDD in individuals who experienced childhood trauma were of particular interest. FKBP5 is a promising biomarker due to the multitude of evidence associating a specific environmental factor with increased susceptibility to development of MDD.[3,11-15,19,20,25-28]

Cattaneo *et al.*[29] and Banach *et al.*[30] examined FKBP5 RNA expression levels following antidepressant treatment. While Cattaneo *et al.*[29] displayed decreased RNA expression following treatment, Banach *et al.*[30] did not observe significant differences. Potential explanations for this disparity, as noted by Banach *et al.*,[30] include the lack of HPA axis dysregulation observed in the studied population. Additionally, Banach *et al.*[30] studied a smaller group of individuals (30 participants) compared to the 74 patients studied by Cattaneo *et al.*,[29] which likely

resulted in lower statistical power for the former. Both studies contain relatively small sample sizes, and a larger group of participants may be necessary to observe the true effects of antidepressants on FKBP5 levels. Of note, Banach *et al*.[30] observed a trend of decreased FKBP5 mRNA expression after administration of sertraline and an increase of expression after venlafaxine therapy, although significance was not reached.

Variants of the FKBP5 rs1360780 allele were associated with both successful antidepressant response and remission and non-response. Stamm *et al*.[33] found that the rs1360780 TT allele carriers were more likely to respond to a standardized algorithm antidepressant treatment regimen and experience more remission compared to CT/CC allele carriers. However, a greater percentage of CT/CC allele carriers also achieved remission in the algorithm treatment group compared to treatment as usual. In contrast, Fabbri *et al*.[34] found the TT/CT genotypes to be associated with non-response to antidepressants and lower rates of remission. These findings suggest the mode of treatment is significant, and genotype alone may not account for differences in antidepressant response. Fabbri *et al*.[34] found that the rs1360780 CC genotype/C allele had nominal associations with response to venlafaxine and remission, and decreased risk of treatment resistant depression in a European and ITAS population. The data from these two studies suggest that both the TT allele and CT/CC allele may have a better response to different treatments. The positive association with FKBP5 polymorphisms and response to different treatments strongly supports that it plays some role in treatment response. However, the differences in treatment provided within the two studies makes it difficult to parse out the true impact of genotype on treatment response, and future studies might consider comparing rs1360780 polymorphisms and antidepressant response to a wider range of different treatment options and drug classes, including a placebo, within the same population.

Fabbri *et al*.[34] also found the rs3800373 AA genotype/A allele showed some evidence of response and remission in two populations, and the CC genotype/C allele was associated with non-response and lack of remission. Additionally, the rs9470080 CC allele was associated with antidepressant response and remission, and the TT genotype was correlated with decreased remission in patients receiving escitalopram. Also mentioned by Fabbri *et al*.[34] as an interesting finding, the closely-linked rs9368882 was associated with non-remission in patients who received citalopram. Although some of these findings were positive, Fabbri *et al*.[34] noted the associations were nominal. Previous studies have similarly linked these polymorphisms to increased susceptibility of MDD in individuals who experienced childhood trauma, suggesting a basis for the association.[3,28] The utilization of three study populations strengthened the likelihood of finding a true association. However, relatively small sample sizes may have prevented strong significant associations from being discovered.

Zobel *et al*.[32] found associations between the FKBP5 rs3800373 AA genotype and rs4713916 and decreased reduction in cortisol secretion after treatment, suggesting a correlation with non-response to antidepressants. However, no significant changes were found in HAM-D scores and these associations were insignificant with multiple testing. Interestingly, both the rs3800373 AA genotype and rs4713916 were also associated with MDD diagnosis in the study. Non-response to antidepressant treatment conflicts with the positive rs3800373 AA genotype association found by Fabbri *et al*..[34] However, the difference in these findings may be due to small effect sizes, as Zobel *et al*.[32] had approximately half of the study population drop out. It should also be noted that those that tended to drop out had a greater average number of depressive episodes and likely were more treatment resistant. This potentially skews their data toward more favorable results, although none were found. Strengths of the study include the use of a dex/CRH test as a biological indicator of antidepressant response. As noted by Zobel *et al*.[32] and Lekman *et al*.,[31] using standardized survey measures to determine response and non-response may be another explanation for disparities in treatment response found in the same polymorphisms.

Lekman *et al*.[31] found rs4713916 was shown to be significantly associated with remission (p=0.049) but not treatment response when studied in all ethnicities and corrected for multiple testing. Zobel *et al*.[32] also found a lack of associated antidepressant response, but the study methods did not account for associations with remission. The study of linkage disequilibrium patterns by Lekman *et al*.[31] showed that the rs4713916 SNP may serve as the functional region of FKBP5, and additional molecular studies may shed light on its involvement in MDD pathogenesis.

Ellsworth *et al*.[35] found two additional SNPs, rs9380514 in the Mayo PGRN-AMPS study and rs352428 in the STAR*D study, that may play a role in functional regulation of FKBP5. Both polymorphisms were found to be associated with poor antidepressant response. However, the study failed to name the number of responders and non-responders, as well as the QIDS-C score that constituted poor response. Although Ellsworth *et al*.[35] found several SNPs that were associated with response and remission, none were found to be significant after multiple testing. The lack of significance may be attributed to limited sample size. To the author's knowledge, rs9380514 and rs352428 have not been studied in individuals with MDD who experienced childhood trauma, but could potentially be examined in future studies. Establishing a molecular mechanism for rs352428 (A/G alleles), a polymorphism associated with transcriptional regulation including transcription factor binding and silencing, may strengthen evidence for its involvement in MDD and treatment response.

A major limitation of many of the studies included in this review were their reports of nominal observed effects, stating that the lack of statistical power was likely due to small sample sizes and lack of heterogeneity. As noted by Zimmerman *et al*.[28] and Hahle, Merz, Meyners, and Hausch,[36] existing genome wide association studies have likely been statistically underpowered to identify FKBP5 associations due to many of the associations being linked with specific environmental factors, including childhood trauma. Additionally, Ising *et al*.[37] notes the importance of considering subgroups that may respond to particular treatments due to shared pathology. Existing studies on molecular mechanisms of the pathogenesis of MDD via increased HPA axis activity point to a particular population for further study, individuals who have experienced childhood trauma.[11,14,16-19] Data supporting the association between polymorphisms and treatment response might be strengthened by specifically focusing on these individuals, as there have been demonstrated lower methylation levels at many of the same foci involved in antidepressant response. Both the rs1360780 A/T allele and the CC allele have been associated with susceptibility of MDD in individuals who experienced childhood trauma, and further study in this specific subpopulation may yield findings of greater significance.[12,13,28]

An additional limitation of the studies is the limited clinical relevance of the data. Specific genotypes have not been associated with successful treatment using a specific antidepressant class. Ideally, FKBP5 polymorphisms could be used to predict what treatment would result in the best response for a specific population of patients. The broad associations in these studies fail to inform treatment decisions in medical care. Another criticism of these studies, particularly the STAR*D trial, is their lack of a placebo treatment option, and therefore it is unknown whether remission would have occurred without antidepressants. Additionally, studies took different approaches to offering treatment. Some utilized a standard algorithm while others allowed physicians prescribing choice. While the presence of associations between FKBP5 and different treatments strengthens the evidence for its use as a potential biomarker, a blinded randomized

study looking at different treatment responses to multiple classes of antidepressants would be ideal.

As demonstrated by the number of positive associations with FKBP5 polymorphisms and antidepressant response in various study designs, it is likely that with an appropriate study population significant association can be discovered. Prior research linking both morphological changes within the brain and a probable molecular mechanism due to epigenetic changes suggests individuals who have experienced childhood trauma are an ideal population for future study. Focused future study on shared and newly discovered polymorphisms linking FKBP5 with MDD and antidepressant response may yield findings of clinical significance and further personalized psychiatric treatment.

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Review

Novel Blood Biomarkers for an Earlier Diagnosis of Alzheimer's Disease: A Literature Review

Shiavax J Rao,[1] Andrew J Boileau.[2]

Abstract

Alzheimer's disease is a neurodegenerative condition associated with neurofibrillary tangles and cortical deposition of amyloid plaques. Clinical presentation of the disease involves manifestations such as memory loss, cognitive decline and dementia with some of the earliest reported deficits being episodic memory impairment and olfactory dysfunction. Current diagnostic approaches rely on autopsy characterization of gross brain pathology, or brain imaging of biomarkers late in the disease course. The aim of this literature review is to identify and compare novel blood-based biomarkers with the potential of making an earlier clinical diagnosis of Alzheimer's disease. Utilizing such techniques may allow for earlier therapeutic intervention, reduction of disability and enhancement of patients' quality of life. Literature review and analysis was performed by screening the PubMed database for relevant studies between July 1, 2014 and December 31, 2019. Sixteen studies were reviewed with biomarker candidates categorized under microRNAs (miRNAs), auto-antibodies, other blood-based proteins or circulating nucleic acids. Three biomarker candidates – serum neurofilament light chain, plasma β-secretase 1 activity and a panel of three miRNAs (miR-135a/193b/384) – reported statistically significant differences in testing between patients and controls, with high discriminative potential and high statistical power. In conclusion, certain blood biomarkers have shown promising results with high sensitivity and specificity, high discriminative potential for Alzheimer's disease early in its progression, and statistically significant results in larger study samples. Utilization of such diagnostic biomarkers could increase the efficacy of making an earlier clinical diagnosis of Alzheimer's disease.

Key Words: Alzheimer's Disease; Diagnosis; Biomarkers; Early Diagnosis (Source: MeSH-NLM).

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, first described by German psychiatrist Alois Alzheimer in 1906, and currently affecting millions of people on a global scale.[1] Approximately 5.8 million Americans are diagnosed with AD and by 2050 this number is expected to increase to 13.8 million.[2] An important characteristic to note is the propensity of the disease to cause dementia – an acquired syndrome resulting in declining memory, executive function and cognitive ability, sufficient to cause interference with daily life and functioning. Globally, an estimated 50 million people have dementia, of which 60-70% of cases are due to AD.[3] Total costs of health care and services in 2015 for all individuals with Alzheimer's or other dementias worldwide were estimated at US $818 billion, placing a substantial financial burden on many families.[3]

The best-known risk factor for AD is increasing age, especially with people aged 65 and older, resulting in a subset of AD known as sporadic or late-onset Alzheimer's disease (LOAD). Old age, however, is not the defining requisite of the disease, as there is also a younger-onset (before age 65) pattern, referred to as early-onset Alzheimer's disease (EOAD), with about 13% associated with particular genes and familial inheritance.[4] One of the earliest cognitive deficits of either form of AD is episodic memory impairment, which presents as a reduced ability to recall events specific to a place and time.[5] As the disease progresses, it manifests as dementia, due to involvement of cortical association areas, with clinical manifestations including progressive memory impairment, deficits in executive functions and semantic memory, disorientation, behavioral changes and mood alterations. The diagnosis of AD is based on both clinical manifestations and gross morphological changes due to disease pathology and neurodegeneration in the brain. Consequently, AD (LOAD specifically) is detected quite late in the disease course, along with histopathological confirmation of neurodegeneration observable on autopsy, or in rare cases, biopsy.[6]

Since their discovery, neurofibrillary tangles (NFTs) and senile amyloid plaques have been the hallmark neuropathological features of AD.[7] Amyloid precursor protein (APP) is a highly conserved and integral membrane protein found in various tissues and is highly concentrated in neural synapses.[5] The sequential cleavage of APP by the enzymes β-secretase 1 (BACE1) and γ-secretase results in the formation of amyloid-β (Aβ). The pathogenesis of AD is hypothesized by some groups to be linked to an imbalance between amyloid-β (Aβ) production and clearance, resulting in the aggregation of Aβ predominantly as Aβ42 and Aβ40, which contribute to amyloid plaques and angiopathy respectively, although Aβ40 can also play a role in plaque formation.[8] The neurotoxicity of these plaques plays an important part in the preclinical phase of the disease.[5] Other groups hypothesize that the causative neuropathology of AD is related to tau, a protein expressed in neurons that plays an important role in the regulation of microtubules and their stability within axons. The functioning of tau is in turn regulated by several post-translational modifications to the protein itself. The most significant modification involves phosphorylation of serine and threonine residues, which can also result in hyperphosphorylation of tau protein, leading to the formation of NFTs.[5]

[1] MD, Medical Graduate, Saba University School of Medicine, Caribbean Netherlands
[2] PhD, Professor and Course Director, Neuroscience & Neurology, Saba University School of Medicine, Caribbean Netherlands

About the Author: *Shiavax Rao is a graduate of the 4-year MD program at Saba University School of Medicine (Saba, Caribbean Netherlands), and an incoming internal medicine resident physician at MedStar Health (Maryland, USA).*

Correspondence:
Shiavax J. Rao
Address: 27 Jackson Road, Suite 301, Devens, MA 01434, USA.
Email: s.rao@saba.edu

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The strongest predisposing risk factor for LOAD is the genotype of Apolipoprotein E (APOE), a gene that encodes the ε2, ε3 and ε4 alleles. Of the three alleles, ε4 is inversely correlated with age of disease onset, as increased expression results in an earlier than usual disease onset. Additionally, one APOEε4 allele and two APOEε4 alleles are associated with a 3x and 12x increase in risk of developing LOAD, respectively.[9] The APOEε4 protein is an important regulator of lipoprotein metabolism and plays a significant role in the aggregation of Aβ as well as its clearance from the central nervous system. These underlying genetic changes ultimately give rise to the gross morphological features seen in the brains of patients with AD.

Autopsy findings in brains from AD patients are grossly characterized by widespread cortical atrophy, especially involving the entorhinal cortex (anterior portion of the parahippocampal gyrus) and the neighboring hippocampal formation.[10] The neuronal atrophic changes in these and other densely cholinergic areas are subsequently accompanied by sulcal widening and gyri narrowing in much of the cerebral cortex. The extensive cortical neuronal atrophy can also give rise to ventriculomegaly and hydrocephalus ex vacuo.[11] Microscopic examination of the affected tissue generally reveals senile plaques composed of Aβ as well as NFTs of hyperphosphorylated tau, as discussed. The disease is also characterized by whole brain reduction in acetylcholine while levels of other neurotransmitters remain relatively unaffected until late stages.[11]

The underlying pathology of AD is known to begin much earlier than the onset of clinical manifestations. As such, a set of new criteria for the staging of AD was proposed by the National Institute of Aging and Alzheimer's Association in 2012. The criteria define three distinct stages of AD: preclinical AD, mild cognitive impairment (MCI) and AD dementia.[12] The preclinical and early MCI stages would be those where AD pathology and possible memory deficits should be present, but cognition would be intact, and as such, disease-modifying therapeutics would be most efficacious in these stages.

Biomarkers have classically been used to characterize the pathology seen in several conditions including AD. The historic and most widely used biomarkers for AD are Aβ and tau, with AD patients having lower levels of Aβ in cerebrospinal fluid (CSF) due to accumulation in plaques, and higher levels of CSF tau.[13] When looking at these markers in blood, studies have reported marginally lower plasma Aβ42 levels,[14] and significantly higher plasma tau levels in AD patients as compared to control subjects.[15] Neuropathological markers such as Aβ and tau can be directly visualized by biopsy and immunohistochemistry. These diagnostic techniques are largely invasive and mostly utilized on autopsy or late during the disease course, once the patient develops cognitive decline and clinical interventions are warranted. Accumulation of Aβ in the brain is a very early event, starting at least a decade before symptoms appear. Well-established Aβ-biomarkers, such as Aβ-binding ligands for in-vivo positron imaging tomography (PET) imaging, can be utilized to measure the Aβ deposition.[16] Imaging methods like PET, however, may be prohibitively expensive. Nevertheless, there is ongoing research investigating plasma Aβ42/Aβ40, with a recent study providing Class II evidence that Aβ42/Aβ40 levels when combined with APOE ε4 status and age, can accurately determine amyloid PET status in cognitively normal individuals.[17]

The involvement of olfactory dysfunction early in the disease course of AD has been reported as early as 1974 and may possibly be one of the earliest manifestations of the disease.[18] The olfactory dysfunction seen in AD is associated with Aβ and NFT deposition in the olfactory bulb – the olfactory pathway's very first synaptic relay.[19] Early AD also affects portions of the olfactory cortex, and degeneration is known to be more pronounced in the left hemisphere of patients with AD. Techniques involving simple olfactory tests have been studied in the past, using stimuli such as a peanut butter. It has been previously reported that such a test can discriminate AD patients from those with MCI and controls with a sensitivity of 100% and specificity of 92%.[20]

Aside from Aβ and tau, there have been advances in the field of other blood-based biomarkers capable of discriminating between those with MCI and healthy controls, and several studies of novel biomarkers detectable in serum and plasma have emerged. Preclinical diagnosis of AD by using such biomarkers, can allow for early therapeutic interventions and new clinical trials, which may result in reduced disability and a better quality of life for patients. This literature review study explores the efficacy of utilizing novel blood-based biomarkers to detect AD earlier in the disease course.

Methods

Search Strategy

The scientific literature used in this review was selected through screening of literature pertaining to the topic of interest by searching the PubMed database. The initial search parameters included combinations of Medical Subject Headings "Alzheimer's disease" or "Alzheimer disease" along with the words "biomarkers", "serum" and "plasma". This initial search yielded 372 articles. Only studies published in English and involving humans were considered for inclusion. A recent systematic review and meta-analysis on CSF and blood biomarkers for AD included studies from July 1, 1984 and June 30, 2014. Carrying forward from then, studies published between July 1, 2014 and December 31, 2019 were considered for inclusion in this review of novel blood-based AD biomarkers. Review articles were filtered out from the search. This yielded 162 articles for further screening and study selection. The abstracts of these articles were thoroughly reviewed to determine eligibility.

Eligibility Criteria

Studies were selected by analyzing the abstracts of the studies for relevancy to the topic of interest. Given the focus of the review is on biomarkers with the potential to detect AD earlier in the disease course, studies not including mild AD or MCI patients in the study sample were excluded. Studies that focused on the ability of biomarkers to differentiate either AD patients, MCI patients, or AD and MCI patients from cognitively healthy individuals were selected. Studies that focused on the ability of biomarkers to discriminate between either AD patients, MCI patients, or AD and MCI patients from patients with other neurodegenerative conditions (such as Parkinson's disease, vascular dementia, etc.), were excluded. Studies that examined the utility of novel biomarkers for the initial diagnosis of MCI, or AD, or MCI and AD were selected; those studies in this subset examining only other effects of biomarker utility, such as AD progression or response to treatment, and not initial diagnosis, were also excluded. After thoroughly reviewing article abstracts and applying these eligibility criteria, sixteen articles were selected.

Data Extraction

The following information was extracted from selected studies and analyzed for this review: Study objectives, sample size and classification, experimental methods, key findings, strengths, limitations and major conclusions.

Results

The sixteen reviewed studies investigated several different blood-based biomarker candidates for detecting AD earlier in the disease course. These candidates included microRNAs (miRNAs), autoantibodies, other proteins and circulating nucleic acids.

microRNA levels

Five studies, summarized in **Table 1,** focused on investigating the utility of miRNAs as biomarkers for earlier detection of AD.[21-25] Four studies included patients with AD and MCI, and one study included patients

Table 1. MicroRNA biomarkers for Alzheimer's disease.

Author, Title, Objective	Study Sample, Selection Criteria	Methods	Key Findings
Yang et al. (2018) **The Serum Exosome Derived MicroRNA-135a, -193b, and -384 Were Potential Alzheimer's Disease Biomarkers.** **Objective: To explore the potential value of serum exosomal microRNAs as biomarkers for diagnosing AD.**	107 AD; 101 MCI; 228 controls Patients admitted to Xuanwu Hospital of Capital Medical University (Beijing, China) between September 2015 and December 2016 were enrolled in the study.	Serum levels of three exosomal miRNAs (miR-135a, miR-193b and miR-384) were measured through exosome isolation, Western blotting and qRT-PCR analysis.	*Serum miR-135a level* Compared to controls: Significantly increased in AD (P<0.05) Significantly increased in MCI (P<0.05) *Serum miR-193b level* Compared to controls: Significantly reduced in AD (P<0.01) Significantly reduced in MCI (P<0.05) *Serum miR-384 level* Compared to MCI: Significantly higher in AD (P<0.05) Significantly lower in controls (P<0.05)
Kumar et al. (2017) **MicroRNA-455-3p as a potential peripheral biomarker for Alzheimer's disease.** **Objective: To identify microRNAs as early detectable peripheral biomarkers in AD.**	10 AD; 16 MCI; 14 controls Sera and DNA samples obtained from patients under the FRONTIERS project (Texas Tech University Health Sciences Center). Inclusion criteria: Age≥45 years; rural community-based West Texas individuals; assessed for cognitive functions. Exclusion criteria: On strong medications; many health complications	After miRNA extraction, primary screening was performed by microarray analysis. Differentially expressed miRNAs were validated by qRT-PCR. miRNA data was further validated by using AD postmortem brains.	*miR-455-3p expression* Compared to controls: Significantly upregulated in AD (P=0.007) *miR-4668-5p expression* Compared to controls: Significantly upregulated in MCI (P=0.016) *Postmortem AD brains* Significant upregulation of miR-455-3p (P=0.016)
Zeng et al. (2017) **Expression of microRNA-222 in serum of patients with Alzheimer's disease.** **Objective: To determine the association between AD and serum microRNA-222 in patients with AD.**	30 moderate AD; 30 mild AD; 30 controls Patients were categorized into groups according to MMSE: mild (15< MMSE ≤26) and moderate (10≤ MMSE ≤15) Exclusion criteria: History of cerebral vascular disease; TBI; toxic/metabolic/other brain disorders; drug therapy prior to diagnosis; blood system disease; dementia by vascular or other causes; no signed informed consent.	After miRNA extraction, primary screening was performed by microarray analysis. Differentially expressed miRNAs were validated by qRT-PCR.	*microRNA-222 expression* Compared to controls: Significantly lower in mild AD (P<0.05) Compared to controls: Significantly lower in moderate AD (P<0.05) Compared to mild AD: Significantly lower in moderate AD (P<0.05)
Nagaraj et al. (2017) **Profile of 6 microRNA in blood plasma distinguish early stage Alzheimer's disease patients from non-demented subjects.** **Objective: To investigate the utility of plasma microRNAs as biomarkers for detecting early AD.**	20 AD; 15 MCI; 15 controls All study subjects were Caucasian individuals from Poland. Blood samples were taken from patients enrolled in the Alzheimer's ward of Central Clinical Hospital of the Ministry of Interior in Warsaw.	The study sample was divided into two groups: a pilot experiment (20 subjects) and a verification experiment (30 subjects). After miRNA isolation, qRT-PCR was performed for both experiments (179 miRNAs for pilot and 15 miRNAs for verification).	*miR-483-5p level* Compared to controls: Significantly increased in MCI (P<0.01 in pilot; P<0.001 in verification) *miR-200a-3p level* Compared to controls: Significantly increased in MCI (P<0.01 in both pilot and verification)
Dong et al. (2015) **Serum MicroRNA Profiles Serve as Novel Biomarkers for the Diagnosis of Alzheimer's Disease.** **Objective: To identify and validate the potential of circulating miRNAs as novel biomarkers for AD.**	127 AD; 30 MCI; 123 controls Study subjects comprised of patients being treated at Shanghai Mental Health Center, Nanjing Brain Hospital and Guangxi Jiangbin Hospital.	After miRNA extraction, quantification of miRNAs was performed by qRT-PCR.	*miR-93 concentration* Compared to controls: Significantly higher in MCI (P<0.001) *miR-143 concentration* Compared to controls: Significantly lower in MCI (P<0.01) *miR-146a concentration* Compared to controls: Significantly higher in MCI (P<0.01)

Legend: **AD:** Alzheimer's Disease; **MCI:** Mild Cognitive Impairment; **miRNA:** microRNA; **qRT-PCR:** Quantitative Real Time Polymerase Chain Reaction; **MMSE:** Mini-Mental State Examination; **TBI:** Traumatic Brain Injury

with mild and moderate AD. All five studies utilized quantitative real time polymerase chain reaction for quantification of differentially expressed miRNAs. Levels of seven miRNAs (miR-135a, -384, -4668-5p, -483-5p, -200a-3p, -93 and 146a) were found to be significantly higher in MCI patients as compared to controls. Levels of three other miRNAs (miR-193b, -222 and-143) were found to be significantly lower in patients with MCI or mild AD as compared to controls.

