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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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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

Leadership and Health: The Scientific Journal's Mission of Spreading Science in Times of Pandemic

Francisco J. Bonilla-Escobar.[1,2,3,4]

It has been 8 years since the International Journal of Medical Students published its first issue.[1] Since that time, hundreds of medical students have been influenced by the journal directly, and thousands more indirectly. Some of them have been members of our select team of Student and Associate Editors, some have been Ambassadors, and others authors, readers or fans on social media.

During these years, we have trained future leaders of medical science in the areas of scientific publication, editorial management, and editorial processing. This early training in research, during and even before medical school, is a way to bridge the physician-scientist gap worldwide.

We come from a legacy of brilliant medical students who put together, against so many difficulties, a scientific journal for medical students and young doctors.[1] Our Editorial Board is made of top-tier international researchers. Similarly, the Editorial Team is full of brilliant and enthusiastic medical students and young physicians who volunteer their time to help other students get their manuscripts strong enough to be published; eventually, this promotes research by medical students worldwide. Our Ambassadors are increasing the reach of the journal and allowing students to gain access to something that not that long ago, and especially for underserved areas, seemed unachievable: the publication of medical student research.

Today, more than ever, the community of medical students and young physicians is at risk. Humanity is going through an unprecedented time for our generation. In this issue, we are highlighting experiences from medical students and young physicians around the globe during this COVID-19 pandemic. This journal is an avenue for the youngest generations to tell the world about their experiences during these difficult times and to show how our peers around the globe are going through similar situations; but we did this specially to highlight the positive aspects of such circumstances. In this issue, you will find the problems, options, perspectives, fears, happiness, opportunities, ironies, and the best that we all can identify and take out of this pandemic.[2-17]

I have not been immune to this situation. Even though I am sitting comfortably writing this editorial, when this situation started, I was in the US. Then, I moved to France to do a fellowship in research, and after the two countries closed their borders, I ended up in my home country, Colombia. I am lucky to be with my family and you can imagine the challenges that I went through moving back home after all the previous efforts to get into top educational institutions. I cannot complain much: my research is being done remotely, and I am participating in academic activities using one of the many programs that we have. But I have learned that not everything is about the "*when*" but about the "*how*". In the Experiences section of this issue, you will find that too.

We have witnessed the globe being polarized. Leaders are forgetting that the economy is sustained by the ones that it serves, the people, and people are forgetting that the healthcare professional is anything but their enemy. We, as future scientists, must never forget that we praise facts over assumptions, and do our work not because of the monetary reimbursement but to serve others. The former is a fact from which some governments have taken advantage of their health care workers, especially in low- and middle-income countries where virus exposure is high and health care workers lack the required living conditions to safely care for others.

We have witnessed how other journals, even the most renowned ones, have run to publish everything. We see authors repeating their cases in more than one article, and series of cases with low number of patients which are not providing any new knowledge about a common enemy. These are desperate times, but we have a moral duty as editors. More transparent science is required as well as higher ethical standards among researchers and scientists. We try to impress these values to our authors through a long and comprehensive editorial process and a declaration of transparency when submitting their articles.[18]

We have not and we are not going to rush to get publications pertaining to COVID-19. Articles will still undergo a peer-reviewed process due to our responsibility as editors and future judges of what we did during these times. Everything would be much better if we were able to judge our current acts knowing what was about to come in the future.

This takes me to the last part of this editorial. Decision makers are responsible for the health of people. We have seen amazing examples of paternalistic health interventions. Yes, people are complaining and, in some cases, protesting, but lives are being saved by governments' decisions. How will history judge those decision makers that did not listen to science? How would it be if governments assumed a more compromised attitude towards prevention and improving people's lifestyle, well-being and health status based on reliable evidence?

We are still far from seeing the end of the tunnel in this pandemic. Things are not going to be the same after this period of our human history. Nevertheless, we need to be sure that we are moving forward. There are several global and local efforts in the shape of collaborations, studies and trials to win the battle against this coronavirus. We have found that we can live without many things and that there are gaps in people's daily lives that we never thought about but that we have found solutions to, or that we are still in the process of finding out how to solve. This is a new opportunity for humanity to grow, and this is also an opportunity for the planet which has a chance to recover, at least a little, from the abusive way we inhabit it.

We will overcome this situation and bright things will come after. We just need to stay strong and together.

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Original Article

Determinants of Residency Program Choice in Two Central African Countries: An Internet Survey of Senior Medical Students

Ulrick S. Kanmounye,[1] Mazou Temgoua,[2] Francky T. Endomba.[3]

Abstract

Background: Central African countries have an increasing burden of disease, low specialist workforce densities, and under-resourced postgraduate medical education. The residency program choice of today's medical students will determine specialist workforce density in the near future. This study aims to elucidate the factors that influence the choice of residency programs among medical students of two Central African countries. **Methods:** We designed an online questionnaire in French and English with closed-ended, open-ended, and Likert scale questions. Links to both forms were shared via the international messaging application, WhatsApp, and data were collected anonymously for one month. Respondents were sixth- and seventh-year medical students enrolled in nine Cameroonian and Congolese schools. The threshold of significance was set at 0.05 for bivariate analysis. **Results:** There were 149 respondents in our study, 51.7% were female, and 79.2% were from Cameroon. Almost every student (98%) expressed the wish to specialize, and a majority (77.2%) reported an interest in a residency program abroad. Preferred destinations were France (13.7%), Canada (13.2%), and the U.S.A. (11.9%). The most popular specialties were cardiology (9.4%), pediatrics (9.4%) and obstetrics and gynecology (8.7%). The choice of specialty was made based on the respondent's perceived skills (85.9%), anticipated pay after residency (79.2%), and patient contact (79.2%). **Conclusion:** Understanding which specialties interest Cameroonian and Congolese medical students and the reasons for these choices can help develop better local programs.

Key Words: Career choice; Internship and residency; Surveys and questionnaires; Cameroon; Democratic Republic of the Congo (Source: MeSH-NLM).

Introduction

Cameroon and Democratic Republic of Congo (DRC) are Central African countries with high burdens of infectious and maternal diseases, low health investments, and high incidences of catastrophic health expenditure due to a lack of universal health coverage.[1,2] The overburdened Cameroonian and Congolese health systems are stressed further by conflicts and disasters.[3,4] Limited medical school admissions and local residency positions are pushing medical graduates to educational migration. Also, a considerable percentage of African medical graduates tend to go abroad because foreign programs are perceived to be of higher quality.[5,6] This decreases the physician workforce density and limits patient access to specialist care in African countries. Specialist care plays a significant role in the healthcare system as it leads to prompt diagnosis, adapted care, and generally better outcomes for patients.[7,8] Postgraduate medical education (PGME) programs should equip their graduates with the skills to tackle the nation's public health challenges. Understanding the determinants of residency program choice can equally help bridge the disparities in certain specialties. For example, women are poorly represented in some specialties[9,10] despite making up more than half of the medical student body.[11,12] This disparity is accentuated in African society, where women tend to be less interested in specialties that are viewed as "demanding."[13,14]

Cameroon has 1,420 general practitioners and 422 specialists serving 25 million inhabitants.[15] Admission into the 7-year medical school programs is through a unique national examination for undergraduates, and successful candidates get into one of 8 medical schools (six public and two private). The first three years are pre-clinical, the next three are clinical, and the last year is reserved for the thesis. At the end of the sixth year, students take a national examination (*Examen National de Synthèse Clinique et Thérapeutique*) made of a written and a practical section. Successful candidates can apply for an academic specialty program known as *internat,* and if selected, they then go on to start their specialty the following year. Those who are not interested in *internat* and those who failed to get into *internat* can apply for another specialty program known as *résidanat* once they have totaled at least two years of general practice.

The DRC, on the contrary, has 84 million inhabitants and 4,500 (2,000 specialists and 2,500 general practitioners) of the country's 25,000 physicians that practice in the capital city. The number of medical schools has grown exponentially.[16] From 19 nationwide in 2010, there are now 25 in the capital city (Kinshasa) alone.[17] Training in the DRC is divided into three pre-clinical years called *graduat* and four clinical years called *doctorat*. The last year of doctorat, *quatrième doctorat*, is spent doing rotations for a period between 14 to 18 months divided into at least: 1-month neurology, 1-month psychiatry, 4-month medicine, 4-month surgery, 4-month obstetrics and gynecology, and 4-month pediatrics rotations. Medical graduates can apply for residency if they pass the admissions tests organized by each program.

Cameroonian and Congolese medical graduates are considered fit to practice as soon as they get licensure from their respective national medical bodies. The state is the major employer in both countries and the state's budget limits recruitment.[18] There are no rural practice

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requirements for recent medical graduates, and most physicians recruited by the state are assigned to rural health centers unless they are admitted into a PGME program, in which case, they will be assigned to a teaching hospital. Little is known about how Cameroonian or Congolese medical students choose their residency programs. We aimed to identify the determinants of residency program choice among senior year medical students in Cameroon and the DRC.

Materials and Methods

Study Design and Participants

We conducted a descriptive cross-sectional study, and our target population was defined as sixth- and seventh-year students enrolled in Cameroonian and Congolese medical schools. We distributed our survey to students of 9 medical schools: 6 Cameroonian and 3 Congolese. Two of the eight Cameroonian medical schools, the University of Dschang and the University of Ngaoundere, were created less than three years ago and had no senior medical students at the time of our study. We recruited students from the Faculty of Medicine and Biomedical Sciences, Yaounde; Higher Institute of Medical Technologies, Yaounde; Faculty of Medicine and Pharmaceutical Sciences, Douala; Faculty of Health Sciences, Buea; Faculty of Health Sciences, Bamenda and Higher Institute of Health Sciences, Bangangte. Cameroon has two official languages, French and English. English is the primary teaching language in the Faculty of Health Sciences, University of Bamenda, and the Faculty of Health Sciences, University of Buea, while French is the primary teaching language in the other medical schools. In the DRC, we recruited from Bel Campus Technological University, Kinshasa; Faculty of Medicine, Kinshasa; and Faculty of Medicine, Kamina. All Congolese medical schools use French as their official language. The study population sampling was consecutive and convenient, and participant consent was sought before beginning the survey.

Questionnaire

The questionnaires were self-administered in both French and English. Links to the online Google Forms (Google LLC, CA, U.S.A.) questionnaires were shared via the official class WhatsApp (WhatsApp Inc, CA, U.S.A.) groups and via text messages. A restriction on the number of survey responses from a single device limited duplicate responses, and all respondents were given information on the aims and risks of the study.

The questionnaire comprised five sections: the first section included sociodemographic data (gender, age, marital status, medical school, medical schools' private/public status, year of study). The second section covered the students' preferred residency programs and the reasons for choosing these programs. The questionnaire evaluated the importance of 11 factors using 5-point Likert scale questions. These factors had previously been identified during a formal group discussion between the authors and a sample of 21 Cameroonian and Congolese senior medical students. This same group was used to pilot the online survey, and their responses were not included in the final analysis. The following section covered the intention to migrate, destination, and reasons for migrating or not migrating. The fourth section explored whether the students had been encouraged or discouraged by someone close to them. Finally, the last section covered whether the medical students had previously changed their minds. Data were collected anonymously, and ethical clearances were obtained from Institutional Review Boards in Cameroon and the DRC.

Specialty classification

We classified specialties into medical specialties (acute internal medicine, allergy, cardiology, clinical genetics, dermatology, endocrinology, gastroenterology, general internal medicine, geriatric medicine, immunology, infectious diseases, medical oncology, ophthalmology, neurology, palliative medicine, nephrology, nuclear medicine, pneumology, rheumatology, and sports medicine), surgical specialties (cardiothoracic surgery, general surgery, neurosurgery, oral and maxillofacial surgery, trauma and orthopedic surgery, otolaryngology, pediatric surgery, plastic surgery, urology surgery, and vascular surgery) and other specialties.

Data analysis

Data was exported from Google Forms to Excel (Microsoft Corp, WA, U.S.A.), coded and analyzed using SPSS v24 (Statistical Package for the Social Sciences, SPSS Inc, U.S.A.). 95% confidence intervals, bivariate, and multinomial regression analyses were run. The alpha value was set at 0.05. The Likert responses were organized into three categories: strongly disagree and disagree, undecided, and agree and strongly agree. Agree and strongly agree were the reference for the level of importance of each determinant, while surgical specialties were the reference category for PGMEs. The visualizations were generated using Tableau Public v2019.4.1 (Mountain View, CA, U.S.A.).

Results

Of the 186 eligible final year medical students approached in Cameroon and the DRC, 149 respondents (response rate: 80.11%) consented to the study, and the same number completed the survey. There were no incomplete surveys, and we were unable to distinguish abandonments from non-response. Following data cleaning and analysis, we did not find ineligible respondents among our sample. The mean age was 25.29 years ± 1.97, 52% of participants were female, 86.6% were single, 79.2% went to school in Cameroon, 56.4% were in public schools, and 75.8% were in their seventh year of medical school. Almost every participant (98%) expressed a firm desire to get into residency, 115 respondents (77.2%) intended to do their residency abroad, and 114 (76.5%) reported that they would come back home after their training abroad. Those who wished to return after their residency training stated the need to help the vulnerable (40.3%) and the need to serve the state (36.9%). Some answers from our respondents are below:

"We lack doctors in my preferred specialty in my country, and I wish to improve the health of my countrymen."

"My country needs me more, plus we were trained to take care of the sick and needy. Patients exist everywhere, so [physicians] should equally exist everywhere."

Most participants (58.4%; 95% CI: 50%-66.4%) had previously changed their minds on their specialty choice. 133 (89.3% 95%CI: 83.1%-93.7%) respondents reported that they had been advised to take up a specialty. These students had been encouraged by a family member (64.4%, n=133), a friend (30.2%, n=133), or a teacher (21.5%, n=133) to choose a specialty over another. The most commonly recommended specialties were obstetrics and gynecology (18.8%, n=133) and pediatrics (12.8%, n=133). Sixty-four students (43.0%, n=149) followed the advice given to them (***Table 1***).

When asked what they would choose between their least favorite specialty abroad and their favorite specialty at home, 104 (69.8%; 95% CI: 61.7%-77%) chose their favorite specialty. 77 (51.7%) students agreed they would accept a residency offer if it entailed having to practice in a rural area at the end of residency while 46 (30.9%) were hesitant. Students that hesitated or refused to accept such an offer reported they might change their minds if rural outposts were better equipped (10.7%) or if they were guaranteed career advancement (5.4%) or if they were given financial incentives (4.0%).

Participants from this study chose Africa (30.2%) as the second most popular continent for residency program choice behind Europe (38.2%). The most popular countries for residency training were France (13.7%), Canada (13.2%), and the U.S.A. (11.9%) (***Figure 1***). The main reason for wanting to train abroad was to get better training (68.5%). Additionally, 6.7% of students wished to train abroad because they felt foreign programs were more prestigious, while 3.4% wished to train abroad because their preferred specialty was not available for PGME in their home country. Some interesting quotes by our respondents:

"I wish to train abroad because education and remuneration are better than at home. There are more opportunities to grow abroad, and I can directly access my specialty without having to wait to gain experience."

"The specialty I wish to do is not available in my country, and I wish to explore another country."

Only seven students decided to train in their country. They cited family (2.7%) and patriotism (2.0%) as reasons for training in their homeland. The destination for residency training was chosen based on the reputation of the country's training programs (45.0%), the host country's language (9.4%), and opportunities (7.4%).

Table 1. Cameroonian and Congolese Medical Students' Sociodemographic Characteristics, Intention to Specialize and Intention to Migrate in Online Survey by Frequency and Percentage.

Characteristic	All (%) [n=149]	Cameroon (%) [n=115]	The DRC (%) [n=34]
Mean Age	25.29	24.91	26.56
Gender			
Female	77 (51.7)	66 (44.3)	11 (7.4)
Male	72 (48.3)	49 (32.9)	23 (15.4)
Relationship status			
Single	129 (86.6)	100 (67.1)	29 (19.4)
Engaged/Married	20 (13.4)	15 (10.1)	5 (3.4)
School year			
Seventh	113 (75.8)	84 (56.4)	29 (19.4)
Sixth	36 (24.2)	31 (20.8)	5 (3.4)
Medical school			
Public	84 (56.4)	71 (47.7)	13 (8.7)
Private	65 (43.6)	44 (29.5)	21 (14.1)
Intent to get into residency			
Yes	146 (97.8)	113 (75.8)	33 (22.1)
Maybe	3 (2.0)	2 (1.3)	1 (0.7)
Intent to migrate for residency training			
Yes	115 (77.2)	84 (56.4)	31 (20.8)
Maybe	27 (18.1)	24 (16.1)	3 (2.0)
No	7 (4.5)	7 (4.7)	0
Intent to return after training if they migrate			
Yes	114 (76.5)	88 (59.1)	26 (17.4)
Maybe	29 (19.4)	22 (14.8)	7 (4.6)
No	6 (4.0)	5 (3.3)	1 (0.7)
Change of mind on the preferred residency program	87 (58.3)	69 (46.3)	18 (12.1)
Advised to go into a particular specialty	133 (89.3)	101 (67.8)	32 (21.5)
Followed the advice	64 (43.0)	47 (31.5)	17 (11.4)
Advised not to go into a particular specialty	66 (44.3)	51 (34.2)	15 (10.1)
Followed the advice	24 (16.1)	22 (14.8)	3 (2.0)

Figure 1. Preferred Destinations of Cameroonian and Congolese Senior Medical Students for Postgraduate Medical Training.

The most popular first choice specialties in our study were cardiology 14 (9.4%), pediatrics 14 (9.4%), and obstetrics and gynecology 13 (8.7%). 24.7% of women chose a surgical specialty, while 14.3% chose pediatrics as their first choice. On the other hand, 44.4% of men chose a surgical specialty, while 4.2% chose pediatrics as their first choice (***Table 2***).

The majority of study participants identified personal skills for the job (85.9%), patient contact (79.2%), and anticipated pay after residency (79.2%) as being essential to choosing a residency program (***Figure 2***). Eighty-eight students (55.7%) estimated the specialist average monthly salary to be above USD $1,070, the median of the specialist monthly wage estimation was USD $982-1,070, and the mode was .USD $1,607 (25.5%). 83 (55.7%) felt there was no factor other than the pre-identified 11 that influenced their residency choice. Other factors reported included a passion for the specialty (8.1%), lesser popularity of the specialty (6.0%), and family (3.4%). The main reason for not liking a specialty was a lack of interest (58.4%).

We found a statistically significant small to moderate association between male gender and having been discouraged from doing a particular specialty (Phi -0.213, p = 0.009). Enrollment at a public or private school (p=0.859), being discouraged (p=0.619), and being encouraged (p=1.000) by someone to do a particular specialty were not found to be associated with specialty choice. No association was found between the intent to specialize on the one hand and deciding on whether to practice in a rural area (p=1.000), being encouraged to do a specialty (p=0.113), and being discouraged from doing a specialty (p=0.013). The choice of specialty was significantly associated with perceived specialty prestige (p=0.04) and previous experience (p=0.05). Multinomial analysis of the level of agreement on the importance of the determinants by preferred specialty revealed that indecision on the importance of prestige (p=0.004) and strong disagreement/ disagreement of the importance of previous experience (p=0.02) to specialty choice were both statistically significant among students who chose specialties that were neither medical nor surgical (***Table 3***).

Table 2. Cameroonian and Congolese Medical Students' First Specialty Choice by Frequency and Percentage.

Specialty	All [n (%)] n=149	Female [n (%)] n=77	Male [n (%)] n=72
Medical specialties	37 (24.8)	21 (14.1)	16 (10.7)
Cardiology	14 (9.4)	7 (4.7)	7 (4.7)
Endocrinology and diabetology	5 (3.4)	4 (2.7)	1 (0.7)
Gastroenterology	4 (2.7)	2 (1.3)	2 (1.3)
General internal medicine	3 (2.0)	2 (1.3)	1 (0.7)
Infectious diseases	2 (1.3)	0	2 (1.3)
Nephrology	6 (4.0)	3 (2.0)	3 (2.0)
Oncology	2 (1.3)	2 (1.3)	0
Pneumonology	1 (0.7)	1 (0.7)	0
Surgical specialties	51 (34.2)	19 (13)	32 (21.5)
Cardiothoracic surgery	6 (4.0)	2 (1.3)	4 (2.7)
General surgery	10 (6.7)	6 (4.0)	4 (2.7)
Maxillofacial and oral surgery	3 (2.0)	3 (2.0)	0
Neurosurgery	10 (6.7)	2 (1.3)	8 (5.4)
Otolaryngology	3 (2.0)	1 (0.7)	2 (1.3)
Pediatric surgery	6 (4.0)	3 (2.0)	3 (2.0)
Plastic surgery	4 (2.7)	1 (0.7)	3 (2.0)
Trauma and orthopedic surgery	7 (4.7)	1 (0.7)	6 (4.0)
Vascular surgery	2 (1.3)	0	2 (1.3)
Other specialties	61 (41)	37 (25)	24 (16.1)
Anesthesia	3 (2.0)	1 (0.7)	2 (1.3)
Clinical and therapeutic pharmacology	1 (0.7)	0	1 (0.7)
Community and sexual reproductive health	1 (0.7)	1 (0.7)	0
Neurology	3 (2.0)	1 (0.7)	2 (1.3)
Obstetrics and gynecology	13 (9)	7 (5)	6 (4.0)
Occupational medicine	1 (0.7)	0	1 (0.7)
Ophthalmology	5 (3.4)	4 (2.7)	1 (0.7)
Pediatrics	14 (9.4)	11 (7.4)	3 (2.0)
Psychiatry	3 (2.0)	1 (0.7)	2 (1.3)
Public health	8 (5.4)	6 (4.0)	2 (1.3)
Radiology	7 (4.7)	5 (3.4)	2 (1.3)
Resuscitation medicine	1 (0.7)	0	1 (0.7)
Sports medicine	1 (0.7)	0	1 (0.7)

Figure 2. Factors Influencing the Choice of a Specialty and the Level of Agreement of Sixth- and Seventh Year Medical Students.

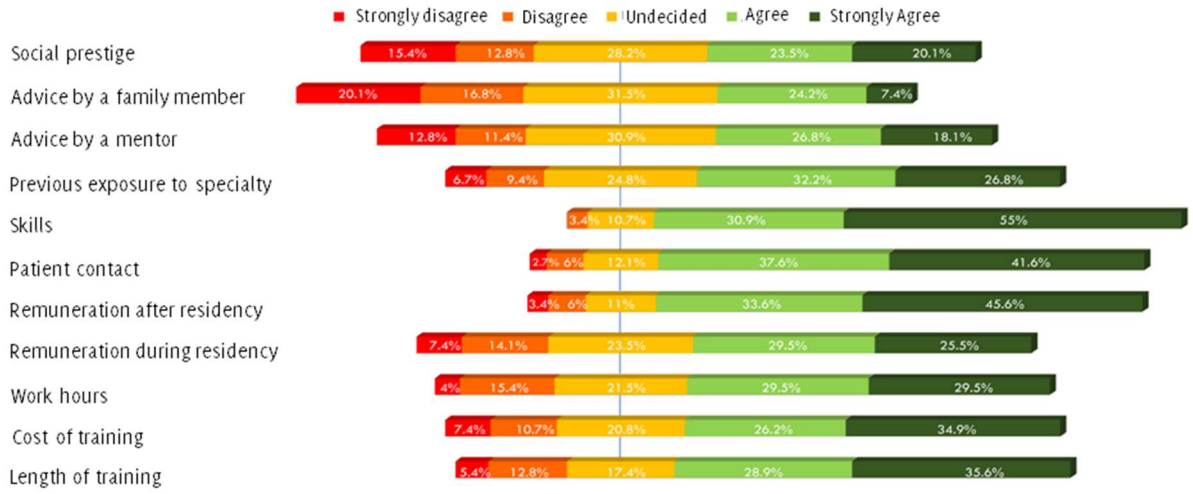

Table 3. Multinomial Regression Analysis of Specialty Determinants and Medical Students' Specialty Choice.

Determinant [a]	Internal medicine [b]			Other specialties [b]			Intercept	χ^2	p-value
	S.E.	Wald	p-value	S.E.	Wald	p-value			
Advice by a family member							25.14	0.62	0.96
Strongly disagree/disagree	0.52	0.07	0.80	0.46	0.27	0.61			
Undecided	0.53	0.03	0.87	0.49	0.21	0.67			
Advice by a mentor							29.55	5.41	0.25
Strongly disagree/disagree	0.54	2.96	0.09	0.48	1.00	0.32			
Undecided	0.51	0.18	0.68	0.46	0.73	0.39			
Cost of training							25.14	1.55	0.82
Strongly disagree/disagree	0.56	0.24	0.62	0.52	0.04	0.84			
Undecided	0.56	0.84	0.63	0.51	1.22	0.27			
Length of training							25.11	3.83	0.42
Strongly disagree/disagree	0.56	1.56	0.21	0.52	4.15	0.04*			
Undecided	0.56	0.23	0.63	0.54	0.22	0.64			
Patient contact							25.11	3.83	0.42
Strongly disagree/disagree	0.73	1.09	0.30	0.72	2.25	0.13			
Undecided	0.73	1.09	0.30	0.56	0.04	0.85			
Prestige							34.30	10.18	0.04*
Strongly disagree/disagree	0.50	2.45	0.12	0.48	2.40	0.12			
Undecided	0.55	1.76	0.19	0.49	8.09	0.004**			
Previous experience							32.92	9.61	0.05*
Strongly disagree/disagree	0.54	0.09	0.77	0.64	5.88	0.02*			
Undecided	0.52	1.56	0.21	0.45	2.69	0.10			
Remuneration after residency							23.77	2.20	0.70
Strongly disagree/disagree	0.77	0.05	0.82	0.64	0.02	0.89			
Undecided	0.67	1.78	0.18	0.68	0.21	0.64			
Remuneration during residency							26.02	2.15	0.71
Strongly disagree/disagree	0.56	0.47	0.49	0.51	1.70	0.19			
Undecided	0.53	0.17	0.68	0.47	0.05	0.82			
Skill							24.13	6.35	0.18
Strongly disagree/disagree	0			0.94	0.06	0.80			
Undecided	0.82	2.54	0.11	0.58	0.65	0.42			
Work hours							33.40	9.90	0.42
Strongly disagree/disagree	0.54	0.03	0.87	0.52	1.60	0.20			
Undecided	0.52	1.64	0.20	0.52	7.84	0.005**			

Legend: [a] Strongly agree and agree are set to zero because they are redundant; [b] The reference specialty category is surgery; * p-value<0.05; ** p-value<0.01

Discussion

Cameroonian and Congolese students, like their Kenyan colleagues, wish to get into residency.[19] PGME fosters learning and mastery of a medical specialty in a formal setting and affords physicians career opportunities, higher social standing, and better remuneration. Cameroonian general practitioners in the public sector earn between USD $262 - $292 on average per month as opposed to the highest Cameroonian specialist earners, surgeons, who earn up to USD $1,491 per month on average.[20] Medical students estimated specialists earned an average monthly salary of USD $1,607, well above the USD $300 – $600 monthly income of the African middle-class, and they felt remuneration after residency was critical when choosing their future specialty.[21]

Cameroonian and Congolese students rotate through surgery, obstetrics and gynecology, pediatrics, and internal medicine. During this period, they develop skills, and they get to build bonds with patients in these departments. They equally experience the challenges of medical practice and PGME training in-country. PGME in developing countries is faced with a lack of financial resources, a dearth of qualified medical educators, and these impact the quality of PGME training.[22,23] Few local residency programs can compete with the resources and prestige of foreign programs. While residency programs of developed nations have successfully integrated innovative solutions to their PGME,[24–26] residency programs in low-resource settings, often lack residency spots and the infrastructure necessary for quality PGME training. Local programs must develop novel, sustainable, and low-cost solutions in order to improve the quality of their PGME and to garner the attention of their medical students. Some programs, like the College of Surgeons of East, Central and Southern Africa, and the West African College of Surgeons, have successfully developed training models that make use of foreign and local resources. This combination has led to an increase in the number of trained specialists and high retention of graduates on the African continent.

Admission to foreign residency programs is extremely competitive and costly.[27] African countries lose financial and human resources to Western countries as those willing to study in world-renowned institutions migrate. Having quality local PGME programs can reduce brain drain from medical workforce migration and reduce capital flight. Similarly to our survey participants, 88.2% of medical students in Malawi[5], and 69% of medical students in Botswana[6] intend to train abroad.

In contrast, South African medical students prefer to study in their home country.[28] South Africa, unlike most sub-Saharan African countries, is advanced economically and scientifically. Its medical education is reputed for its quality medical education and research.[29,30] This might explain why less South Africans are willing to go abroad for their specialization while most Cameroonians and Congolese wish to go to more developed countries like South Africa for their PGME. This difference is corroborated by the fact that most survey respondents chose to train in their favorite specialty at home instead of training in their least favorite specialty abroad.

Although most medical students intend to migrate, they are equally willing to return home once they complete their training. Return to practice in a low-resource setting can be a daunting task for a physician who has become accustomed to working in the Western world. Often newly graduated specialists return home to hospitals that lack equipment and often have to build a service from the ground up. If a residency program is not available in-country, training in an African country offers an environment similar to the home country. It is encouraging that a considerable number of students chose African countries as their destination for PGME training.

Specialties that offer medical students with greater exposure to patients tend to elicit a greater sense of confidence. The confidence that medical students have in their clinical ability increases with supervision, and transition from the lab to the bedside.[31] Both previous exposure to future specialty and perceived skill were essential factors in the choice of future medical specialty to our participants. Similarly, Brazilian medical students emphasize previous experience, perceived skill, and patient contact.[32] Remuneration is equally vital in the choice of a specialty. Although American military medical students choose their specialty based on interest when compensated reasonably, they are more likely to choose less-desirable specialties.[33] We posit that the choice by our respondents of pay after residency can be attributed to the fact that medical training is costly, lengthy and demanding. Medical school tuition can cost as much as USD $2,279 in some Cameroonian and Congolese private schools, and training lasts at least seven years in both countries. In the DRC, it is not uncommon for medical students to graduate with a delay of up to 18 months. This delay, *année élastique* (elastic year), often occurs during the seventh academic year. This is a stressful period for students given that they do not have a medical license, they cannot take up remunerated jobs and therefore depend on their parents for financial assistance. This in part explains the strong desire to train abroad where there are less uncertainties.

Sub-Saharan Africa has the lowest regional medical workforce despite having the highest burden of disease in the world.[34] We must pay attention to those specialties that have a high burden of disease to workforce ratio through strategies aimed at those who are least interested or least represented. Local governments should partner with their medical diaspora and foreign partners to develop quality residency programs and opportunities for medical students. The medical diaspora and foreign medical bodies have the skills, resources, and experience to help bring these plans to fruition [35], but it is up to local governments to develop policies that incentivize their participation.

Limitations to the study include the small sample size and low representation of Congolese medical students. Their low representation might be due to the expensive cost of broadband, USD $1 buys between 130-165 Mb of broadband in the DRC, and most students cannot afford the internet daily. Secondly, by choosing a cross-sectional study design, we could only establish correlation and not causation. The fact that 58.4% of respondents reported having changed their mind before on their specialty choice suggests that some might change their minds in the future. Ideally, we should have followed our participants from medical school to their admission into residency to establish if they had changed their minds. However, this was not possible due to a lack of resources. Next, surveys are prone to a multitude of biases, which can complicate their interpretation. We minimized social response bias by guaranteeing anonymity to our respondents and addressed non-response bias and self-selection bias by sharing our survey by text and WhatsApp while sending reminders every ten days. Despite these limitations, we believe our findings give an insight into some of the motivations of Cameroonian and Congolese medical students who wish to get into a residency program. Future studies should focus on whether these future African medical doctors get into the residency program of their choice, whether they succeed in migrating to the country of their choice and whether they return once they have been trained abroad. Such studies can inform the decision-makers as they design PGME programs.

Medical students from Cameroon and the Democratic Republic of Congo are eager to get into a specialty. They wish to have the best PGME and are willing to travel for this purpose. Their preferred destinations for training are France, Canada, and the United States. Cardiology, pediatrics, and obstetrics and gynecology are the most popular specialties, and their choice is influenced by skills, patient contact, and remuneration after residency. Local program directors must evaluate the quality of programs currently available and modify them to meet the expectations of medical students.

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Original Article

Teaching Cultural Competency through Global Health Education at Weill Cornell Medicine

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Abstract

Background: Educating medical students to better understand the complexities of cultural competence, the social determinants and environmental determinants of health that are important and integral components of the medical school curriculum. **Methods:** In 2014, Weill Cornell Medicine (WCM) implemented a new curriculum, the adoption of which provided the means to enhance an existing global health program, informally introduced in 2009, and to address the issues of cultural competency. In this article, we share WCM's experience in building and expanding its global health curriculum. **Results:** A hallmark of our program is the successful collaboration between students and faculty to create a multi-disciplinary global health program that incorporates electives, clinical field placement, and collaborative research. **Conclusion:** Key lessons learned through our experience include the necessity for strong faculty-student collaboration, full support from the administration, and building global partnerships. Our example could be a useful guide for other medical schools seeking to establish a global health education curriculum.

Key Words: Global health; Cultural competency (Source: MeSH-NLM).

Introduction

The Liaison Committee on Medical Education lists 'Cultural Competency and Health Care Disparities' as an important element in its12 accreditation standards. Section 7.6 clearly states that the medical school curriculum should include "…opportunities for medical students to learn to recognize and appropriately address gender and cultural biases in themselves, in others, and in the health care delivery process."[1] Educating medical students to better understand the complexities of cultural competence and the social and environmental determinants of health are viewed as integral components in the medical school curriculum.[2-3] Focusing on global health is also viewed as a means of addressing diversity and cultural competency.[4-7] Within the past decade, many medical schools have introduced a global health component into their curricula, although the structure of which varies widely in scope and content. The most prevalent example of a global health program is offering an international elective experience. Between 1998 and 2008, medical schools in the United States and Canada experienced a 270% increase in the number of students participating in an international experience.[8] As of 2013, the latest year for which we found available data, at least two-thirds of medical schools offered global health opportunities.[9] However, little standardization across programs existed in terms of requirements for didactic, clinical, scholarly, and cultural components.[10]

There is no "right way" to present global health, and the scope and content of global health curricula vary among medical schools. Some schools have the capacity to organize and administer their own global health program, while others may have to rely on outside entities to do so. For example, the American Association of Medical Colleges (AAMC) Visiting Student Learning Opportunities (VSLO) program merged two existing visiting student programs: the Visiting Student Application Service (VSAS®) and the Global Health Learning Opportunities (GHLO®). The VSLO program provides assistance to institutions located in the U.S. that either send their students to other U.S. medical schools or receive students from other U.S. medical schools. The Global Network component of the VSLO program assists institutions located in the U.S. and overseas to enable students to participate in an international elective at a host institution.[11]

In this article, we describe WCM's innovative and integrated approach to offering global health teaching in the medical school curriculum. A hallmark of our program is the successful collaboration between students and faculty who work together to create a multi-disciplinary global health program focused on education, clinical field placement, and collaborative research. Throughout all aspects of the program, cultural competency is an essential and valued component.

Methods

About the Weill Cornell Medicine Global Health Program

Global health opportunities, including applied experiences and research abroad, have been available to Weill Cornell Medicine (WCM) students since the 1970s. Over time, the scope and focus of the program greatly expanded from initial research and training sites in Haiti and Brazil, to partnerships with medical schools and hospitals across six continents. In 2004, the Office of Global Health Education (OGHE) was established by the Office of the Dean of the medical school to coordinate global health educational activities. The intent was to expand and enrich international opportunities available to WCM students and to foster partnerships with leading medical schools around the world. This engagement has led to collaborative research and bilateral educational opportunities. A previous article describes this early development of WCM's global health program.[12]

Despite the growth of the applied experience component of the global health program at WCM, there was no formalized curriculum for students to learn about global health. In 2009, a small group of WCM faculty members, the Global Health Teaching Associate, an

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administrative assistant to the global health program, and medical students developed the Global Health Curriculum (GHC), which initially consisted of an informal collection of a global health activities, including applied experiences abroad and seminars. In order to create a formal global health course, we relied on the set of core competencies published by the Consortium of Universities for Global Health.[13] An interdisciplinary curriculum for the formal global health course addressed five core competencies:

1. Global Burden of Disease
2. Health, Equity and Social Justice
3. Globalization of Health and Healthcare
4. Capacity Strengthening of Global Public Health Programs
5. Comparative Health Systems and Health Care Delivery

This initiative would not have succeeded without the full support and collaboration of faculty, students, and the administration.

Results

Evolution and Change of the Global Health Curriculum

In 2014, WCM, along with many other medical schools, adopted a revised medical school curriculum. At this time, almost all (98%) of U.S. medical schools enacted curricula changes that "enhanced integration of basic science content (e.g., an organ-system/case-based curriculum)" and 95% of U.S. medical schools made changes that "enhanced clinical correlations in the preclinical years."[14] At WCM, the new curriculum, among other things, increased emphasis on early clinical exposure during the first year, which allowed students to interact with patients beginning in the first semester of medical school. Issues relating to health care diversity are included in all modules. Curriculum revision also enabled the integration of global health into the four-year curriculum through the newly created Areas of Concentration (AOC) curriculum course that also spans the four years of medical school.

The AOC course mandates that students declare a research focus, and after the completion of the core clinical clerkships, conduct a dedicated six-month scholarly research project under the mentorship of a WCM faculty member. Global Health was approved as an AOC option for students. As such, it became imperative that the nascent GHC expand to meet the qualifications of the AOC program. What emerged was a robust multi-focused program that enabled global health to be incorporated into the medical school curriculum in a comprehensive way.

Global Health Electives and Research Opportunities

The global health program includes electives, seminars, and opportunities abroad that span the four years of medical school.

Courses and Electives: *Introduction to Global Health*, an elective offered in the second semester of the first year, focuses on a range of global health topics, including the global burden of disease, comparative health systems, infectious disease, and non-communicable diseases in low- and middle-income countries. *Foundations in Global Service*, an elective offered in the second semester of the first year, focuses on preparing students to conduct global health field work. This elective enables students to explore practical and ethical considerations before taking electives abroad. The *Global Health Preceptorship* is offered as an option in the required clinical preceptorship program during the first and second semesters of the first year.[15] The global health clinical preceptorship was established to enable first-year students to participate in healthcare delivery to marginalized, resource-limited populations in New York City. Students are assigned to a clinic or physician's office located in under-served area of the city, and spend one afternoon each week shadowing physicians over a five-week period. Students also complete weekly readings to learn about the clinical and social approaches to working with vulnerable populations in New York City. These topics include, the social determinants of health, immigrant health, language discordance, and healthcare as a human right. To complete the course, students attend a critical reflection session which allows students to process and share their experiences with their peers.

Global Health Lecture and Seminar Series: *Global Health Grand Rounds* are scheduled several times during the academic year. Renowned global health leaders from around the world are invited to speak on timely global health topics. *Global Health Career Seminars*, scheduled monthly throughout the academic year, offer students the opportunity to have conversations with WCM clinical and research faculty who are engaged in global health work. These small group sessions (~25 students) provide a more informal way for students to appreciate how global health can be incorporated into clinical medicine.

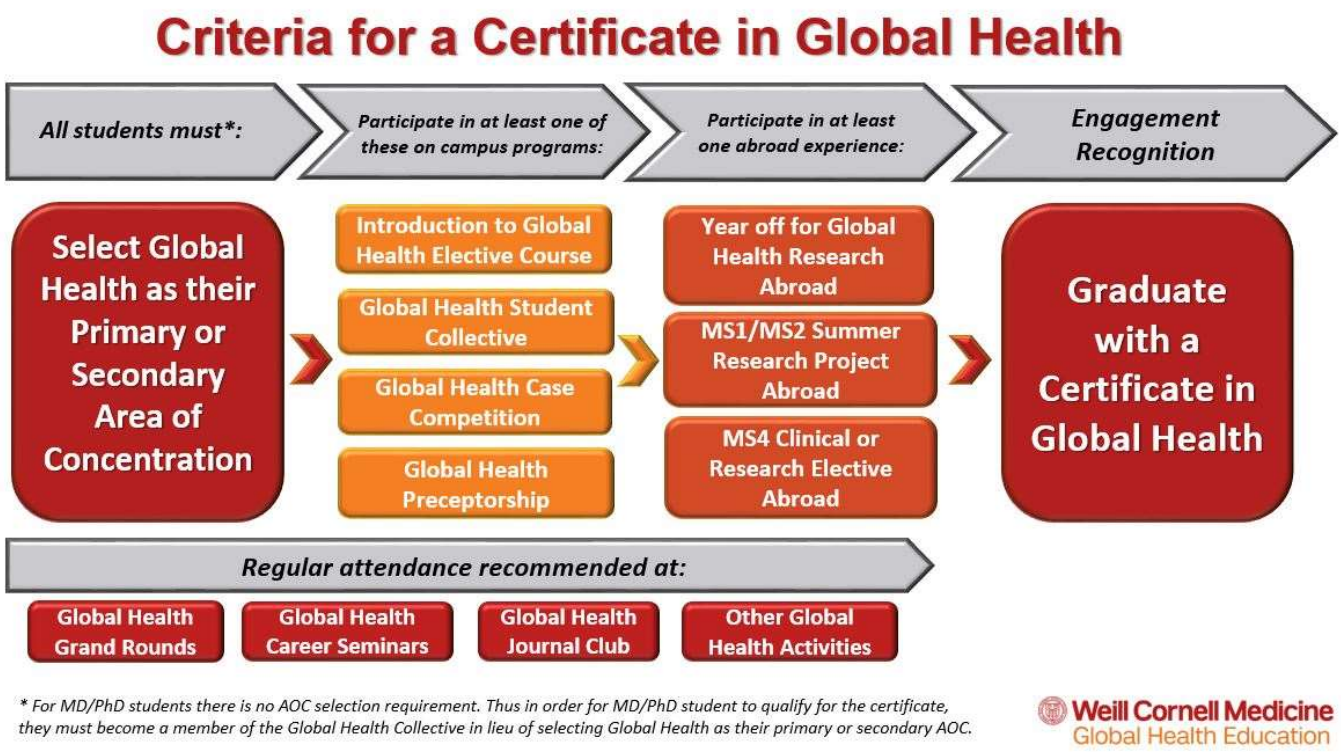
Applied Global Health Experiences: During the summer between the first and second years, WCM students can take an 8-week *first-year international summer elective* under the supervision of a host mentor. Projects typically focus on population/community health research, as students do not have sufficient clinical skills at this point of time in their medical school training. Students participate in an ongoing research project under the mentorship of the host researcher. Of the approximately 100 students in each class, about 7-12 students take advantage of this opportunity, for which work-study funding is available (~$3,000). During their final year of study, students are offered another opportunity to complete an applied global health experience, known as the *fourth-year international elective*. Approximately 35-40 percent of the fourth-year students take an international clinical elective, which ranges from four-to-eight weeks in length. The Office of Global Health Education (OGHE) oversees these international clinical electives (see www.med.cornell.edu/international). Some programs focus solely on clinical care while others combine clinical care with learning more about the healthcare system of the host country.

Students receive a travel stipend ($3,000) from which airfare, accommodations, and living expenses can be paid for. The stipend, allocated by OGHE to all students who take a clinical elective abroad, is funded by gifts, donations, and endowments made to OGHE by donors. A small percentage of students (1-3%) take a *research year* off between the 3rd and 4th year to do global health research at a host institution. A small stipend (~$1500) is also provided to help defray the cost of living. Many students also receive research grants (.i.e., NIH, Foundation funding) to help defray the costs of conducting research abroad.