Serum autoantibodies

Two studies, summarized in **Table 2,** focused on investigating serum autoantibodies as diagnostic biomarkers for early detection of AD. The studies included patients with MCI or mild AD and utilized the enzyme-linked immunosorbent assay technique for antibody detection. Levels of anti-phosphatidylserine-dependent antibody (aPSd), anti-phosphatidylethanolamine-dependent antibody (aPEd) and anti-phosphatidylcholine-independent antibody (aPCi) were found to be significantly elevated in the serum of MCI patients as compared to controls.[26] Antibodies against the angiotensin 2 type 1 receptor (anti-ATR1) were found to be significantly higher in mild AD patients without hypertension or diabetes.[27]

Table 2. Autoantibodies as biomarkers for Alzheimer's disease.

Author, Title, Objective	Study Sample, Selection Criteria	Methods	Key Findings
McIntyre et al. (2015) **Antiphospholipid autoantibodies as blood biomarkers for detection of early stage Alzheimer's disease.** **Objective: To investigate redox-reactive antiphospholipid autoantibodies as a diagnostic tool for mild pre-AD.**	30 AD; 30 MCI; 30 controls Coded serum samples assigned to the three study groups by the Alzheimer's Disease Neuroimaging Initiative were used.	aPLs dependent on plasma-protein binding before binding epitopes on PLs were designated as aPLd, and those directly to epitopes on PLs were designated as aPLi. Four different types of R-RAA aPLs were quantified in each group using ELISA, each with dependent and independent subtypes: (aPSd and aPSi), (aCLd and aCLi), (aPCd and aPCi) and (aPEd and aPEi). Quantitative ELISA was run on coded serum samples and R-RAA aPL activity was expressed as the difference in optical density between buffer-controlled samples and those treated with hemin (a redox reactive reagent which would unmask the aPLs and allow their detection).	*Serum IgG R-RAA aPSd* Compared to controls: Significantly elevated in MCI (P=0.011) *Serum IgG R-RAA aPEd* Compared to controls: Significantly elevated in MCI (P=0.005) *Serum IgG R-RAA aPCi* Compared to controls: Significantly elevated in MCI (P=0.001)
Giil et al. (2015) **Autoantibodies Toward the Angiotensin 2 Type 1 Receptor: A Novel Autoantibody in Alzheimer's Disease.** **Objective: To investigate the association between anti-AT1R and AD, and to investigate the association between clinical/biomarker features of anti-ATR1 and AD.**	92 mild AD; 102 controls Study subjects were recruited from the Dementia Study in Western Norway during 2005-2007 from three participating hospitals. Exclusion criteria: acute delirium/confusion, terminal illness, recently diagnosed major somatic illness, previous bipolar/psychotic disorder.	Measurement of serum anti-ATR1 antibodies was done in duplicates by using a solid-phase sandwich ELISA. Absorbance was measured using an ELISA plate reader.	*Serum anti-ATR1 level* Compared to controls: Significantly higher in mild AD patients without hypertension (p=0.04) Compared to controls: Significantly higher in mild AD patients without diabetes (p=0.008)

Legend: **AD:** Alzheimer's Disease; **MCI:** Mild Cognitive Impairment; **aPLs**: anti-phospholipid antibodies; **aPSd:** anti-Phosphatidylserine-dependent Antibody; **aPEd:** anti-Phosphatidylethanolamine-dependent Antibody; **aPCi:** anti-Phosphatidylcholine-independent Antibody; **R-RAA:** Redox-Reactive Auto-Antibodies; **ELISA:** Enzyme-Linked Immunosorbent Assay; **anti-ATR1:** anti-angiotensin 2 type 1 receptor antibody.

Other blood-based proteins

Eight studies, summarized in **Table 3,** focused on other blood-based proteins as biomarkers for earlier detection of AD. Dynamics of neurofilament light chain (NfL) have been found to predict neurodegeneration and clinical progression in presymptomatic AD.[28] Serum NfL rates of change were significantly elevated in individuals carrying highly penetrant autosomal-dominant mutations in the amyloid beta precursor protein (*APP*), presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*) genes, as compared to non-carriers. Furthermore, the rates of change of serum NfL in symptomatic mutation carriers were significantly associated with rates of cortical thinning in the precuneus.[28]

Keratin type-2 expression, neuronal pentraxin 1 (NP1) levels and BACE1 activity were all found to be significantly elevated in MCI patients compared to controls.[29-31] Angiotensin converting enzyme (ACE) serum activity was significantly higher in AD patients as compared to controls and MCI patients, but no significant difference existed between MCI patients and controls.[32] Levels of soluble endothelial protein C receptor (sEPCR) and Galectin-3 (Gal-3) were found to be significantly elevated in AD patients compared to controls, but no significant difference existed between MCI patients and controls.[33,34] Expression of albumin was significantly decreased in MCI patients compared to controls.[29]

Mean exosomal levels of extracted phospho-serine-type 1 insulin receptor substrate (P-S312-IRS-1) were significantly higher in early AD patients compared to controls.[35] Mean exosomal levels of extracted

Table 3. Other blood-based protein biomarkers for Alzheimer's Disease.

Author, Title, Objective	Study Sample, Selection Criteria	Methods	Key Findings
Preische et al. (2019) **Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease.** **Objective: To demonstrate that NfL levels in CSF and serum are correlated with each other and are elevated at the presymptomatic stages of familial AD.**	243 mutation carriers; 162 non-carriers DIAN Data and biospecimens were used in the study. DIAN participants were members of families carrying autosomal-dominant mutations in *APP, PSEN1 or PSEN2*. Family members not carrying the mutations served as controls.	Single-molecule array immunoassay technology was used to measure NfL in CSF and serum of 405 participants at the initial visit. 196 participants returned for another 1-5 visits over a median observation time of 3 years from initial visit. Among these, mutation carriers were further subdivided into pre-symptomatic (CDR=0 across all visits), converter (initially CDR=0, and CDR>0 at subsequent visits) or symptomatic (CDR>0 across all visits). Serum NfL rates of change were determined for these participants. Additionally, regression analysis was performed between NfL rates of change and rates of change in brain imaging.	*Serum NfL rates of change* Significantly elevated in pre-symptomatic carriers compared to non-carriers (P=0.000671) Significantly elevated in converters compared to Non-carriers ($P=3.05 \times 10^{-7}$) and Pre-symptomatic mutation carriers ($P=0.00119$) Significantly elevated in symptomatic mutation carriers compared to Non-carriers ($P=8.78 \times 10^{-12}$) and Pre-symptomatic mutation carriers ($P=0.000151$) *Rates of precuneus cortical thinning:* Significantly associated with rate of change of serum NfL in symptomatic mutation carriers ($P=0.018$)
Kumar et al. (2018) **Proteomics based identification of differential plasma proteins and changes in white matter integrity as markers in early detection of mild cognitive impaired subjects at high risk of Alzheimer's disease.** **Objective: To identify and quantify differentially regulated plasma proteins in MCI subjects vs healthy controls.**	50 MCI 50 controls Inclusion criteria: Ability to converse in Hindi/English; age › 50; memory complaint for › 6 months; stable and controlled medical conditions such as HTN, DM, hyperlipidemia. Exclusion criteria: Having other neurological diseases (stroke, severe small vessel disease, any other systemic problem).	2D-PAGE of plasma protein in MCI (n=50) and controls (n=50), and identification of differentially regulated proteins with MALDI-TOF and MS-MS. Western blotting for quantification of Keratin 2 and Albumin expression in serum of MCI (n=12) vs controls (n=12).	*Serum expression of Keratin type-2 protein* Significantly increased in MCI compared to controls (p≤0.001) *Serum expression of Albumin* Significantly decreased in MCI compared to controls (p≤0.01)
Ma et al. (2018) **Neuronal pentraxin 1: A synaptic-derived plasma biomarker in Alzheimer's disease.** **Objective: To evaluate NP1, a potential CNS-plasma derived biomarker of excitatory synaptic pathology.**	33 MCI; 31 controls Human plasma samples were obtained from APOE- genotyped controls and patients from the ImaGene Study conducted through the UCLA Easton Alzheimer's Center.	Quantification of plasma NP1 by sandwich ELISA.	*Plasma NP1 level* Compared to controls: Significantly higher in MCI (p<0.05)
Shen et al. (2018) **Increased Plasma BACE1 May Predict Conversion to Alzheimer's Disease Dementia in Individuals With Mild Cognitive Impairment.** **Objective: To identify the presence of BACE1 activity and determine potential BACE1 activity alterations in subjects with MCI.**	75 probable AD; 96 MCI; 53 controls Study subjects were recruited from three independent international academic AD research centers and memory clinics (Munich, Sweden and USA). This included patients with cognitively stable MCI (non-converters) and those with MCI who converted to AD (converters).	Plasma BACE1 activity was measured by a synthetic fluorescence substrate ELISA. Protein expression of BACE1 was assessed by Western blotting.	*Plasma BACE1 activity (V_{max})* Compared to controls: Significantly increased by 62.8% (p=0.001) in MCI converters Significantly increased by 68.9% (p<0.001) in AD *Plasma BACE1 concentration* Compared to controls: Significantly increased in AD (p<0.05)

Author, Title, Objective	Study Sample, Selection Criteria	Methods	Key Findings
Zhuang et al. (2016) **Angiotensin converting enzyme serum activities: Relationship with Alzheimer's disease.** **Objective: To determine serum activities of ACE as a marker in diagnosis of AD.**	59 moderate-severe AD; 19 mild AD; 45 aMCI; 39 controls Study subjects were recruited from patients enrolled in Qingdao Municipal Hospital and through advertisements at senior clubs (2013-2014). Exclusion criteria: non-AD dementia; severe CHF; severe liver or kidney disease; severe COPD; cancer; symptoms of depression/anxiety/OCD; taking ACEi, ARB or other medication that could influence cognition.	ACE activity was measured by sandwich ELISA.	*Serum ACE activity* Compared to aMCI: Significantly higher in AD, considering different stages altogether (P=0.03) Compared to aMCI: Significantly higher in moderate-severe AD (P=0.02) Compared to controls: Significantly higher in AD, considering different stages altogether (P=0.01) Compared to controls: Significantly higher in moderate-severe AD (P=0.01)
Zhu et al. (2015) **Serum sEPCR Levels Are Elevated in Patients With Alzheimer's Disease.** **Objective: To examine serum sEPCR levels in patients with AD, MCI and controls, and to determine its association with the degree of cognitive impairment (measured by MMSE).**	45 AD; 36 MCI; 42 controls Study subjects were recruited from the Department of Gerontology at the Huangshi Central Hospital Affiliated to Hubei Polytechnic University.	Serum sEPCR levels were measured by ELISA.	*Serum sEPCR level* Compared to controls: Significantly higher in AD (P=0.0005)
Wang et al. (2015) **Elevated Galectin-3 Levels in the Serum of Patients With Alzheimer's Disease.** **Objective: To compare serum Gal-3 levels in patients with AD, MCI and controls, and to evaluate its association with the clinical features of the disease.**	41 AD; 32 MCI; 46 controls Study subjects were recruited from the Department of Neurology in Yuhuangding Hospital and Qilu hospital of Shandong University.	Serum Gal-3 levels were measured by ELISA.	*Serum Gal-3 level* Compared to controls: Significantly higher in AD (P=0.017)
Kapogiannis et al. (2014) **Dysfunctionally phosphorylated type 1 insulin receptor substrate in neural-derived blood exosomes of preclinical Alzheimer's disease.** **Objective: To investigate IRS-1 and its phosphorylated forms in neurally derived plasma exosomes of patients with AD.**	32 AD; 16 aMCI; 81 controls Study subjects (aMCI, n=16; mild/moderate dementia, n=10) included identified patients who had donated blood once in the CRU-NIA of Harbor Hospital (Baltimore, MD) or at Jewish Home of San Francisco (San Francisco, CA). For longitudinal studies, 22 additional AD patients were identified, who had given blood twice at Mayo Clinic of University of Kentucky (first when cognitively normal, second when diagnosed with AD).	After isolation of exosomes from plasma, quantification of exosome proteins was performed by ELISA.	*P-S312-IRS-1 level* Compared to controls: Significantly higher in AD ($P<0.0001$) *P-panY-IRS-1 level* Compared to controls: Significantly lower in AD ($P<0.0001$) *Insulin Resistance Index, R* Compared to controls: Significantly higher in AD ($P<0.0001$) *Longitudinal Analysis of R* Accurately predicted development of AD up to 10 years prior to symptom onset

Legend: **NfL:** Neurofilament Light Chain; **CSF:** Cerebrospinal Fluid; **AD:** Alzheimer's Disease; **DIAN:** Dominantly Inherited Alzheimer Network; **APP:** Amyloid Precursor Protein; **PSEN1:** Presenilin 1; **PSEN2:** Presenilin 2; **CDR:** Clinical Dementia Rating; **MCI:** Mild Cognitive Impairment; **HTN:** Hypertension; **DM:** Diabetes Mellitus; **2D-PAGE:** Two-Dimensional Polyacrylamide Gel Electrophoresis; **MALDI-TOF:** Matrix Assisted Laser Desorption/Ionization Time of Flight; **MS-MS:** Mass Spectrometry; **NP1:** Neuronal Pentraxin 1; **CNS:** Central Nervous System; **APOE:** Apolipoprotein E; **UCLA:** University of California Los Angeles; **ELISA:** Enzyme-Linked Immunosorbent Assay; **BACE1:** Beta-Secretase 1; **ACE:** Angiotensin Converting Enzyme; **aMCI:** Amnestic Mild Cognitive Impairment; **CHF:** Congestive Heart Failure; **COPD:** Chronic Obstructive Pulmonary Disease; **OCD:** Obsessive-Compulsive Disorder; **ACEi:** Angiotensin Converting Enzyme Inhibitor; **ARB:** Angiotensin II Receptor Blocker; **sEPCR:** Soluble Endothelial Protein C Receptor; **MMSE:** Mini-Mental State Examination; **Gal-3:** Galectin-3; **IRS-1:** Type 1 Insulin Receptor Substrate; **CRU-NIA:** Clinical Research Unit of the National Institute on Aging-

phospho-tyrosine-type 1 insulin receptor substrate (P-panY-IRS-1) were significantly lower in early AD patients compared to controls. The ratio of P-S312-IRS-1 to P-panY-IRS-1 (Insulin Resistance Index, R) was significantly higher in early AD patients. Insulin resistance reflected by R values could accurately predict development of AD up to 10 years prior to symptom onset.[35]

Circulating Nucleic Acids

One study, summarized in **Table 4,** focused on circulating nucleic acids (CNAs) as diagnostic biomarkers for AD. Patients with probable-AD were found to have higher CNA concentrations compared to controls. DNA methylation of the *LHX2* gene was also found to be significantly higher in these patients.[36] Furthermore, upon subclassifying probable-AD patients by MMSE scores, CNA concentrations peaked in the MCI subclass (significantly higher compared to controls).[36]

Discussion

A novel biomarker, which is sensitive and specific to the development of AD pathology would be an ideal candidate for the preclinical detection of the disease. As such, an ideal biomarker for early AD diagnosis should distinguish between cognitively normal elderly controls and patients with MCI, with great accuracy, sensitivity and specificity. The ideal biomarker should also reasonably predict conversion from cognitively healthy individuals to MCI, and progression from MCI to AD. For each biomarker reviewed, the discriminative potential quantified by measures of diagnostic accuracy, if available, is summarized in **Table 5.**

Table 4. Circulating Nucleic Acids as biomarkers for Alzheimer's disease.

Author, Title, Objective	Study Sample, Selection Criteria	Methods	Key Findings
Pai et al. (2018) **The Role of Methylated Circulating Nucleic Acids as a Potential Biomarker in Alzheimer's Disease.** **Objective: To explore the role of methylated CNAs as potential biomarkers for diagnosing AD.**	27 probable-AD; 9 controls Study subjects were recruited from National Cheng Kung University Hospital (cases) and outpatient clinics (controls). Exclusion criteria: Evidence of stroke; diabetes; trauma; autoimmune disorders; known malignancy.	CNAs were extracted using the QIAamp CNA Kit. Purified CNAs were quantified by qRT-PCR for the human β-globin gene. DNA methylation of the LHX2 gene was analyzed by pyrosequencing after performing genome-wide amplification of the plasma CNAs.	*CNA concentrations* Compared to controls: Significantly higher in probable-AD group ($p < 0.01$) Peaked in probable-AD patients classified as mild cognitive impairment, by MMSE ($p< 0.05$) *LHX2 methylation* Compared to controls: Significantly higher methylation of CpG sites 1 and 5 in probable-AD group.

Legend: **CNA:** Circulating Nucleic Acid; **AD:** Alzheimer's Disease; **qRT-PCR:** Quantitative Real Time Polymerase Chain Reaction; **LHX2:** LIM Homeobox 2; **CpG:** Cytosine-phosphate-Guanine

Table 5. Discriminative potential of novel biomarkers, quantified by measures of diagnostic accuracy

Study	Diagnostic marker	Control vs AD		Control vs MCI	
		Sensitivity	Specificity	Sensitivity	Specificity
Yang et al.	miR-135a, miR193b, miR-384	-	-	99%	95%
	miR-135a	-	-	90%	95%
	miR-193b	-	-	78%	77%
	miR-384	-	-	85%	90%
Nagaraj et al.	miR-483-5p (pilot study)	80.0%	100%	83%	100%
	miR-483-5p (verification study)	92.0%	100%	87%	100%
McIntyre et al.	aPSd, aPEd and aPCi	-	-	80%	83.3%
Shen et al.	BACE1 activity	64 – 84%	86 – 88%	66 – 70%	86 – 88%
Pai et al.	CNA concentration	67%	89%	-	-

Study	Diagnostic marker	Control vs presymptomatic MC		Control vs symptomatic MC	
		Sensitivity	Specificity	Sensitivity	Specificity
Preische et al.	Serum NfL (baseline)	92.0%	14.0%	85.0%	75.0%
	Serum NfL (rate of change)	58.0%	78.0%	82.0%	89.0%

Legend: **AD:** Alzheimer's Disease; **MCI:** Mild Cognitive Impairment; **miR:** microRNA; **aPSd:** anti-Phosphatidylserine-dependent Antibody; **aPEd:** anti-Phosphatidylethanolamine-dependent Antibody; **aPCi:** anti-Phosphatidylcholine-independent Antibody; **BACE1:** Beta-Secretase 1; **CNA:** Circulating Nucleic Acid; **NfL:** Neurofilament Light Chain; **MC:** Mutation Carrier

Over the last decade, researchers have focused on developing non-invasive tests for AD based on detection of miRNAs in the blood. These non-coding, small nucleotide molecules have been found to be differentially regulated in the blood, CSF and even brain tissue of patients with AD.[37] The panel of three miRNAs (miR-135a, -193b, -384) studied by Yang et al. (2018) showed the most promising results, with high discriminative potential and study power.[21] Another biomarker candidate, miR-483-5p, studied by Nagaraj et al. (2017), also revealed high discriminative potential for both AD and MCI, as well as statistically significant results in both pilot and verification studies.[24] This study, however, was limited by the small sample size and consequently, low study power. The other miRNA studies, which presented statistically significant results, either failed to investigate discriminative potential or had low statistical power.

Autoantibodies are another area of focus when looking for non-invasive blood-based biomarker candidates for AD. The study by McIntyre et al. (2015) identified redox reactive antiphospholipid antibodies as serum autoantibodies detectable upon exposure to oxidizing agents, and potential biomarkers of early AD.[26] A limitation of the study lied in the redox reactive oxidizing reagents required for detection, due to cost and limited availability of reagent in different areas. Nevertheless, there is increased ability to generalize the technique to patients having early and late LOAD, due to inclusion of MCI patients in the sample. The resulting discriminative potential was also quite high for MCI patients. Giil et al. (2015) studied anti-ATR1 as a biomarker candidate, which yielded statistically significant differences in antibody levels for mild AD patients.[27] The utility of this biomarker can be severely limited, as the significant results were only applicable to patients without hypertension or diabetes, two highly prevalent systemic diseases. Future steps in evaluating autoantibodies include performing studies on a larger scale to increase statistical power and checking for accuracy of discriminating values.

Preische et al. (2019) conducted an extensive study on serum NfL in relation to the onset and progression of AD.[28] Longitudinal analysis of rates of change in serum NfL yielded significant elevations in subclasses of carriers of mutations in *APP, PSEN1* or *PSEN2* genes, which contribute to the heritability of EOAD.[38,39] The strong association between NfL changes in CSF and blood is indicative of blood-based NfL changes reflecting changes in the brain in AD.[40] The significant association between serum NfL rates of change and rates of precuneus cortical thinning is a noteworthy finding, since this area has been shown to be most sensitive to AD progression.[41,42] The study results coupled with high statistical power show that longitudinal measures of serum NfL are a relatively cheap, non-invasive and reliable method of evaluating neurodegeneration and clinical progression. Future direction for longitudinal NfL studies warrants closer follow-up intervals to determine the association between the time period of rate of change and clinical predictability. Future work should also address translation of these findings to sporadic AD.

Another promising blood-based protein studied was BACE1, which showed statistically significant increases in activity in AD patients, and those with MCI who eventually converted to AD.[31] With a larger sample, the study had relatively high statistical power, and was also highly generalizable since patient groups were recruited from different populations in multiple countries. ACE activity was also similarly studied in a large population but revealed no statistically significant differences between MCI patients and controls. Nevertheless, the study reported significant data and utility of ACE activity pertaining to progression from MCI to AD.[32] NP1, keratin type-2 and albumin had significantly different levels in MCI patients compared to controls, but discriminative potential of these biomarkers was not investigated and the studies had low statistical power and poor generalizability.[29,30] Future studies warrant replication in larger, more representative study samples for validation of results.