AOC Research: An important component of the AOC course is the *Scholarly Project* (SP). In second year, every student identifies an area of clinical research interest and prepares a research proposal that forms the basis of their SP. A WCM faculty member serves as the primary mentor who oversees the student's research, and the final, journal-style written report is reviewed and approved by two independent AOC faculty members. The project must be original research that is part of an existing grant-funded project or conceived by the student. Built into the curriculum is a dedicated six-month period during the third year in which the student is not taking any clinical rotations or electives. The block of time is specific to conducting research. The research may be conducted at Weill Cornell, at another medical school in the U.S., or abroad. A faculty mentor at Weill Cornell and a research mentor at the host institution are responsible for overseeing the student's work, and the WCM mentor has the responsibility of approving the finished product. All projects must have Institutional Review Board (IRB) approval from the institution at which the research is being done. Examples of past scholarly projects that focused on some aspect of global health include research in palliative care in India, hypertension in rural Tanzania, and multi-drug resistant TB in Sub-Saharan Africa.

Certificate in Global Health: To earn a Certificate in Global Health, an acknowledgment of active participation in the global health program at Weill Cornell, students must select global health as their primary or secondary AOC for their scholarly project. Additionally, students must be actively engaged in at least one global health program on campus (i.e., Global Health Grand Rounds, Global Health Career Seminars) and take at least one international elective abroad. The Certificates are awarded at a special event prior to graduation. Since the inception of the Certificate, approximately 15-25 students in each graduating class (N=100) have received the Certificate in Global Health. (***Figure 1***).

Figure 1. Requirements to earn a Certificate in Global Health.



Faculty Involvement

All global health programs and initiatives have faculty input. A multi-disciplinary group of faculty throughout WCM, known as the Global Health Faculty Advisory Group, reviews all student applications requesting an international elective. If faculty approval is not given, the student is invited to revise and resubmit their proposal. For example, if the proposal does not clearly state what the student is planning to do during this elective, or if the host mentor is deemed inappropriate, the Advisory Group will request further information and clarification. Students whose proposals are ultimately not approved are ineligible to take part in the international elective and to receive funding. The Global Health Faculty Advisory Group also plans new curricular initiatives, establishes new international and local partnerships, and serves as student mentors. Their role is essential to the continued success of the program.

Student-Led Initiatives

OGHE has carefully fostered a global health community of interested students and faculty members. Student involvement is hugely important to the success of our global health program. The *Global Health Teaching Associate*, a full-time position in OGHE, serves as the bridge between students and faculty. The position is usually filled by a recent college graduate with strong global health experience. This individual also coordinates the global health courses and program activities.

A student group, *the Global Health Collective,* was formalized in 2014 to work collaboratively with the global health faculty in organizing lectures and seminars, as well as to give the students a voice in designing new global health initiatives. One of the main objectives of the Collective is to work with OGHE to foster a sense of community among students and faculty within the global health network at WCM. In an effort to achieve this goal, the Collective, in collaboration with OGHE, organizes various global health career seminars and student panels discussing experiences abroad. The global health career seminars, in particular, are very popular among the students. These informal, small group (N=25) sessions enable interested students to meet with faculty members who are engaged in global health activities as well as clinical care and to understand better how to integrate clinical medicine and global health into a career.

The Global Health Collective has also developed many student-led initiatives, such as the *Global Health Journal Club,* as a way for students to learn about new research in global health, as well as to have discussions on current global health topics. The Journal Club is now organized as a monthly event in which a Weill Cornell student presents a scientific article and leads a discussion with the student audience on the topic.

The *Infectious Disease (ID) Interest Group* seeks to inform students about careers related to ID, connect them to ID faculty, and link them to research opportunities within the WCM community. The group disseminates information on ID research opportunities, organizes shadowing experiences, and convenes faculty panels so that students can learn about ID-related career opportunities, as well as meet potential mentors. It also organizes events surrounding World AIDS Day and other important global health events to increase student understanding and awareness of specific global health topics.

The *Cornell Water Society* offers students the opportunity to participate in a clean water project (i.e., installation of a solar-powered water pump and filtration system) in rural Shinyanga, Tanzania. This project is the result of an international collaboration of non-governmental organizations (NGOs)GOs, local community members, and WCM students. The Weill Cornell Water Society is currently conducting research to assess whether the water pump system has contributed to reduction in the incidence of diarrhea in children under five years of age. In doing so, students gain experience participating in international public health initiatives and research in a meaningful way.

The Center for Human Rights is a Weill Cornell Medicine faculty and medical student-run human rights clinic dedicated to providing forensic medical evaluations to individuals seeking asylum in the United States. The clinic is staffed by physician volunteers, and students are afforded first-hand experience in the assessment of human rights violations.

Strengthening Opportunities for Faculty Mentorship
Building a roster of Global Health Faculty mentors was essential to the success of the program. These individuals guide interested students in finding projects and opportunities abroad, and connect them to mentors at the host institutions. OGHE has created a database of over 60 WCM faculty members and researchers who are involved in global health activities in over 28 countries. Additionally, OGHE hosts Social Hours between faculty members and students in order to facilitate networking and share updates on ongoing research projects. Prior to this, navigating the multitude of global health mentorship opportunities was cumbersome. The global health faculty database and Social Hours have improved the process of finding an appropriate global health mentor.

Communicating global health activities, updates, and new initiatives to the WCM community and general public is crucial for the efficient functioning of the program. OGHE's website has been restructured to provide students with current information and insight about various global health opportunities. Included is a robust set of student resources, including a Travel Handbook and a Global Health Student Guidebook that outline our programs and list all WCM faculty who are currently conducting global health research.

Administrative Support and Funding
Support for global health by the WCM Administration has been essential to the strength of our program. WCM leadership has been highly supportive of our initiatives and activities. While global health programs at other medical schools may receive their primary funding from their school administration, OGHE is self-funded thanks to the large number of endowments provided by generous donors as well as by elective fees charged to visiting international students who take clinical electives at WCM and its affiliated hospitals. We realize that our financial situation may be quite different from other schools and are grateful to our donors for their support of our programs.

Discussion

Next Steps
The WCM global health program continues to be a work in progress—growing substantially over the past decade and continuing to learn how to navigate and overcome challenges that arise. Its integration into the medical school curriculum was a tremendous step in validating the importance of this area of study and its necessary place in the curriculum. After its integration, it was imperative that accessibility be expanded so that any student could participate regardless of financial constraints. Further, didactic coursework and applied experiences were expanded to expose students to an array of issues and topics, which serve to broaden and deepen the traditional medical school curriculum. Given the diverse educational, professional, and cultural backgrounds of students, and their different levels of exposure to global health topics, creating a learning environment that encompasses the global context enables students to develop the skills required of physicians in today's world.

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Original Article

Clinical Presentation and Therapy of Primary Immune Thrombocytopenia Resistant to Splenectomy

Aleksandar Kara-Jovanović,[1] Nada Suvajdžić-Vuković. [2]

Abstract

Background: A satisfactory therapeutic response is achieved with splenectomy in 60–80% of the patients diagnosed with immune thrombocytopenic purpura (ITP). There is an ongoing consensus on the short-term efficacy of splenectomy, however, its long-term efficacy remains controversial. Our aim was to establish the frequency of resistance and relapse after splenectomy, the occurrence of complications, the therapeutic strategies and the drug efficacy in splenectomy-resistant ITP. **Methods:** We retrospectively analyzed 138 adult ITP patients who had been previously diagnosed and treated at the Clinic of Hematology, Clinical Center of Serbia, and who underwent splenectomy between 1987 and 2018. **Results:** Of the 138 ITP patients, 20.3% (n=28/138) were refractory to splenectomy, 11.6% (n=16/138) relapsed and 8.7% (n=12/138) were primarily resistant. The average post-splenectomy follow-up period was 117 months (range 3-474). The average follow-up period of the patients resistant to splenectomy was 147 months (range 23-474). Of the patients refractory to splenectomy, 67.8% (n=19/28) showed a good therapeutic response: 49% (n=14/28) complete remission and 18.8% (n=5/28) partial remission. The response was usually achieved using the following drugs: romiplostim (100%), eltrombopag (75%), cyclosporine (66.67%), mycophenolate mofetil (50%), danazol (50%) and corticosteroids (40.9%). Hemorrhagic and non-hemorrhagic complications occurred in 78.6% (n=22/28) and 28.6% (n=8/28) of the patients, respectively. **Conclusion:** Splenectomy remains a very efficient therapeutic modality for the treatment of ITP patients with a high percentage of splenectomy-resistant patients achieving remission. Thrombopoietin receptor agonists have shown exceptional results so far in the treatment of refractory ITP patients.

Key Words: Immune thrombocytopenia; Idiopathic thrombocytopenic purpura; Refractory immune thrombocytopenia, Thrombopoietin receptor agonists (Source: MeSH-NLM).

Introduction

Immune thrombocytopenic purpura (ITP) is an immune-mediated acquired disease of adults and children characterized by a transient or persistent decrease of the platelet count below 100×10^9/L in the absence of evident predisposing factors, and by an increased risk of bleeding.[1-2] The incidence of primary ITP in adults is 3.3/100 000 adults per year with a prevalence of 9.5 per 100 000 adults.[1] In 2009, the International Working Group (IWG) presented standards for definitions, classification criteria, and outcome measures. The classification scheme included division by disease phase: newly diagnosed ITP (<3 months), persistent ITP (3–12 months), and chronic ITP (>12 months). Refractory ITP is defined as a disease that does not respond to or relapses after splenectomy and that requires treatment to reduce the risk of clinically significant bleeding.[1]

The clinical presentation of ITP is most often asymptomatic or with a varying bleeding tendency. The severity of bleeding frequently correlates with a low platelet count and older age. However, many patients with ITP do not experience significant bleedings despite having severe thrombocytopenia.[3-4] Mucocutaneous bleeding (epistaxis, menorrhagia, gingival and gastrointestinal bleeding) is the most common clinical manifestation of ITP. Intracranial hemorrhage is the most worrisome complication of ITP, with an incidence of 6/340 adults newly diagnosed with ITP.[5] Patients with ITP have an increased risk of thrombotic events in comparison to adults without ITP, as well as fatigue, infections, hematologic malignancies and reduced quality of life.[5]

The diagnosis of ITP is made when all other causes of thrombocytopenia are ruled out.

The therapy objectives are to achieve a safe number of platelets (often $>30\times10^9$/L), to avoid life-threatening bleeding and long-term treatment, and to sustain a normal quality of life.[1] The therapy should be tailored according to the clinical presentation, presence of additional bleeding risk factors (such as anticoagulant therapy, dialysis, surgical procedures), comorbidities, individual side effect tolerance, as well as the platelet count. Treatment should begin when the platelet count is $<30\times10^9$/L, or when bleeding symptoms present in spite of a high thrombocyte count (***Table 1***).[6-7]

Splenectomy is reserved for patients unresponsive to or intolerant to corticosteroids. By performing splenectomy, antibody-coated platelets are no longer removed *via* the spleen and spleen antiplatelet antibodies are no longer produced. Splenectomy should be postponed, if possible, for 6–12 months, considering a possible spontaneous or therapeutically induced remission.[1,6,8-9] Good therapeutic response is achieved in 60–80% of patients with ITP.[8] Even though there is a consensus regarding the short-term efficacy of splenectomy, findings on its long-term efficacy and side-effects are controversial. Particular studies show that splenectomy leads to long-term remission in 60–80% of patients, while other studies imply that all patients with ITP relapse after a sufficiently long follow-up period. In most published studies, remission is achieved in 60% of patients, with 75% of relapses recorded in the first 4 years. The response was achieved in 83% of patients who needed further

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treatment after splenectomy, which implied that splenectomy can convert a drug-resistant patient to a patient with a good response.[10] Currently, there are many therapeutic modalities for patients resistant to splenectomy. Approximately 75% of patients with refractory ITP eventually achieve remission, although it occurs slowly. Patients who do not achieve remission instead experience an extremely difficult disease course with significant morbidity and mortality rates. It is possible that newer forms of treatment, such as rituximab, thrombopoietic factors, and monoclonal antibodies, may alter the outcomes for this extremely resistant subgroup.[11]

The aim of our study was to establish the frequency of resistance and relapse after splenectomy, the occurrence of bleeding, infections and thrombotic events, the therapeutic strategies and the drug efficacy in a group of patients with splenectomy-resistant ITP.

Table 1. The Therapy of Immune Thrombocytopenia (ITP).[6]

First-line management (initial treatment)	• corticosteroids (prednisone, methylprednisolone, dexamethasone) • intravenous immunoglobulins (IVIg)
Second-line management	• splenectomy • azathioprine; cyclosporine A; vinca alkaloids; cyclophosphamide; thrombopoietin receptor agonist (TPO-RAs); mycophenolic acid; danazol; dapsone; rituximab
Third-line management (for refractory ITP)	Category A: • thrombopoietin receptor agonists (TPO-RAs)
	Category B: • combination of medications from the 1st and 2nd line management

Patients and Methods

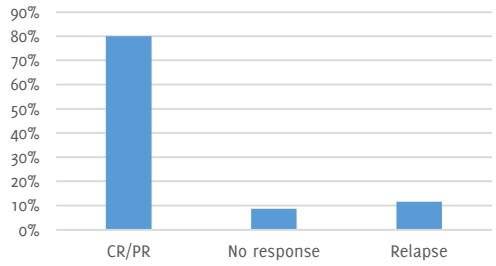
We retrospectively analyzed 138 adult patients with ITP who had been previously diagnosed and treated at the Clinic of Hematology, Clinical Center of Serbia, and who underwent splenectomy between 1987 and 2018. The following laboratory tests were run for each patient: blood tests - erythrocyte, leukocyte and platelet (PLT) counts, hemoglobin value, and leukocyte formula, hemostasis tests - fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), morphological and cytochemical analysis of the bone marrow, thyroid status, abdominal ultrasonography and platelet kinetics (in most patients). Splenectomy was indicated in cortico-resistant (PLT<30x10^9/L) or cortico-sensitive patients. In order to attain the recommended platelet count for splenectomy (PLT>50x10^9/L), patients were premedicated with corticosteroids, intravenous immunoglobulins (IVIg) and platelet transfusions. A "Complete response" (CR) is defined by the IWG as any platelet count of at least 150x10^9/L. "Partial response" (PR) is defined as any platelet count >50x10^9/L. Refractory ITP is defined as any platelet count <30x10^9/L. Relapse is defined as any platelet count <150x10^9/L in patients who previously achieved a CR or 50x10^9/L in patients who previously achieved a PR.[2] The software used for the statistical analysis was "Microsoft Office Excel 2007"

Results

In this retrospective study, we analyzed 138 patients with adult ITP who had been previously diagnosed, treated and splenectomized at the Clinic of Hematology, Clinical Center of Serbia, from 1983 to 2018. From 138 patients who were splenectomized, 28 (20.3%) were refractory to splenectomy. Of these, 16 (11.6%) relapsed and 12 (8.7%) had no response (***Figure 1***). The average follow-up period after splenectomy was 117 months (3-474). Only one patient (0.79%) was observed for less than a year. We observed 37.8% (n=52/138) of the patients for longer than 5 years, and 40% (n=55/138) for more than 10 years.

Hemorrhagic syndrome developed in 22/28 (78.6%) patients. Patients most commonly had hematomas, petechiae, and ecchymoses (61%, n=17/28), epistaxes and gingival bleeding (18%, n=5/28), menorrhagias and metrorrhagias (18%, n=5/28). There was no reported intracranial hemorrhage. Incidence and localization of bleeding are shown in ***Figure 3***. Non-hemorrhagic complications or other comorbidities were recorded in 8 (28.6%) patients: Non-Hodgkin's lymphoma (2/28, 7,1%), acute renal failure (1/28, 3.6%), systemic lupus erythematosus (1/28, 3,6%), abscesses (2/28, 7.1%) or infections (3/28, 10.7%). There were no reported death outcomes.

Figure 1. Patient Distribution Relative to Splenectomy Response.



Legend: CR = complete response. PR = partial response.

The average follow-up period of the patients resistant to splenectomy was 147 months (23-474). Most relapses occurred in the first year after splenectomy (6/28, 21.4%), while in one patient (1/28, 3.6%) relapse occurred after 18 years (***Figure 2***). Laparotomy was performed in 64% (n=18/28) of the patients, and laparoscopy was performed in 36% (n=10/28) of the patients, with no significant differences in response. Of the patients refractory to splenectomy, 67.8% (n=19/28) showed a good therapeutic response: 49% (n=14/28) complete remission and 18.8% (n=5/28) partial remission.

Figure 2. Relapse Incidence after Splenectomy.

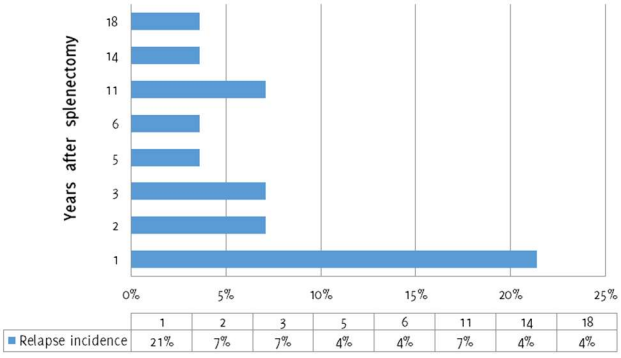
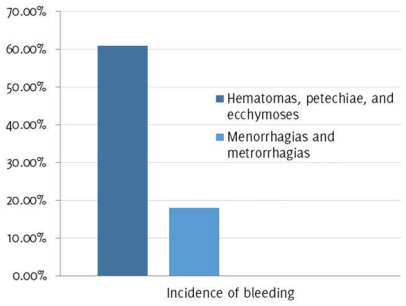


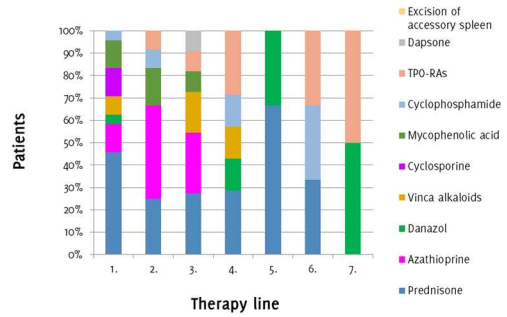
Figure 3. Incidence and Localization of Bleeding.



Out of the 28 splenectomized patients with refractory ITP, 27 patients underwent further treatment. Therapeutic lines and modalities are shown in ***Figure 4***, and the therapeutic effect is shown in ***Figure 5***. Prednisone was used in 22 patients (81.5%) and lead to a good therapeutic response (CR+PR) in 9 patients (40.9%). Romiplostim was used in 2 patients (7.4%) who achieved a good response (100%). Eltrombopag was used in 4 patients (14.81%), leading to a good

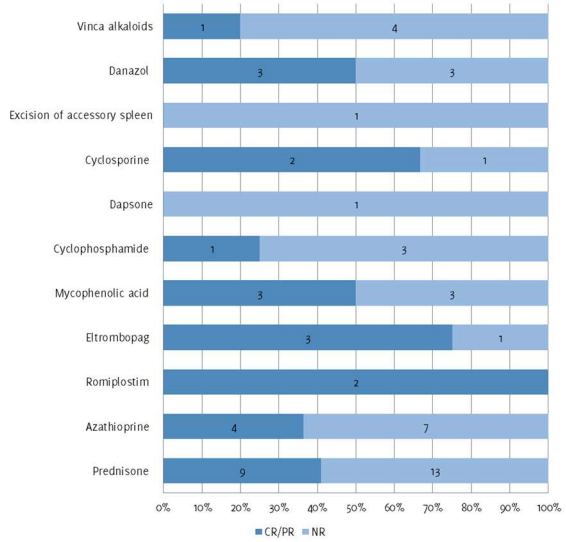
therapeutic response in 3 patients (75%). Cyclosporine was used in 3 patients (11.1%), leading to a good therapeutic response in 2 patients (66.7%). Mycophenolic acid was used in 5 patients (18.5%), leading to a good therapeutic response in 3 patients (60%). Danazol was used in 6 patients (22.2%), leading to a good therapeutic response in 3 patients (50%). Azathioprine was used in 11 patients (40.7%), leading to a good therapeutic response in 4 patients (36.4%). Cyclophosphamide was used in 4 patients (14.8%) with only one patient (25%) achieving a good therapeutic response. Dapsone was used in one patient (3.7%) without response. Excision of an accessory spleen was performed in one patient (3.7%) without effect. Vinca alkaloids were prescribed in 5 patients (18.5%), with only one patient (20%) achieving a good therapeutic response.

Figure 4. Distribution of Patients based on the Employed Therapeutic Modalities after Splenectomy.



Legend: TPO-RAs = Thrombopoietin Receptor Agonists.

Figure 5. The Effect of Therapy.



Legend: CR = complete response. PR = partial response. NR = no response.

Discussion

Our study included 138 adult patients with ITP, out of whom 20.3% (n=28/138) were refractory to splenectomy. Relapse occurred in 11.6% (n=16/138) of patients, whilst 8.7% (n=12/138) of patients had no response to splenectomy. The average follow-up period of patients resistant to splenectomy was 147 months (23-474). Most relapses occurred in the first year after splenectomy (n=6/28, 21.4%), while in one patient (3.6%) relapse occurred after 18 years. The study of Mcmillan et al., which involved 105 ITP patients refractory to splenectomy, reports a frequent occurrence of relapse (66%), most often in the first 3 months after splenectomy (45% of patients), and no response in 22% of cases after splenectomy was performed.[11] Vianelli et al., who studied 233 splenectomized patients, reports a relapse rate of 75% (after 48 months) and no response in 40% of cases.[12] In the retrospective study of Ahmed et al., involving 167 patients, relapse occurred in 30% of the cases (after 54 months) and 14% of the patients experienced no response.[13]

After splenectomy, our study reported a good therapeutic response with different therapeutic modalities in 67.8% of the patients: CR 49% and PR 18.8%, similarly to Mcmillan's study (71.4%).[11] A stable therapeutic response was achieved with the following medications: romiplostim (2/2, 100%), eltrombopag (3/4, 75%), cyclosporine (2/3, 66.67%), mycophenolic acid (3/6, 50%), danazol (3/6, 50%), prednisone (9/22, 40.9%). Also, 29.6% (8/27) of the patients had no response to therapy. Mcmillan et al. showed that a stable therapeutic response was achieved with following medications: danazol (33.9%), cyclophosphamide (25.7%), prednisone (19%), and azathioprine (15.8%); 28% of the patients did not respond to therapy. The percentage of patients resistant to all therapeutic modalities is similar in both studies.[11] However, Mcmillan's study does not take TPO-RAs into consideration, which may be the reason for the discrepancy between our studies. In the study of Saleh et al., 299 patients (115 splenectomized) were treated for 3 years with eltrombopag. Good therapeutic effect was noted in 80% (92/115) of the splenectomized patients, as well as in 50% of the multi-resistant patients (treated with more than 4 therapeutic lines). The effect was maintained for 2 years.[14] In the research of Kuter et al., 292 ITP patients (95 splenectomized) were treated with romiplostim for 5 years with a good therapeutic effect in 67% (64/95) of the splenectomized patients. The effect was maintained for 2 years also.[15] Consequently, the results of our study coincide with results of Saleh et al., as well as with the results of Kuter et al. Our study reported hemorrhagic syndromes in 22/28 (78.6%) of the patients: hematomas, petechiae, ecchymoses (61%), epistaxes and gingival bleedings (18%), menorrhagias and metrorrhagias (18%), with no intracranial hemorrhage reported. Non-hemorrhagic complications or comorbidities were seen in 8 (28.6%) of the patients: Non-Hodgkin's lymphoma 2/28 (7.1%), acute renal failure 1/28 (3.6%), systemic lupus erythematosus 1/28 (3.6%), abscesses 2/28 (7.1%) and infections 3/28 (10.7%). There were no reported death outcomes. Mcmillan et al. did not describe morbidity, but only a mortality regarding hemorrhagic events of 10% (intracranial hemorrhage 90%), malignancy and cardiovascular disease 13.9%. Other noted complications/comorbidities in Mcmillan's study were deep venous thrombosis (12.4%), systemic lupus erythematosus (2.9%), Non-Hodgkin's lymphoma (1.9%) and Hodgkin's lymphoma (2.9%).[11] The study of Saleh et al reported a lower incidence of hemorrhagic complications after the use of eltrombopag (from 56% to 11% during the next 3 years), thromboembolic events (4%) and elevation of liver enzymes (2%).[14] The study of Kuter et al, reported hemorrhagic complications in 57% of the patients: hematomas and petechiae (32%), epistaxes and gingival bleeding (41%).[15] In comparison, our study had a higher incidence of complications, but without death outcomes.

Conclusion

Splenectomy represents a very efficient therapeutic modality for patients with ITP. Patients who remained resistant after splenectomy had a higher rate of CR. In our study, 20.3% of the patients were refractory to splenectomy, out of whom 11.6% relapsed (with the highest incidence in the first year after splenectomy, 21.4%), and 8.7% were resistant to splenectomy. Our research showed that 67.8% of the patients refractory to splenectomy achieved a good therapeutic response (49% CR and 18.8% PR). A stable therapeutic response was achieved with the following medications: romiplostim (100%), eltrombopag (75%), cyclosporine (66.67%), mycophenolic acid (50%), danazol (50%), prednisone (40.9%). Thus, thrombopoietin receptor agonists exhibited the greatest success so far in treating patients with refractory ITP. The limitations of our study were a small sample of patients with a resistant form of ITP treated with thrombopoietin receptor agonists, as well as a heterogeneous follow-up period after splenectomy.

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Review

Next Generation of Advanced Non-Small Cell Lung Cancer Therapy: Targeted and Immuno-Therapies

Sze Wah Samuel Chan,[1] Elliot Smith.[1*]

Abstract

Lung cancer is one of the deadliest cancers in the world. Current clinical trials are focused on developing the next generation of therapies that target novel anti-cancer mechanisms. One approach is to prime the immune system, as the cancer has been known to suppress immune cells in the tumor microenvironment. Using immunotherapy, the immune system can be unleashed and suppress the cancer's growth. Another pathway is targeting known oncogenic genes that are important for the cancer's growth and survival. In lung cancer, the epidermal growth factor receptor and several other mutated proteins are targets of small-molecule inhibitors that have been shown to drastically improve patient survival and quality of life. Discussed in this review are broad highlights of the different immunotherapies and small molecule targeted therapies that have been studied in the latest clinical trials for lung cancer.

Key Words: Lung neoplasms; Non-Small-Cell Lung Carcinoma; immunotherapy; EGFR tyrosine kinase inhibitor; Molecular targeted therapy (Source: MeSH-NLM).

Introduction

Globally, cancer is increasingly one of the greatest health burdens, with an estimated 20% probability of being diagnosed with cancer before age 75 and a 10% chance of dying from it.[1] According to GLOBOCAN in 2018, lung cancer had the highest incidence, with nearly 2 million cases and the highest mortality at almost 1.7 million deaths. In the United States, similar trends were observed where 234,030 lung cancer cases were diagnosed, accounting for 25% of cancer deaths.[1]

Lung cancer is histologically divided into small cell lung carcinoma (~15% of lung cancers) and non-small cell lung carcinoma (NSCLC) (85% of lung cancers).[2] NSCLC is further subdivided into squamous, adenocarcinoma, and large cell carcinoma. These histopathological divisions help decide further investigations and management. Many of the development of the next generation of medical therapies has focused on stage IV, metastatic lung cancers and will be the focus of this review. Until recently, the first-line chemotherapy regimen for metastatic NSCLC is chemotherapy with two drugs, one of which is a platinum agent (known as platinum-doublet chemotherapy); where appropriate, maintenance chemotherapy with a single agent may take place after the end of 4-6 rounds of platinum-doublet chemotherapy.[3,4] Few effective treatments are available after disease progression and mainly involve single-agent chemotherapy such as docetaxel.[3]

For treatment-naïve patients, identification of who benefits from immunotherapy is contingent on several main factors: lack of a driver mutation (e.g. *EGFR* or *ALK* as immunotherapies are likely less effective than targeted therapy in this population) and biomarker status.[5] PD-L1/PD-1 is the most commonly used biomarker status for lung cancer as the approved therapies all target this immune blockade.[6] The PD-L1/PD-1 axis is a mechanism by which cancer cells induce T cell anergy and exhaustion, and avoid anti-tumor immune cells. PD-L1/PD-1 antibodies block this interaction and allow the immune system to recognize and then suppress the cancer cells.[7] The goal of this review is to provide a broad yet comprehensive overview of the different next-generation cancer therapies in NSCLC and provide a summary of the evidence rationalizing each therapy. The following section will focus on immune modulators that re-educate the immune system to attack the cancer cells based on phase III clinical trials data. The second section will discuss targeted therapies for lung cancers with driver mutations. Finally, the last section will propose an algorithm for treatment decision making based on the current evidence.

The adverse events and clinical trials described in this review use the Common Terminology for Adverse Events (CTCAE) terminology system which aims to unify the nomenclature in assessing the severity of each adverse event. Grade 1 represents mild adverse events and intervention is not needed to grade 4 where there are life-threatening consequences requiring immediate intervention.[8,9] Grade 5 is reserved for cases where the adverse event led to death. An example of a grade 1 event in vomiting means it requires no intervention a grade 2 event is determined by the need for outpatient IV hydration, a grade 3 event requires hospitalization or tube-feeding and grade 4 carries life-threatening consequences. ***Table 1*** has examples of different common adverse events reported in oncology clinical trials and their grading definitions.

Immunotherapy with Monotherapy

Nivolumab as second-line monotherapy for metastatic NSCLC

Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody and has been approved for second-line therapy regardless of PD-L1 status. In the CheckMate 017 and CheckMate 057 trials, nivolumab was compared to docetaxel for patients with disease progression after first-line therapy for both squamous and non-squamous histology. Nivolumab lowered the risk of death compared to docetaxel in squamous (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.44 to 0.79, P <0.001, minimum follow-up was 11 months) and non-squamous (HR 0.73, 95% CI 0.59 to 0.89, P = 0.002, minimum follow-up was 13.2 months) cell types.[10,11] CheckMate 026 evaluated nivolumab monotherapy in the first line, which showed non-significant differences in overall and progression-free survival.[12] However, the nivolumab group reported 18% grade 3-4 adverse events as opposed to 51% in the standard chemotherapy group, mainly with more fatigue and hematological

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adverse events such as neutropenia, thrombocytopenia, and anemia in the chemotherapy group.[12]

Atezolizumab monotherapy as second-line therapy for metastatic NSCLC
Atezolizumab is a humanized monoclonal IgG1 PD-L1 antagonist. The OAK trial demonstrated in second-line therapy that atezolizumab improved overall survival (OS) (HR 0.73, 95% CI 0.62 to 0.87, P = 0.0003) compared to docetaxel with a median follow-up of 21 months.[13] Similar to nivolumab, the difference was significant regardless of PD-L1 tumor expression. Fewer grade 3-4 adverse events were observed with immunotherapy (15% vs. 43%), where chemotherapy had more hematological adverse events such as anemia, neutropenia, and febrile neutropenia.[13]

Table 1. Common Terminology for Adverse Events (CTCAE) v5.0 examples.

Grade 1	Grade 2	Grade 3	Grade 4
Rash – Maculo-papular			
<10% Body surface area (BSA)	10-30% BSA, limiting activities of daily living, or >30% BSA but no or mild symptoms of burning, pruritis, or tightness	>30% BSA with moderate to severe symptoms; limiting self-care ADLs	Grade not available
Diarrhea			
<4 stools per day over baseline, mile increase in ostomy output	Increase of 4-6 stools per day over baseline, a moderate increase in ostomy output, limits instrumental ADL	Increase of >7 stools per day over baseline, hospitalization is indicated, severe increase in ostomy output, limiting self-care ADLs	Life-threatening, urgent intervention required
Neutropenia			
<LLN including 1500/m^3, 1.5 x 10^9 / L	<1500 – 1000/mm^3, <1.5 – 1.0 x 10^9 / L	<1000 – 500/mm^3, <1.0 – 0.5 x 10^9 / L	<500/mm^3, <0.5 x 10^9 / L
Anemia			
Hemoglobin < LLN, including <10.0 g/dL, <6.2 mmol/L, <100 g/L	Hemoglobin <10.0-8.0 g/dL, <6.2-4.9 mmol/L, <100-80 g/L	Hemoglobin <8.0 g/dL, <4.9 mmol/L, <80 g/L; transfusion is indicated	Life-threatening, urgent intervention required

All definitions were extracted directly from the Common Terminology for Adverse Events (CTCAE) v5.0, developed by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) published in November 2017, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Each adverse event is graded according to severity, where grade 1 is the least severe with no intervention to grade 4, which requires urgent intervention and grade 5 is reserved for deaths related to the adverse event. Self-care activities of daily living (ADL), according to CTCAE, refer to bathing, dressing, undressing, feeding self, using the toilet, taking medication and not bedridden. Instrumental ADLs refer to preparing meals, shopping for groceries or clothing, using the telephone or managing money.

Pembrolizumab as monotherapy in first- or second-line metastatic NSCLC
Pembrolizumab, a humanized monoclonal IgG4 PD-1 receptor antagonist, was first tested in 2016 where the Keynote 10 trial compared pembrolizumab vs. docetaxel in the second-line, which showed superior overall survival (HR 0.61, 95% CI 0.49 to 0.75, P <0·0001, median follow-up was 13.1 months) driven mainly by patients with PD-L1 immunohistochemical staining of at least 50% (OS HR 0.50, 95% CI 0.36-0.70,P <0.0001) for which it was mainly powered to detect.[14] In the same year, Keynote 24, with a median follow-up of 11.2 months, confirmed the benefit in the . 50% PD-L1 setting now in the first-line setting. Pembrolizumab treatment induced longer overall survival (HR 0.60, 95% CI 0.41 to 0.89, P = 0.005) compared to platinum-based doublet therapy.[15] Furthermore, grade 3-5 adverse events were less in the immunotherapy group (26.6% vs. 53.3%), which were similar to nivolumab and atezolizumab, where the chemotherapy group had more hematological suppression. One key point from the trial was that immunotherapies demonstrated more immune-related adverse events such as more severe skin reactions, pneumonitis and colitis.[15] Keynote 42 was a follow-up trial that indicated that tumors with . PD-L1 1% treated with pembrolizumab showed superior overall survival (HR 0.81, 95% CI 0·71 to 0·93, P=0·0018) at a median follow-up of 12.8 months with a similar side effect profile demonstrated in the previous trials.[16]

Sequential Durvalumab Monotherapy after Chemoradiation in Unresectable Stage III NSCLC
Durvalumab is an IgG1 kappa monoclonal antibody against PD-L1 that was investigated in the PACIFIC trial in stage III surgically unresectable NSCLC without disease progression after . 2 cycles of platinum-based chemoradiotherapy compared to placebo. Durvalumab-treated patients demonstrated superior overall survival (HR 0.68, 99.73% CI 0.47 to 0.997, P = 0.0025, median follow-up 25.2 months). For grade 3 or 4 adverse events due to any cause, 30.5% of the durvalumab treatment group reported these events compared to 26.1% in the placebo group. Most of the grade 3-4 event differences were due to increased pneumonia and radiation pneumonitis in the immunotherapy group.[17,18] Durvalumab is unique as the only approved consolidation immunotherapy single agent for NSCLC.

Immunotherapy Combination Therapies

Immunotherapy with Chemotherapy for first-line metastatic NSCLC
The latest clinical trials have expanded beyond the monotherapy realm to investigate more effective front-line therapies. One strategy is to combine chemotherapy and immunotherapy, and there is evidence to suggest they can work synergistically in melanoma trials.[19,20] In the first-line setting, Keynote 189 compared standard platinum-based chemotherapy ± pembrolizumab in non-squamous NSCLC. The immunotherapy with chemotherapy group demonstrated better overall survival (HR 0.49, 95% CI 0.38 to 0.64, P <0.001) and the trend was preserved regardless of PD-L1 expression, where median follow-up was 10.5 months.[21] Adverse events of grade 3 or higher were found in 67.2% for the combination group compared to 65.8% for the chemotherapy group. The main difference in grade 3 or higher events in the combination group was more febrile neutropenia.[21] Keynote 407 (median follow-up of 7.8 months), which studied carboplatin + paclitaxel ± pembrolizumab in squamous NSCLC, showed similar improvements for the combination group (HR 0.56, 95% CI 0.45 to 0.70, P <0.001), with similar number of grade 3 or higher adverse events (69.8% vs. 68.2%) with more pneumonitis and autoimmune hepatitis in the combination group.[22]

One of the CheckMate 227 secondary goals compared first-line platinum-doublet chemotherapy ± nivolumab in the <1% PD-L1 population, which showed improved OS compared to chemotherapy alone (HR 0.78, 95% CI 0.60 to 1.02, P = 0.035, minimum follow-up was 29.3 months).[23] IMpower 131 was a trial comparing first-line carboplatin and nab-paclitaxel ± atezolizumab in squamous NSCLC, where there was improved progression-free survival (HR 0.715, 95% CI, 0.603 to 0.848; P = 0.0001) but no differences in overall survival (P = 0.16).[24,25] The IMpower130 was a similar trial for non-squamous histological subtypes and reported at the European Society of Medical Oncology (ESMO) 2018 that atezolizumab + carboplatin and nab-paclitaxel had superior OS (HR 0.79, 95% CI 0.64 to 0.98, P = 0.033) and PFS (HR 0.64, 95% CI 0.54 to 0.77; P <0.0001) compared to carboplatin and nab-paclitaxel alone.[26]

Dual Immunotherapy
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another target of immunotherapy blockade, which combined with PD-L1 blockade, has demonstrated improvement in metastatic melanoma.[27] The rationale is to target different T-cell activation pathways to induce a more robust tumor response. In CheckMate 227, another secondary goal was to compare nivolumab and ipilimumab treatment with nivolumab monotherapy in PD-L1 .1%. This comparison showed trends towards benefit for the PD-L1 .1% population (HR 0.90, 95% CI 0.76-1.07) and PD-L1 .50% (HR 0.87, 95% CI 0.68-1.12), but there were more grade 3-4 events in the dual immunotherapy group compared to the monotherapy group (35.5% vs. 19.4%). More specifically it included more rash, pruritis, diarrhea and adverse events with suspected

immune etiology affecting the pulmonary, gastrointestinal, skin and endocrine systems.[23]

The MYSTIC trial investigated patients with PD-L1 . 25% with a durvalumab and tremelimumab (anti-CTLA-4) combination in the first-line setting. Unfortunately, the immunotherapy combo was unsuccessful in showing PFS or OS improvements over chemotherapy but had less grade 3-4 treatment adverse event profiles (22.1% in combination vs. 33.8% in chemotherapy).[28] The NEPTUNE trial (durvalumab + tremelimumab vs. chemotherapy) includes ALK and EGFR patients, and is set to reveal results soon.[29]

Immune-Related Adverse Events in Immunotherapies

Immunotherapies are not harmless despite a safer side effect profile compared to chemotherapy. Physicians caring for patients undergoing immunotherapies must be keenly aware of the unique and dangerous side effects compared to chemotherapy patients (***Table 2***). The unique danger in immune-oncology is an overstimulation of the immune system, which can induce an autoimmune condition. The most common immune-related adverse event (irAE) is dermatological rash/pruritis, with an estimated prevalence of 30% in nivolumab or pembrolizumab patients.[30] Grade 1 toxicities do not necessarily necessitate stopping treatment and can be treated with topical steroids or symptomatic systemic treatment. Serious irAEs that require clinicians to be vigilant about are colitis, pneumonitis, endocrinopathies, neurological syndromes, and cardiovascular compromise (***Table 2***). For all toxicities, grade 1 events should be monitored for progression while grade 2 and above may necessitate withholding treatment or permanently discontinuing treatment and immunosuppressive treatment depending on the specific irAE.[31] Specific irAE risk stratification and treatment strategies are summarized in the American Society of Clinical Oncology Clinical Practice Guidelines and the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group.[30,31] Due to the potential for high morbidity and mortality associated with pneumonitis, colitis, neurological syndromes and cardiovascular toxicity, these warrant consideration of immediate discontinuation and referral to additional specialists. The mainstay of systemic treatment for grade 2 and above adverse events is corticosteroids, such as prednisone at 0.5-2 mg/kg/day depending on the grade of the toxicity, along with appropriate prophylaxis therapies.[31] If refractory, immunomodulatory therapies could serve as the next step; for instance, infliximab has been reported in the use of refractory colitis.[31–33]

Table 2. Potential Adverse Events for Immunotherapies for Oncology Treatment.

Common Adverse Events	Uncommon Adverse Events	Indications to Stop Treatment
Maculopapular rash	Renal involvement	Pneumonitis
Pruritis	Neurological syndromes	Colitis
Fatigue	Exocrine pancreas involvement	Neurological syndromes
Infusion-related reactions	Cardiovascular toxicity	Potentially for cardiovascular toxicity
Diarrhea	Hematological related	Grade 2-4, reassessment for restarting treatment after symptom resolution
Hepatitis	Ophthalmological inflammation	
Hypothyroidism	Myositis	
Hypophysitis	Pneumonitis	
Arthralgia	Colitis	

Legend: The table was adapted from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group, reference 31: Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):1–28.

Targeted Agents for NSCLC Patients Carrying Actionable Mutations

Epidermal Growth Factor Receptor

Epidermal Growth Factor Receptor (EGFR), a receptor tyrosine kinase responsible for cell proliferation and survival, is one of the most commonly identified driver mutations in NSCLC. The prevalence of EGFR aberrations in NSCLC varies drastically based on geographical distribution, varying from 10% in North American and Western European cases to 30% in East Asian cases.[34,35] Studies have reported a higher prevalence in females and non-smokers.[34,36] From a histologic perspective, it is most frequently seen in adenocarcinomas compared to any other NSCLC histologic subtype, with a rate of 30% compared to 2% of another diagnosis.[35,36] The most common of these intracellular TK mutations include the L858R mutation in exon 21, or short in-frame deletions in exon 19, which both contribute 90% of the aberrations in this domain.

Gefitinib

Gefitinib is an EGFR inhibitor that competitively inhibits ATP. It is approved for first-line therapy of EGFR+ metastatic NSCLC. The IRESSA Pan-Asian Study (IPASS) was a seminal phase III trial demonstrating remarkable efficacy. In the EGFR+ subgroup, gefitinib was superior to carboplatin-paclitaxel, with an improvement in PFS (HR 0.48, 95% CI 0.36-0.64, P<0.001) and overall survival (HR 0.78, 95% CI, 0.50-1.20).[37] Median follow-up in this study was 527 days. In the EGFR- subset, patients treated with the gefitinib showed a worse PFS (HR 2.85, 95% CI 2.05-3.98, P<0.001).[37] From a toxicity perspective, in IPASS, gefitinib was associated with fewer grade 3-4 adverse events (28.7% vs 61.0%).[37] The most common toxicities for gefitinib included rash, diarrhea and mucositis, while neurotoxicities and hematologic toxicities were significantly lower compared to chemotherapy.[37]

Erlotinib

Erlotinib, like gefitinib, is an EGFR inhibitor and has a similar mechanism to gefitinib. It is approved for locally advanced or metastatic EGFR+ NSCLC. In the EURTAC trial, erlotinib was compared to cisplatin-docetaxel or gemcitabine in a first-line setting and found to have a significantly improved PFS (HR 0.16, 95% CI 0.10-0.26, P<0.0001).[38] The median follow-up in this study was 18.9 months in the erlotinib group. Other phase III trials using erlotinib in the first-line setting compared against platinum-based combination chemotherapy regimens, such as OPTIMAL and ENSURE, have shown similar results with erlotinib achieving a significant improvement in PFS.[39,40] Erlotinib has also been studied as a combination therapy through the FASTACT trial where erlotinib intercalated with gemcitabine and platinum therapy versus chemotherapy with placebo was compared in patients with NSCLC. The erlotinib combination, in EGFR+ mutated NSCLC, showed a significant increase in PFS (HR 0.25, 95% CI 0.16-0.39, P<0.0001).[41] Erlotinib intercalated chemotherapy also showed significant improvements in overall survival (HR 0·48, 95% CI 0.27–0.84, P = 0·0092).[41] Median follow-up in the erlotinib plus chemotherapy was 28.2 months. In the EURTAC trial, erlotinib had fewer grade 3-4 adverse events than chemotherapy (45% vs 65%). Rash and elevated aminotransferase concentrations were the most frequent adverse events in the erlotinib group compared to neutropenia and anemia being the most frequent adverse events in the chemotherapy group.[38]

Afatinib

Afatinib is a second-generation EGFR tyrosine kinase inhibitor (TKI) and exhibits its effect by irreversibly binding to the kinase domain in all erbB family tyrosine kinases. LUX-LUNG-1 was a phase IIB/III trial that studied afatinib versus placebo in NSCLC patients who have previously received chemotherapy and have failed on a previous EGFR TKI. While there was no significant difference in OS, PFS was improved (HR 0.38, 95% CI 0.31–0.48, P<0·0001) with afatinib, and these patients were followed for an estimated two years.[42] In addition, in patients who previously developed resistance, PFS was significantly improved by

afatinib treatment, which supports its role as a treatment-following resistance development in first-line EGFR TKIs. Adverse events were similar between afatinib and chemotherapy, where the most frequently encountered events include rash, diarrhea and mucositis. In LUX-LUNG-8, afatinib showed improved PFS and OS compared to erlotinib.[43]

Osimertinib

Osimertinib is a third-generation EGFR TKI and, similar to afatinib, acts by binding irreversibly to the EGFR receptor. Intriguingly, this drug shows a pharmacological effect in patients with sensitizing mutations such as exon 19 deletion or exon 21 L858R as well as patients with the exon 21 T790M mutation, typically conferring resistance to EGFR TKIs. In the AURA3 trial, osimertinib was compared to platinum-pemetrexed in patients who had previously failed on first-line EGFR TKI. Osimertinib showed superior progression-free survival (HR 0.30, 95% CI 0.23-0.41, P<0.001) and fewer grade 3-4 adverse events than chemotherapy (23% vs 47%). Median follow-up for all patients in this study was 8.3 months. The most common side effects within the osimertinib group were paronychia, rash and diarrhea compared to anemia and GI-related adverse events, which were the most common toxicities seen in the chemotherapy group.[44] The FLAURA trial showed osimertinib provided a significant improvement in progression-free survival versus gefitinib or erlotinib in the first-line setting (HR 0.46, 95% CI, 0.37-0.57, P<0.001). Median follow-up for the osimertinib group was 15 months and 9.7 months in the standard EGFR-TKI group.[45] The drug has recently been approved for first-line treatment of metastatic EGFR+ NSCLC.