The studies investigating sEPCR and Gal-3 showed statistically significant differences in levels of each serum protein for AD patients, but there were no significant differences between MCI patients and controls.[33,34] Further study is warranted in larger study samples to validate these results and determine discriminative potential. Pai et al. (2018) reported significantly elevated CNA concentrations in patients with MCI compared to controls, but the study had low statistical power.[36] The marker may show promise but warrants future work in larger MCI patient samples and investigation of discriminative potential for MCI patients specifically.

Brain tissues from AD patients are noted to have abnormal expression of insulin receptors, as well as an alteration in the phosphorylation pattern of IRS-1, as is seen in patients with type II diabetes mellitus.[43] Kapogiannis et al. (2014) investigated differential phosphorylation of the serine and tyrosine type-1 insulin receptor substrate (IRS-1) secondary to insulin resistance and reported statistically significant differences in these proteins in MCI as well as AD patients, as compared to controls.[35] Furthermore, significant longitudinal study findings supported this biomarker candidate's ability to accurately predict AD development, up to 10 years prior to onset of clinical symptoms. The power of the study was a significant limitation due to the low sample size. Future work with IRS-1 should focus on replication in larger study samples, with a focus on subjects with MCI and determination of discriminative potential when differentiating MCI from controls.

This review summarizes sixteen journal articles investigating various novel biomarkers potentially capable of aiding in the earlier diagnosis of AD. The studies were conducted in several different countries, giving a global perspective on the issue, but several studies had low statistical power due to relatively small sample sizes. Nevertheless, certain biomarkers such as NfL, BACE1 activity and the panel of miR-135a/193b/384 showed promising results with high relevance towards development of a non-invasive, clinically applicable AD diagnostic biomarker.

The articles included in this study were limited to publications in English, which may have potentially excluded important and relevant manuscripts pertinent to the topic. Additionally, several reviewed articles used study samples from specific populations, leading to selection bias. Another limitation includes one database being used to search and identify publications relevant to the topic. The search was conducted by one investigator and selection of relevant articles depended on a single investigator's judgement, potentially allowing for selection and reporting bias.

Conclusion

The blood-based biomarkers for an earlier AD diagnosis presented in this review encompassed microRNAs, autoantibodies, other proteins and circulating nucleic acids. Some of the novel biomarkers reviewed will require future studies for validation of results in larger study samples, or for determination of discriminative values. Further work, in terms of validation of these study results in larger samples and careful evaluation of the diagnostic technique, is warranted to identify the strongest diagnostic biomarkers with high potential and applicability to a clinical setting. A combinatorial approach is also possible and should be considered. Certain biomarkers – such as NfL, BACE1 activity and the panel of miR-135a/193b/384 – have shown promising results with high sensitivity and specificity, high discriminative potential for early AD (MCI patients vs. control subjects) and valid, statistically significant results. Utilization of such biomarkers will increase the efficacy of making an early clinical diagnosis of Alzheimer's disease and begin interventions sooner. Such interventions could potentially reduce disability, delay severe disability, and enhance patients' quality of life.

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Case Report

ECG Artifact by a Spinal Cord Neurostimulator: A Case Report

Shyla Gupta,[1] Cathy Shaw,[1] Sohaib Haseeb,[1] Adrian Baranchuk.[1]

Abstract

Background: Neurostimulator devices produce electrical oscillations that may prevent accurate diagnosis of an ECG. **The Case:** We present the case of a 68-year-old man who came to the emergency department with chest pain and a spinal cord neuromodulator device in situ to treat his polymyalgia rheumatica. A 12-lead ECG was obtained to determine the cause of the chest pain, and atrial fibrillation was wrongly diagnosed. **Conclusion:** This case reiterates the value of recognizing this uncommonly encountered ECG artifact to avoid unnecessary mistakes in interpretation of heart rhythms.

Key Words: Neurostimulator devices; ECG artifact; Atrial fibrillation (Source: MeSH-NLM).

Introduction

Acquisition of high-quality surface 12-lead electrocardiograms (ECGs) in the emergency department (ED) is paramount to facilitate interpretation of different clinical presentations.[1] Inability to obtain adequate recordings significantly diminish the capacity of the interpreter, leading to potentially serious medical errors.

The Case

We present the case of a 68-year-old male with a history of polymyalgia rheumatica with pain refractory to usual care and implanted with a neuromodulation device (MyStim Neuromodulator Device, Medtronic) (**Figure 1A**). The patient reported a history of metastatic lung cancer, for which he underwent surgical removal of a lung mass via thoracotomy. On this occasion, he presented to the ED with complaints of chest pain. A 12-lead ECG was obtained; however, the automatic analysis of the ECG machine was unable to determine whether the patient had a pacemaker. From this ECG, there was an erroneous diagnosis of atrial fibrillation (**Figure 2A**). The patient had an external programmer (MyStim Programmer Model 97740, Medtronic) with the ability to inactivate the neurostimulator and adjust the stimulation level (**Figure 1B**). After the neuromodulation device was switched off, a repeat ECG showing normal sinus rhythm was obtained (**Figure 2B**).

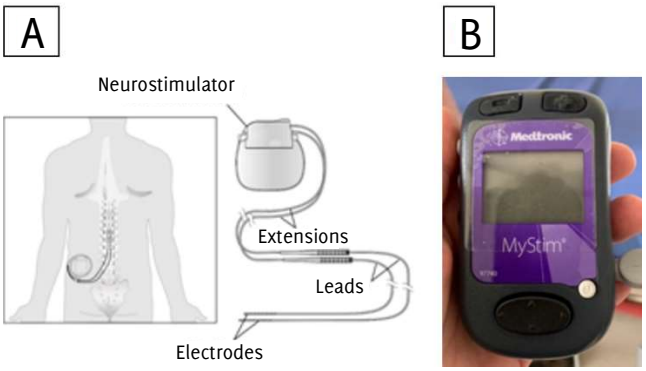
Discussion

Neuromodulation stimulators are inserted in a wide variety of patients in the context of a range of conditions. Devices like these target different anatomical sites, such as the deep brain and spinal cord. Neurostimulator devices produce electrical oscillations that may hinder the procurement of an ECG and can generate artifacts that may interfere with the accurate diagnosis of the data attained.[2] The neurostimulator controller is a miniature hand-held, wireless device, similar to a remote controller. It delivers electrical signals to the epidural space near the spine through lead-wires.[3] It is used for the treatment of polymyalgia rheumatica chronic pain. Spinal cord stimulation reduces chronic pain and improves the ability to go about daily activities by modifying and masking the pain signal before it reaches the brain.[4]

Highlights:

- This case report brings to light important information regarding ECG artifact to prevent misdiagnosis of atrial fibrillation or other heart rhythms.
- The information will help physicians and technicians identify sources of electromagnetic interference when patients are getting ECGs.
- The case report will draw to light the importance of obtaining sufficient ECG recordings to make valid medical decisions.

Figure 1A: Implanted Parts of an Internal Neurostimulator System. **B:** External Programming Unit of the MyStim Spinal Cord Neurostimulator Model 97740.



The device works by adjusting amplitude, pulse width, and rate of pulses delivered per second, according to the therapy prescribed by the physician.

The stimulation induces artifact in the ECG tracing, posing different difficulties to a precise analysis of the surface ECG. In this case, momentarily impairing the device provided an accurate ECG recording, showing a normal ECG instead of wrongly diagnosing atrial fibrillation (or any perceived arrhythmia). Other common sources of interference,

[1] Undergraduate student. Queen's University. Kingston Health Sciences Centre, Ontario, Canada.
[2] RN. Kingston Health Sciences Centre, Ontario, Canada.
[3] BSc. Kingston Health Sciences Centre, Ontario, Canada.
[4] MD, FACC, FRCPC, FCCS. Kingston Health Sciences Centre, Ontario, Canada.

About the Author: *Shyla Gupta is an undergraduate student at Queen's University, pursuing her bachelor's degree in Health Sciences. Sohaib Haseeb is a 1st year medical student of James Cook University College of Medicine and Dentistry in Townsville, Queensland, Australia.*

Correspondence:
Adrian Baranchuk, MD, FACC, FRCPC, FCCS
Address: 76 Stuart St, Kingston, ON K7L 2V7, Canada
Email: barancha@kgh.kari.net

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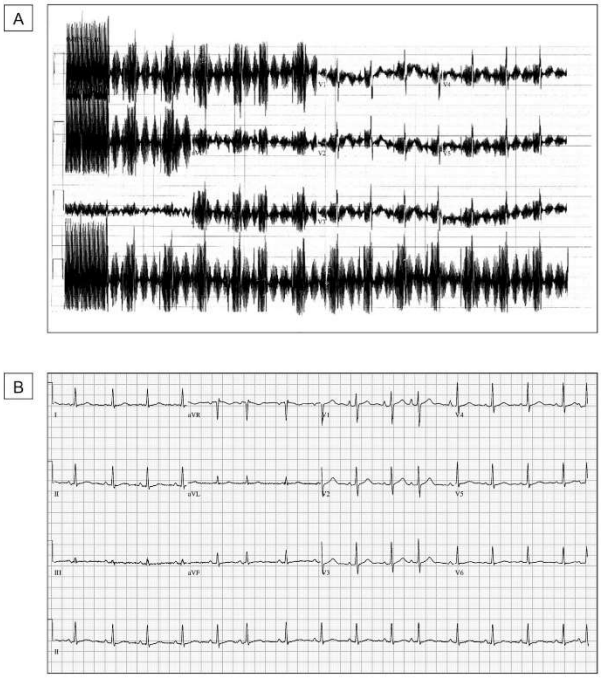
***Figure 2A*:** ECG with atrial fibrillation obtained with neuromodulator active. **B:** ECG without artifact, obtained after turning off the neuromodulator device.



such as Parkinson disease and tremors, hearing aid devices or sacral neuromodulators, may also act as a barrier to accurate electrocardiographic diagnosis. [5]

Similarly, deep brain stimulation is another form of electrical interference that has been shown to cause ECG artifact. Because the ECG can pick up electrical activity created by these stimulators, this brings to light other potential sources of interference, artifacts are only visible when neurostimulators are in monopolar mode. [6] This is likely because in bipolar mode, the electrode contact in the brain does not possess enough magnitude to create a notable interference.

Another example of interference comes from transcutaneous electrical nerve stimulators (TENS). TENS produce electric currents that interfere with ECG machines.[7] Artifact can occur depending on the frequency and amplitude through which skin electrodes are placed. Additionally, artifact can occur if ECG leads are placed incorrectly, and mimic pathology like in this case.[8] Proper ECG interpretation depends on several aspects of clinical care.

Recognizing different sources of artifact, learning how to facilitate a situation where ECG artifact is minimized, and being able to collect a proper ECG is quite essential to maintaining high level care.[9] Being aware of the effects of different neuromodulator devices is important for both ECG technicians and physicians.[10] Rapid recognition of sources of electromagnetic interference improves surface ECG recordings quality facilitating the accurate diagnosis or exclusion of different medical conditions relating to cardiac electrophysiology.[11]

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ULS

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Case Report

Clinical Course of a Covid-19 Patient with Gastrointestinal Symptoms- A Case Report

Sidra Agarwal,[1] Hemanshi Mistry.[2]

Abstract

Background: COVID-19 most commonly presents with respiratory symptoms. However, it can involve the gastrointestinal tract causing symptoms like diarrhea and the resultant shedding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in feces. This is due to the virus adhering to angiotensin-converting enzyme 2 receptors largely present in the gastrointestinal tract. This case report recommends routine stool Real-Time Reverse Polymerase Chain Reaction (rRT-PCR) testing for patients presenting with gastrointestinal symptoms. **The Case:** A healthy 36-year-old male healthcare worker in New York who tested positive for SARS-CoV-2 infection through rRT-PCR of the nasopharyngeal swab. After 7 days of convalescence, he recovered from influenza like symptoms after which he predominantly developed diarrhea, nausea, vomiting and extreme fatigue. Cough was the only lower respiratory symptom during the 3rd week of the clinical course. Anosmia or ageusia preceding the onset of respiratory symptoms was also reported. Due to the outbreak of the pandemic and New York being the epicenter at the time, the patient was recommended to self-isolate with supportive management through antipyretics and electrolyte replacement. **Conclusion:** This case highlights a SARS-CoV-2 PCR positive patient with predominant gastrointestinal symptoms. The reports regarding virus shedding in feces suggest that SARS-CoV-2 could be transmitted via fecal-oral route and thus routine stool rRT-PCR testing can aid in transmission-based precautions. Furthermore, reports of viral ribonucleic acid present in the stool, suggests direct infectivity of the virus on the intestinal tract. Therefore, screening in patients with only gastrointestinal symptoms can potentially help to contain the virus spread.

Key Words: COVID-19; SARS-COV-2 pandemic; Gastrointestinal symptoms; ACE2 receptor; Fecal-oral transmission; Case report (Source: MeSH-NLM).

Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with rapid spread worldwide, has now become a public health emergency.[1] A growing number of publications are shedding light on the frequency and nature of the gastrointestinal symptoms of coronavirus disease-2019 (COVID-19).[2] SARS-CoV-2 is thought to make its way into the gastrointestinal tract by adhering its spike proteins to angiotensin-converting enzyme 2 (ACE2) receptors, which are located in the lungs but also widely present in the gastrointestinal tract.[3]

A review article noted that diarrhea and vomiting was the most common symptom in children, diarrhea in adults whereas abdominal pain and gastrointestinal bleeding was mostly seen in severely ill patients, and it also showed that the incidence of gastrointestinal symptoms was higher in the later than in the early stages of the clinical course.[4]

Han et al, described a unique subgroup of COVID-19 patients with mild disease severity marked by the presence of digestive symptoms. This study demonstrated that the time between symptom onset and viral clearance was significantly longer in this subgroup and this longer disease course might reflect a higher viral burden in comparison to those with only respiratory symptoms.[5] Parasa et al, also found that these patients are more likely to test positive for COVID-19 viral Ribonucleic acid (RNA) in the stool, suggesting direct infectivity of the virus on the intestinal tract.[2]

A study by Xiao et al, highlighted the clinical significance of testing viral RNA in feces by real-time reverse transcriptase polymerase chain reaction (rRT-PCR).[6] According to the Centers for Disease Control and Prevention (CDC) guidance for the disposition of patients with SARS-CoV-2, the decision to discontinue transmission-based precautions for hospitalized patients with SARS-CoV-2 was dependent on the negative results of Real-Time Reverse Polymerase Chain Reaction (rRT-PCR) testing for SARS-CoV-2 from at least 2 sequential respiratory tract specimens collected ≥24 hours apart.[7] It was found that in more than 20% of patients, although the viral RNA in the respiratory tract were negative, it remained positive in feces indicating that the viral gastrointestinal infection and potential fecal-oral transmission [8] can last even after the virus has cleared from the respiratory tract.[2] It has been recommended that rRT-PCR testing for SARS-CoV-2 from feces should be performed routinely due to the high prevalence of positive stools in patients with COVID-19.[5] Here we described a case of a healthcare worker with predominant gastrointestinal symptoms who tested positive for COVID-19. We obtained written consent, and the Human Infection with COVID-19 Person Under Investigation (PUI) and Case Report Form was filled by the patient.

Highlights:

- This case report highlights another possible option for the pathophysiology of the SARS-CoV-2 infection.
- It presented a case of predominant gastrointestinal symptoms in COVID-19 compared to lower respiratory symptoms.
- The case report depicts importance of rRT-PCR testing for fecal-oral transmission.
- Further research is needed to probe the role of fecal-oral transmission.

[1] MBBS, Shadan Institute of Medical Sciences, Telangana, India.
[2] MBBS, Medical College Baroda, Gujarat, India.

About the Author: *Sidra Agarwal, an International Medical Graduate in the US and a MBBS from Shadan Institute of Medical Sciences, Telangana, India.*

Correspondence:
Sidra Agarwal
Address: Peeranchuruvu, Hyderabad, Telangana 500086, India.
Email: sidraa530@gmail.com

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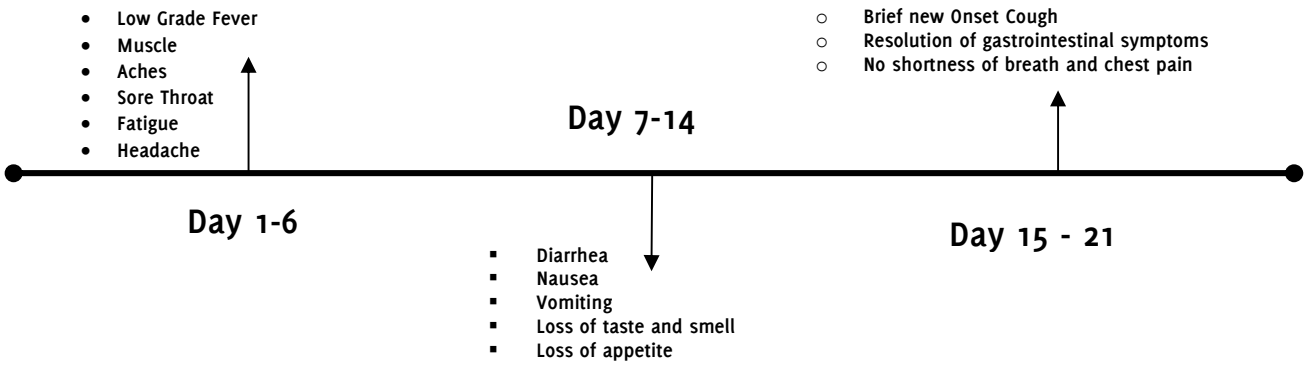
The Case

An otherwise healthy 36-year-old male, healthcare worker in New York, with no recent travel history and no history of diabetes mellitus, coronary artery disease, or hypertension presented to an urgent care with flu like symptoms (***Figure 1***).

The patient first noticed flu-like symptoms such as low-grade fever, chills, muscle aches, sore throat, weakness, and headache after possible healthcare contact with a COVID-19 case-patient. Vitals showed a temperature of 100.4 °F, blood pressure of 124/78 mmHg, heart rate of 95 beats per minute, and respiratory rate of 18 and pulse oxygen saturation of 97%. The National Early Warning Score (NEWS) was 1 (from 0 to 20, the score is related with clinical risk). The physical examination was normal otherwise. He was tested negative for Influenza Rapid Ag using the OSOM Ultra Flu Influenza A & B Test: Sekisui Diagnostics, LLC. A nasopharyngeal swab sample was performed on Day 1 of onset of symptoms to check for SARS-CoV-2 infection by using CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel protocol (CDC, Atlanta, Georgia, USA) that confirmed SARS-CoV-2 by positive result on polymerase chain reaction assay. No Radiological study (radiography or chest scan) was performed on the patient. He was placed under home isolation with daily monitoring for development of cough, dyspnea along with daily temperature and vital sign measurements. The patient was not prescribed antibiotics. Treatment during this time was largely supportive which included Acetaminophen 1000 mg every 8 hours as needed and a multivitamin a day. The patient started to notice improvement in his flu-like symptoms towards the end of the first week.

Figure 1. Timeline of the patient's symptoms after a possible healthcare contact with another COVID-19 patient.



On Day 7, the patient noticed sudden reappearance of fever, aches, chills, and weakness. He developed symptoms of diarrhea associated with nausea, vomiting, and complete loss of taste and smell. The patient mostly had watery stools that occurred 3-4 times a day for 1 week, no blood or mucus. He also had loss of appetite, inability to tolerate solid foods, significant weakness, and fatigue with no energy to perform daily activities. The patient did not undergo coproscopy and coproculture. There was no history of other infectious diseases such as HIV. There was no epidemiological link related to gastrointestinal symptoms such as food consumption, intoxication or fast food. The patient was on electrolyte replacement and plenty of oral fluids throughout the course of the illness due to gastrointestinal symptoms.

He had no cough, shortness of breath or chest pain. Vitals signs were: temperature 100.6 °F, blood pressure 95/60 mmHg, heart rate 104 beats per minute, respiratory rate 19, and pulse oxygen saturation of 99%. The NEWS was 4. At home supportive management with electrolyte replacement and plenty of oral fluids was the mainstay therapy.

In the 3rd week of convalescence at day 16, the patient developed a new onset cough but no shortness of breath, difficulty breathing or chest pain. He continued to have loss of taste and smell, but the diarrhea resolved.

At day 22, symptoms completely resolved but the patient continued to have some weakness and lethargy. The patient was not prescribed any antibiotics and did not require hospitalization, mechanical ventilation/intubation or ECMO (***Table 1***).

After the resolution of symptoms, the patient was followed-up by using CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel protocol (CDC, Atlanta, Georgia, USA) on Day 40 after the initial symptoms to assess clearance of viremia which was negative. He also underwent SARS-CoV-2 AB IgG test on day 138 that was positive indicating adaptive immune response to SARS-CoV-2.

Table 1. COVID-19 patient convalescence and findings

Duration	Presentation
Day 1-6	Low grade fever, chills, muscle aches, sore throat, weakness, and headache; started to feel better
Day 7-14	Worse again with sudden reappearance of fever, aches, chills, weakness, non-bloody watery diarrhea, nausea, vomiting, anosmia, ageusia, loss of appetite, fatigue.
Day 15-21	New onset cough, no shortness of breath or chest pain.
Day 22	Complete resolution of symptoms

Discussion

This case report describes a COVID-19 positive patient who initially presented with flu-like symptoms which was followed by diarrhea, nausea, vomiting, loss of appetite that lasted for most part of the illness with cough being the only respiratory symptom.

Receptor-mediated viral entry into a host cell is the first step of viral infection. SARS-CoV-2 enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor, and this receptor is expressed in the glandular epithelial cells of the stomach, duodenum, rectum, and via the absorptive enterocytes of ileum and colon.[9] These receptors are rarely found in esophageal epithelium because the esophagus is lined by the squamous epithelium and ACE2 receptor mainly targets the glandular epithelium. Viral nucleocapsid protein staining in the gastric, duodenal, and rectal epithelium confirmed the presence of SAR-COV-2 in these locations. Although the viral RNA could be detected in the esophageal mucosa, failure to stain the viral nucleocapsid protein shows low infectivity in the esophagus. In addition, ACE2 expression is higher in the gastrointestinal tract than in the lungs.[10] Patients with digestive symptoms have more virus in the gut based on the stool RNA testing, and thus potentially greater damage to the gut mucosa.

The tissue tropism of the SARS-CoV-2 in the intestinal tract has a major role to play in the clinical presentation and viral transmission.[11] In a systematic review and pooled analysis of published and preprint literature of SARS-CoV-2 infection and gastrointestinal symptoms, it was found that approximately 10% to 12% of patients with COVID-19 experience gastrointestinal symptoms, such as diarrhea (7.4%) and nausea or vomiting (4.6%).[2] Similarly, with our case, diarrhea was mostly watery without any blood or mucus and abdominal pain was minimal in most cases.[2]

The longer disease course in patients with digestive symptoms might be because of higher viral burden in these patients in comparison to those with only respiratory symptoms.[12] As the intestinal wall is invaded by SARS-CoV-2, there may be increased permeability and diminished barrier function allowing easier invasion of pathogens across the intestinal surface area.[5] Recent evidence has shown that fecal nucleic acid is readily detected in the stool of patients with COVID-19 and rectal swabs are also positive in some patients.[4] Han et al, stated that given the high prevalence of positive stools and the correlation between diarrhea and stool positivity, routine rRT-PCR testing of feces should be recommended in COVID-19 patients, especially those presenting with digestive symptoms.[13]

Recommended management for these cases is based on supportive measurements,[5] as described here. The patient was not exposed to any other potential cause of gastrointestinal symptoms and the length of duration of his gastrointestinal symptoms without any comorbidities calls the attention towards the role of this potential way of infection.