NSCLC patients carrying Anaplastic Lymphoma Kinase translocations

Anaplastic Lymphoma Kinase (ALK) is a receptor tyrosine kinase normally found on chromosome 2. Under normal circumstances, it is expressed at low levels in the small intestines, neural tissue, male testes and has a role in neural development.[46] It is found mutated and fuses with other partner genes in approximately 1-5% of NSCLC cases and, similarly to EGFR, is found in predominantly non-smokers and adenocarcinoma histology.[47]

Crizotinib

Crizotinib is a TKI that inhibits ALK. PROFILE-1007 was a phase III study comparing crizotinib to chemotherapy in ALK-positive NSCLC following failure on the first-line, platinum-based doublet chemotherapy. Crizotinib showed a significant PFS improvement to chemotherapy (HR 0.49, 95% CI 0.37-0.64, P<0.001).[48] The median follow-up in the crizotinib group was 12.2 months. Crizotinib also showed a more tolerable toxicity profile compared to chemotherapy, where the most common adverse events were visual disorder, GI-related symptoms, and elevated aminotransferase levels. PROFILE 1014 studied crizotinib in chemotherapy-naïve ALK-positive NSCLC and found PFS to be significantly improved in the crizotinib group compared to chemotherapy (HR 0.45; 95% CI 0.35-0.60, P<0.001, median follow-up of 17.4 months).[49]

Ceritinib

Ceritinib is a next-generation TKI approved for ALK mutated NSCLC. As a more potent inhibitor, ceritinib has displayed activity in certain cases that have developed resistance and progressive disease on crizotinib. The ASCEND-1 trial studied ceritinib in patients who were previously treated and progressed on crizotinib, and found that 56% responded (95% CI, 49-65%), and the median PFS was 6.9 months (95% CI, 5.6-8.7 months). Median follow-up was 11.1 months. The most common adverse events included GI-related symptoms, primarily grade 1 or 2 in severity, including elevated aminotransferase concentrations.[50]

Alectinib

Alectinib is another next-generation ALK-targeted TKI that has shown activity against crizotinib-resistant NSCLC. Of particular interest, this drug is not a P-Glycoprotein substrate and therefore, can achieve significantly improved intracranial concentrations for targeting CNS metastases. Alectinib was then compared to crizotinib in the first-line setting in two clinical trials, J-ALEX and ALEX, with improved PFS for alectinib and 12-month event-free survival rate, which was 68.4% vs. 48.7% (95% CI, 61-76% vs. 40-57%).[51] Furthermore, CNS progression occurred in 12% of the alectinib group compared to 45% of the crizotinib group. Median follow-up in this study was 17.6 months in the crizotinib group and 18.6 months in the alectinib group. Overall, alectinib had more adverse events than crizotinib; however, when comparing based on severity, alectinib had marginally fewer grade 3-5 adverse events (41% vs 50%). The most common adverse events in the alectinib group include GI-related symptoms, elevated aminotransferase concentrations, peripheral edema and myalgia. Most impressively, the ALEX trial found a PFS of over 34 months compared to 12 months in patients treated with crizotinib, setting the stage for a change in first-line recommendations to alectinib soon.[51]

Brigatinib

Brigatinib is an additional next-generation ALK TKI that has shown activity in this NSCLC subtype. In the ALTA-1L phase III trial, brigatinib was compared to crizotinib in a front-line setting. Median follow-up in this trial was 11 months in the brigatinib group and 9.3 months in the crizotinib group. Brigatinib was found to be more efficacious for PFS (HR 0.49, 95% CI 0.33-0.74, P<0.001).[52] In addition, brigatinib was found to show increased activity against CNS lesions with an observed response rate of 78% (95% CI, 52-94%) compared to 29% (95% CI, 11-52%) in the crizotinib group.[52] The brigatinib group had a higher frequency of grade 3-5 adverse events, occurring in 61% of patients compared to 55% of the crizotinib group, the most common of which were elevated creatine kinase, elevated lipase levels and hypertension.[52]

Treatment Algorithm for Advanced NSCLC

The treatment of patients with metastatic or unresectable NSCLC is rapidly evolving and increasingly complex based on the most available data. The immunotherapy summary is adapted from the expert opinion provided by the Society for Immunotherapy of Cancer 2018 NSCLC consensus statement as well as the compilation of the targeted therapy trials highlighted above (Figure 1).[53]

With the diagnosis of advanced NSCLC, standard staging should first be conducted if not already completed. Following that, driver mutation analysis, histological subtype and PD-L1 expression are some of the most basic molecular profiling to decide on initial treatment decisions.

For patients with non-squamous histology and an actionable driver mutation, TKI therapy would be initiated first in almost all cases. For EGFR positive patients, afatinib, erlotinib, gefitinib and osimertinib may be used in first-line with osimertinib used in treatment-resistant cases. For ALK-fusion tumors, crizotinib is considered first-line with ceritinib and alectinib following progression; however, this is likely to change soon given the superiority of alectinib in both efficacy and toxicity profiles in the first-line setting because of the ALEX trial results. Also, upcoming trial data of lorlatinib, a fifth ALK inhibitor, has some preliminary evidence of efficacy in patients who have failed multiple other ALK inhibitors; however, phase III trial data is not yet available.[54]

For tumors carrying ROS1 fusions, there is evidence that crizotinib and lorlatinib are effective; entrectinib is another drug that is showing promise.[55,56] For BRAF-mutated tumors, dabrafenib and trametinib can be considered.

For patients who have failed targeted therapy, platinum doublet therapy should be considered as second-line therapy due to previous poor efficacy of immunotherapy in this subpopulation.[53] Third-line would include immunotherapy monotherapy, including atezolizumab, nivolumab or pembrolizumab. Patients with no identifiable, actionable driver mutation have the choice for pembrolizumab/immunotherapy alone or a combination for first-line therapy. While Checkmate 227 showed some initial promising data for dual-immunotherapy vs

monotherapy, it was not powered enough to detect a meaningful difference, and there were some initial concerns of immune-related adverse events. For patients with PD-L1 < 50%, there is evidence for pembrolizumab with chemotherapy for both squamous (carboplatin + nab-paclitaxel or paclitaxel) and non-squamous cell histology (platinum + pemetrexed). For PD-L1 . 50% non-squamous cell, there is benefit from either pembrolizumab monotherapy or pembrolizumab + chemotherapy that is dependent on symptomology and how fast the cancer is progressing. For PD-L1 . 50% in squamous cells, there are similar choices but less strong evidence for combination therapy. Pending the peer-reviewed published results of IMpower 130, atezolizumab + carboplatin and nab-paclitaxel may be an alternative option for squamous cell carcinomas.

For patients who progress on immunotherapy, the second-line would include either pemetrexed (non-squamous) or docetaxel (squamous) based on standard second-line chemotherapy regiments. Furthermore, with patients with isolated sites of progression or "oligoprogression," there is a consideration for local therapy, but the management is not within the scope of this review.

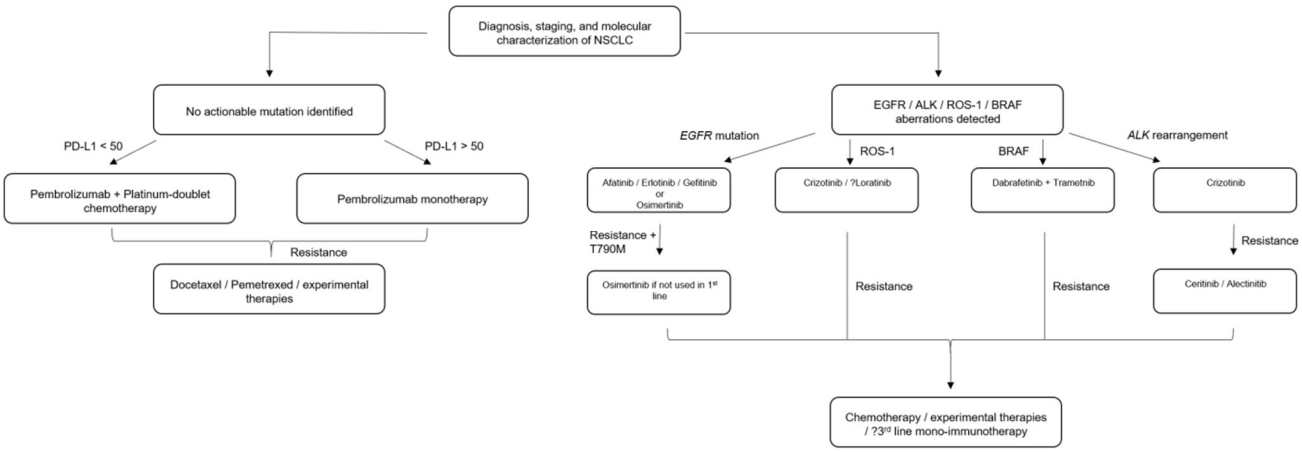
Conclusion

In summary, immunotherapies have transformed metastatic lung cancer care by providing more durable responses and more effective responses compared to traditional chemotherapy. There is no doubt about the clinical benefit of immunotherapies; however, the current question is identifying the patients who would benefit. Only 40-50% of PD-L1 positive patients clinically benefit from immunotherapy, while 15% of PD-L1 negative patients also benefit.[57] This highlights the complexity of the mechanism of these immunomodulatory drugs that are not explained fully by PD-L1 expression. Tumor mutational burden, cytotoxic T cell infiltration, immune gene signatures and immune compositive biomarkers are emerging biomarkers.[58] For targeted therapies, the race between drug targets and resistance will continue, and novel strategies for identifying resistance and combination therapy will be the key to future success in controlling these oncogene-addicted cancers.

Given the substantial survival benefit with minimal side effect profile of targeted therapies, there should be a greater awareness in the medical education community to understand that even poor functional status patients with actionable mutations can benefit from these small molecule inhibitors. Furthermore, with the paradigm shift of immunotherapies in oncology where the goal is stimulation of the immune system, rather than immunosuppression as more classically taught with immune modulators, there should be greater education in learning about these mechanisms and immune-related adverse events.

One additional consideration for this new generation of therapies is the cost to the patient and the healthcare system. There are some studies that suggest that first-line pembrolizumab and consolidation durvalumab are cost-effective with a similar conclusion for EGFR+ and ALK translocation directed therapies in NSCLC.[59–65] Future studies will help identify patients who can most benefit from these next-generation therapies and help minimize toxicities and undue financial burden.

Figure 1. Treatment Algorithm for Advanced NSCLC.



Legend: The treatment of patients with advanced NSCLC is detailed here in the first-and second-line setting. Patients with no identifiable driver mutations follow along the treatment course on the left, while patients with EGFR/ALK/BRAF/ROS1 molecular alterations follow the right side. Patients with NSCLCs that carry BRAF and NTRK molecular alterations were excluded from this algorithm as there is not enough evidence to suggest a straightforward treatment path and will be up to the discretion of the treating physician based on evidence discussed above. All treatment decisions should be tailored to a patient's specific performance status, biomarkers, prior treatments and the physician's clinical judgement. Parts of the figures were adapted from the Society of Immunotherapy, see reference 53, Herbst RS, Davies MJ, Neal JW, Sagorsky S, Gandhi L, Antonia SJ, et al. and The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). J Immunother Cancer. 2018;6(1):1–15), while the targeted therapy part was adapted from the studies in this paper.

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Case Report

Polymyositis as a Rare Musculoskeletal Manifestation of Chronic Graft-Versus-Host Disease: A Case Report of a 33-Year-Old Patient

David Ben-Nun.[1]

Abstract

Background: Musculoskeletal manifestations of chronic Graft-Versus-Host Disease (GVHD) are rare and unfamiliar to most clinicians. Here we discuss the pathophysiology of chronic GVHD, current treatments and direction of research for improved therapy and prophylaxis and focus on the common and less common musculoskeletal complications of this unfortunately prevalent and burdensome disease. **The Case:** This is a case report of a 33-year-old male with a past medical history of Acute Myeloid Leukemia (AML) who presented with a 1-month history of generalized, proximal weakness and was found to have polymyositis secondary to chronic GVHD. Elicitation of further history showed that the patient had had multiple manifestations of both acute and chronic graft-versus-host disease in the two years following hematopoietic stem cell transplantation (HSCT). **Conclusion:** It is important for clinicians to be familiar with polymyositis secondary to chronic GHVD, which may appear in patients more than 100 days following allogenic HSCT and typically presents as diffuse, generalized myopathy with preserved sensation and elevated CPK and aldolase. The current mainstay of treatment is glucocorticoids with or without a calcineurin inhibitor, however due to the side effects associated with long term treatment, more effective prophylactic and therapeutic treatments are needed to address this and other manifestations of chronic GVHD.

Key Words: Polymyositis; Graft-Versus-Host Disease; Muscular Diseases; Acute Myeloid Leukemia; Hematopoietic Stem Cell Transplantation (Source: MeSH-NLM).

Introduction

Graft-Versus-Host Disease (GVHD) is a pathological process that occurs when immune cells from a donor graft recognize host antigens as foreign and trigger an immune response. GVHD is the most common life-threatening complication of allogenic hematopoietic stem cell transplantation (HSCT) and is classified into acute and chronic based on the length of time after which the immune response occurs following transplantation.[1] Acute GVHD is considered any manifestation of graft T cell immune activation within the first 100 days following HSCT.[2] Typical signs and symptoms of acute GVHD include a maculopapular rash, hyperbilirubinemia with jaundice, nausea and vomiting, anorexia, and watery or bloody diarrhea with crampy abdominal pain.[3] By some estimates, incidence of acute GVHD may be as low as 9% or up to 50% of patients who undergo HSCT from Human Leukocyte Antigen (HLA)-matched sibling donors, which indicates that it is a significant medical problem especially given the fact that HSCT is a relatively common procedure.[4–6] Between the years 2013-2017, the Center for International Blood and Marrow Transplant Research reported that 106,112 HSCT procedures were carried out in the United States. Out of that total, approximately 43,962 were allogeneic transplants, which is an average of 8,792 allogeneic HSCTs annually.[7]

Chronic GVHD was first described in 1978 and has been defined as any alloimmunity that results in clinical manifestations that occur more than 100 days post HSCT.(2) Chronic GVHD occurs in 30 to 70% of patients who have undergone allogeneic HSCT of nonmanipulated donor grafts and have received standard prophylaxis with a calcineurin inhibitor and an antimetabolite.(1) Chronic GVHD can have protean manifestations that range from fibrotic skin disease resembling systemic sclerosis, bronchiolitis, salivary and lacrimal gland disease, and eosinophilic fasciitis.[8]

The pathophysiology of chronic GVHD is believed to involve three phases: early inflammation and tissue injury, chronic inflammation and dysregulated immunity, and aberrant tissue repair often accompanied by fibrosis.(9) In the first phase, there is translocation of bacteria and fungi across epithelial tight junctions, which are believed to be made more porous as a result of tissue damage that may occur following cytotoxic cell conditioning with chemotherapy or radiotherapy during the process of HSCT. This porosity leads to the release of immunogenic molecules that are not normally found in the extracellular space, which triggers clonal expansion of B cells and differentiation of T cells into type 1, type 2, and type 17 helper T-cells. This expansion of T cells causes a concomitant increase in the amount of auto-reactive T cells that escape immune regulation both in the thymus and in the periphery. Autoreactive T cells, along with toxic effects of the conditioning regimen, prophylaxis with calcineurin inhibitors, and immunoglobulin deposition lead to further thymic injury which further degrades the immune system's ability to filter out autoreactive immune cells in the thymus. In the final phase, activated macrophages secrete fibrotic growth factors such as Transforming Growth Factor Beta (TGF-β) and Platelet-Derived Growth Factor (PDGF), which stimulate fibroblasts to lay down extracellular collagen and causes widespread fibrosis and sclerosis in various organs.[1]

In 2005, the National Institutes of Health (NIH) compiled a formal set of guidelines regarding diagnosis of chronic GVHD, which were updated in 2014, that stipulate that the diagnosis of chronic GVHD requires "at least 1 diagnostic manifestation of chronic GVHD or at least 1 distinctive

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manifestation, with the diagnosis confirmed by pertinent biopsy, laboratory tests, or radiology in the same or another organ" along with distinction from acute GVHD and exclusion of other possible causes.[4] The mainstay of treatment of chronic GVHD requiring systemic treatment is and has been glucocorticoids, along with a calcineurin inhibitor. If patients require additional therapy following the prolonged use of glucocorticoids, secondary agents including rituximab, cyclophosphamide, imatinib, mycophenolate mofetil, IL-2, extracorporeal phonophoresis, methotrexate, bortezomib and as well as other novel immunosuppressive treatments are used.[1,10]

Musculoskeletal manifestations that result from chronic GVHD are uncommon and likely to be missed by many clinicians who are unaware of this entity. The goal of reporting on the case below is to emphasize the importance of being aware of the presentation, diagnostic guidelines and recommended treatment of polymyositis secondary to chronic GVHD in patients who have undergone HSCT.

The Case

Here we report on the case of a 33-year-old male living in central Israel with a past medical history of Acute Myeloid Leukemia (AML) diagnosed two years prior who presented to his local hospital with a 1-month history of generalized weakness that was more pronounced in the lower body. The patient's chief complaint was that he was having difficulty accomplishing tasks of daily living such as lifting items around the house, getting out of bed, preparing food and driving. He had initially gone to see a neurologist in his community, who noted that he had profound upper and lower body weakness and referred him to the local hospital. The patient stated that the weakness had begun to progress more rapidly in the 10 days leading up to his presentation and that he now needed to use crutches in order to walk. He reported no sensory deficits or urinary incontinence. He also denied a family history of neurological or musculoskeletal disease, significant history of substance abuse, recent notable travel or sick contacts or occupational exposures to toxic chemicals.

The patient had been generally healthy prior to his diagnosis of AML two years prior. At that time, he had presented with complaints of fever, weakness, vertigo and headache for one week. Following an extensive work up, the patient was diagnosed with FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) positive AML, which is named for its similarity to a tyrosine kinase that binds macrophage or monocyte colony-stimulating factor and is encoded by the Feline McDonough Sarcoma (FMS) oncogene.[11] He was treated with a "7+3" regimen of daunorubicin and cytarabine plus midostaurine as well as prophylactic antibiotics and steroids. The patient ultimately underwent allogenic HSCT two months after his initial presentation with a donor who was a 10/10 match (both alleles matched at HLA loci A, B, C, DRB1, and DQB1). One month following his HSCT, the patient was hospitalized with a febrile illness and found to have elevated CMV titers as well as elevated AST and ALT enzymes. He was treated at the time for a suspected viral infection with valganciclovir, piperacillin/tazobactam and prednisone. The patient later developed facial skin rashes and oral ulcers and his prednisone dose was increased. Soon afterward, he also suffered from a febrile illness with respiratory symptoms including cough and slight oxygen desaturation. He underwent bronchoscopy and a biopsy was taken from his respiratory tract, which was later found to be positive for Corynebacterium and he was treated with antibiotics. Later that same year, the patient presented with a complaint of gross hematuria and he was again prescribed prednisone and the hematuria eventually resolved.

At the patient's presentation for a chief complaint of generalized weakness, he was taking voriconazole, acyclovir, and trimethoprim-sulfamethoxazole for antibacterial and antiviral prophylaxis as well as sorafenib for maintenance AML treatment. He was tapering his dose of prednisone and currently taking 5mg daily, which was a decrease from 60mg daily a few months prior.

At the hospital, the patient's vital signs showed that he was afebrile with a regular pulse of 85, a blood pressure of 107/55 and a respiratory rate within normal limits. The patient's extraocular muscle movements and visual fields were intact. Both arms and legs were hypotonic and patient could not hold them up against gravity, however no pronation was noticed. Arm muscle strength was rated as 4+/5 bilaterally both proximal and distal. Wrist flexion was rated as 5/5. In the lower body, hip flexion was rated as 3/5 bilaterally, knee flexion was 4+/5 bilaterally, knee extension was 4+/5 bilaterally and foot plantar flexion and dorsiflexion was rated as 5/5 bilaterally. The patient's reflexes were 2+ throughout without any pathological reflexes. Superficial touch was intact in upper and lower body. The patient's gait was narrow-based with left foot dragging and he required a crutch in order to move around in his hospital room.