More research is needed to identify the reliability of testing suspect patients based on oropharyngeal samples only vs. the addition of stool samples. Can a patient have a respiratory resolution (a negative test) but the virus can continue its pathogenesis in the gastrointestinal system? Can the patient restart respiratory symptoms through reinfection? These are a few questions that we are pending to answer.

Conclusion

Our case report highlights predominant gastrointestinal involvement in a COVID-19 patient due to intestinal tropism of SARS-CoV-2. Studies regarding virus shedding in feces suggest that SARS-CoV-2 could be transmitted via the fecal-oral route and thus routine stool rRT-PCR testing can aid in transmission-based precautions among patients with SARS-CoV-2 infection. Furthermore, COVID-19 viral RNA present in the stool, suggests direct infectivity of the virus on the intestinal tract. We would also recommend screening for SARS-CoV-2 infection in patients presenting with only gastrointestinal symptoms and possible symptomatic management.

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Experience

Medical Volunteerism in Times of COVID-19: Burden or Relief?

Dimitris Potolidis.[1]

The Experience

The COVID-19 pandemic has significantly changed our daily lives in the way we see the world and understand the events occurring around us.[1] We suddenly realized further the importance of being healthy and we became more appreciative of it. Greece, after a severe and lengthy financial crisis, is now coping with this pandemic and it seems that the country is admittedly doing it with success by having embraced science-driven measures. Towards this endeavor, eager to keep our society healthy, medical students across the nation, as well as across the globe, have expressed their willingness to voluntarily participate in tackling COVID-19.[2-4]

Recently, medical student volunteering has dominated public discourse and it is being discussed in various fora and groups with final-year medical students expressing intriguing opinions on how they could help in addressing the pandemic and provide assistance to the national health system. In times of a crisis, this kind of mobilization is truly moving and gives us hope for the future. However, the participation of medical students in the daily clinical routine could possibly pose risks and have a negative impact on society as a whole for a couple of reasons.

First of all, there is no denying that volunteerism per se amid a crisis, be it a health crisis or the climate crisis, is something to be encouraged and embraced. Outside a crisis, volunteering, as a way of living, has positively affected our communities and has played a key role in bridging gaps and mitigating social issues like poverty and social disparities. As far as the medical field is concerned, we have seen, over the years, numerous international and domestic medical volunteer placements, which have undoubtedly enhanced the health care delivery in various settings, such as refugee camps or poverty-stricken countries. Many of these placements were given to medical students, which, under the proper guidance, assisted however they could. These endeavors should be strongly encouraged, as they unquestionably foster solidarity and equality. Consequently, in times of a given crisis, volunteerism plays a crucial role in overcoming difficulties throughout various fields, and more specifically in healthcare delivery.

However, albeit volunteerism in healthcare settings by medical students is highly useful, at the present moment, they could be both a burden on the healthcare system and a risk to the society, should the necessary conditions be not present. As SARS-CoV-2 has proven to be a highly infective virus, the participation of medical students in the daily clinical practice could lead to quicker transmission to the rest of the society, and particularly to the most susceptible, like the elderly.[5] Furthermore, there is already a medical personal protective equipment scarcity in the healthcare system[6] and this problem could get worse, as students will certainly need huge amounts of this equipment. While the aforementioned factors are worth serious consideration, we should also take into account the ever-increasing and constantly updated knowledge on our understanding of viral pathogenesis. Ill-preparedness and unawareness of the latest insights and guidelines could pose a threat to public health in general. Thus, only with suitable conditions and a meticulously planned policy would the students be able to actively engage in the daily nosocomial routine.

Lately, many argue that volunteering, and more specifically in healthcare delivery, is not the solution to the difficulties our health system has been experiencing over the years and is facing now, during the pandemic, as it will most probably perpetuate the problem. It has also been expressed that the serious and long-term issues in our understaffed and overworked national healthcare system will definitely not be resolved through volunteering, and that further measures should be implemented. It could be true but solutions to long-term problems should assuredly be sought out after the crisis and when, hopefully, all of us will be there to open the relevant discussions. For now, action should be taken. We can see many of our co-citizens undertaking voluntary projects, such as the development of protective equipment for the health personnel. These actions highly relieve the crisis burden and there are many similar examples that highlight the importance of volunteering.

Having said that, medical students are right in expressing their keenness to voluntarily engage and help in every way they can. Such initiatives give us hope to move forward as an active and responsible society. Being properly prepared, having acquired up-to-date insights, and having adequate protective equipment they could actively become involved in tackling the pandemic, with safety and responsibility. As COVID-19 is a rapidly evolving situation and it seems that it will continue to be present in our daily lives, it's not too late for the medical students to gain all the necessary expertise and be ready for future waves of the infection.

[1] Medical Student, Democritus University of Thrace, Greece.

About the Author: *Dimitris Potolidis is currently a final-year medical student of the 6-year program at Democritus University of Thrace, Greece.*

Correspondence:
Dimitris Potolidis
Address: Vasilissis Sofias 12, Xanthi 671 00, Greece.
Email: potolidis.dimitris@outlook.com

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Experience

The Role of Telemedicine in Ecuador During the COVID-19 Crisis: A Perspective from a Volunteer Physician

Bryan Nicolalde.[1]

The Experience

Ecuador is one of the countries with the most cases of COVID-19 by surface area in Latin America. According to The New York Times, the number of COVID-19 cases could be 15 times higher than the statistics cited by the government.[1] The large number of cases that may exist threaten to lead to an oversaturation of the country's healthcare services. In a middle-income country where the availability of emergency rooms is scarce, a pandemic such as this one can be overwhelming since many mild cases of COVID-19 could exhaust the limited healthcare resources available. For this reason, the Ecuadorian Ministry of Public Health has created a crisis call-center and has invited volunteer doctors to join the fight against this pandemic.[2] I decided to lend a hand during the COVID-19 crisis and immediately volunteered.

The world health organization defines telemedicine as: "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries".[3] Within these parameters and with current technology, telemedicine can be practiced from several different platforms such as video calls, standard calls, text messages, emails and other online platforms. However, the diagnostic accuracy may vary according to the method used, since receiving a text message will not present the same data as conversing with a patient on the phone or seeing him or her on video.[4-5] According to the latest survey by the national institute of statics and censuses, 70.6% of people in Ecuador have a smartphone, 32.7% of people have Internet, 50.1% of people have computers at home and 90.7% have a standard phone.[6] The Ecuadorian Ministry of Health has proposed the delivery of telemedicine solely via the use of conventional phone calls. This may be a result of the fact that there is greater cellular coverage and because of the limited Internet usage in rural areas. However, this type of physician-patient interaction may significantly decrease the quality of the evaluation when compared to a video call. The objective of telemedicine during this crisis in Ecuador is mainly to perform medical triage and to be able to desaturate the medical systems, for this a telemedicine algorithm has been proposed where 4 possible scenarios are possible: patients who are stable, patients who are stable and have any comorbidity, patients who are critical and, patients who ask about other diseases.

Since I started volunteering, I have faced several difficulties that I have transformed into opportunities.[7] Being able to assess a patient's condition without a physical examination is challenging, especially since I only recently graduated from medical school. Many patients call with complaints about fever, dyspnea, cough, runny nose, confusion and chest pain and being able to translate these symptoms into a scale of severity or relate them to COVID-19 is complicated, since many of these symptoms may have alternative explanations. For example, chest pain and dyspnea may be secondary to anxiety rather than pneumonia. Some tools that I have used to assess the severity of a patient's complaint is listening to understand if the patient can complete sentences without signs of respiratory distress, teaching relatives to identify the patient's respiratory rate and asking relatives if there is some degree of change in mental status in the patient. These tools can convert subjective details into objective metrics that may help us improve our efforts to triage via the telephone.

One of the main objectives of this hot line is to desaturate the health systems. Therefore, it is necessary to achieve excellent coordination between the emergency systems and telemedicine services to reach this goal and avoid delays when personal attention is necessary.

Telemedicine also has a psychological role during this pandemic. Many people call because they have seen their relatives die and are afraid. The role I have played during these occasions has been to provide psychological support. Additionally, many patients have also chosen to self-medicate, which can be much worse than the disease itself. Some patients have used dangerous pharmacological combinations at toxic dose, including hydroxychloroquine plus azithromycin, which without the proper monitoring or a suitable indication may have a fatal outcome. In this case, the patient education that a doctor can provide can play an important role.

This crisis has allowed for the widespread use of telemedicine in Ecuador. However, due to the lack of coverage and lack of digital education it is not being used in an optimal manner. The difficulties that can be faced in using telemedicine are related to establishing the severity of a patient's condition via subjective means alone. The role that the doctor plays during this crisis is fundamental from an educational, preventive and psychological point of view.

[1] MD, Colegio de Ciencias de la Salud, Universidad San Francisco de Quito, Ecuador.

About the Author: *Bryan Nicolalde is a MD who graduated in 2019 from Universidad San Francisco de Quito in Ecuador (6-year program). He graduated Summa Cum Laude with a final GPA of 3.93. ORCID: https://orcid.org/0000-0002-7043-5515.*

Correspondence:

Bryan Nicolalde

Address: Diego de Robles s/n y Pampite. Quito, Ecuador.

Email: bryan.nicolalde@alumni.usfq.edu.ec

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Experience

A Surgical Resident's Perspective about COVID-19 Pandemic: Unique Experience and Lessons Learnt

Madhuri Chaudary,[1] Prakash Kumar Sasmal.[2]

The Experience

History has been repeating itself in the form of pandemics like cholera, swine flu, and smallpox, to name a few, which affect humanity by killing a substantial number of people with each occurrence. After nearly a decade of the swine flu pandemic which caused massive loss of human lives all over the world, the presently ongoing COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has wholly paralyzed the globe with a rising death toll. COVID-19 or SARS-CoV-2 illness was declared to be a public health emergency of international significance on 30th January 2020. The outbreak, as first reported in December 2019 in Wuhan province of China, has now spread in almost the entire world, affecting most of the countries worldwide.[1] In India, though cases started to appear towards the end of January 2020, now cases are skyrocketing despite stringent measures to contain the disease.[2] Every pandemic teaches people new ways of lifestyle, like the Black Death, which in the year 1346 left us ending the system of serfdom in Europe and introduced the concept of quarantine.[3]

As a surgical postgraduate trainee, I had never thought in my life to be experiencing such a situation, especially in the early part of my career. In this short article, I will be sharing my experience during this challenging time, regarding the management of the health crisis in a tertiary care center of a lower-middle-income country.

What I Experienced

Patient Care: Ever since the outbreak of the COVID-19 in India, the government has implemented a standard operating procedure (SOP) to manage the diagnosed or suspected cases in the hospital. There is frequent training of the residents, irrespective of the specialty, regarding donning and doffing of personal protective equipment (PPE) and handling the ventilators to manage the critically ill patients. The infectiousness and fatality of the SARS-CoV-2 virus have not only spread apprehension amongst the public but created chaos amongst the health care providers.

As a surgical trainee, I am used to handling high-risk surgical patients taking universal precautions, but managing a highly infectious medical condition is the need of the hour. As a surgical resident, I never thought of managing cases with a medical illness, including collecting swabs for RT-PCR and running the screening outpatient departments.

During this critical time, it has become even more difficult to manage a patient with a genuine surgical emergency. Due to the apprehension in my mind about unknowingly encountering a COVID-19 patient and getting exposed, a surgical disease is often clinically missed. At present, there is postponing of all elective surgeries barring emergency procedures. As a front-line worker, the trainee is supposed to prepare and post an emergency case for operation. It was a time when I used to enter the operating room with so much enthusiasm and zeal to learn and treat patients. These surgeries, with which I used to assist with passion three months ago, have become stressful now. The operating room which once used to be a place of learning is now entirely a silent and stressful zone. Thinking back, I remember assisting high-risk seropositive cases with apprehension but not to this extent. But despite all this I am bound to treat and take care of patients, whatever the conditions or diseases might be, as I had taken the Hippocratic Oath on the start of this journey.

Academics during the COVID-19 times: Due to the strict imposition of the rules of social distancing by the administration, which is the key to break the chain of transmission of this highly infectious virus, there is a withholding of regular classroom academic seminars and classes. Also, the bedside teaching in clinical grand rounds is temporarily suspended to avoid crowding near the patients. It comes with the drawback that medical students in their clinical years will suffer from a lack of clinical experience impacting the skills they require to make on-point clinical decisions, which is of utmost importance.[4] More amount of e-learning is promoted presently with online seminars and webinars on managing COVID-19 and other non-COVID-19 diseases, which is overall a new experience during this critical time. Few students find it very comfortable to take online theory classes at home, still, at the cost of missing the clinical courses.[5] There is a risk of depression among students and having online courses is not always very pleasant due to frequent voice disturbances with connection problems and online examinations.[6]

Mental health among medical students: We, medical students, are used to group study sessions and hangouts. Due to strictly abiding social distancing, the present situation has increased isolation of medical students and had a significant impact on mental health. In general, medical students are more prone to psychological distress and mental illness, leading to suicidal ideation.[7]

Strategy to overcome the COVID-19 crises: All elective surgical procedures are on hold, and the semi-elective cases are deferred if possible, by conservative treatment or radiological interventions. By this, a lot of resources, including indoor beds and PPE, are preserved, can be redirected for use by health care workers dealing directly with the COVID-19 patients. Also training all health care workers, irrespective of specialties, in critical care management for future preparedness, updating ourselves regarding recent happenings of the disease and helping in the active screening of all suspected patients is

[1] MBBS, DCH. Surgical Resident, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India
[2] MBBS, MS, FNB (MAS), FALS (Metabolic Surgery), FAIS. Additional Professor of Surgery, AIIMS, Bhubaneswar, India.

About the Author: *Madhuri is pursuing her academic surgical training in the second year of a three years degree program. She has completed her two years of training in child health after her graduation.*

Correspondence:
Prakash Kumar Sasmal
Address: Sijua, Patrapada, Bhubaneswar, Odisha 751019, India
Email: surg_prakash@aiimsbhubaneswar.edu.in

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going to help fight against the dreadful disease until an effective medicine or vaccine is available.

Lessons Learnt

I just thought where we stand despite all the advancement in technology, improved health care and better diagnostic facilities possible today. Globally, a virus has disrupted the entire health system, economy and has taken a significant toll of precious human life. Seeing the present scenario, every nation and medical university needs to adequately increase the infrastructure to tackle similar situations and also train their future generation of health care providers more broadly to be able to manage critically ill patients during epidemics. It is high time – the global community should unite to fight against this invisible enemy of humanity strategically, or else it will cause colossal devastation, more so than the world war.

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Experience

Stuck in Limbo: Coping with an Unusual Circumstance as an International Medical Graduate from India

Sanjana Chetana Shanmukhappa.[1]

The Experience

The world is on a war path. A war against a seemingly invincible disease that has driven humanity into a state of chaos and confusion. With over a hundred countries under some form of lockdown, people are striving to adjust to the new "normal" of social distancing and restricting themselves to the confines of their homes. In a country like India, a population of over 1.3 billion poses unique challenges. The lockdown in this country has been in place since the 24th of March. The once bustling streets are now empty. Only essential services remain open and there too strict social distancing norms are being adhered to. The government and police are working tirelessly to identify, trace and quarantine contacts. With over 60000 cases (as of 11th of May), these precautionary measures are all the more prudent now to prevent the occurrence of an unimaginable yet ever-looming threat: the overburdening of our healthcare system.

I am a young medical doctor from Bengaluru, India. I have been preparing for a medical residency in the United States. This is a process that involves years of time, money, effort and dedication. In the crux of my journey to achieve my dreams of training in the most advanced country in the world, my path has been brought to a staggering halt. I am now faced with a million uncertainties, a worry that's heightened by my idle mind. I'm anxious about the pandemic situation not just in India but in the United States as well. Watching the news, listening to the grim tales of death and despair has left me feeling distressed about the precariousness of the upcoming days.

This is true for thousands of aspirants like me across the globe. To be a competitive residency applicant, a lot of importance is placed on having a resume that is devoid of gaps or one that shows unproductive time periods. However, at present, electives are being called off, emails unanswered, flights cancelled and visa embassies closed indefinitely. Facebook groups are filled with posts of students worrying about the future. The panic is tangible. And contagious. With no end to this pandemic in sight, restrictions can extend even till the end of the year. What does that mean for International Medical Graduates?

Unfortunately, this cannot be answered at this time. I fight these questions of unsureness every day and have developed several strategies to spend my time constructively:

Volunteering

When the lockdown began, many junior doctors like me were asked to leave our jobs owing to insufficient funds and lack of Personal Protective Equipment (PPE). To be young and able, and yet not given the opportunity to contribute to the healthcare system can be frustrating. But if we look hard enough, opportunities show up in other forms. From volunteering as medical doctors to finding Non-Government Organizations (NGOs) involved in distributing food and basic amenities to vulnerable populations, there are ways to continue to help the society. Personally, I have been part of the Child Rights and You (CRY) Organization and have joined their efforts to compile online lessons for children from underprivileged communities.

Teleconsultation

We can join practices that are moving to teleconsultation and telehealth services. The discussion on incorporating these methods to meet the demands of the health care system began long before the present-day crisis.[1] Now through these online means, young doctors can continue to remain in touch with clinical practice and ease the burden off of senior professionals who work in the front lines. Contrary to my initial skepticism towards the practicality of teleconsultation, it has in fact been an eye opener because of its profound and far reaching impact. As part of a private organization I work with a team of primary care doctors to consult, treat and triage patients from remote parts of the country. We also mentor nurses (who form the backbone of the healthcare system in rural India) and guide their decisions in patient management.

Online learning

As medical schools around the world move to online classes, this can be a great use of technology for medical graduates as well.[2-4] There are a wide variety of courses available at our fingertips. Many universities and organizations are even offering courses for free/nominal prices. We can look for online conferences, webinars and Continued Medical Education (CME) courses. This will help pick up some skills and gain more knowledge. As for me, I am using this time to brush up on my understanding of biostatistics (which, without a doubt, I would not have done under normal circumstances!)

Research

For individuals interested in research, this is the perfect time to join online research groups (or form one of our own) to begin online research projects, journal clubs etc.[5] This becomes a platform to share information and knowledge, for beginners to get their foothold on research methodology or biostatistics and to develop critical thinking. Additionally, this gives us a chance to meet other young researchers and doctors to collaborate with on new studies. I am part of groups and organizations and am constantly on the lookout for mentors or research partners, new projects and inspirational ideas.

[1] M.B.B.S. Aster CMI Hospital, Bengaluru, India.

About the Author: *Dr. Sanjana Chetana Shanmukhappa is a graduate from Dr. B.R Ambedkar Medical College, Bengaluru, India. She is currently working as a Junior Resident at Aster CMI Hospital, Bengaluru. She was conferred "The Most Promising Student" award in her high school graduation and is a recipient of the State Government Scholarship for medical school education. She has presented papers in National conferences and has received accolades for an oral presentation of one of her papers in the National Conference on Family Medicine and Primary Care, India.*

Correspondence:

Sanjana Chetana Shanmukhappa

Address: New Airport Road, NH 44, Sahakar Nagar, Hebbal, Bengaluru, Karnataka 560092, India

Email: sanjcs92@gmail.com

Editor: Mihnea-Alexandru Găman
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In conclusion, these times are unprecedented and it can be difficult to add valuable experiences to our resume during a lockdown. These are some of the ways I have been keeping myself occupied. It is also important to remember that there are hundreds of people in similar situations of being stranded at life's crossroads and that we are not alone. While the world fights back this deadly disease, hope, optimism and support can drive those of us at home towards productivity and help stray away from fear and mindless panic.

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Experience

COVID-19 Pandemic: Medical and Pharmacy Education in Nigeria

Yusuff Adebayo Adebisi,[1] Progress Agboola,[2] Melody Okereke.[1]

The Experience

Coronavirus Disease 2019 (COVID-19) pandemic poses a major threat to education globally and medical and pharmacy education in Nigeria is not an exception. Although the focus has been to treat the infected persons and reduce the spread of the virus as much as possible, the emergence of COVID-19 has disrupted education and this requires prompt attention from stakeholders.[1,2] The pandemic effect on healthcare students' education would be more pronounced because of its peculiarities as it involves clinical rotation exposure, laboratory experiences, internships, in-person didactic lectures and tutorials, presentations, clinical clerkship, observing and assisting relevant medical and surgical procedures.

A good number of healthcare students including medical and pharmacy students are in the process of preparing for or undertaking assessments that require clinical exposure. The effect of COVID-19 pandemic on healthcare students' education in Nigeria could therefore be considered significant, causing a disastrous effect to performance in examination post-pandemic and competency of these future healthcare professionals. As students, we cannot help but concern ourselves with how the COVID-19 pandemic will affect our career trajectories. The pandemic has equally reiterated the value of the skills and trainings that we gain in school. We are happy and proud to see healthcare students including medical and pharmacy students starting and organizing different programs aimed at improving public understanding and supporting responses to the COVID-19 outbreak.

Medical and pharmacy education were halted as a proactive measure to further curtail the spread of the virus. The National Universities Commission has ordered universities in Nigeria to close for a month beginning from 23 March 2020.[3] As there is an upsurge in number of COVID-19 confirmed cases on a daily basis, schools across the country are likely to be closed indefinitely until there is a standard treatment option or vaccine for COVID-19. Consequently, medical training has been invariably affected, however, some private universities have explored the use of virtual platforms like Zoom, Telegram, WhatsApp, Google Classroom, and emails for academic activities. The effectiveness of these learning platforms in Nigeria has been questioned because of poor internet connectivity, relatively expensive out-of-pocket spending on internet data bundles and epileptic power supply.

Additionally, the COVID-19 pandemic has also affected proposed examinations in medical schools across the country. For instance, Progress Agboola's Bachelor of Medicine Part 2 assessment was postponed a few days to the exam due to the COVID-19 pandemic. It is without a doubt that this will have impact on students ranging from competency, mental health status to academic performance.

Crises like this provide opportunity for educators to leverage technology to sustain undergraduate and postgraduate medical education.[4] To leverage on these opportunities, e-learning platforms can be utilized to deliver lectures remotely at one's convenience. Faculty, instructors and medical educators, residents, and students can then log in at scheduled time for discussions, which can be facilitated live using video and audio conferencing. In addition to lectures, video conferencing can also be leveraged to teach medical procedures and surgical techniques.[5] However, required facilities to cope with these modern teaching approaches in Nigeria remain a major challenge.

Also, the COVID-19 pandemic has had its toll on pharmacy education globally and Nigeria is not left out. The pharmacy practice is continuously evolving worldwide and so is the need for a corresponding evolution of learning methods,[6] which is especially crucial at this period of crises. The unprecedented nature of the pandemic has led to the unanticipated closure of all pharmacy schools in Nigeria thereby causing disruption and interruption of the pharmacy curriculum and examinations. For instance, Melody Okereke's exam was suspended indefinitely. This present situation has challenged the pharmacy education sector to also devise a coordinated response and deploy feasible interventions that will ensure uninterrupted learning and student assessment in case of any unforeseen crises.

The benchmark for pharmacy education in Nigeria encourages the use of lectures, tutorials, case studies, presentations, and practical sessions as methods of imparting knowledge to pharmacy students.[7] The most commonly used method is didactic method. While e-learning methods are employed in some pharmacy schools,[8] the reality is that not all pharmacy schools are equipped with the necessary infrastructure and technological innovations to strive in the face of the pandemic. This, however, is due to the fact that infrastructure, access to teaching resources, development of academic staff, and quality research remain persistent challenges to the delivery of quality pharmacy education in Nigeria and other developing countries.[9] While the e-learning approach seems to be plausible, some practical courses in both pharmacy and medical curriculum require a hands-on approach.

The lockdown policy and the need to practice physical distancing also have a significant effect on clinical rotations, internships and graduation of pharmacy and medical students as they are forced to

[1] BPharm. Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria.
[2] MBBS. Department of Medicine & Surgery, Faculty of Clinical Sciences, Ladoke Akintola University of Technology, Oyo State, Nigeria.
[3] BPharm. Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria.

About the Author: *Yusuff Adebayo Adebisi just finished his final exams at the Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria. Progress Agboola is a 4th year medical student from the Faculty of Clinical Sciences, Ladoke Akintola University of Technology, Oyo State, Nigeria. Melody Okereke is a 2nd year pharmacy student from the Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria.*

Correspondence:
[Yusuff Adebayo Adebisi
Address: Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria.
Email: adebisiyusuff23@yahoo.com

Editor: Francisco Javier Bonilla-Escobar
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remain at home until the pandemic is over. For instance, Yusuff Adebayo Adebisi completed his final examinations on 25 February 2020 but his induction into pharmacy profession was halted due to the COVID-19 pandemic. Him and his classmates are in state of dilemma whether they are still a student or graduate. This disruption has also cost some students opportunities to advance their career. Going forward, this trend may also lead to a possible decline in the pharmacy workforce capacity, which has been documented in literature as one of the major challenges facing pharmacy practice in Nigeria.[10]

The COVID-19 pandemic creates a complex mixture of threats and opportunities for medical and pharmacy education in Nigeria and globally. The need to encourage e-learning in the modern world of education becomes clearly evident.[11] In light of this, COVID-19 crisis makes it much-needed for the academic community, stakeholders and the Nigerian government to learn from this unprecedented pandemic to further review the future of medical and pharmacy education in Nigeria because there is no better time than now.

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Experience

A Positive Attitude to Negate a False Positive Test Result: An Intern's Experience with COVID-19

Vanessa N. Youmbi.[1]

The Experience

I am an intern at a tertiary referral hospital in the Democratic Republic of Congo (DRC). On March 19, 2020, during a night shift at the emergency department, I received a 23-year-old Caucasian female who had been volunteering at a local pediatric health center for two weeks. She had presented with dyspnea, tachypnea, and was desaturating. Given her sunstantial travel history and the current public health emergency of international concern, we suspected her symptoms were consistent with COVID-19. This suspicion came after we had examined her without the appropriate personal protective equipment (PPE). At the time, the DRC had not registered a case of COVID-19 and thus hospital administrations had not yet made PPE available to all personnel.

As soon as we reported our findings to our consultants, drastic measures were taken. All personnel who had been in contact with the patient were immediately isolated. We were placed in separate rooms, away from the rest of the hospital. The room that I was allotted was chilly. My knees became weak, and I found it hard to breathe. The room was bounded by security tapes that read, "Caution, do not enter." The tapes designated a "red zone" in which no one was to leave or enter without clearance. I am an active and sociable person. Being in this room was a stressful experience. I spent my days imagining my colleagues at work, I was eager for this to be over, and I could not help but wonder what will happen if I had contracted the novel coronavirus.

We were told that the results of the patient's swab would be available in 48 hours. This moment was the most prolonged 48 hours of my life! I was impatient yet courageous at times. I thought to myself: "a positive attitude will lead to a negative result." Things became scary when the result came back positive. My first thought when I heard the news was, "I was silly for infecting myself and putting the rest of my team in danger." Upon reflection, I should have handled this better.

The next days were painful. Colleagues with whom we had shared a close bond avoided us as much as possible. It was the right thing for them to do physically, but it just did not feel right mentally. I felt ostracized. Once in a while, a few of our colleagues would stop by to cheer us up – from a distance. I received calls and texts from acquaintances, but the feeling of rejection, loneliness, and stigma was overwhelming. I remember once, to send us our medication, they pushed the tray on the floor. It was the last straw – I cried my heart out in this new prison. The thought of being an outcast in the hospital I had worked in took a toll on me.

A new test was ordered to confirm the previous result of the patient, and a few days after this, the results came back. The results read – negative(!) The first test was a false positive. We were liberated from our holding cells but not from our new status. In the corridors, the uneasiness was palpable and audible. We became known as the "corona doctors." Unfortunately, the impact of COVID-19 is not limited to medical students like myself who are on the frontline.[1-5] The resulting stress due to uncertainty is taking a mental toll on student-physicians.[6]

As physicians, when we chose medicine, we know that we will be exposed to several challenging situations including risks. However, if these risks are preventable, we should avoid them. Emergency department staff are at higher risk of developing COVID and adverse psychiatric outcomes.[7,8] Singapore, for example, has recognized this and have integrated psychological interventions in their national COVID-19 response.[9]

I have experienced isolation, and I understand that some of my patients went through this without ever complaining. The feeling of rejection can be as much of a problem as the actual disease and we physicians should do a better job at preventing and managing that.

[1] BS. Faculty of Medicine, Bel Campus University of Technology, Kinshasa, Democratic Republic of Congo.

About the Author: *Vanessa Nono is currently a seventh-year medical student at the Bel Campus University of Technology, Kinshasa, DRC of a 7-year program. She is also a recipient of the Dean's Award for academic excellence.*

Correspondence:

Vanessa N. Youmbi

Address: 17, 8ème Rue Limete / Quartier Industriel, Congo - Kinshasa

Email: youmbi06vanessa@gmail.com

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Balancing Our Identities as Medical Students and Global Citizens in the Wake of COVID-19

Ramesha Ali.[1]

The Experience

Our role as students never ceases. Medical training spans a lifetime, seamlessly transitioning from medical school, to postgraduate training, and to our practices. This lifelong commitment to learn and be a student holds a few accelerations, periods that have great determining potential. The transition from medical school to post-graduate training is largely influenced by six critical months at the cusp of third and fourth year. These months encompass the follow up to our university finals, twelve weeks of electives that are carefully planned to hopefully yield the strongest letters of reference, and multiple licensing exams. As a Canadian student studying Medicine in Ireland, these months are the fruit of meticulous planning, balancing time zones to catch emails at the right time, scheduling international exams between electives that are yet to be confirmed, and the pressure to not let a single day fall short of its potential. These six months culminate with the start of residency applications and fall between March and September of 2020.

In Ireland, at the start of March, our University Hospital had one COVID-19 case - the only one in our city and one of forty national cases.[1] Similar to the experience of medical students in Europe, North America and Asia, we were pulled from clerkships and our learning quickly transitioned to virtual lectures and clinics.[2-6] As we made this transition, upcoming electives, internships, and exams also began getting cancelled, one by one over an agonizing number of days, leaving unplaceable anxiety and uncertainty in their wake.[7] We struggled to search out any remaining opportunity, only to have it snatched away a few days later. At this time, the pandemic was rising, but the looming, national sense of emergency was distant. In a matter of days, global circumstances shifted. We were suddenly flying back home to our families in Canada, months before we had intended and without having written any exams. As we approached our homes, feelings of diminished hope heightened, and the idea of facing a residency director in autumn, with no account of shining clinical moments, burdened us.

Thoughts of the pandemic inevitably circled back to how we were going to fill the days ahead. It was a state of unawareness that perhaps represented how naïve and optimistic we were about the global trajectory COVID-19 would take. When we came home and as the COVID-19 cases reached millions, the thoughts that filled our minds were far more unsettling and humbling. Cases rose disproportionately in my home province compared to the rest of Canada, and like many other students arriving home, I worried about the well-being of my loved ones and my own health.[8] Many of us were self-isolating and upholding our own mental well-being became a very conscious process.[9] These were feelings that were understandable, even predictable, but had deliberately been left by the wayside.[10] Back in Ireland, it had been easy to focus on our responsibilities as students, but now that we were back home in Canada, and surrounded by our loved ones, it was hard not to worry at a very intimate and personal level. We had been putting our identity as medical students above our identity as global citizens living in distressing times. COVID-19 had challenged both of these identities, and we had been doing a disservice to ourselves by not accepting that we were also vulnerable to ill-health and the loss of loved ones. We were working to dedicate ourselves to a lifetime of service, to uphold the care of others regardless of the threat against it. Along the way, however, we stripped ourselves of the same privilege. We neglected our own well-being in a constant struggle to come out on top of the pandemic, to negotiate the opportunities that were no more.

It was easy to feel hopeless at the loss of structure, loss of opportunity, and loss of certainty. It was even harder to accept that we were feeling this way when the loss was so much greater than that. Suddenly, we were facing a significant loss of life, loss of health, and loss of security. Just in North America, cases reached and surpassed one million before our self-isolation period had even ended.[11] Moments of sadness at our personal losses were followed by self-identification as an insensitive and apathetic individual, or worse yet, a future healthcare provider. The contrast between these was complex and resulted in confusion, in terms of what mattered most to us. After all, we chose medical school to care for patients. And now that patient care was in a delicate position, globally, our individual challenges seemed insignificant.[12] How could one feel disappointment at a cancelled elective or postponed exam when the health and well-being of millions were suddenly threatened in a manner that we could not even have fathomed?

[1] BSc in Medical Sciences (Honours). University College Cork

About the Author: *Ramesha Ali is currently in her final year of Medicine at University College Cork, in Cork, Ireland.*

Correspondence:
Ramesha Ali
Address: Gaol Walk, University College, Cork, T12 YN60, Ireland.
Email: 117105162@umail.ucc.ie

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Experience

To Help or Not to Help: A First Year Canadian Medical Student's Dilemma During the COVID-19 Pandemic

Janhavi Patel.[1]

The Experience

On March 13, 2020, we received our first email concerning COVID-19. This was followed by a large flurry of emails and soon our inbox was flooded with, *"there will no longer be any large group lectures"…"no clinical skills classes"… "all anatomy programs have been suspended"* and so forth. The e-mails kept coming in, and with them came a wave of confusion about the future. For me, a first-year medical student, I was shocked. I understood that many universities across the globe were taking steps toward social distancing but an online medical school? That had to be a mistake. Suddenly, another email came in, suggesting that all the upper-year students on clerkship were discharged from clinical duties and that all medical students were expected to not visit any healthcare facilities unless necessary. After reading the last email, I was no longer feeling uncertain about the future; instead, I felt apprehensive. Although, I could not pinpoint the reason for my feelings.

Then my phone rang, it was my supervisor calling to check in. He asked what my thoughts were about medical students being suspended from clinical duties. Before I could say anything, he said that in this time when physicians should be helping out more, why should the medical students be discouraged from helping and doing their part? His idea was that we did not come to medicine to step away when the need arises, but to take proper precautions, and stand up in solidarity to provide care. Listening to him, I felt validated. I took a deep breath as I realized that the sentiment I felt was of being stripped of the opportunity to play my part. I kept thinking back to the day of our white coat ceremony just a few months ago, where we pledged to serve our communities with kindness, care, and justice. Now, a time when more than ever before, we had the opportunity to stay true to our oath, we were told that our services will no longer be required. Talking further, we both explored the other side of the issue. We did discuss how having medical students at the hospital increases liability as well as puts students at risk. However, reconciling with those ideas, and staying inside the house was difficult.

Sensing that many medical students felt the same as me yet recognizing our responsibility to engage in social distancing like all citizens, the next few days went into finding a sweet balance. Within days, we started seeing a rise in initiatives started by medical students to help with the COVID-19 relief.[1] Initiatives like helping frontline workers by doing grocery runs or providing child-care services. It was heart-warming to see how students from all across the globe were collaborating, reaching out, innovating and trying to support the frontline heroes.[2] Personally, I found myself drawn to reducing anxiety and aiding in the mental health of community members. As an Education Committee member of the Ontario Medical Students Association, I began working with medical students from all over Canada to create a series of infographics sharing resources and encouraging medical students to stay informed (***Figure 1***). I began checking in with senior residents of my building, and we tried to reassure and encourage each other. Somehow, in an attempt to physically distance, people were indeed coming together emotionally.

As days pass by, and we begin to adjust to our new online curriculum, I find myself surrounded by new dilemmas. Every news or social media outlet that I surfed was filled with ideas of being productive. From cooking challenges to exercising, and spending time with family, everyone seemed to be in a race to make efficient use of this unexpected gift of time. I am guilty of thinking similarly. I found myself being pulled in all directions. It was important for people to recognize that not doing anything productive, and simply taking care of ourselves was equally important. Just as it was important is to seek support when needed, and to realize that it is okay if we all do not come out as chefs, or athletes after this lockdown."

Even though I am not at the frontline, I feel a sense of responsibility by being associated with the profession of medicine. In some ways, living everyday through this pandemic and seeing the world cope, seems to teach me something new every day. Even though our classes are now online, and it seems scary to think we might not learn all the necessary clinical skills, I am determined to work harder. Most of all, stories of sacrifice and triumph of healthcare professionals motivate me to be a better version of myself, to be a better student, and a better physician in the future. To end off, just like all the email communications we received, I hope you are all keeping safe during these uncertain and changing times.

Learn more about education in Ontario, Canada (including infographics), volunteering opportunities and wellness during COVID-19 at the Ontario Medical Students Association website: https://omsa.ca.

[1] Bachelor of Medical Sciences (BMSc), MD Candidate, Michael G. DeGroote School of Medicine, McMaster University, Canada.

About the Author: *Janhavi Patel is currently a first-year medical student at the Michael G. DeGroote School of Medicine, McMaster University, Niagara Regional Campus (St. Catherines), Canada of a three-year program. She is a recipient of Ontario Medical Students Association Innovator Grant and McMaster Medical Student Research Excellence Scholarship.*

Correspondence:
Janhavi Patel
Address: 100 Main St W, Hamilton, ON L8P 1H6, Canada
Email: janhavi.patel7397@gmail.com

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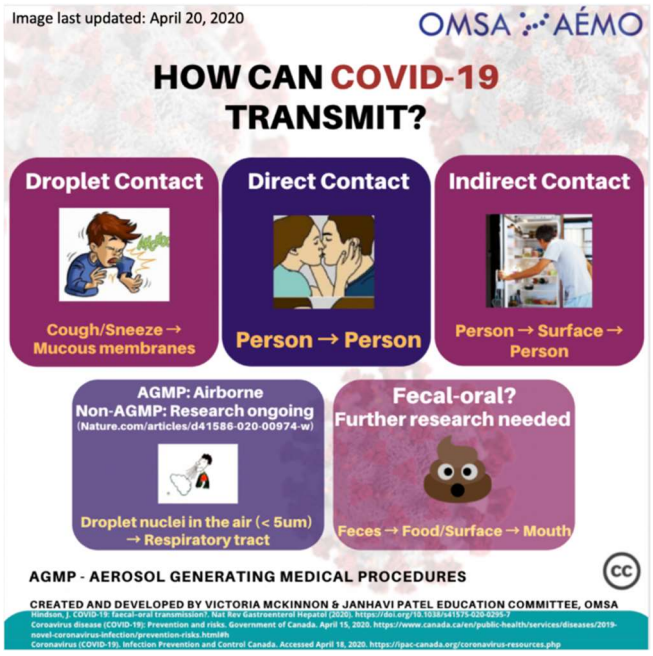
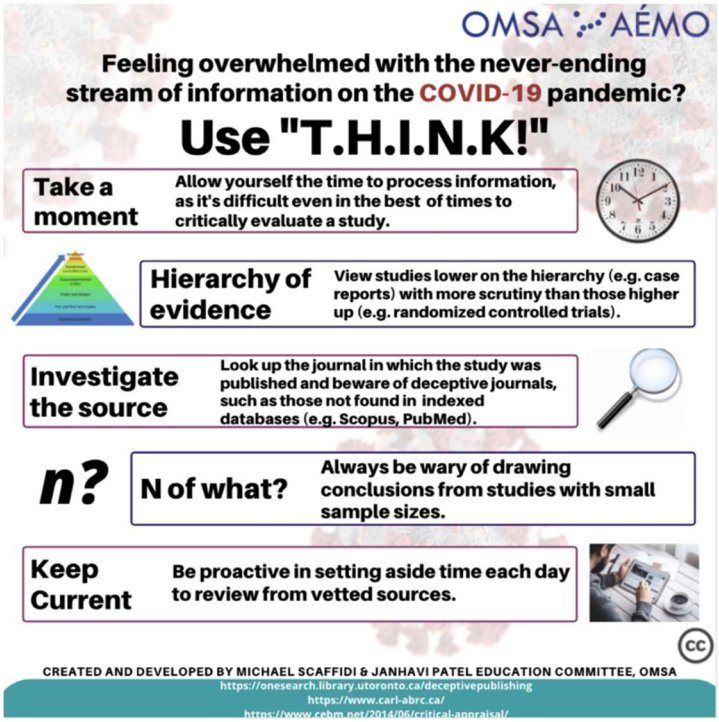
Figure 1. Infographics created with students of the Education Committee of the Ontario Medical Students Association





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Experience

The Effect of COVID-19 Pandemic on US Medical Students in their Clinical Years

Raed Qarajeh,[1] Farah Tahboub,[2] Nikita Rafie,[3] Nurry Pirani,[4] Mary Anne Jackson,[5] C. Douglas Cochran.[4]

The Experience

Since December 31, 2019, when China identified the first cases of SARS-CoV-2 respiratory disease, this topic has dominated all news outlets, medical journals, and household conversations. On January 30, 2020, the World Health Organization (WHO) announced coronavirus disease of 2019 (COVID-19) to be a global health emergency following identification of cases from 18 countries outside of China including 8 cases of human to human transmission. The declaration called on countries to implement consistent evidence-based decisions, identify gaps in resources, share knowledge and experience, and move forward on vaccine development. The first coronavirus pandemic was announced on March 11, 2020 following confirmed infections in 114 countries. Within the US, hot spots developed first in Washington State and then shifted to New York. The surge in disease overwhelmed resources and the ripple effect impacted the entire medical community. Medical students, like many others, are experiencing the repercussion of COVID-19 firsthand and are not exempt from its many lasting effects.[1] The Association of American Medical Colleges (AAMC) announced, on March 17th, 2020, a minimum two-week suspension of medical students' participation in patient contact activities with possible longer suspension left to medical school discretion.[2] Herein, we present challenges, concerns, and impacts of the COVID-19 pandemic on medical students across the nation as well as suggestions for possible solutions.

The Safety of Medical Students

With the epidemiology, transmission, and treatment of COVID-19 still not fully understood, the safety of medical students is a major concern. Many medical students have never been trained to don and doff personal protective equipment (PPE) and are not N95 fit tested. The AAMC's decision to suspend clinical rotations was twofold: to ensure the safety of both students and patients, and conserve PPE. Lessons can be drawn from medical student suspension in the 2003 SARS outbreak in Hong Kong and Canada which were successful in setting up several plans to be implemented based on escalation of the situation.[3,4] If this pandemic becomes prolonged, return of medical students to rotations should be considered after receiving infection control and transmission prevention training, and should be excused from interacting with suspected or confirmed COVID-19 cases.

Changes to Clinical Rotation Structure and Exposure

From institutional and personal perspectives, every stakeholder in medical education is concerned of the detrimental effect that loss of face to face clinical teaching can have. Medical schools have been quick to propose innovative ways for students to continue learning using online teaching. Tufts University easily merged existing online teaching programs into "flip classrooms" which involve small video discussion groups with specialized software programs. Successful models already in place can be adopted by other programs. Hospitals have cancelled all elective procedures and resorted to telemedicine for clinics. This is a good time for medical students to learn and participate in telemedicine.

Changes to remaining clerkships and electives length to allow missed clinical experience to be made up would ensure students have adequate exposure to core clerkships. Many students faced cancellation of electives inside and outside their institutions, including opportunities overseas. These electives expose students to fields of interest and different patient populations and health care systems from their own home institutions. The cancellation will impact the knowledge and experience of medical students and their residency applications. Students should be given the opportunity to re-enroll in outside electives in subsequent years.

Medical students have the unprecedented experience of a pandemic, a new disease with unknown epidemiology, etiology and treatment. The skills learned during this time will give students new insight to their approach to medicine, patients, knowledge, and research. Students can reach out to their home institutions to explore volunteer opportunities during clinical suspension. Some existing projects include answering phone queries via telehealth technology, using decision trees and prepared scripts, assisting with research, determining trial eligibility, mask collections and sewing, making infographics, blood donation drives, and restocking hospital warehouses.

In response to the need for health care providers, Harvard Medical School (HMS), Boston University, Tufts University, and University of Massachusetts issued an option for medical students to graduate early.[5] The ACMGE warned of "serious ramifications to early appointment Centers for Medicare and Medicaid Services (CMS) reimbursement for direct graduate medical education (DGME)/indirect medical education (IME) and Match participation agreements, among many others" and urged medical schools to carefully consider these ramifications before making their decision.[6] Many programs in the harder hit areas have opted for early graduation, however, the majority of programs are following their original calendar and are virtually graduating students on time.

[1] MD, Department of Internal Medicine, University of Missouri-Kansas City, Missouri, USA.
[2] Medical Student, University of Jordan School of Medicine, Amman, Jordan.
[3] Medical Student, University of Missouri–Kansas City School of Medicine, Missouri, USA.
[4] MD, Assistant Professor, Department of Internal Medicine, School of Medicine, University of Missouri-Kansas City, Missouri, USA.
[5] MD, Professor of Pediatrics, Division of Infectious Diseases, Children's Mercy Hospital. University of Missouri–Kansas City School of Medicine, Missouri, USA.

About the Author: *Raed Qarajeh is currently a PGY-2 at the University of Missouri-Kansas City internal medicine residency program*

Correspondence:
Raed Qarajeh
Address: 5000 Holmes St, Kansas City, MO 64110, United States
Email: qarajehr@umkc.edu

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Medical school examinations, USMLEs, and residency applications
Administering traditional exams given CDC recommendations against social gatherings is a challenge. Medical schools should explore alternative options like changing exams to case presentations simulating true clinical settings or by utilizing online resources such as Lock Down Browser® and Zoom®. Evaluations can be assessed based on interaction of students in online sessions and discussions. Grades should be compared with previous rotations to ensure they are reflective of the students' performance; any discrepancies should be addressed.