Laboratory results showed that the patient had a macrocytic anemia of 12.3 g/dL with a MCV of 99.4 (normal 80-94), thrombocytopenia of 90 K/micl (normal 130-400), leukocytosis of 13.32 K/micl (normal 4.8-10.8) with eosinophilia of 4.3 K/micl (normal 0.0-0.8). All of these abnormal blood test findings were confirmed to have been noted on prior labs. The patient had CRP a 1.86 mg/L (normal 0.0 – 5.0) and ESR of 29 (normal 0.0 – 8.0). Basic metabolic and coagulation panels were within normal limits. Patient's CPK and TSH were within normal limits. A lumbar puncture was performed which revealed an opening pressure of 12 cm of H20, 1 WBC/uL, no erythrocytes, glucose of 47 mg/dL and no xanthochromia. A flow cytometry test was negative for any abnormal cell populations in CSF and CSF culture and a Biofire panel for various microbiological pathogens was also negative. Patient serum and CSF was checked for antibodies including ANA, anti-dsDNA, anti-Jo1, anti-Scl-70, anti-voltage-gated calcium channel, anti-acetylcholine receptor, anti-GM-1 among others and were all negative. Hepatitis and HIV tests were also negative.

The patient was sent for a non-contrast head CT which showed a minor lesion in the right pons that was interpreted as an old finding that was likely an artifact.

The patient was also sent for electromyography (EMG), which revealed no spontaneous activity upon needle insertion and low amplitude, polyphasic motor unit action potentials with decreased duration along with increased recruitment in all nerves including the median, ulnar, peroneal, tibial and axillary nerves. Nerve conduction studies showed distal motor latency and conduction velocity were preserved for both sensory and motor components.

The patient was treated with 60mg of methylprednisolone IV and was referred to hematology for treatment of presumed polymyositis secondary to chronic GVHD. Muscle biopsy was also recommended in order to confirm the working diagnosis but deferred since it seemed reasonable to assume this was a manifestation of chronic GVHD given the patient's history and findings. Following a stay in the hemato-oncology department, the patient's dose of steroids was changed to 50mg daily of prednisone. The patient was instructed to continue taking prophylactic antibiotics and schedule a follow up appointment with his hematologist for continued treatment of chronic GVHD manifestations.

Discussion

This report details the case of a patient with a history of FLT3-ITD positive AML and acute and chronic GVHD who presented with progressive weakness of one month's duration and was diagnosed with presumed polymyositis secondary to chronic GVHD. According to the NIH Consensus Criteria on Chronic GVHD, polymyositis is a recognized diagnostic finding in chronic GVHD (***Figure 1***) and, in this case, it was confirmed via EMG, which clearly demonstrated a myopathic pattern in multiple nerves in the upper and lower body. Other causes of myopathy including prolonged steroid use, auto-immune disease, hypokalemia, hypothyroidism, infection and otherwise were ruled out and the patient's presentation timeframe of more than 100 days post HSCT excluded acute GVHD as a potential cause.

Musculoskeletal manifestations of chronic GVHD are very rare and when present do not usually manifest as myositis. In a retrospective chart review of all cases of myositis that developed in 7161 patients who underwent HSCT at the Fred Hutchinson Cancer Research Center in Seattle, Washington between 1969 and 1999, only 12 patients out of 1859 (0.6%) who developed chronic GVHD also developed myositis between 7 and 55 months after HSCT.[12] In another case series of 381 patients with chronic GVHD, Parker at el. reported that myositis occurred in 11 patients out of 318 (3.5%).[13] The incidence of myositis in the first study at the Hutchinson Cancer Center was calculated to be 23 per 100,000 person-years for all HSCT patients and 49 per 100,000 person-years for HSCT patients who had previously reported chronic GVHD manifestations.[12] For a comparison of prevalence in the general population, in a large study that looked at 35 million commercially insured individuals in the US, the incidence of idiopathic inflammatory myositis (including dermatomyositis, polymyositis and sporadic inclusion body myositis), was found to be between 5.8 to 7.9 per 100,000 person-years from 2003-2008.[14]

Figure 1. Section of Scoring Card from NIH Chronic Graft Versus Host Disease Criteria Relevant to Musculoskeletal Manifestations.

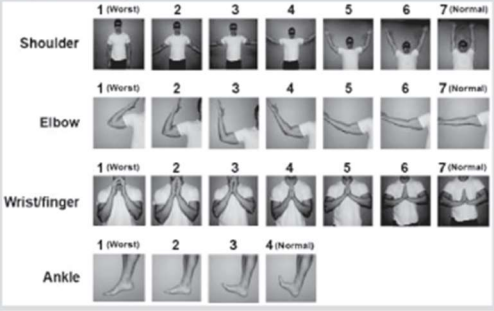
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



Legend. Section of organ system scoring card relevant to musculoskeletal complications of chronic GVHD as drafted by The National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease in 2014. The scoring card focuses mostly on musculoskeletal changes related to joint contractures, fasciitis and their related manifestations with a photographic range of motion scale provided for ranking perceived joint range of motion. There is also a box that can be ticked with a related severity scale of 1-3 in case of noted polymyositis.[15]

In patients who do develop musculoskeletal complications of chronic GVHD, the most common manifestation is fasciitis that is characterized by sclerosis of the overlying skin and subcutaneous tissues causing joint contractures, edema and restricted range of motion.[15] ***Figure 1*** shows the section of the scoring card that is pertinent to musculoskeletal manifestations provided by the National Institutes of Health to rate the severity of chronic GVHD. In that section, a scoring system is shown that allows clinicians to rate the severity of joint contractures and to tick a box if polymyositis, peripheral neuropathy and/or myasthenia gravis are present and, if so, to indicate the degree of severity. Besides evaluating for joint contractures, clinicians caring for patients with musculoskeletal symptoms of chronic GVHD should always monitor a patient's respiratory rate and oxygen saturation since there are reports of respiratory failure as a result of weakness of the respiratory muscles in chronic GVHD.[16]

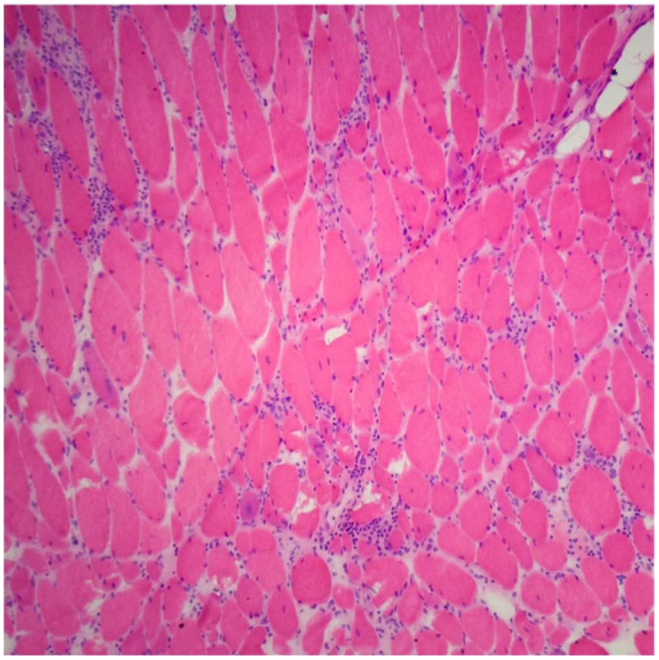
Another etiology of myositis that was considered in this patient was medication-induced myositis. The patient has been regularly taking sorafenib, a tyrosine kinase inhibitor that has been shown to increase event-free survival in patients younger than 60 years old with FLT3-ITD positive AML albeit with increased toxicity.[17] While Sorafenib has been reported to cause myositis in at least one case report, however it was not believed to be the culprit in this patient's case since the patient had been taking the drug for several months before the onset of weakness and myopathic symptoms appear to be a relatively rare side effect.[18] As a result, the patient was instructed to continue taking sorafenib as maintenance for AML.

This patient presented with normal levels of CPK, which may make this presentation unusual since in one review of 36 cases of polymyositis due chronic GVHD, it was reported that the majority of patients presented with elevated CPK and aldolase levels.[19] Aldolase was not measured in this patient, so unfortunately we cannot know if it was elevated or not. As for the normal level of CPK, while this enzyme typically parallels disease activity in most patients with myositis, it may be normal or only slightly elevated in different types of myositis.[20] This patient did have a history of acute GVHD, which may or may not be present in common presentations of this disease. In the same case series that reported data on elevated CPK, Couriel et al. found that about half of the patients did not have any history of an episode of acute GVHD prior to their presentation with symptoms of polymyositis.[19] This also means that a significant percentage of patients are likely to present with myositis without any prior indications of graft-versus-host disease.

In muscle biopsies taken in cases of myositis secondary to chronic GVHD, one should expect the same findings as in idiopathic polymyositis, namely perimysial and endomysial infiltrate of CD4+ and CD8+ T cells in the myofibrils.[19] This is confirmed in a report by Takahashi et al., who reported CD4+ and CD8+ T cells in the perimysial infiltrate and primarily CD8+ infiltrate in the endomysial layer in a 22-year-old patient with polymyositis secondary to chronic GVHD.[21] Examples of pathology slides showing expected findings can be seen in ***Figure 2*** and ***Figure 3***.

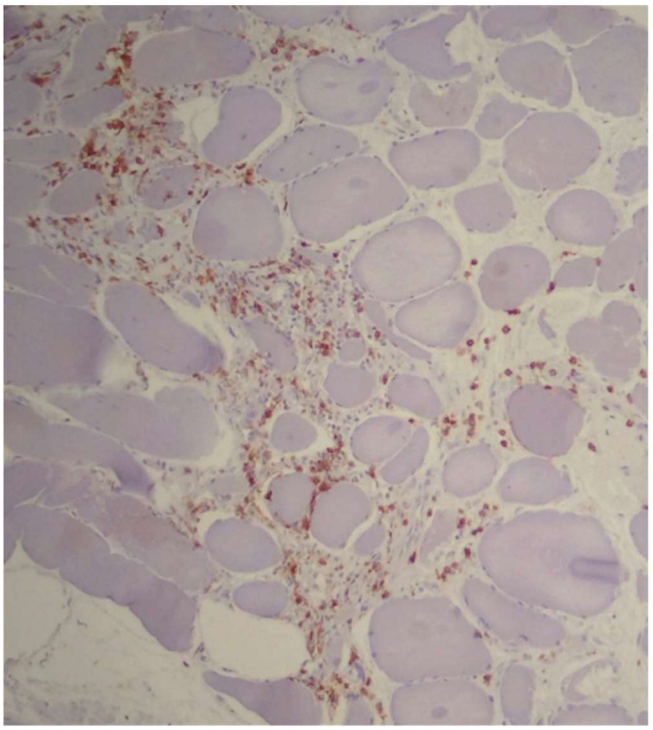
This case shows that it is important for clinicians to be familiar with the phenomenon of polymyositis as a manifestation of chronic GVHD, especially since the etiology of myopathy in these patients may easily be mistaken for something else since they often suffer from multiple co-morbidities and are often on immunosuppressive therapy as well as other medications. Furthermore, more research is necessary to find more effective prophylactic and therapeutic treatments for chronic GVHD that possess a lighter side effect burden with long-term use. Current directions of investigation, which include impeding B cell signaling and germinal center formation, increasing regulatory T cells populations, targeting pro-fibrotic interleukins and T and B cell recruiting chemokines have shown some promise but require more patients and clinical trials to be further validated.[1]

Figure 2. Lymphocytic Infiltrate in Muscle Tissue.



Legend; An H&E section of a muscle tissue showing infiltration of lymphocytes as well as myopathic features including smaller, rounded myofibers with increased internal nuclei. Courtesy of Meggen Walsh, D.O., M.S.-P.A.[22]

Figure 3. CD8+ T Cell Infiltrate in Muscle Tissue



Legend: Immunostaining of muscle from H&E section showing that infiltrate is composed of CD3+ CD8+ T cells. Courtesy of Meggen Walsh, D.O., M.S.-P.A.[22]

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ULS

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Case Report

ST-Segment Elevation and Normokalemia in Acute Diabetic Ketoacidosis: Case Report and Brief Literature Review

S. Bryn Dhir,[1] Abbas Husain.[2]

Abstract

Background: Diabetic Ketoacidosis (DKA) is a life-threatening complication of Diabetes Mellitus Type 1 (DM1) and requires prompt management; however, benign transient electrocardiographic (ECG) abnormalities with normal serum potassium levels can be seen in diabetic patients secondary to metabolic changes. Understanding the varying presentation among patients provides valuable insight into the management of this seemingly uncommon and benign diagnosis. **The Case:** A 24-year-old male with a history of DM1 presented to the Emergency Department (ED) with ST-segment elevation, normal potassium levels and metabolic acidosis. The patient was found to be in DKA with benign cardiac manifestations. **Conclusion:** The correction of underlying metabolic abnormalities in DKA and the awareness of the benign cardiac pseudo pathology on ECG allows for effective management and personalized patient care.

Key Words: Diabetic ketoacidosis; Diabetes mellitus type 1; Myocardial infarction; Pseudo pericarditis; Normokalemia (Source: MeSH-NLM).

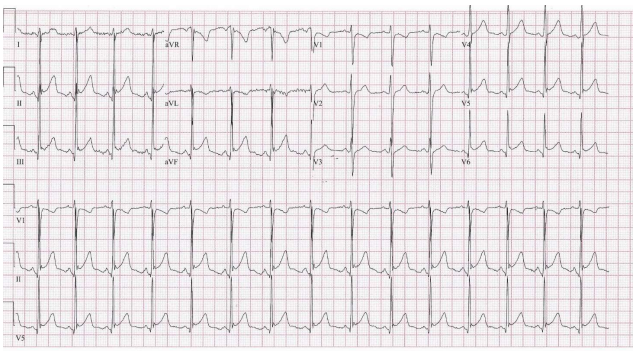
Introduction

Patients with DM are at risk for life-threatening complications such as cerebral edema, noncardiogenic pulmonary edema, DKA, and a subset of complications secondary to metabolic imbalances. Among the most concerning, DKA requires rapid diagnosis and is often associated with viral illness, infections, compliance of insulin therapy, stroke, trauma, surgery, alcohol abuse, pregnancy and severe dehydration. DKA is responsible for acute metabolic complications with fluid-electrolyte and acid-base abnormalities such as increased potassium levels, errors in metabolizing fat, carbohydrates and protein, and ECG abnormalities. However, the presentation of DKA varies greatly between patients and is often unrecognized or misdiagnosed.[1] To the best of our knowledge, this is the first case report to highlight the clinical presentation and management in a young male patient with DM1 in DKA with normal serum potassium levels and ST-segment myocardial infraction (STEMI) in the Emergency Department (ED) and Intensive Care Unit (ICU) at the Staten Island University Hospital, Staten Island, New York, USA.

The Case

A 24-year-old male with a history of insulin-dependent DM1 presented to the ED with abdominal pain, nausea, and fifteen episodes of non-bloody, non-bilious vomitus for 24 hours. Admission vital signs evidenced tachycardia with no other abnormalities: right arm blood pressure 118/82 mmHg; pulse rate 102; respiratory rate 18; oxygen saturation on room air 97%; oral temperature 35.8°C; auscultation of the heart and lung fields revealed normal S1, S2, rate and rhythm; bilateral breath sounds without rales, rhonchi or wheezes. The patient was awake and oriented to person, place, time, situation and spoke coherently. Associated symptoms included: diffuse, intermittent, cramping epigastric pain without fever or chills. On exam, his abdomen was soft, non-tender, without guarding or peritoneal signs, and positive for bowel sounds in all four quadrants. He denied recent travel, tobacco or illicit drug use and indicated regular compliance of his insulin pump with the exception of the previous day. On further evaluation, he indicated consumption of approximately two to three beers and two to three cups of hard liquor the previous day at a party. Initial and repeated 12 lead ECG showed a STEMI (***Figure 1***) and an anterior-posterior chest x-ray was unremarkable for evidence of acute cardiopulmonary disease (***Figure 2***). Laboratory work up of cell counts, metabolic and urine profile, and cardiac biomarkers were investigated and significant results were noted for acetone, serum glucose, urine glucose and ketones (***Table 1***).

Figure 1. ST segment elevations on ECG investigation.



The patient was diagnosed to be in DKA with acute kidney injury (AKI). Management with 0.9% sodium chloride, potassium chloride, 20mg famotidine, 4mg ondansetron hydrochloride, and continuous insulin infusion was initiated in the ED. A third ECG continued to showed pathology for a STEMI. Upon consultation with a cardiologist, percutaneous coronary intervention was not indicated at the time. The care plan included optimizing medical management with adjustments to subcutaneous (SC) insulin, and inpatient care in the ICU under critical care. The total time in the ED was approximately 2.5 hours.

Approximately eight hours after the patient presented to the ED, the cardiac manifestations resolved and the AKI secondary to mild dehydration showed improvement. The patient was comfortably ambulating and tolerating food orally (approximately 20 and 24 hours later). Repeat laboratory work-up at 20 hours and 46 hours showed

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anion gap and metabolic improvements. Upon detailed review of the case and medical education, the patient was discharged approximately 48 hours after ICU admittance.

Figure 2. Anterior-Posterior Chest X-Ray.

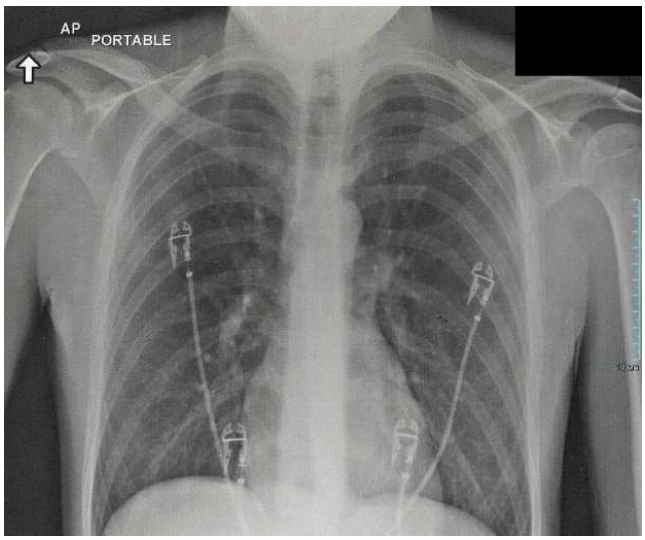

Table 1. Laboratory Investigation and Results: Basic Metabolic Profile.

Basic Metabolic Profile	0 hrs	20 hrs	46 hrs
Anion Gap *(mmol/L)*	23	12	11
Glucose *(mg/dL)*	441	163	231
Blood Urea Nitrogen *(mg/dL)*	28	14	10
Creatinine *(mg/dL)*	1.75	0.91	0.75
BUN:Cr Ratio	16	0.154	13.3
GFR	48	102	128
Sodium *(mmol/L)*	133	135	137
Potassium *(mmol/L)*	4.2	3.9	3.7
Chloride *(mmol/L)*	97	1.4	99
Calcium *(mg/dL)*	10.5	9.1	9.1
CO2 *(mmol/L)*	13	19	27
Lactic Acid *(mmol/L)*	2.7		

Legend: GFR - Glomerular Filtration Rate, BUN:Cr - Blood Urea Nitrogen to Creatinine ratio.

Discussion

DKA is a life-threatening complication of DM and requires rapid diagnosis by medical care teams involved in patient care, and closed-loop communication aids favorable outcomes. The understanding of the vastly different patient presentations can allow for cost-effective and appropriate personalized care, as was seen in this patient case. Medical management of DKA includes correction of electrolyte abnormalities, in particular potassium and phosphate; fluid replacement; as well as the administration of bicarbonate, though controversial. Recommendations for insulin therapy guided by serum potassium indicate that low-dose IV insulin should be used if the serum potassium is greater than or equal to 3.3 mEq/L, whereas therapy should be delayed if the level is less than 3.3 mEq/L in order to allow for potassium replacement.[1] Imaging and investigations are often guided by patient presentation as well as hospital and physician practices, and can range from conservative to invasive with costly measures such as coronary angiography imaging.

As outlined in this case, the transition of insulin therapy from IV to SC in the ICU is a widely adopted practice by hospitals managing DKA, and various algorithms and criteria exist for the safe transition.[2] Other treatment options, such as the use of IV heparin in severe cases of DKA for the prevention of pancreatic complications in patients with hypertriglyceridemia, was not indicated for this case. In addition to evidence-based medicine and applying clinical research literature to decipher uncommon disease presentations, the understanding of ECG abnormalities and insulin compliance allows for appropriate patient care with favorable and uneventful outcomes. Furthermore, although serum potassium levels may be normal or elevated in DKA, a total body potassium deficit may exist. This means understanding the pathophysiology of the cellular movement of potassium can eliminate further decreased levels caused by rehydration dilution, urinary loss, acidosis correction, or reentry into cells. Metabolic changes are often reversible with rehydration as well as the correction of the underlying abnormalities, and ECG can be a useful tool to guide potassium replacement.[3] Other factors influencing benign transient ECG changes in DKA include idiopathic pericarditis, nonspecific cardiac enzymes abnormalities, vasospasms, autoimmune diseases and viruses as metabolic acidosis and Brugada syndrome do not solely contribute to ST-segment changes.[4]

Despite the widely accepted and common practices of medical management for the disease, the diagnosis is often unrecognized or mistaken for another infection (alcohol abuse, drug use, lactic acidosis, STEMI) and the presentation of DKA vastly differs between patients. The awareness among physicians, health care workers and the scientific community is lacking and remains ambiguous. Novel insight into DKA and DM was first provided by seminal cases published in the medical literature by Campbell et al., 1977, and identified the complications associated with uncontrolled diabetes. The abnormal metabolic states were attributed to the severe changes associated with water and electrolyte imbalances, and manifested as subepicardial injury presenting as pseudo pericarditis with ECG abnormalities such as the displacement of the J point and ST-segment elevation without a QRS complex.[5] In addition, the effects of DKA and hyperkalemia were observed in the patients from the Campbell and colleagues (insert year article was published here) study, in which dry pleurisy was associated with pleural pain and friction rub.[6] Furthermore, idiopathic causes of benign acute pericarditis in diabetic patients with hyperkalemia and pseudo-anterior wall infarction are also described in early cases reported by Bennett and Blake (1971).[7] Although our patient presented with a normal serum potassium level, compared to patient cases described above, this case report is similar in that pathology attributed to infectious causes were ruled out early because of lacking clinical signs and symptoms (friction rubs, chest pain, pericardial effusion, fever, changes to white blood cell counts).

Case reports such as this highlight the differences and similarities in the presentation of signs and symptoms of a young patient in DKA. The young patient in DKA with seemingly alarming ECG abnormalities and normal potassium levels contrasts with adult male patients that have Type 2 DM, noncompliant with oral insulin therapy and may present with acute inferior pseudo infarction, normal potassium levels, and extended hematemesis.[8] Further, noncompliant teenage males with normokalemia can present with T wave inversion in leads II, III, aVf, V4-6.[9] Hyperkalemia in male patients with DM1 in the same age range as our patient is also possible, and ECG can show ST-segment elevation in leads I, II, aVL, aVF, V2–V6, as well as ST-segment depressions in lead aVR.[10] Although the presentation of patients with DM in DKA with ECG abnormalities is often unrecognized or misdiagnosed, understanding the cardiac manifestation mimicking STEMI and correcting metabolic abnormalities is essential in providing rapid, cost-effective personalized care to patients.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Case Report

Encephalopathy an Atypical Presentation of Intussusception: A Case Report

Venma Mampilly, Sasikumar Manalumukkil Sankaran, Ramaraj Subbiah.[1]

Abstract

Background: Intussusception Encephalopathy is a pediatric emergency where a stuporous child presents with or without abdominal symptoms. Neurological manifestations of intussusception are an atypical presentation of this condition. It often misleads clinicians to other differential diagnoses of encephalopathy. **The Case:** We present you a case of 11-month-old child presented with encephalopathy, acute in onset with underlying intussusception. **Conclusion:** Intussusception encephalopathy is a pediatric emergency. It should be kept as a differential diagnosis when a child presents with complaints of acute onset of drowsiness with or without abdominal symptoms. Early diagnosis could save grave complications and improve the prognosis

Key Words: Metabolic encephalopathy; Intussusception; Pediatric Emergency Medicine; Drowsy (Source: MeSH-NLM).

Introduction

Intussusception is the commonest cause of bowel obstruction in children under 2 years of age. It occurs in 1.4 per 1000 live births.[1] Intussusception is a rare presentation, being the first case reported by Goetting in the year 1990.[2] It is characterized by the telescoping of one segment of bowel (intussusceptum) into its neighboring segment (intussuscepiens), situated most commonly near the ileo-cecal valve (ileocolic).[3] Children suffering from this emergency condition will not show its cardinal symptoms. It is often confused with sepsis until blood and stool cultures result in sterile growth and detected by ultrasonography. Therefore, early diagnosis could prevent the time delay in treatment and improve global prognosis.

The aim of this study is to describe an uncommon presentation of intussusception towards its inclusion in the differential diagnosis when having a child with encephalopathy in clinical practice.

The Case

A 11-month-old baby girl was brought to pediatric emergency with complaints of excessive drowsiness, vomiting where vomitus was not bilious in nature, decreased feeding and history of intake of stale food in the previous night. The mother described that the child woke up in middle of the afternoon with severe cry and fell into sleep after a few minutes. The child had an episode of blood-stained stools in the next morning. Parents did not mention any past history of exanthematous fever, respiratory infections and gastrointestinal infections. The family didn't suffer from similar complaints. Baby was born at term with no antenatal or postnatal complications. Currently, she is on family diet.

On general examination, child appeared lethargic, drowsy, pale and afebrile. Modified Pediatric Glasgow coma scale was calculated to be 11/15. Vitals were stable with pulse rate-120/min, BP-110/70 mm Hg, respiratory rate- 28/min and Sp02-97%in room air. The extremities felt warm. ear, nose and throat examination done and found normal. On abdominal examination a mass was palpable in the epigastrium .She had no features of hepatosplenomegaly and bowel sounds were heard 3/min .On neurological examination, pupils were isochoric and bilateral plantar flexor. There were no other neurological deficits were found. Child showed no signs of meningeal irritation .Other systems were found within normal limits. Anthropometric measurements were assessed and found appropriate for the age. Child was admitted at pediatric intensive care unit for further management (***Table 1***).

Table 1. Clinical manifestations[7]

Symptoms	Signs
Altered level of consciousness	Decreased AVPU scale
Excessive sleepiness	Tender abdomen
lethargy	Sausage shaped mid-abdominal mass
Abdominal pain-colicky type	
Vomiting	
Sudden, loud cry	

Legend: AVPU scale: Alert,Verbal,Pain,Unresponsive

Routine blood investigations were carried out .A Hemogram showed elevation of total counts of white blood cells of 16.2 x 10^9 per liter, with Hemoglobin 9.3 g/dl and platelet counts of 644x 10^9 per liter. Both renal and liver function tests were found within normal limits. Serum electrolytes showed mild hyponatremia with Sodium (Na+) of 134, Potassium (K+) of 4.5 and HC03 of 18. Arterial blood gas analysis was done and showed compensated metabolic acidosis (pH: 7.31, Pco2: 38.0, Po_2: 48.4, HC03: 18.5). CT brain was taken and detected no features suggestive of intracranial abnormality. Ultrasonography abdomen was done immediately and showed features of ileo -colic intussusceptions (as in ***Figure 1***). A pseudo kidney like bowel related mass lesion of size 8.2 x 4.2 x 3.8 cm formed by herniation of bowel loop along with mesentery into another bowel loop in upper abdomen was suggestive of intussusception with no features of strangulation. Mild ascites was also found in the ultrasound.

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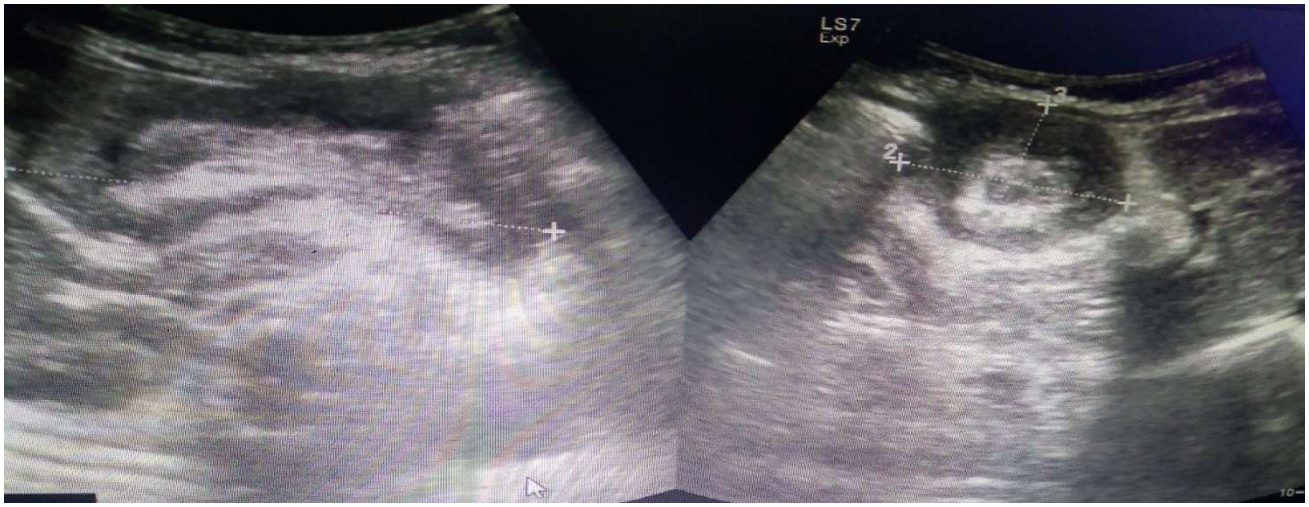
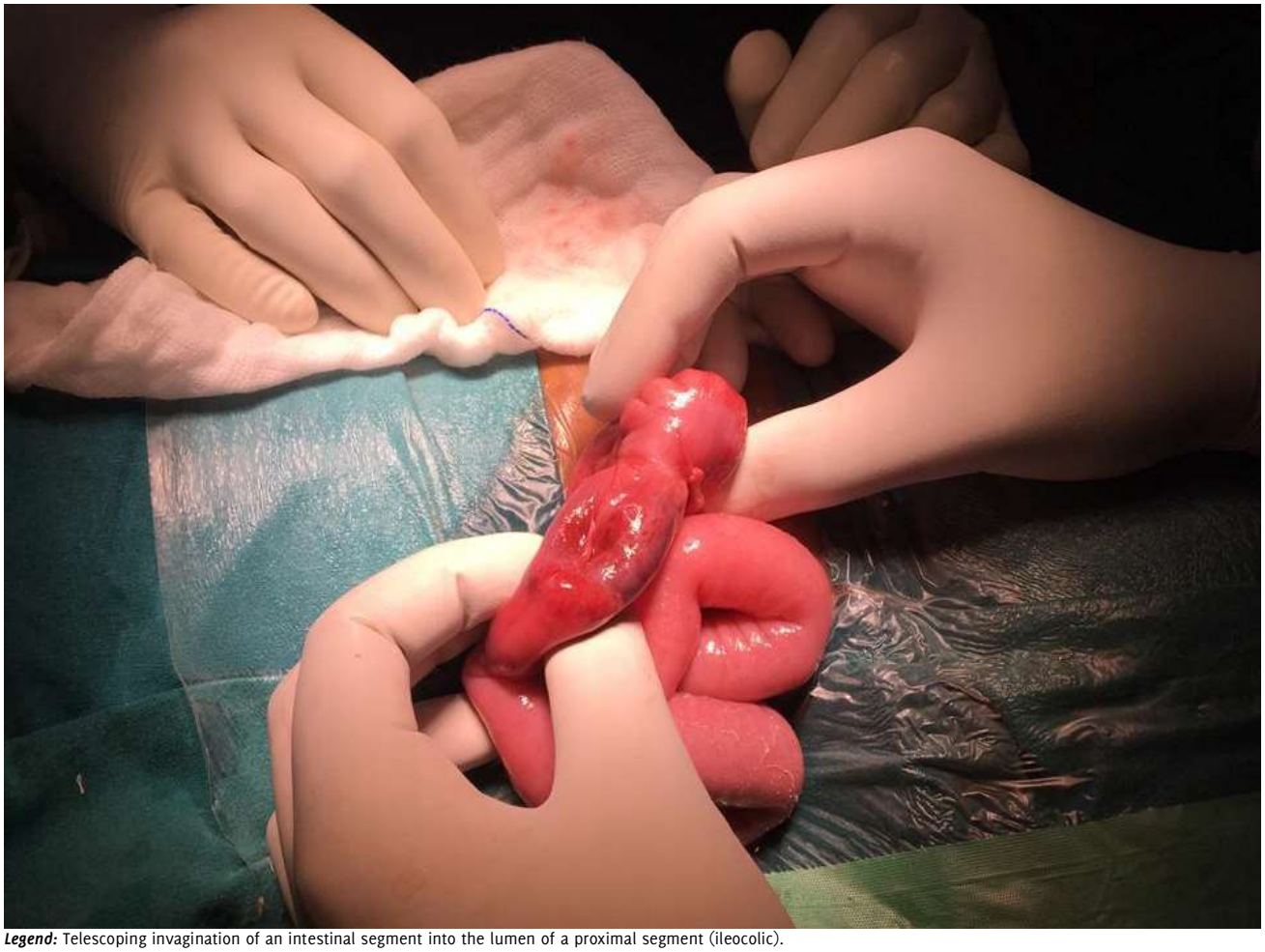
Figure 1. Ultrasonographic appearance of the abdomen of the child



Legend: Target sign of intestinal Intussusception.

Stool and blood were sent for culture and sensitivity to rule out shigellosis and septicemia. Both cultures showed sterile growth. The child was immediately consulted by pediatric surgery and posted for hydrostatic reduction which failed and therefore exploratory laparotomy and reduction was done subsequently (***Figure 2***). Postoperatively, the child was managed with antibiotics and other supportive measures. Postoperative period was uneventful. The child became more wakeful the next day. Vitals were stable. Surgical site was examined in the following days and there were no features of wound infection seen, hence she was discharged.

Figure 2. Laparoscopic reduction



Legend: Telescoping invagination of an intestinal segment into the lumen of a proximal segment (ileocolic).

Discussion

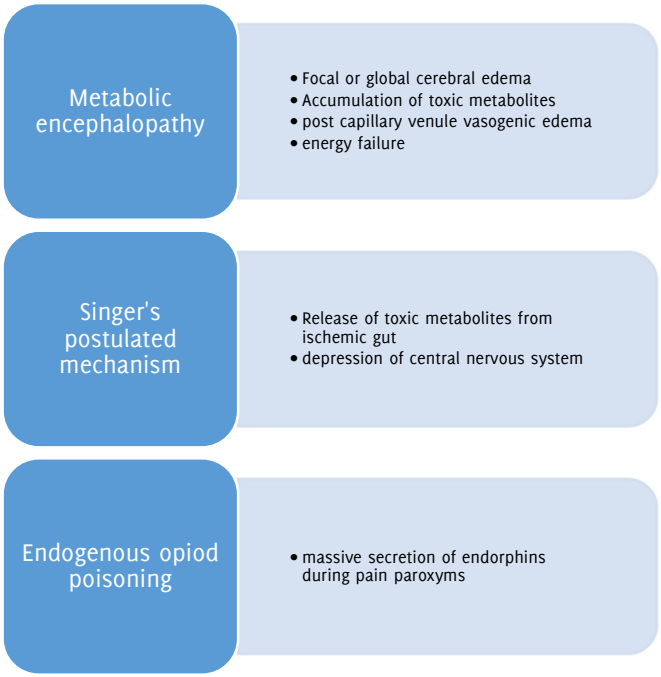
Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive or static. Etiologies include infectious, toxic, metabolic, genetic and ischemic causes.[1] The brain which is the most active organ of the human body has a fast-metabolic rate .It requires high level of oxygen to meet this high efficiency. On the other hand, its capacity of energy deposition is very low. When an etiology leading to acute change in consciousness is treated ,neurological improvement occurs and the prognosis good.[4]

Intussusception could be initiated by introduction of new food, gastrointestinal infection and acute respiratory tract infection .It results in swollen peyer's patches in the terminal ileum.[4] Intussusception encephalopathy is an atypical neurologic manifestation of intussusception. The neurological symptoms include paroxysmal episodes, global hypotonia, acute weakness and fluctuation of level of consciousness.[5] Therefore intussusception encephalopathy should be kept as differential diagnosis when children are presented with altered level of consciousness or other neurological symptoms with or without abdominal features.[6-7]

Three possible hypotheses for this encephalopathy have been postulated. First hypothesis is due to the systemic action of toxic metabolites released from ischemic gut that depress the central nervous system as postulated by Singer in his article.[9] Another hypothesis proposed for similar manifestation is that a possible endogenous opioid poisoning by massive secretion of endorphins during pain's paroxysm.[8] This pathophysiology is not clearly understood and a subsequent study demonstrated no difference in plasma beta endorphins levels in patients admitted with intussusception compared to the controls.[11] Finally, when there is an acute abdominal pathology, it is possible that there will be derangement in the electrolyte and subsequently a metabolic encephalopathy could set in (***Figure 3***).

Kinnier Wilson coined the term metabolic encephalopathy to describe a clinical state of global cerebral dysfunction induced by systemic stress.[11] Metabolic encephalopathy can set in due to various mechanisms such as focal or global cerebral edema ,alterations in transmitter function, the accumulation of uncleared toxic metabolites, post capillary venule vasogenic edema and energy failure.[11] In our case , arterial and venous blood analysis shows metabolic acidosis ,thereby metabolic encephalopathy may be a possibility in this scenario. This case highlights that one should have a high index of suspicion when a child presents with altered level of consciousness with or without abdominal features suggestive of intussusception.

Figure 3. Hypothetical mechanisms causing Intussusception encephalopathy



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Interview

Fostering Europe's Future Physician-Scientists: An Interview with European MD/PhD Association Chairman Dr. André dos Santos Rocha

Paul M. Ryan,[1,2] André dos Santos Rocha.[2,3]

The Interview

Dr. André dos Santos Rocha is a Resident Physician in Intensive Care Medicine & Anaesthesiology and a current MD-PhD student in the Department of Acute Medicine at the University of Geneva (***Figure 1***). In parallel, he is also the current Chairman of the European MD/PhD Association (EMPA), a role in which he coordinates a diverse group of highly-driven MD-PhD students. EMPA is a not-for-profit organisation which was founded with the central aims of bringing together MD-PhDs from across Europe, fostering a comfortable setting for networking, promoting European scientific collaborations and support for research, and mobilizing European MD-PhD students. One of the main mediums through which EMPA achieves a number of these lofty goals is their annual conference, which is typically held in conjunction with one of the national associations. I met with Dr. Dos Santos Rocha after the recent European and Swiss MD-PhD Conference in Geneva to discuss his experience in this role and what the future holds for EMPA.

Figure 1. Dr. André dos Santos Rocha, University of Geneva MD-PhD Student & EU MD/PhD Association Chairman. *Pictured here with a Geneva EMPA Conference attendee.*

Paul MacDaragh Ryan (PMR): *Good afternoon, André. Many thanks for agreeing to educate us on EMPA and your involvement in the organisation. To start,* ***can you tell us a bit about your career to date, your research and what drew you into medicine initially?***

Dr. André dos Santos Rocha (ASDR): Hi Paul! Thank you for joining EMPA and especially for reaching out to me for this conversation. My career to date has been divided between a number of European countries. I attended medical school in Lisbon, completing the final two years of my undergraduate education in Paris and London, respectively. It is somewhat difficult for me to go back to the very first moments that drove me into medicine. I must have been 12 or 13 years old when, already fascinated by the natural sciences, my older cousin brought me to visit the Intensive Care Unit (ICU) "space shuttle" room at one of the biggest hospitals in Portugal. Of course, it was difficult not to be fascinated by this back at that age. Many years later, I was attracted by medicine for its humanistic aspects, the art of its practice and the endless innovation which keeps it in motion.

After graduating from my undergraduate studies in 2013, I launched into residency in ICU/Anaesthesiology in Switzerland. Subsequently, in 2017, I put my clinical training on hold to pursue an MD-PhD programme in Geneva. My research focuses on respiratory biophysics and pathophysiology during mechanical ventilation. Naturally, my choices and career in research were guided by my experience in the ICU.

PMR: What is the one piece of advice which you would give to someone who is currently considering applying to an MD-PhD program?

ADSR: I would rather say that if someone is actively considering applying to such a research track, they very likely possess the core skills which fuel research: motivation and scientific curiosity. With this in mind, now is the right moment to dive into it without fear. It might seem long, laborious and disconnected from the usual clinician track, but you will probably become one of a kind amongst your peers. To hold an MD-PhD title and education is rarely undervalued.

PMR: What have been the biggest challenges and rewards of the MD-PhD route for you so far?

ADSR: I guess the challenges and struggles are quite similar to all of us: to find enough financial and personal support, as well as to have guidance for both our experiments and careers. It is of course challenging to attain a salary which is equivalent to our peers/colleagues who are solely performing clinical duties. On a personal note, I would say that becoming a student again many years after leaving medical school was the biggest challenge. As a junior doctor, my sense of autonomy and fulfilment increased exponentially. You can imagine what it was like at first to go back to didactic lectures, amphitheatres and a laboratory bench as a full-time job.

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Figure 2. Delegates of the 8th EU MD/PhD Association Conference. *More than 70 delegates representing 15 nationalities attended the meeting at Campus Biotech, Geneva, Switzerland.*

However, I would not dare to complain since a range of otherwise unattainable rewards revealed themselves along the way – jobs, positions, prizes & grants, the EMPA presidency – but the greatest reward is the respect and recognition from my physician peers whenever I go to seminars and conferences to present my experimental data.

PMR: In your opinion, what are the key features of an impactful or successful Physician-Scientist?

ADSR: This question has no easy answers. Through EMPA, I have had the chance to meet and interact with many colleagues from different countries, programmes and backgrounds. Each career seems so unique and they all are meant to lead to a successful physician-scientist profile. From my perspective, two aspects deserve special attention whether one wants to successfully combine clinics and research: career planning and mentorship. While your PhD is still ongoing, dedicate some time to discuss with your mentors your next steps and future plans, apply to grant opportunities and manage research protected time with your institution. I believe that these key features will help pave the way to a fruitful career.

PMR: What are your future career and scientific aspirations?

ADSR: Regarding medical training, I will pursue my Anaesthesiology & ICU specialised training. Simultaneously, I am managing a non-interventional clinical trial that aims to bridge and validate my preclinical data within clinical scenarios. I was lucky to be awarded Swiss National funding to support my research during residency and, therefore, I am planning to acquire clinical research skills alongside medical training. Regarding my long-term career aspirations, the plan is to take a path such that academia and research can accompany my clinical duties.

PMR: Can you tell us about the history of EMPA and where it found its origins?

ADSR: MD-PhD gatherings at the European level started in London in 2012. Back then, EMPA did not exist but the informal association between students from European MD-PhD programmes started by bringing together annual international MD-PhD conferences throughout Europe. It was in 2015, during the 4th European MD-PhD Conference in Groningen, The Netherlands, that EMPA was born with an official registration in the Chamber of Commerce, its statutory terms, its Executive and Advisory Boards. The heritage from this "birth" is that our website servers, financial and legal headquarters are still in Groningen today.

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PMR: When and how did you become involved in EMPA?
ADSR: It was back to 2017, when I attended the 6th Swiss and European MD-PhD Conference in Basel. I got to know EMPA's goals and projects during the General Assembly and I was recruited to join the movement, just as happened to you in Geneva lately. By the way, thank you for becoming the National Representative for EMPA in Ireland.