On March 16th, 2020, the United States Medical Licensing Examination (USMLE) Step 2 Clinical Skills (CS) examinations were suspended until further notice and the Prometric center announced temporary closure of testing centers for 30 days starting March 18th.[7] The USMLE program announced that it cannot resume the Step 2CS exam in its current format and is exploring plans to employ a telehealth model via a web browser and is expected to resume after July. Prometric resumed partial testing for USMLE exams starting May 1st, however Prometric test centers were erroneously listed as open but examinees were met with closed doors, and USMLE program is looking for alternatives outside of Prometric to increase capacity. Schools requiring Step 1 to start clinical training and Step 2 Clinical Knowledge (CK) to start fourth year should extend deadlines to account for test center reopening and scheduling. Delay in test taking, and thus reporting will also impact fourth year medical students unable to have their scores by residency application deadline.

The AAMC announced a change in the date where residency programs may begin reviewing applications from the usual September 15th to October 21st. This change in deadline will help accommodate the cancelled testing and application requirements, however, the examination situation remains unclear and is uncertain if the testing capacity will meet the needs and if the scores will be available for the new date. The AAMC also issued a statement encouraging medical schools and teaching hospital faculties to "conduct all interviews with potential students, residents, and faculty in a virtual setting - either by phone or through video conferencing".[8] Safety is the priority and whilst virtual interviews will eliminate the need for travel and will help maintain social distancing, much of the interview activities such as taking tours of the campuses, meeting with the residents and attendings, having in person interviews, and experiencing the feel of the program and campus would be lost.

Scholarly activities
Medical students' research projects are also impacted by the COVID-19 pandemic. In a letter to the HMS Community, Dean George Q. Daley wrote, "I understand that everyone is concerned about the very real loss of research productivity", as 'stay at home orders' have necessitated "for the emptying of our laboratories and encourage all to pursue alternative scholarly activities in isolation".[9] The inability to continue research will result in loss of data, hours invested, having to redo parts of research and delays in completion and publication. Fourth year medical students who will not continue residency at their school's institution, may not complete their research prior to leaving, resulting in significant loss of research output. Allowing remote access to necessary documents and databases and setting up at-home laboratories within technological capability can help alleviate research loss.

Cancellation of scholarly conferences and important milestones
All conferences and meetings have been cancelled causing students to lose the opportunity to present their work and meet with peers and experts in the field. Conferences should identify virtual options that allow students to present their research and provide a chat or comment feature so traditional discussions with experts at these meetings are not lost and the advancement of medicine and discussion is continued.

An important milestone that medical students look forward to are match day activities which have been cancelled forcing institutions to carry out virtual activities. Graduation ceremonies will likely be cancelled. Alternatives to the traditional celebration such as virtual graduation ceremonies allowing students and their families to actively participate in this milestone should be explored.

Psychological effects of COVID-19
Rotenstein et al.'s metanalysis estimated that "the prevalence of depression or depressive symptoms among medical students was 27.2% and that of suicidal ideation was 11.1%".[10] Adding the COVID-19 pandemic to stressors can increase the severity and number of medical students with depression. The uncertainty of schedules, rotations, clinical requirements, exams, and cancellation of important milestones including graduation and matching can further heighten depression symptoms. Health care workers have suffered serious repercussions from COVID-19, even death, which will negatively impact medical students' mental health. Medical schools should proactively address this and provide resources, including psychotherapy. Medical schools should also provide students with as much transparency as possible in updating medical students via short, regular email notices or allowing virtual town hall meetings.

International Medical Graduates
International medical students (IMGs) faced cancellation of electives required for US residency positions as well as cancellation of Step 2 CS. Many students plan months in advance for travel and are now faced with visa constraints and financial strain and would benefit from applications deadline extension. Perhaps the most immediate impact on the health care system is on IMGs that have recently matched in residency programs in the US that are set to begin this July. There is a possibility that IMGs will not be able to travel to the US and will be forced to delay the start date of residency. This would negatively impact the health care system and cause a shortage of residents that hospitals are in dire need of.

Conclusion
The impact of the COVID-19 pandemic on medical students' safety, education, research, clinical rotations, residency applications and mental health are important issues to address. Managing the needs of medical students, finding innovative alternatives, and involving students with dialogue and solutions are extremely important. Medical students will soon enter the healthcare system as new doctors, and how they are handled will have a direct impact on the future of the healthcare system.

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Clinical Skills Abilities Development During COVID-19 Pandemic in Mexico City

Lourdes Adriana Medina-Gaona.[1]

The Experience

It was February 29, 2020, when the first 4 cases of COVID-19 were reported in Mexico.[1] It did not take long for this country of approximately 130 million people[2] to enter a critical stage of this pandemic. By May, Mexico was already in the top 10 countries in number of deaths due to COVID-19.[3] Despite the ongoing efforts of the Mexican government and citizens, it has become hard to reduce the rapid spreading of this virus. As a result, students of all grades were forced to study at home, including medical students. In Mexico, training of doctors takes place in the classroom for most of the first two years, taking courses such as anatomy, physiology, biochemistry, to name a few. Nevertheless, the subsequent years are considered critical for the future healthcare worker in developing clinical skills, not only learning to carry out several procedures, but also communication, establishing the patient history, and physical exam competencies. This step is crucial for the early development of skills to help foster a satisfactory doctor-patient relationship.[4] Before the pandemic, Mexican students went to hospitals to observe and learn how to interact and build confidence with patients. When COVID-19 reached Mexico, medical schools decided to stop sending medical students to the hospital, but continued online learning, ultimately ending the opportunity for patient interaction.

As a 4th year medical student in Mexico City, this sudden change was a particular challenge for me as I was starting to develop clinical skills that had to be practiced in simulation laboratories. COVID-19 brought us a new barrier, the development of empathy through a computer, not seeing the person face to face, doing semiology correctly, by observation, palpation, percussion, and auscultation, was lost. Our doctors have never lived this situation and teaching clinical skills through a computer, seemed impossible.

There is no doubt that the learning of medicine, thanks to technology, has been changed, as compared to 50 years ago. New tendencies of practicing with robots and simulations have become an amazing tool to avoid the use of animals or human bodies to learn anatomy or different procedures. For example, Tecnológico de Monterrey started in 2018 to implement a center of clinical simulation, this space allows students to interact with medical equipment. Doctor Rios, director of this center, explained that these places allow participants to complete several procedures without putting patients in danger.[5] Despite all these advancements, physical examination training remains a challenge, even more in times of pandemic. Doctors could argue that it may not be necessary to examine the patient due to existing technology that could give us a precise diagnosis. To this argument, we could say that human trust has to be won by the doctor, not only to give the best treatment available but also to be able to respect the human aspect of medicine and take care of a person, not a disease.[6] In Mexico, according to the National Commission for Medical Arbitration (Comisión Nacional de Arbitraje Médico, CONAMED) in 2015, 11,529 complaints to doctors were submitted, of which 2,516 were due to the doctor-patient relationship.[7] These doctors had a chance to learn in person; what is going to happen with those trained in pandemic times?

A teacher of mine told us once "Technological imaging or any other technology should be used only to confirm a diagnosis that you already have in mind, thanks to a good semiology and physical examination". This way of thinking, especially in a country, where resources are limited, is one of the main tools used by clinicians to came with a correct diagnosis, avoid misusing limited resources, and provide optimal treatment.[8-9] It is of great concern for my generation that these skills have not been developed. How can we gain the trust of people? Clinical skills are part of medical training and so new solutions have emerged through the pandemic.

In my experience, our school has developed an online simulated medical consult, where the clinical educator acts as a standardized patient, and we took the history. In my opinion, this was a great opportunity to develop a skill to recognize symptoms and practice history taking, nevertheless, signs may be missed. Our generation has learned to adapt and use the new technologies. COVID-19 is a new opportunity for medical schools and students to develop new ways to practice clinical skills, including doctor-patient interaction through different platforms. Another option for simulating teaching platforms is virtual reality, an option that is still under development.[10]

Technologies are required and can be used in the whole medical career. Their level of complexity should be tailored to each year or stage of training. In 2014, a survey was done among medical students to know their perception about the learning through technological devices.[11] Most had perceived usefulness of different tools for learning, nevertheless, 3rd-year students agreed that clinical skills could be affected with that type of training. In my perspective, after learning the theory in the first year, practicing based on it becomes essential to start understand better those concepts and contextualize them in everyday practice. The use of smartphones has become one of the most important tools for learning in several countries. Technology brings us the possibility of flexible learning. The development of new tools, by the support of other disciplines such as computer and engineering, has to be done for medical students to develop the ability of building trust, empathy, listening, observation, and others, all to give the best medical attention to our future patients.

[1] Medical Student, Instituto Tecnológico y de Estudios Superiores de Monterrey, Mexico City Campus.

About the Author: *Lourdes Adriana Medina is currently a 4th year medical student of a 7-year total program. She published in 2018 an original article in the International Journal of Medical Students and worked in summer programs in Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán researching on diabetes.*

Correspondence:

Lourdes Adriana Medina-Gaona

Address: María Auxiliadora 7, Coapa, San Bartolo el Chico, Tlalpan, 14380 Ciudad de México, Mexico

Email: A01337201@itesm.mx

Editor: Francisco Javier Bonilla-Escobar
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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

COVID-19 and Clinical Rotations in the Democratic Republic of Congo

Olga Djoutsop Mbougo,[1] Vanessa Youmbi Nono,[1] Ulrick S. Kanmounye.[1]

The Experience

Authors ODM and VYN are Cameroonian students in their final year of medical school in the Democratic Republic of Congo (DRC). Both were enrolled initially in Cameroonian medical schools but had to transfer to the DRC after their schools were closed. ODM was in her second year of medical school out of seven years while VYN was in her third year. ODM transferred the same year the schools were closed, while VYN spent a year out of medical school before she transferred. For the two students, the DRC is their new home – it welcomed them when their home would not. In their seventh and final year of medical school, the two are on a twelve-month rotation at the Mother and Infant Monkolé Hospital Center, a 158-bed referral hospital in the capital of the DRC.[1]

Before ODM and VYN began their rotations, they were apprehensive and lacked certainty. As time went by, they grew professionally and gained confidence. They had a busy seven-day schedule – day shifts, three-night shifts, and one off-duty day (***Figure 1***). Their interactions with the staff were informative, and most surgical interventions were planned so the students could read up on the cases. The students learned to perform appendectomies, cesarean sections, ultrasonographies, and gastroscopies under the supervision of the senior residents and attendings.

On March 10, 2020, the DRC registered their first case of COVID-19 in the region, and it also marked the point in time in which our outlook towards COVID-19 shifted.[2] Before the first case of COVID-19, the general feeling was that the diseases affected other countries. Even after the first case was registered in the DRC, we were still unconcerned in our hospital. However, we were proven wrong on March 19, 2020, when we admitted our first COVID-19 case. It was inevitable given that our hospital is one of the premier health facilities in the country. The diagnosis resulted in a panic within the hospital. Confusion and fear replaced the natural feeling of assurance despite the rapid and practical measures that had been put in place.

Fortunately, the hospital leadership responded promptly. The hospital dedicated an entire building to the isolation and quarantine of COVID-19 cases. Also, infrared thermometers and taps were made available in every wing, entrance, and exit points. A work from home protocol was initiated for those whose work did not warrant their physical presence at the hospital, and a new triage protocol was put in place.

We had all been briefed on what to do and when to act. This situation was new but still old. New because of the global reach of COVID-19, and old because we had dealt with epidemics of cholera and Ebola viral disease before.[3,4] Inexplicably, though, there was panic. The staff and students were upset that they did not have regular supplies of personal protective equipment (PPE). The hospital administration, unable to get enough PPE, then decided to limit the clinical personnel in-hospital. Although the administration felt the students had a role to play in the COVID-19 response, they made the hard decision to suspend student rotations indefinitely. The students felt helpless; they wished they could help.

On March 19, 2020, the Congolese president announced a national "stay at home" and gave the citizens a couple of days to get provisions. This decision had the undesirable effect of causing stampedes in produce markets and supermarkets. Some cupid traders used price gouging to make the most of their new "business opportunity." The price gouging led to more panic buying among the high- and middle-class but left the most vulnerable without everyday necessities. These tragic events led to a reversal of the presidential decision and a firm decision by the authorities on unnecessary exposure to COVID-19.[5,6]

We have been at home, hoping for all of this to come to an end. Staying at home and not being able to help is difficult. We wonder what happened to all those patients who had malaria, typhoid fever, strokes, acute appendicitis, postpartum hemorrhage, and neonatal infections. We do understand that staying at home is the best way we can help right now, given the situation. The last thing we need is for health personnel to be infected in a country with a limited workforce density. So, we are playing our part to the best of our abilities.

Three times a week, we go from one home to another and test patients in the suburbs. We report and isolate suspected cases, and we educate the seronegative entourage on how to interact with their seropositive acquaintance. Besides testing patients, we raise funds and distribute clean water, soap, and hydroalcoholic hand sanitizers. Unfortunately, none of the medical schools are organizing online classes, so we organize weekly group study sessions on Zoom.

Post-COVID, we anticipate there will be an economic crisis. In a country where more than half of the population lives on less than USD $1.90 and where the number of physicians is insufficient,[7] this pandemic will push more people into poverty, increase the burden of disease, and decrease the number of physicians.[8-10] The personal economy is a major social determinant of health, and the new state of poverty will undoubtedly translate to a new disease burden. As future physicians, we must think about innovative strategies to manage the new disease burden because this is just as important as learning to perform a cesarean section or graduating on time. While at home, we are strengthening our research capacities and reading up on potential solutions to propose measures to combat the spread of COVID-19 to the Congolese people.

[1] Faculty of Medicine, Bel Campus University of Technology, Kinshasa, Democratic Republic of Congo.

About the Author: *Olga Djoutsop Mbougo is currently a seventh-year medical student at the Bel Campus University of Technology, Kinshasa, DRC of a 7-year program. She is also a recipient of the Dean's Award for academic excellence.*

Correspondence:

Olga Djoutsop Mbougo

Address: 17, 8ème Rue Limete / Quartier Industriel, Congo - Kinshasa

Email: olgadjoutsop@gmail.com

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Life will no longer be the same, and it is up to us to define what the new "normal" will be.

Figure 1. Shift schedule of final year medical students.

Day Shift

7.30-8.00	8.00-9.00	9.00-13.00	13.00-14.00	14.00-15.30	15.30-17.00	17.00-18.30
Update on the status of the inpatients	Rounds with the residents	Rounds with the attendings	Pause	Presentations supervised by the senior resident	Assessment of inpatients	Tutoring and labs (once or twice a week)

Night Shift

15.00-17.00	17.00-20.00	20.00-22.00	22.00-6.00	6.00-7.30	8.00-9.00	9.00-10.00
Update on the status of the inpatients	Update on the status of the patients at the emergency department	Rounds with the doctor on duty	Call	Write cases to be presented during the rounds	Rounds with the residents	Rounds with the attendings

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ULS

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

NHS Nightingale North West: A Medical Student on the Front Lines

Lewis Holt.[1]

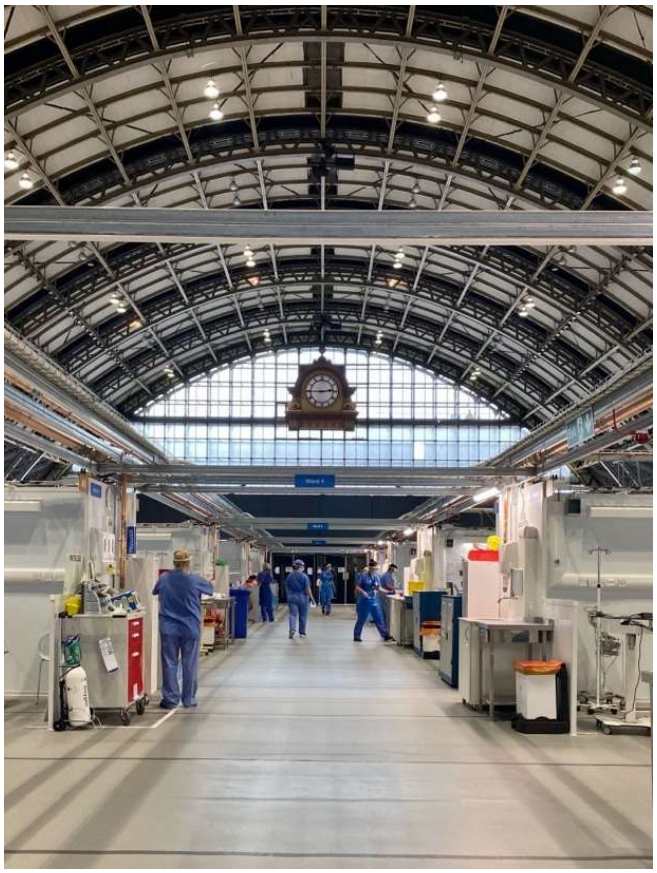
The Experience

"I never lose an opportunity of urging a practical beginning however small for it is wonderful how often in such matters the mustard seed germinates and roots itself" – Florence Nightingale;[1] fitting words for my strange current circumstances. I have been working on the frontline against COVID-19 at a National Health Service (NHS) COVID-19 field hospital, in the North West of the United Kingdom (UK), in the midst of a pandemic that has shaken the globe. Deployed as a healthcare assistant, I found myself learning more along the way than I could have imagined.

Life as a British medical student changed dramatically within the space of a fortnight in light of the COVID-19 crisis. The World Health Organization (WHO) officially declared the pandemic on the 12th of March 2020 and by the 13th of March universities, placements, and exams across the UK had been suspended indefinitely.[2] Within a week, all students were granted automatic progression and I moved into fourth year. All teaching was moved online and learning updates were provided via regular videoconferences. I found myself with an idle mind, lots of free time, and no way to spend it under a national lockdown. I was keen to maintain some form of clinical work, as a leave absence from patient contact is not ideal for any healthcare student, but was met with resistance from my family. They feared for my health and reiterated chilling scenes seen on the news from high dependency COVID-19 wards across the world, worrying that this was what I was heading to face. It also meant moving away to live in a hotel with my colleagues, as to not risk bringing COVID-19 home and risking the health of my family. It was a very fast paced situation in a scary time. Nonetheless I wanted to help in whatever way I could, so much to my family's upset I applied to be a care support worker; a nursing assistant role designed to assist with basic needs and personal care of patients. This desire to help in a time of crisis has been echoed by medical students worldwide, as seen with students in the US assisting those in need within their communities.[3] Similarly, in the UK, a database called National Health Supporters was devised to put medical students in contact with health professionals to alleviate pressures of basic needs such as child care and shopping, whilst preoccupied with the emerging pandemic.[4]

The UK's national response to COVID-19 included the seemingly overnight construction of a series of field hospitals across the UK, called the Nightingale Hospitals.[5] The Nightingale ward structure dates back to the time of Florence Nightingale and is eponymously named as such, utilizing long stretches of patient beds all within the line of sight.[6] My application was accepted in days and within the week I underwent induction to prepare me for what I might face. The peak of the infection still hadn't hit by this point in the UK and it was unclear whether our NHS would be overwhelmed with cases —a daunting prospect. By this point, the hospital was still under construction but within two weeks it was completed, set inside a repurposed train station turned convention center; a marvel of design and ingenuity. Days after completion we were sent in, working beneath towering arched ceilings, as seen in ***Figure 1***. It was a surreal experience for myself and I couldn't help wondering how patients were feeling, many of whom had delirium and confusion.

Figure 1. The towering ceilings reminding us of the hospital's past as a train station. The large clock remained illuminated throughout the night shifts and was quite a sight.



[1] MBCHB, University of Manchester, United Kingdom.

About the Author: *Lewis Holt is a 4th year medical student studying the 6-year MBCHB course at the University of Manchester. Recipient of the Nightingale STAR award for outstanding contribution to Nightingale North West Field Hospital.*

Correspondence:

Lewis Holt

Address: Oxford Rd, Manchester M13 9PL, United Kingdom

Email: lewis.holt@student.manchester.ac.uk

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The days started at 6AM, after watering and feeding myself, I would enter the personal protective equipment (PPE) donning area, put on my kit for the day, which consisted of scrubs, a visor, fluid repellent surgical mask, apron and gloves before heading through to the ward also known as the 'red zone'. This area was a central corridor with branching rows of nightingale wards for hundreds of COVID-19 positive patients, built to prepare for the worst-case scenario the UK could face. A strict one-way system was enforced; donning and doffing PPE areas separated, with a specific sequence of steps to remove contaminated PPE safely. Different classes of PPE were used depending on the environment and the level of intervention being used for the patient. The PPE shown in ***Figure 2*** was our usual day to day PPE and was considered 'Light'. 'Heavy' PPE is required for aerosol generating procedures such as resuscitation and was available in the event of an emergency. Nightingale North West was designed as a step-down facility for patients on the road to recovery from COVID-19, so these types of interventions were rarely required.

COVID-19 is a harrowing and unpredictable infection. The crackly breathing of patients can be heard from the end of the bed, many patients struggling with labored breathing and supported by high flow oxygen. Removal of the masks for even minutes resulted in desaturation to critical levels; already frail patients were truly worn out within hours as a consequence. Some patients sadly did not recover during their time with us, but for the first time I experienced caring for end-of-life patients, and it was moving to support and be there with them in their final days. There were, however, many positives in the form of patient discharges. Both staff and patients were elated when a patient had finally swabbed negative for COVID-19 and were clapped off the wards, by lines of healthcare workers, to be reunited with their families after weeks in hospital.

As the Nightingale now goes into standby and the COVID-19 curve is flattened, I feel proud to have been part of this outstanding team. I am glad our services are no longer needed, as it means we are winning the fight against this awful disease, but I am still nervous for the future.

As I prepare to continue my medical studies, I wait for the call that the hospital is to reactivate in response to a second wave; however, only time can tell if we will be needed once again.

Figure 2. Myself and Celia, one of the clinical nurse advisors in our full PPE kit.

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Experience

Experiences of a London Medical Student in the COVID-19 Pandemic

Alin-Ioan Suseanu.[1]

Introduction

On the 12th of March 2020, World Health Organisation declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic.[1] At this point, there were 596 confirmed cases of COVID-19 in the United Kingdom a figure that seemed alarmingly high at the time.[2] I had just finished a rotation in Emergency Medicine and Critical Care during my fourth year at medical school and was eagerly awaiting my final rotation in Women's Health. The concern regarding coronavirus was palpable in the hospital but there were still no signs of a lockdown from the government and our placement was scheduled to go ahead as planned.[3] In fact, the only change to our timetable was an hour earlier start to our first induction day to allow for a talk on coronavirus. This day never came.

As precautions were taken to curb the spread of COVID-19, clinical rotations were cancelled and medical students around the world had to adapt to a new norm.[4-6] In my country, the National Health Service (NHS) moved into major-incident mode forcing the university to quickly mobilise to deliver an unprecedented online curriculum.[7] Overhauling the delivery of the curriculum is no easy feat as our fourth year is entirely clinical with very few lectures scattered throughout the year. Our time in surgical theatres and outpatient clinics was replaced by laparoscopic videos with detailed voiceovers and interactive lectures; clerking patients in the emergency department was replaced by interactive case-based discussion. All key content was to be provided via videoconference for the foreseeable future. The university has already been using Zoom video-conferencing for occasional teaching sessions so the transition was not as jarring as one would expect. However, I encountered several problems with the transition.

One problem is the sheer size of the year's cohort with some sessions having as many as 250 students in attendance, meaning only the clinician leading the session could interact audio-visually. The students were instructed to interact using an embedded chat tool. I experienced first-hand how overwhelming this could be in case-based teaching. While the quality of the discussions was excellent, and they remain some of the best teaching sessions I have ever had, I quickly became intimidated despite the fact that I had scored well on my previous exams and felt confident with my learning. It will always be more difficult to interrupt and ask questions in front of such a large group of people, compared to the 5-6 students we would normally have in hospital teaching. Additionally, the speed at which some students were able to answer obscure and challenging questions left me and my colleagues impressed by our fellow students, but also anxious and self-doubting. At times I would struggle to even read the question before answers started filling the chat. It became the perfect environment to compare ourselves to each other, where some students were negatively impacted and others were positively motivated.

I am writing down my experiences one week after finishing my final year-four exam. The exam was quickly changed to an online format, with extra time being granted. The exam was then made open-book, pushing me into uncharted territory. I stopped memorising obscure paediatric milestones or side effects of rarely used diabetes drugs, and instead focused on improving my ability to generate differential diagnoses. Imperial College London was the first to make this change claiming it would not be possible to complete the exam by looking things up online.[8] I personally found this to be true. Case-based questions, which made up most of the exam, worked best in this format. Just as with a real patient, these questions challenged us to figure out the diagnosis, consider the patient's history, and make decisions regarding management. The questions rely on our diagnostic acumen and cannot be answered by two minutes of internet searching. I think we will see a shift in the direction of online and/or open book exams over time. COVID-19 seems to have only pushed forward the inevitable in terms of incorporating technology into our medical exams. My impression is that the university has recognized the need to train doctors who are able to competently use online resources. For example, in our Objective Structured Clinical Examinations (OSCEs) we have access to both paper copies of our drug dictionary, the British National Formulary, and virtual copies on tablet devices. This is reflective of actual clinical practice, as it only takes one day on the wards to see how often clinicians will use their phones to look up drug dosages, national guidelines or peer-reviewed articles concerning less common conditions.

We also decided as a cohort to scale up our previous exams, essentially making our final year-four exam pass or fail. Changing our exams in this fashion was immensely stress-relieving, allowing us to focus on our own wellbeing and the wellbeing of our loved ones during the pandemic without the guilt that we should be studying more. Additionally, it allowed those who wished to contribute to the effort against the pandemic to do so without it affecting their academic ranking. The Medical Schools Council was very quick to provide us with guidance and the opportunity to work up to 16 weeks in paid volunteer roles in the NHS.[9] I noticed that interest in volunteering was particularly strong as we were inspired by the fifth years graduating early to work in the NHS.[10]

Two months into lockdown and with three months of online learning ahead of us, I find myself thinking of a news article headline I read early in January about 44 confirmed cases of "a mysterious viral

[1] Undertaking MBBS. King's College London, UK.

About the Author: *Alin is a 4th year medical student of King's College London, United Kingdom undertaking a 5-year programme. He has been awarded Merit in "From Science to Clinical Practice".*

Correspondence:

Alin-Ioan Suseanu

Address: Strand, London WC2R 2LS, United Kingdom, UK.

Email: suseanua@yahoo.com

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pneumonia" spreading in Wuhan.[11] I immediately showed some friends a 2015 TED talk from Bill Gates titled 'The next outbreak? We're not ready'.[12] Whether our country was ready remains to be seen. What I can say is that our medical school, my fellow medical students, and our clinical teachers were more than ready to ensure we could continue our education. I believe this public health crisis has demonstrated the importance of resilience and adaptability in 21st century educational institutions and the need for them to instil these same values in our generation of doctors.

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Experience

South Africa and COVID-19: A Medical Student Perspective

Sahil Maharaj.[1]

The Experience

From humble beginnings in a seafood market in Wuhan, the deadly SARS-Cov-2 virus festered to a global pandemic.[1] The seemingly invisible virus was crippling health systems across the world within weeks. First world countries such as the United Kingdom, Germany and France were entering lockdowns to curb the spread of the disease.[2] News reports documented struggling health care staff and their accounts of futile efforts to treat the disease. Due to a high burden of Human immunodeficiency virus (HIV) and tuberculosis (TB), coupled with a strained public health system and weakening economy, South Africa was set to be severely affected. We anxiously witnessed the world being captured, knowing that our time would soon come. With bated breath, we awaited the arrival of the deadly SARS-Cov-2 virus.

On March 5th , South Africa reported its first confirmed case of COVID-19.[3] It was a 38 year old male who had returned from a ski trip in Italy, one of the epicenters of the disease.[4] At the time, I was in the neonatal intensive care unit at Greys Hospital, Pietermaritzburg. I was only 3 weeks into my pediatrics rotation when this news broke, spurring a nationwide panic.

In the following days, fear and doom suffocated the atmosphere. As I walked through the corridors, I watched a darkness veil the once smiling nurses. Preparations were underway for the expected influx of COVID-19 patients that would ensue. Resources were being provisioned and stricter hygiene protocols were being enforced. There was uncertainty as to whether medical students would be allowed to continue learning at the hospital. The university had already lost 3 weeks of the academic year due to a student protest in February. Any more time lost would severely impact students and may risk losing the academic year. Ultimately in a bid for student safety, all medical students were sent home on 15 March.

South Africa hosts the greatest HIV epidemic in the world with 7.7 million infected individuals.[5] This is complimented by a high prevalence of TB and non-communicable diseases such as cardiovascular disease and diabetes.[6] Data collected on the COVID-19 disease highlighted an increased risk of mortality amongst these populations.[7] Coupled with a lack of health care facilities and an already burdened public health system, the country would be unable to cope with the surge in new COVID-19 infections, and many lives would be lost. Consequently, on March 27th, President Cyril Ramaphosa announced a nationwide lockdown for 21 days which was subsequently extended. All operations, with the exception of essential services, had ceased.

The nationwide lockdown was weakening an already struggling economy. Many South Africans rely on a single source of income, and many more live at or just below the poverty line. Due to lockdown restrictions, many were unable to work and thus provide food for their families. In an effort to mitigate the financial impact, the South African government implemented a risk adjusted approach to the lockdown, advised by the National Department of Health. This strategy involves the gradual easing of lockdown restrictions, progressing from level 5 to level 1.[8] Each step down allows for greater freedom of movement and for more businesses to open than the previous. The transition to lower levels is guided by local epidemiological trends including infection rate, daily deaths and daily new cases of COVID-19. As of 1st June 2020, South Africa is under level 3 of lockdown.

Under level 3, only final year medical students have been allowed to return to university. At the end of every year, final year medical students qualify as medical doctors. In the first week of January, these doctors are deployed to mandatory internship posts in the public health system. Due to the delays brought on by the lockdown, final year medical students are now expected to qualify by the end of January 2021. This will result in a significant deficit in the public sector due to the reliance on internship doctors.

The remainder of the medical student population still remain at home since the lockdown began. The university has shifted to an online model of learning to mitigate time lost. We have not had any assessments, and there is no indication from the university on the remainder of the academic year. Due to poor socioeconomic backgrounds, many students have been unable to access online learning and thus remain isolated from their studies. Such is the manner in which COVID-19 highlights the socioeconomic disparities that plague South Africa. To date, the university has successfully engaged with telecommunications companies to provide free mobile data packages to all students. Laptops have also been procured for certain students.

South Africa is walking a tightrope delicately balancing the slowing economy, a strained public health system, return to education and the health of the people. In the time it is most needed, the government has displayed high-quality leadership in reaction to COVID-19. Our response has been lauded by officials from the World Health Organization for the prompt implementation of the lockdown, rapid deployment of mobile screening units and ramping up testing capacity.[9,10] In unprecedented times such as these, we are all forced to adapt to a new way of life that goes against the very nature of our social being. I am hopeful that we shall emerge from this scourge as a stronger and more united country.

[1] MBChB, University of Kwa-Zulu Natal, Durban, South Africa.

About the Author: *Sahil Maharaj is currently a 5th year medical student at Nelson R. Mandela School of Medicine in Durban, South Africa. The total program is 6 years. He placed amongst the top 5 students provincially in the national matriculation examinations. He has a research placement at the Centre for the AIDS Program of Research in South Africa (CAPRISA). He was awarded the Pius Langa Scholarship and is the South African representative for the Golden Key International Honor Society.*

Correspondence:

Sahil Maharaj

Address: 238 Mazisi Kunene Rd, Glenwood, Durban, 4041, South Africa.

Email: maharajsahil98@gmail.com

Editor: Francisco Javier Bonilla-Escobar
Student Editors: Shawn Albers & Samreen Fathima
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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Utilizing Health Education and Promotion to Minimize the Impact of COVID-19

Nidhi Thomas.[1]

The Experience

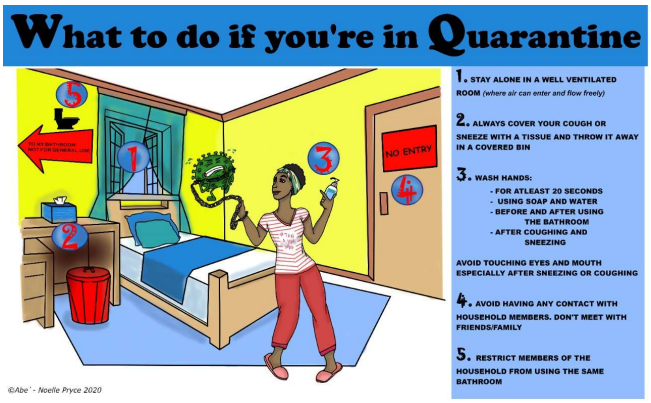
March 10, 2020 marked Jamaica's first confirmed case of coronavirus disease 2019 (COVID-19). With this news, public panic was imminent. By March 13, 2020, proactive measures were implemented to include deploying police and soldiers to restrict movement within the communities, closing schools at all levels and air travel ban.[1] Before the virus reached our shores, and the situation became worse overseas, I was filled with dread; expecting total utter chaos, leaving my country ravaged and crippled. As a medical student at The University of the West Indies (UWI) doing clinical rotations, I was well aware of the limitations of our resources.

The Jamaican government actively kept the public informed; but misconceptions and false information were proliferating at an alarmingly rapid rate. This could lead to life threatening consequences,[2] and eventually cripple the health system. Although medical students cannot be on frontline, we could still make a positive impact.[3,4] After all, "prevention is better than cure" and being a part of the Standing Committee on Medical Education of the Jamaica Medical Students' Association, had taught me the importance of social accountability. Consequently, through my initiative, COVID-19 Health Education and Promotion program was implemented on March 14 with the aim to educate the general public on COVID-19 as well as possible mitigative measures that are more targeted towards the current situation but could be applied in the future via social media such as Facebook, Instagram and so on.

In ventures like this one, support, especially in large numbers, is a key factor to ensure success and sustainability. Ninety-five members from across the healthcare spectrum joined the team of medical students. They included UWI dentistry, nursing, physical therapy, pharmacy and radiology students, as well as medical students from the Caribbean School of Medical Sciences, Jamaica. Our team also included nurses; medical doctors (from interns to consultants) and members of academia. With the blessing of our dean and enrolling the program with the International Federation of Medical Students' Associations (IFMSA), the credibility of our activity was fully established.[5]

As our members were from across the Caribbean, this project extended beyond Jamaica. Four working groups were established: Graphics, Information Analysis, Misconceptions and Myth Debunkers, and Question and Answer. Graphics is a vital component in the success of the program; we managed to find students who were able to make interesting infographics, ranging from posters to comic strips (***Figure 1***).

Figure 1. Some quarantine measures that should be heeded that was posted on our social median platforms



The Information Analysis team was responsible in evaluating the different sources to determine the information that needed to be promoted more. The ultimate goal of our project was to not only create our own graphics but to also bring credible information from Caribbean and Global non-governmental organizations to the public's eye that may be buried in the myriad of misinformation. Our Misconceptions and Myth Debunkers team worked at keeping up with the latest research to find the studies that could counteract these misconceptions, and by using the expertise of our healthcare professionals (***Figure 2***). Finally, the Question and Answer team were tasked with dealing with questions on COVID-19 that were either going unnoticed or were not fully addressed.

Now that we had the information, we needed it to be available in a simple and understandable format to the public. Our information was first vetted by working group members to ensure that information was not only accurate but comprehensible. We then sought the opinions of non-medical personnel to confirm that the information was effectively being communicated. Due to the effectiveness of social media in ensuring maximal dissemination of the content,[6] our members posted it via their various personal social media platforms. We targeted community, family and church groups. Our organization's social media platform was also utilized, and our content was reposted by the Jamaica Medical Students' Association and the International Federation of Medical Students' Associations community.

[1] Bachelor of Medicine, Bachelor of Surgery (MB, BS) - UWI, Mona (2021 Candidate). University of the West Indies, Jamaica Medical Students' Association (JAMSA) Standing Committee on Medical Education, International Federation of Medical Students' Associations (IFMSA).

About the Author: *Nidhi Thomas is 5th year medical student at the University of the West Indies, Kingston, Jamaica of a 5-year program. She is an active member of the Jamaica Medical Students' Association Standing Committee on Medical Education and is the recipient of Jamaica Medical Students' Association (JAMSA) President's Award for Excellence 2018-2019 and JAMSA Council Member of the Year 2018-2019.*

Correspondence:
Nidhi Thomas
Address: Kingston 7, Jamaica, W.I.
Email: nidtreas@gmail.com

Editor: Francisco J, Bonilla-Escobar
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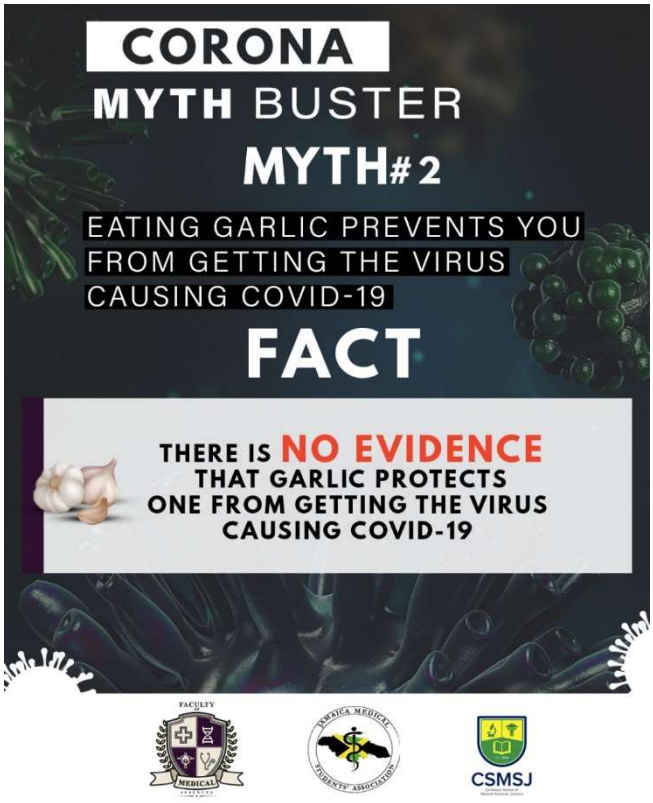
Figure 2. An example of a common myth that was debunked that was posted on our social media platform.



Although, I had the support of my team, it was undeniable that I felt overwhelmed at leading a project of such caliber. Will I be up to the task? Will I have the soft skills to manage the people under my leadership? Will we be able to make content that will replace the public's misconceptions? Although these doubts taunted me, I was still filled with pride that so many students and healthcare professionals were interested and willing to participate.

We were able to see the positive impact of our program, as more people sought advice from us. However, we faced challenges; we started this project when our classes were postponed, and our university sought to change to an online platform to safely accommodate and educate the students. Once classes restarted, it became increasingly hard to juggle our academic studies and create content. Also, the interest from our members started dwindling and this significantly impacted the production of our content. Currently, we are looking for strategies to reignite student engagement such as by having one-on-one interactions with students to indicate their opinions and interest matters.

Health literacy is imperative to driving behavioral modification.[7] By engaging students and healthcare professionals in health education and promotion, we can reap long term benefits for not only Jamaica but also the Caribbean.

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ULS

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Experience

Medical Students during COVID-19 Pandemic: Lessons Learned from Response Teams in Greece

Nikolaos Vlachopoulos,[1] Emmanouil Smyrnakis,[2] Panagiotis Stachteas,[3] Maria Exindari,[4] Georgia Gioula,[4] Anna Papa.[4]

The Experience

Novel Coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged from Wuhan, China before rapidly spreading globally, affecting millions of people worldwide. On March 11, 2020, the World Health Organization (WHO) characterized the infection caused by SARS-CoV-2 as a pandemic.[1] This health crisis has posed an unprecedented challenge for medical education. As social distancing measures were universally implemented to curtail virus transmission, medical training during these times was inevitably disrupted, especially in clinical settings. The clinical exposure of medical students was hindered, and clinical attachments were abandoned in many medical schools around the globe.[2-5]

Transition to a new era

In general terms, Greece was mildly affected by the virus, but the Hellenic National Healthcare System (NHS) confronted a significant shortage in personal protective equipment (PPE) and medical staff. As a result, Hellenic medical institutions were forced to cancel in-person classes and clinical medical education, according to the guidelines of the Ministry of Education.[6] Medical educators at our institution immediately consolidated distance learning environments by converting in a few weeks the majority of face-to-face theoretical sessions to online sessions. As also happened in other countries, written exams have been converted into orals, which have been administered via web platforms.[7,8] Although current evolving web-based ventures can host and possibly substitute the majority of didactic lectures, results were mixed; not all educators and students had previous experiences on remote learning platforms, thus they could not always adapt successfully to the new circumstances. Technical issues, such as poor internet connection, lack of appropriate equipment, and complicated e-learning environments, but also lack of motivation and learners' boredom to participate in long, consecutive webinars were barriers to online learning. Apart from this, students' clinical exposure remains an indispensable part of their training, and online learning seems insufficient to compensate for, or simulate, clinical exposure.[9]

Students' willingness to participate

The pandemic outbreak put many medical students under psychological pressure due to uncertainty for the future and withdrawal from their daily routine.[10] Those coming from other cities or countries had to self-isolate themselves for 14 days before they travel back home. Despite global instability, the medical students' commitment to contribute to a helpful response was remarkable, even at the initial stages of this health crisis. At our institution, a medical students' organization called for the massive engagement of senior-year students and newly-graduated doctors; their deep conviction has been that these individuals have already developed a solid background knowledge, making them more useful than any other group of volunteers who could be drafted to support the overworked healthcare professionals.[11] This desire for student response was echoed in many other medical schools of the country.[12]

What did we do?

At our institution, the Laboratory of Microbiology, we were assigned with the demanding task of analyzing hundreds of COVID-19 samples coming from patients around Northern Greece, as we were equipped with the long-term experience from seasonal flu testing. The workload was exponentially augmented, but the recruitment of new personnel was not possible; work staff only consisted of two Associate Professors (Maria Exindari, Georgia Gioula) and three molecular biologists. Thus, laboratory medical staff was soon led to frustration due to overworking. To meet the increasing needs the laboratory's director, Professor Anna Papa, came up with the idea of creating a student response team.

Consequently, soon after the cancellation of lectures and clinical placements, eight students were deployed to voluntarily offer their services. To ensure student safety, it was decided that they would not participate in any process of sample testing, instead, they worked in the laboratory's call center. After a short period of training and practice under supervision, students were able to carry their duties alone. Their responsibilities included running the laboratory's hotlines, distributing vital information regarding test results to clinical doctors, and solving some practical issues regarding the delivery of samples. Furthermore, students were familiar with all of the guidelines from the National Public Health Organization and were ready to answer questions on how to take swabs, how to fill out the medical release form for COVID-19 testing, and how to manage suspected or confirmed cases. Their contribution had a two-month duration and was necessary as a substantial relief for the overworked staff. Furthermore, it is undeniable that students received a unique real-life learning experience in crisis management; they had the opportunity to observe NHS functioning and shortages; they grew well-informed of the most up-to-date pandemic protocols; and they developed their professional identity by cultivating useful communication and collaboration skills (including a sense of duty, altruism, adaptability, persistence, and competency).

Our experience of student involvement was not the only one in the country. At "Sotiria," Athens General Hospital, the Third Department of Internal Medicine invited students to actively participate in the battle

[1] Final-year Medical Student, Medical School, Aristotle University of Thessaloniki, Greece – Hellenic Military Academy of Combat Support Officers, Thessaloniki, Greece
[2] Laboratory of Primary Health Care, General Practice and Health Services Research, Medical School, Aristotle University of Thessaloniki, Greece
[3] Post-graduate Medical Student in Primary Health Care, Aristotle University of Thessaloniki, Greece
[4] Department of Microbiology, Medical School, Aristotle University of Thessaloniki, Greece - National Influenza Centre for N. Greece

About the Author: *Nikolaos Vlachopoulos is currently a final-year medical student of a six-year program at Medical School, Aristotle University of Thessaloniki, Greece. He is also a decorated cadet of Hellenic Military Academy of Combat Support Officers, enlisted in the Health Corps of the Hellenic Air Force.*

Correspondence:
Nikolaos Vlachopoulos
Address: Thessaloniki 541 24, Greece
Email: vlacniko@gmail.com

Editor: Francisco Javier Bonilla-Escobar
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Vlachopoulos N, et al.

against coronavirus.[12] Students responded with excitement, received intensive training on PPE usage and hygiene protocols, and afterwards voluntarily engaged in the response to COVID-19 cases by carrying out supervised tasks for frontline providers. Also, they were responsible for providing comprehensive care to chronic patients who tested negative for coronavirus; they contributed by taking down medical histories and by executing common daily procedures; they also offered patient education, literature briefings, and scientific information distribution via social media.

Conclusions

In summary, medical students seem to be ready to accept the moral responsibility and volunteer in pandemic management. As our experience indicates, students can be deployed in several different roles under proper supervision as long as safety is properly prioritized. Under these circumstances, the presence of medical students on the first line joined by experienced professors offers a valuable lesson for them, but also a significant contribution to the overburdened healthcare system.

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Experience

The Outbreak of the Century: A Chronicle Experience by a Medical Intern

Chinmay Divyadarshi Kar,[1] Dipti Mohapatra.[2]

The Experience

Throughout history it has been evident that when men try to control nature, it drags them to their knees with a discovery of something virulent.

It was the dawn of a new decade with mankind on a journey to upgrade their lives both online and offline, when the current outbreak of a new type of coronavirus disease (COVID-19) originating from the Wuhan province of China initiated a global health emergency with a rising death toll. The outbreak, as first reported in December 2019, has now spread in almost the entire world, affecting 215 countries and taking away the lives of more than eight hundred thousand people worldwide and counting. In India, although cases started appearing late as compared to other countries, a population of 1·3 billion across diverse states, health inequalities, wide economic and social disparities, and distinct cultural values presents unique challenges. Every challenge teaches people new ways to cope and, in these months, we have all experienced an upending in our lives.

As a newborn medical intern, I never thought of experiencing such a crisis so early in my life. Having my rotation in the Departments of Emergency Medicine and Pulmonary Medicine during the peak of this outbreak was an experience which got me excited and anxious at the same time, making me realize what exactly I signed up for when I got the degree for being a Doctor.

"Maintaining order in chaos and the fear of impending doom"

In my initial days, I was posted in the Department of Emergency Medicine for the night shifts. Although news of the COVID-19 outbreak from China was prevalent, none of us as healthcare professionals ever thought that this could reach our workplaces, remolding a place of learning into stillness and fear.[1] The influx of the patients was mainly due to road traffic accidents (RTA); still, there was lurking fear amongst the hospital staff that the virus was nearly at our doorstep, could enter any moment and we can do nothing except deliver our utmost care to the patient. With a setup of triage, initial protocols ordained that all patients and attendees be questioned about their travel history and symptoms of virus infection.[2] The patient entering the trauma center is itself an emotional victim fallen prey to the lackadaisical emergency system because of which he is repeatedly being referred from one trauma center to another. In such a situation, it becomes challenging to ask questions. Some patients even started doubting our code of ethics and willingness to provide treatment. It seems the sacred trust in the doctor-patient relationship gets severely affected in these times of crisis.

"The last sip of nervous breakdown"

Due to the imposition of a nationwide lockdown, the usual RTA cases were now in decline. But after some days, we encountered patients being brought to the emergency with profuse sweating, vomiting and sometimes hallucinations, indicative of alcohol withdrawal. There was a sudden spurt of alcohol withdrawal cases in view of the lockdown resulting in the closure of bars, pubs and liquor shops. In response, some state authorities issued orders directing patients suffering from these symptoms to approach only doctors in public hospitals to acquire passes for obtaining liquor.[3] This resulted in local medical associations approaching the courts against this order and obtaining a stay.[4] Such situations also test the harmony between various stakeholders at the forefront of COVID-19 control measures.

"The season of virus transmission"

Towards the end of my rotation in emergency duties, I was having fever along with fatigue and headache at regular intervals. The initial thought was, it may have been exertional pyrexia, but fears of having been infected by the potentially deadly COVID-19 virus were present. I was keeping a close track of all the patients I had come in contact with started practicing social distancing, limiting my interaction with others to a minimum. This routine kept going until a senior doctor noticed blisters in my right ear lobule. He immediately diagnosed me with chickenpox, wrote me a prescription and advised isolation. Hearing this news that I had been carrying a relatively contagious virus came as a surprise. Luckily, I was diagnosed early; hence no one who came across me during the posting got affected. It was the season of transmission of viruses like varicella as well and I could not help but remember that 7-day post-partum lady who had come with complaints of blisters in her forearm and was diagnosed with same in the Emergency Department. After successfully recovering, I was able to resume my duties in the Department of Pulmonary Medicine.

"What has changed and what to expect in future"?

The hospital had setup triage screening for every patient visiting the outpatient department and protocols for screening for symptoms of COVID-19. A mandatory pulmonary consultation was given to all patients coming through Emergency Department with travel history outside the city with red zones and orange zones.[5] As our hospital was one of the first in the nation to open a dedicated COVID-19 hospital,[6] most of the doctors in Pulmonary Medicine had their job cut out. A month had passed and all proper guidelines were followed in the hospital regarding management of patients in COVID-19 times.

[1] MBBS, Medical Intern, Institute of Medical Sciences and SUM Hospital, Bhubaneswar, India.
[2] MBBS, MD. Professor, Department of Physiology Institute of Medical Sciences and SUM Hospital, Bhubaneswar, India.

About the Author: *Chinmay has completed his bachelor's degree of MBBS in IMS And SUM Hospital and is now pursuing his mandatory clinical rotation as a medical intern. He has also successfully conducted research under ICMR in the Short-term Studentship Program and has received the best debut Author of the year for his book under non-fictional category.*

Correspondence:
Dipti Mohapatra
Address: K8 Lane 1, Kalinganagar, Bhubaneswar, Odisha 751003, India
Email: drdiptimohapatra@gmail.com

Editor: Francisco Javier Bonilla-Escobar, Mihnea-Alexandru Găman, & Paul MacDaragh Ryan
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Our university, like many others has started conducting the undergraduate classes online with teachers coming to classrooms and recording the lectures.[7] Though the medical curriculum is being fulfilled still a lot of my juniors have expressed their concerns regarding the importance of clinical rotation and bedside learning,[8] along with the anxiety faced by them regarding the university exam for the next semester. The COVID-19 times have also raised the issue of stress and burnout faced by the many interns like me and the junior non-resident doctors all over the world as the national level exams for entering into residency were postponed for an indefinite period of time.[9] Many banners were set to educate the public about social distancing and personal hygiene. The Emergency Department was provided sufficient masks, gloves and personal protective equipment kits required during management in triage. In the initial two months of the year, no one would have presumed that soon this virus will be declared a global pandemic and that every person in every nation would have to adapt and accept a significant change in their lifestyle in order to move on and contain this virus. We have to remain optimistic and drive our attention to become productive, prioritizing our physical as well as mental health.[10] It is times like this when the whole humanity stands at trial and we get to see the power of unity in mankind[11] - the unity in diversity.

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Experience

Adapting to COVID-19: New Orleans Medical Students Respond

Jacob F. Boudreaux.[1]

The Experience

During March 2020, what was initially viewed as an invisible disease in distant China became an ever-present reality to hundreds of millions of Americans, as fears of the novel coronavirus disease (COVID-19) began to cause mass cancellations of sporting events and gatherings, a nation-wide physical distancing policy, and shortages of surgical masks and cleaning supplies.[1,2] These new practices saw the nationwide closing of schools and increased feelings of isolation as sheltering in place, and frequent handwashing were the only known preventative measures in reducing viral spread. For medical students, this pandemic brought many changes to their traditional third and fourth year of medical education, where students complete rotations in surgery, medicine, obstetrics, and psychiatry and posed challenges to adapting medical rotations to online and virtual learning. Despite these challenges, medical students throughout the New Orleans area, a region particularly impacted during the early pandemic, responded to these challenges in innovative ways. The city's first diagnosed case of COVID-19 was on March 9th, and the medical student response began shortly after.[3]

There are three medical schools located in New Orleans: Louisiana State University School of Medicine, Tulane University School of Medicine, and University of Queensland/Ochsner Clinical School. Each school responded to the coronavirus by shifting the majority of instruction to online learning modules and video conferenced lectures, while students were removed from the clinical environment due to PPE shortages and the risk of exposure. Unable to assist in delivering patient care during the pandemic in a hospital setting, dozens of medical students found a way to contribute to their communities through answering COVID-19 phone lines, organizing blood drives and PPE donations, assisting with free food delivery services, or setting up virtual visits for those with symptoms to see a physician.

Students at Louisiana State University volunteered outside the clinical setting and organized a community drive entitled "Spirit of Charity" for PPE donation from local clinics, veterinary hospitals, and local businesses that yielded thousands of masks for the frontline health care workers. As the disease spreads via respiratory droplets, these supplies were critical to preventing viral spread among health care workers. Students additionally encouraged blood donations throughout the community. Because of fears of contracting the novel coronavirus, many blood banks throughout the region experienced increased need as their reserves ran low. Local medical students increased public awareness of the need to donate blood and that it can be done safely with low risk. Additionally, during physical distancing measures, students participated in food delivery programs created around the city for vulnerable residents who were unable to leave their homes during this time of social isolation.

At Tulane School of Medicine, students operated one of the city's largest PPE donation sites, where members of the public donated spare masks and gloves to be used by frontline staff. Phone lines were also established where students volunteered to call elderly community members to check in on how they were doing during physical distancing, providing mental health support for those most at-risk for contracting the virus. To support those in health care who might have young children, Tulane students additionally organized a free childcare system for frontline workers who were called to work longer hours in the hospitals.

Third- and fourth-year students from University of Queensland/Ochsner Clinical School operated a specific telephone hotline where they triaged patients for potential COVID-19, recommended testing sites with up-to-date testing guidelines and answered general questions and concerns about the signs and symptoms of infection to those willing to learn to recognize the virus and avoid its spread. When students staffed the triage line, the average wait time decreased from nearly 2½ hours to only a few minutes. This was a great opportunity to practice telephone communication, history taking, and triage skills while performing a needed service during a challenging time. UQ/Ochsner students also staffed a dedicated obstetric COVID-19 hotline where concerns specific to pregnancy and coronavirus were answered. Additionally, some students who had a background in clinical research helped to develop and implement a rapid testing program at the hospital.

More broadly, these reactions were not limited to medical students in Louisiana. Across the United States, similar community-based volunteer programs began to be drafted, implemented, and led by medical students who were uniquely positioned "to help answer many questions of [their] friends, loved ones, and neighbors" and to utilize their "work ethic, leadership skills, and social skills to meet the wide range of needs of [their] community."[4] No matter the location, medical students demonstrated a deep understanding of their local communities' needs and the role that they could play in addressing them, whether it be hosting PPE or blood donation drives, childcare services, or educational outreach. This ability to understand the needs of their patient populations and how to best affect change in the community, will be an advantageous skill for future full and empathetic practice.

As a medical student, during the beginning of the pandemic, I found it challenging to adjust to the deluge of information, health recommendations, and mounting infection count, which seemed to increase at an alarming rate, but it was alongside my fellow medical students that we were able to form a united response to the pandemic. Every medical student was impacted by the novel coronavirus, and all the students demonstrated ways in which their skills could benefit their community. This pandemic upended the usual progression of medical studies, but students throughout Louisiana—and across the United

[1] BS, BA, University of Queensland/Ochsner Clinical School.

About the Author: *Jacob F. Boudreaux is a fourth-year medical student at the University of Queensland/Ochsner Clinical School. The program, which allows students to undertake their medical training on two continents, is located in Queensland, Australia and Louisiana, United States.*

Correspondence:
Jacob F. Boudreaux
Address: St Lucia QLD 4072, Australia
Email: v-jacboudreaux@ochsner.org

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States—rose to the occasion and found unique opportunities where their training, dedication, and knowledge could be put to good use. Now more than six months into the pandemic, most medical students have returned to the wards under new COVID-19 guidelines, limiting their potential exposure to the virus. Despite their return to rotations under this new normal, medical students are continuing to serve their communities through ongoing educational outreach, demonstrating the value of mask-wearing, and speaking about the importance of following physical distancing guidelines with friends, family, and the public. Through the trials of these last several months, the medical student response to the novel coronavirus has displayed one of the most important skills required for the clinical practice: adaptation.

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Experience

Fighting COVID-19: What's in a Name?

Thomas Kun Pak,[1] Aline Sandouk,[2] Phuong Le.[3]

The Experience

Coronavirus Disease 2019, or COVID-19, first appeared in Wuhan, China, in late December 2019.[1] Since little else was known about the outbreak, the then-unidentified disease became associated with the city where it was first identified by the scientific community, followed by the press and then the public, and became known as the "Wuhan virus". In the weeks that followed, speedy research efforts and consultations between scientists and clinicians revealed the pathogen responsible to be a Coronavirus, now officially recorded as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Though the name "Wuhan virus" was initially adopted for ease of reporting and in the absence of any details about the cause, we now know much more about COVID-19 beyond its geographic origins. Yet, the obsolete "Wuhan virus" remains in use, to the detriment of anyone or anything even remotely linked to Asia, and indeed, to all of our detriment. Similar to the current pandemic, the 2009 H1N1 Influenza virus led to World Health Organization (WHO)-classified pandemics, spurred national emergency declarations in the United States (US), and led to widespread morbidity and mortality.[2] However, unlike SARS-CoV-2, the 2019 H1N1 Influenza virus was first detected here in the US. While SARS-CoV-2 has erroneously continued to be referred to as the "Chinese Coronavirus", the H1N1 Influenza virus has never been referred to as the "American Virus", even though it was first identified in the American state of California. Instead, it has sometimes been referred to as "Swine Flu".[3] H1N1 benefits from being referred to by its scientific name, even as other closely-related influenza viruses continue to be called the "Asian Flu" (1957) and "Hong Kong Flu" (1968).

In a world free of racism, these terms would be harmless. But as the US struggles to contain a global pandemic that has left more than 125,000 Americans dead, people are concerned about their health and that of their family and friends, and unfortunately, also quick to cast blame. The medical and research communities have attempted to avoid perpetuating this naming trend by adhering to the accepted scientific name of the new virus once the strain was identified. We have seen this adherence in the *International Journal of Medical Students* COVID-19 Hub (http://ijms.info/IJMS/coronavirus). In addition, we conducted a brief review of the literature using Google Scholar and Pubmed, searching for the terms "Wuhan Virus", "Wuhan Coronavirus", "Chinese Virus", and "Chinese Coronavirus". In the earliest days of the pandemic, when little else was known about the outbreak, scientists resorted to using "Wuhan virus" in reference to the location where the first cases of COVID-19 clustered and came to clinical attention, not necessarily in reference to where the virus may have originated or in an effort to disparage the Asian community. Positively, we found only occasional use of "Wuhan virus," "Wuhan Coronavirus," and "Chinese Coronavirus," but determined that these instances pre-dated discovery of SARS-CoV-2 and were employed as a matter of practicality in the absence of more substantive information about the outbreak, not as an indictment of the people of Wuhan or China. Furthermore, we did not find any publications that have continued to use the non-scientific names after the term SARS-CoV-2 came into use, except as keywords, which we interpreted as an effort by authors to ensure accessibility of their work to the widest possible audience.[4-9] This use of the term is in stark contrast to national leaders and elected officials continuing to use these now-out-of-date and misleading terms in order to sow division and stoke xenophobia.[3]

As during other historical pandemics, there has been a significant exchange of wildly inaccurate health information, from ineffective DIY hand sanitizer to telemarketing calls boasting limited-time offers to a COVID-19 vaccine that does not yet exist. Among the inaccuracies in circulation is the ongoing use of the "Wuhan virus" name, with significant consequences. Referring to SARS-CoV-2 as a "foreign", "Chinese" virus has reinforced the inaccurate narrative of blaming Asians and Asian Americans for the pandemic, even though by now China is considered to have taken effective steps to contain the epidemic within its borders.[10] An Ipsos poll showed that 32% of Americans witnessed someone blaming Asian people for the Coronavirus pandemic.[11] Consequently, this has contributed to a significant number of public outbursts of verbal attacks, discrimination, and outright violence against Asian-Americans, exhibiting a similar pattern of abuse against specific ethnic groups seen in past pandemics.[12] Most concerning is the speculation that SARS-CoV-2 was genetically engineered in Wuhan, despite extensive analysis of the virus' genome concluding that the virus originated naturally from wildlife, as noted by public health experts.[13] In response, the Asian Pacific Policy and Planning Council (A3PCON) – a US-based coalition of Asian American and Pacific Islander civil rights organizations representing Americans of Asian descent, including Chinese, Japanese, Korean, Cambodian, and Thai Americans – established a resource for reporting anti-Asian incidents, the STOP AAPI Hate Reporting Center; so far, over 2100 reports have been made since March 2020.[14] As the COVID-19 death toll continues to rise, the FBI has warned of an ongoing rise in crime against Asian Americans due to COVID-19.[15]

It is worth noting that other viruses causing outbreaks that, at least in part, stemmed from or progressed by region-specific cultural practices have not been named according to the geographic area from which they originated or were first identified. For example, during the deadly 2014-2015 Ebola virus outbreak in West Africa, WHO officials identified

1 Bachelor of Arts, University of Iowa Carver College of Medicine, Iowa City, Iowa, United States
2 Bachelor of Science, University of Iowa Carver College of Medicine, Iowa City, Iowa, United States
3 Bachelor of Science, University of Mississippi Medical Center, Jackson, Mississippi, United States

About the Author: *Thomas Pak is an Asian American medical student in the dual-degree MD/PhD Medical Scientist Training Program (MSTP) at the University of Iowa in Iowa City, Iowa. Thomas has also published in USA Today. Phuong Le is a 4th year medical student at the University of Mississippi in Jackson, Mississippi. Phuong was a Rhodes Fellow and a recipient of the 2018 Medical Student Anesthesiology Research Fellowship. Aline Sandouk is also an MSTP student at the University of Iowa and in her final year of graduate training before returning to medical school to finish her undergraduate medical training. Previously, Aline was a 2013-2014 Fulbright Fellow to Germany and a 2009-2011 Post-baccalaureate Intramural Research Training Award (IRTA) Fellow at the National Institutes of Health (NIH).*

Correspondence:
Thomas Kun Pak
Address: 375 Newton Rd, Iowa City, IA 52242, United States
Email: tpak.jhu@gmail.com

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traditional burial and funeral practices as a major mode of transmission, accounting for some 80% of cases in Sierra Leone.[16] These rites involve close, if not direct, contact with the body of a person who died of Ebola virus, such as bathing in water used to wash the deceased or spending several nights sleeping near the deceased.[16] Containment of the virus became critically dependent on modifications of these practices.[17] Similarly, resurgence of the Measles virus in recent years in the US can be attributed almost entirely to vaccine hesitancy fueled by a now-retracted and heavily-discredited 1998 article positing a link between immunization and the development of autism.[18] Yet, neither West Africans nor Americans have been subjected to the indignity of having their association with these outbreaks forever memorialized in the naming of these viruses as the "West African virus" or the "American virus", and rightly so. Identifying and modifying practices that facilitate the spread of deadly diseases is a responsible way to respond to our current situation; making sweeping generalizations about entire communities, regions, countries, or cultures is not. The basis for the inclusion, or exclusion as it were, of the area of assumed "origin" from names of epidemic pathogens in popular media, appears to be a manifestation of underlying racial prejudices, not scientific data. More important than biology and semantics, however, are the very real economic and social impacts of using non-scientific names for human diseases. The effects are considerable and include jeopardizing trade, travel, tourism, and overall community welfare to such an extent as to have motivated the WHO to develop and publish guidelines in May 2015 for the naming of new diseases that exclude geographic location or ethnicity in an important effort to minimize stigma.[19]

As physicians-in-training, we consider it our mission to understand the human body and the natural world that acts on it to the greatest extent possible limited only by the available technology of our times. It is our understanding that race and ethnicity are effectively social constructs. Viruses exist all over the world, originate from all over the world, and spread all over the world, to any available host without discrimination. At this point, SARS-CoV-2 has extended its reach far beyond China's borders, with the US now leading in COVID-19 cases and mortality.[20] Indeed, our best chance now at stopping the spread are the evidence-supported, universally-accepted measures of good hand hygiene and strict social distancing, not just from those of non-native origins or foreign descent, but from everyone. With lives hanging in the balance, this is not a time to sow division, but promote cooperation against a shared adversary, the COVID-19 virus. It is a time to turn to each other, not against each other, in solidarity. We urge everyone to exercise their most analytical, critical, and ethical judgments. Regardless of where or how COVID-19 began, the undeniable reality is that it is now everywhere. A pandemic is, by definition, a worldwide phenomenon, and as such, demands a worldwide response. Let's give it one.

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Experience

Online Final Medical School Exam in a Low-Income Country During COVID-19 Pandemic

Caroline Vimbainashe Gona.[1]

The Experience

The COVID-19 pandemic has affected every sector of society. The usual delivery of medical education and assessment of undergraduate medical students has had to temporarily change in the midst of this global crisis. Online academic assessment of medical students has long been used and keeps developing.[1] However, when I returned from my medical school in China to do my final year of clinical electives in my country, Zimbabwe, I never imagined I would be writing my final medical school examination in my own home.

Traditionally, the medical school I attended holds their final graduation exam in two parts, both of which are paper based tests that are invigilated. The first part being taken before a year of clinical elective attachments at chosen hospitals approved by the school and the second part which is taken after the electives which subsequently leads to the attainment of the Bachelor of Medicine and Bachelor of Surgery (MBBS) degree.

I had read news of final year medical students in other parts of the world being fast tracked and quickly finishing the last part of their undergraduate medical education in order to increase the frontline workforce on the battle against COVID-19.[2] My medical school took a similar course of action shortly after this, announcing my final examination would be written online with time limits, as originally planned by the school. This came as a relief to me because I had been worried about not graduating on time because of the uncertainties surrounding the SARS-CoV-2 pandemic and the hassle of applying for a new visa to China in the event that the pandemic did not die down and travel restrictions were not lifted (which ended up being the case).

Online education or assessment in a low-income country comes with numerous challenges including unavailability of the internet in many homes, slow connectivity and electricity power cuts.[3] Now I had to plan for a 3 hour long online final medical school examination which would hopefully be uninterrupted.

All candidates were informed of the inclusion of subjective type questions in the examination, which was the only difference from the norm, but a significant difference in my opinion as it affected my methods of preparation for the exam.[4]

A few weeks passed and finally it was the day of the examination. Ironically, the electricity was unavailable and I had to use a back-up generator during the exam. I was impressed with the platform used to conduct the examination which had an auto-save function and this was reassuring because if adverse circumstances had interrupted my examination, when I restarted, my answers would have been recorded. Thankfully, I had no disturbances for the entire duration of the examination once the generator was running. At the end of my exam, I was excited about what my experience could mean for the future of medical education and assessment, for undergraduate medical students especially in low income countries, like Zimbabwe.

When I had attended the leading medical school in Zimbabwe during my clinical elective attachments, most things were done manually, the use of pen and paper were commonplace and assessments were done physically which has great advantages such as building the confidence of the physician by oral presentations. A group of final year medical students at the top medical school in Zimbabwe were unable to complete their degree program on time owing to a previous doctors' strike compounded by the effects of the COVID-19 pandemic.[5] Perhaps owing to the style of teaching and assessment, these medical students have had to wait many months before they can be formally assessed which has brought staffing implications for a healthcare system that is already facing capacitation challenges related to a hyperinflation economic environment. In this case, I wondered if the possibility of conducting online examinations was considered and if it was, would it have worked for all the candidates considering the economic state of the country?[6]

How can online medical education and assessment be initiated and formalised by medical schools in low income countries? From my experience, I observed that connectivity is key in the fast changing technological world we live in today and medical schools or institutes may need to provide reliable internet connectivity to their students, not only on campus but remotely as well.[7] However, the reality is that face-to-face discussions and streaming which simulate the usual learning environment are inaccessible to everyone. The online platform most students can relate with is WhatsApp and remains a favoured option for case studies, discussions and handing in of assignments. WhatsApp has been the mode of online learning adopted by university students in Zimbabwe as it is a cheaper way of continuing studies and staying connected. In my opinion, online learning and assessment in Zimbabwe and other low-income countries is likely to become more popular in the post-pandemic era as this difficult time has served as an eye-opener to non-traditional methods of learning and examination.

The COVID-19 pandemic and its effects on the world have caused sheer distress but I think that adversity breeds innovation. The challenges faced allow us to think of ways to improve ourselves and the world including the day-to-day delivery of medical education and assessment, even in the face of a pandemic.[8]

[1] Bachelor of Medicine, Bachelor of Surgery (MBBS). China Medical University (PRC), Shenyang, China.

About the Author: *Caroline Vimbainashe Gona is a recently qualified medical doctor who trained at China Medical University (PRC) in Shenyang, China. She currently resides in her home country, Zimbabwe, where she hopes to start her internship in the following year.*

Correspondence:

Caroline Vimbainashe Gona

Address: 77 Puhe Rd, Shenbei, Shenyang, Liaoning, China.

Email: caroline.nash.gona6@gmail.com

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