PMR: You recently successfully orchestrated the 2019 European and Swiss MD-PhD Conference in the beautiful Campus Biotech setting of Geneva, Switzerland. Can you tell us a bit about this?
ADSR: Having joined EMPA in Basel as I mentioned, it was now my turn to bring the European MD-PhD Conference to Swiss ground once again and to spread EMPA's mission to new members from European Universities. In partnership with the Swiss MD-PhD Association, in which I am the international liaison, we co-organised the 8th annual EMPA conference at Campus Biotech, the Life Sciences' Hub for the region of Lake Geneva (***Figure 2***). Dedicated to *Biotechnology in Health*, this year's conference gathered over 70 MD-PhD candidates and graduates, allowing young doctors to present their unique research work and to network with peers, while enjoying a rich scientific programme delivered by a range of experts in the field from across Europe and the United States.

PMR: What were the major highlights and take-home messages of the conference for you?
ADSR: The major highlight was the presence of more than 70 attendees, from 15 nationalities with a wide range of ages, backgrounds and interests. About twenty original scientific works were selected for oral presentation, in addition to a range of poster presentations, and the high quality of the research done by students during their PhD pursuits was remarkable. These pluralistic demographics is the proof that EMPA shall foster international collaborations, given the rich and highly diverse curricular framework throughout Europe.

PMR: While Europe was certainly the home to many of the first true physician-scientists, the United States was the first country to develop the formal MD-PhD program more than 50 years ago.[1] What is the current state of MD-PhD programs in Europe?
ADSR: Thanks for raising this issue, which is so dear to me. Indeed, the Old Continent has certainly an older and richer scientific history, but for some reason we were far slower than our American peers in developing MD-PhD programmes. It was in the late 80's and early 90's that the first programmes appeared in the UK, France and Switzerland. Efforts have been growing (albeit slowly) ever since and other countries and universities have begun to design PhD programmes tailored for medical students and clinicians. Despite this, the current state in Europe could still be vastly improved, since many countries still lack these programmes entirely. In line with this, we have made it a priority of EMPA over the past few years to host national events and forums in different countries in order to promote tailored programmes for medical doctors wishing to follow PhD tracks.

PMR: What do you hope to achieve during your term as Chairman and what is the long-term future of EMPA?
ADSR: My biggest goal as chairman is to be a facilitator and promotor of international collaborations. In the past, the divergent design of MD-PhD programmes in Europe created some divisions between countries.[3] To heal old wounds, we came up with a new definition and modified our statutes accordingly in 2019 to include in our ranks all health care professionals and students with an interest in biomedical research, in particular physicians, pharmacists and dentists.

As a most sincere personal and associative goal, I hope to achieve consortiums and consensus between the different players inside and outside Europe. I am happy to announce that we have been signing memorandums of agreement with many universities and associations to provide better network and training opportunities for our members. To mention just one, we established the *International Consortium of Clinician Scientist Trainees' Organisation* together with American, Canadian, Asian, French and Swiss physician-scientists associations.[2]

PMR: How can interested students find more information about EMPA and get involved in the organisation?
ADSR: We have several channels of communication through which we are eager to connect, such as Facebook,[4] Twitter[5] and LinkedIn,[6] along with our website,[7] where an events calendar and useful information are continuously updated. Finally, I would be happy to receive and reply to any inquiries directly *via* the EMPA email address, eumdphdassociation@gmail.com.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Being an Italian Medical Student During the COVID-19 Outbreak

Nicolo G. Biavardi.[1]

The Experience

Many students around the world have been wondering how their life will change since the very first outbreak of COVID-19. I am Italian. I am from Milan. I am into the storm. Said plainly, I had never imagined that my life as a medical student could have changed as such. Since February 21st 2020, when the first case of COVID-19 was recorded in Italy, the National Healthcare Service, which offers universal access to healthcare, has faced increasing pressure, with 73780 total cases of COVID-19 and 6801 deaths as of March 26, 2020.1 On March 10th, the Italian Ministry of Health has issue a legislative decree, effective until April 13th, 2020. The said ordinance limits the movement of individuals in the whole national territory unless due to unmovable working issues or any compelling reason which have to be proven. Universities, primary and secondary education are suspended. Any form of social interaction or cultural entertainment, including cinemas, theaters, museums, cultural centers must be shut down. Gathering in public spaces is strictly forbidden, therefore any sport event and funeral must be cancelled. Only those shops that are selling essential goods, such as supermarkets, are allowed to stay open, admitted that they can ensure a distance of at least 1.5 m between customers.2 Since then, I have not been out of my home.

How Did Academic Institutions Respond?

Not taking into consideration the psychological effects of this forced quarantine, which have been reported to range from post-traumatic stress symptoms to confusion and anger, one on the biggest concerns has been to ensure academic education.3 Each chancellor of the university has issued a different decree, despite some formal differences, the common rationale has been to implement online lessons and convert whenever possible written exams into orals. Oral examinations have thereafter been administered thanks to streaming platforms.4

How Have Medical Schools Evolved?

Medical school is notoriously arduous, the difficulty of medical school boils down to the breadth of subjects that are included under its banner, the almost infinite depth to which each of those subjects could be explored and the lack of clarity regarding how much knowledge of each of them is sufficient. Lectures are indeed essential for a deep understanding of the subject. The necessity of a conversion from in-class lectures to on-line ones has posed several interrogatives. For instance, the most debated question has been: "Is achievement affected when attendance is face-to-face versus online?". The said question, along with other digital scholarship related interrogatives have been analyzed by McLean et al.5 It has been reported that it does not appear to affect student achievement whether they observe lectures live or online.

Nevertheless, my experience with online lesson has been troubled, though it is necessary to contextualize. I am a Medical student at San Raffaele University Milan, which attached to the worldwide renowned San Raffaele Hospital. Milan really is the epicenter of the COVID-19 crisis in Italy, being that it is the capital of Lombardia, the region which has been facing the most dramatic outbreak of cases. With that said, it is straightforward to understand that our lecturers, who are before everything else physician, had to overshadow teaching. Nonetheless, all faculties have tried to at least record their lessons so that we could have them available online. Unsurprisingly I have seen lectures recorded by professor still wearing coats, sometimes with scars left from face-masks and with an evidently worn-out face. Moreover, I have also had live-streaming lessons, which all in all have been considerably good. I did have faced connection issues, which are however related to the tremendous pressure posed on the internet by the almost one trillion bit per second of traffic registered in Italy as March 14, 2020.6 Likewise, many medical schools in Italy have tried to do their best to implement online lectures and, on the whole, we can affirm that medical schools have not arrested their activities.

In summary, Italy has been facing the biggest crisis, both economically and socially speaking since the end of World War II. The whole peninsula has been locked down since March 10, 2020. Universities have behaved accordingly by implementing e-learning platforms with results that are all in all satisfying, considering the issues that this situation is posing. Nevertheless, if this crisis will continue, it is necessary to improve the quality of the service provided by universities using a student-centred approach as suggested by Stodnick & Rogers in 2008.7 On March 11, 2020 the WHO declared the COVID-19 viral outbreak pandemic.8 Therefore, more countries will have to implement e-learning strategies and Italy must be used as a benchmark.

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Experience

Medical Education in Naples, Italy, at the Time of SARS-CoV-2

Gianluca Pagano,[1] Gaetano Luglio.[2]

The Experience

Lockdown, quarantine. These are the key words on top of our agendas in Italy and in the most part of the world during these difficult times. The spread of an invisible airways invader has dramatically changed our daytime routine and is affecting social dynamics in their entirety.[1] As part of our everyday life, medical education has been remarkably involved too. Here below we will discuss about our experience, the one of a final-year medical student who is about to be remembered as one of the "Coronavirus-generation graduates" and of a young assistant professor of Surgery.

During the last three years of their long road to graduation, medical students are involved into both surgical and clinical internships not only to achieve exams credits but specially to work on their final thesis. In fact, they are able to choose a specific medical area in which focusing their effort. Due to safety restrictions, medical students are now suspended from attending their internship. As well as students' clinical/surgical activities, scientific research has been slowed down too. As far as our experience is concerned, this is the case of some observational studies promoted by nation- and Europe-wide collaborative groups which are now, reasonably, suspended.[2,3]

The way of teaching has temporarily changed as classic live face to face lessons have been replaced by streaming ones via Microsoft Teams® (MT), a very useful software in educational and smart-working systems, as shown in ***Figure 1*** and ***Figure 2***. However, we think that this unfortunate calamity pushed us to get familiar with the online teaching, something we were not used to take into proper consideration.

Moreover, lessons can be recorded upon teachers consent in order to have them available for further review and listening; tests will be remotely performed on line, which will grant increased transparency especially as far the oral ones.

As a matter of fact, MT platform allow students to interact more efficiently with teachers when compared to classic lessons: teachers found a greater number of questions asked during the online ones, perhaps dictated by the fact that, being the lesson online, that feeling of embarrassment in asking an oral question in a class was diminished. From this perspective, MT is a teaching resource perfectly mirroring our *social-era* relationships where human warm is kind of lost but we are more confident in voicing our feelings through a keyboard and beyond a screen.

By contrast, we urge to stress out that online classes will never be able to replace clinical practice which has to be taught and learned at the patient's bed, visiting and touching him.

But now six years have passed. For a medical student this means that he/she is about to achieve his/her long-life goal: graduation. Never in their lives would they have imagined the graduation ceremony to be telematic. In fact, both the discussion of the final thesis work and the graduation announcement will be made via MT. *Graduation Evaluation Commission* members will be joining candidates in a conference videocall in which each student will show the results of their studies. At the end of the last discussion, there will be the official graduation proclamation. Both professors and students will participate from their homes/offices (***Figure 3***). As it may be clear, during the graduation day there will not be any public or private celebration for this once-in-a-lifetime achievement. In line with other Italian universities policy, the Rector of *Federico II University of Naples*, in Italy, assured that an official ceremony will be held once this emergency status is over.

Figure 1. Online General Surgery focus with Professor Luglio and his Graduate Students.

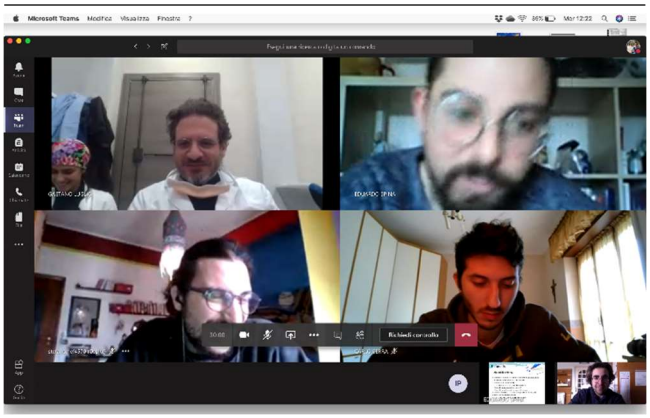

Figure 2. Live Face-to-Face Lesson at the School of Medicine and Surgery, Federico II University of Naples, Italy.

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Figure 3. A Brand-new Graduate in Medicine and Surgery at Federico II University of Naples, Italy.

Often, during the years of a student's internship, the professor's role changes: at the beginning he is the academic but, month by month, he becomes a mentor. From this perspective, it is easily understandable how disappointing it could be for him not to be side by side with his pupil in the plenary hall in front of an audience.

It is true, we all are annoyed to live in a limbo but we should keep our feelings under control. People are suffering, are dying, are losing their jobs. Then, let's stay home as we are not stuck but just safe.

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ULS

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Experience

Uncertainty in the Air. In the Emergency Room with COVID-19 in Pakistan

Abuzar Siraj,[1] Muhammad Waleed Khan.[2]

The Experience

News of the novel Coronavirus spreading like wildfire in China definitely made it to us, but it always seemed so foreign, so far. It was not until 11th March 2020, when WHO declared it a pandemic, that the gravity of the situation became apparent to us.[1] Ever since Pakistan confirmed its first 2 cases on 26th February 2020, the numbers keep piling up. As of writing this, the number of confirmed cases stands at a grand total of 3277.[2]

Fresh out of medical school, my classmates and I were looking forward to finally begin our professional career in medicine. I've always wanted to escape from the realm of books and presentations to actually participate in patient care and make a difference in someone's life. When I found out my first rotation was going to be in the medical emergency room (ER), I was both excited and anxious at the same time.

Emergency rooms in Pakistan are one of the busiest in the world.[3] They also happen to be terribly under-staffed, overcrowded and under-resourced. Usually, you are expected to triage patients, decide who needs your urgent help, and administer life saving measures while also catering to the needs of those patients who are not in any immediate threat, all in the span of a few minutes. This balancing act was made exceptionally complicated by the current pandemic.

I arrived on my first day without any personal protective equipment (PPE), barring an old surgical mask from last week. And within a few minutes, my first critically ill patient came into the ER. Pale as a ghost, ice cold to the touch with no palpable pulse, the attending called for immediate CPR (Cardiopulmonary Resuscitation). Our entire team of junior doctors participated with great zeal; chest compressions, blood drawing, intubation. But all in vain, as the patient failed to respond and the code was called off. Thoughts of sadness were quickly turned to that of worry when the attendant explained that the patient had developed a dry cough and fever earlier that day. Ironically, the masks we had could not hide the fear we were wearing on our faces. The tension was palpable in the air. But there was no time to ponder, as the second batch of patients made their way through the ER doors.

I could not help but think about that patient. We did not know for sure if he had COVID19 (Corona Virus Disease 2019) because he was never tested. But what if he did? Does this mean I have it too? Am I passing it on to all the other patients I see or will see? Will I give it to my loved ones at home? If so, I was violating the most critical dictum of the Hippocratic Oath, "first, do no harm."

My shifted ended, and I left for home physically and mentally exhausted. I locked myself in my room, disinfected everything I had with me in the ER. This unseen threat left me with plenty to think about for the night.

On the day of my second shift, the hospital ordered that all outpatient services will be discontinued in an attempt to minimize unnecessary exposure. This meant a greater volume of patients made their way to the ER for conditions that did not need emergent care. Our ER got even more congested which further increased the likelihood of transmission of the virus.

The entire situation was immensely taxing as dozens of suspected cases came through and asked to be treated, which we young doctors had to provide them, without any PPE. It got to a point that the sound of the nebulization machine, which is implicated in spreading aerosols and so increasing transmission[4], sounded like a grenade going off, spreading contagious debris everywhere.

Experts say the situation will go from bad to worse in the days to come, with the total number of cases projected to reach 50,000 at the end of April 2020. Pakistan is a third world country; our health care system was barely hanging on before this pandemic. Add to that personal risk, outraged relatives, and a culture of mistrust between health care professionals and its civilians, you get a sense of impending doom and gloom, with young doctors at its very center.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

COVID-19 amongst the Pandemic of Medical Student Mental Health

Leah Komer.[1]

The Experience

If being a medical student is hard, being a medical student who struggles with mental health is grueling. Everyday feels like an uphill battle, starting with just getting out of bed after a restless sleep. Just when I thought I was getting a grip on this beast, the unexpected happened. As I was nearing what I thought would be the plateau in this seemingly never-ending climb, COVID-19 sent me up an even steeper path. My original journey had me attending regular counselling sessions and doctors' appointments, with summer electives scheduled, board exams booked, and even small getaways planned with friends. COVID-19 rerouted me to a closed university, no access to counselling services, travel restrictions, a call from the Canadian government to return home, cancelled electives, and oddly, and unpredictably, a toilet paper shortage. While no one was prepared for what the coronavirus pandemic had to bring, it seemed that an already existing problem had been lost in the chaos of it all - what I like to call the pandemic of mental health amongst medical students.

With the demands and pressures that medical students face, it is no surprise that our mental, physical and spiritual wellbeing can be compromised. Ironically, a field that advocates the promotion of health and wellness in patients falls behind in supporting and addressing the needs of its students and residents. In a cross-sectional survey comparing psychological distress and mental illness amongst the medical student population to that of postsecondary graduates, Canadian researchers found that medical students had significantly higher rates of diagnosed mood disorders, suicidal ideation, and psychological distress.[1] In addition to these higher rates, female medical students were more likely than their male counterparts to have a mood disorder, lifetime suicidal ideation, and more severe psychological distress.[1] This is not a unique issue to Canada, and there is a plethora of evidence that medical students worldwide experience significant rates of burnout, psychological distress, and psychiatric morbidity.[2-5] Despite the abundance of research and blatant problem at hand, in my experience, the support is largely lagging behind the evidence.

Even before the world shut down due to COVID-19, awareness and promotion of mental health in the medical community were difficult to acquire. Throw a viral pandemic into the mix and finding a roll of toilet paper became easier than finding support. With so much uncertainty accompanying the events unfolding globally, the added stress of school responsibilities, cancelled medical placements, board exams, and self-isolation, the weight of it all became too much. I felt like I was succumbing to the beast. I struggled to get out of bed in the morning. I had minimal interactions with friends and family. I would stare at my computer screen for hours on end trying to find the motivation to study. To add fuel to the fire, the expectation was that I would have all this "free-time" to dedicate to my work and that I needed to capitalize on everything shutting down and become immune to the distress the rest of the world was facing. In reality, however, I was struggling with another pandemic. While other students were worried about exams, I was worried about accessing my medication. Amidst medical placements getting cancelled, so were my counselling sessions. I had to uproot from my supports in Ireland to come back home to Canada and self-isolate for 14 days.

I know my situation is not unique. There are thousands of medical students who face similar challenges, and more, on a daily basis, especially now given the evolving COVID-19 situation. I believe that now more than ever, our medical community needs to recognize this and act. Understand that we are more than just students and future healthcare providers, but that we have lives outside of medicine. We are not above the stressors thrown our way due to the global crisis that is unfolding. We are people first and our profession second. Just as our patients need care and support, we owe it to ourselves to return the favour.

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Experience

The Utility of Online Resources in Times of COVID-19: A Mexican Medical Student Point of View

Aldo Mijail Pacheco Carrillo.[1]

The Experience

It has been four months since November 2019 when the SARS-CoV-2 outbreak started in Wuhan, China. At the beginning there were medical students who did not believe that the disease would reach Latin America and that news was overstated, as of right now coronavirus disease is a particular burden on the health care systems of many countries including Mexico, mainly due to the lack of resources in public hospitals. It also impacts on the medical education of the country because all universities commanded their students to stay home so the government could handle the situation, firstly for 3 weeks, but it seems that the time of quarantine might be more. Meanwhile many students and professors are still battling to do online lectures because, in contrast to the U.S.A. education system,[1] here in Mexico most of the lectures at university require the student in the classroom, that is why teachers are not used to web lessons.

I have noticed that many of my classmates did not really know the existence of online courses and the quality they may have, it occurs the same with web workshops and other certificate offering resources that many people, including myself, have used to gain extracurricular knowledge in matters of research, clinical applicated knowledge and more. So far in a week I have taken a course about antibiotics provided free by Stanford university, another one about how to use Mendeley by Elsevier online campus and one more course about important information about covid-19 by the Mexican Institute of Social Security, while I attending my regular lectures using the app Zoom to chat with my professors and classmates. I must admit that the quality of online regular lectures are not the same as the presential lectures I get at the university. One out of ten times the internet connection will make very loud interference noise causing the online reunion to end prematurely. However, I see more advantages than disadvantages, for example, I take most of the classes at my desk or bed, to be honest, I feel comfortable doing it. I also have more time to exercise at home and to cook healthy food, on the other hand, the only bad thing I see is the risk of social isolation leading to depression.[2] In my case, I stay with my family and keep contact with my friends by using social media, but for the people living alone the situation could be dangerous. Additionally, I have noticed that many of my friends are spending more time in social media and streaming platforms instead of investing time exploring online academic resources. Maybe because they don't know of their existence.

How are online resources a great window of learning opportunity?

There are plenty of online courses and many of them allow you to fulfill their objectives in a very generous space of time. For example, I took a course about how to write a paper in English with twenty hours of lectures through 8 weeks. Besides the time efficiency, a student can learn something he hasn't seen yet but he will soon, turning the online courses into a *flipped classroom* that has been proved to generate strong positive perceptions on evaluation surveys and benefit the student knowledge and learning process.[3]

Are online resources proven to be beneficial to students?

Depending on the resource, it has been proved that online platforms providing study tools have a positive effect as long as the student participates actively (answering questions and taking notes).[4] Further, open online courses have reported to have a huge potential improving soft-skills and research skills,[5] and although they cannot replace the traditional model, they can be added as a complement and a way to encourage self-directed learning skills.[6] A previous study demonstrated that touch screen device apps improve information retrieval and conceptual understanding.[7]

Are online courses and study platforms valid options in times of COVID-19?

Considering the long time, we will not be able to go out, the short answer is yes. Online resources have shown benefits for learners in terms of engagement, convenience, attainment and enjoyment.[8] I think they are comfortable as well as they generate compromise. In fact, they could be entertaining. Despite the limitations, I think they represent an important tool for medical students around the world.

In summary, we live in an unprecedented time, the covid19 outbreak has paralyzed the world including medical students. They remain in quarantine in the hope that the pandemic will end. The Latin America countries are particularly affected by their lack of resources and the time when medical students return to the universities is lengthening. Meanwhile the use of online platforms to resume the classes and the variety of online courses to complement the learning seems promising and should be more widely disseminated.

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Experience

Studying Medicine in Barcelona During the COVID-19 Pandemic

Enrique López-Ruiz.[1]

The Experience

Here, in Spain, life has rapidly been pushed into an indoor-restricted life as a consequence of the ongoing COVID-19 pandemic. The measures towards an indoor-life started in Barcelona when, on March 12th, the Government of Catalonia published a resolution declaring that presential educational activities must stop.1 Two days later, this resolution was followed by a Royal Decree issued by the Spanish Government, which suspended classes on the whole country and established much more strict measures, such as the obligation to stay at home —with some exceptions, like shopping for groceries or working—.2 Since then, COVID-19 cases have not stopped rising, making Spain the European country with the most confirmed cases, exactly 152,446 on April 9th.3 Because of the strong bond between health institutions and medical training, medicine faculties are being the most affected ones by this worldwide crisis.

What has changed for medical students?

For me, a second-year medical student at the University of Barcelona, presential classes have not been replaced with recorded or real-time online classes as fast as has been done in other faculties4 —and some classes have not been replaced at all—. Workload has not decreased, and libraries are closed, leaving us without the possibility of consulting a wide range of recommended bibliography. In some subjects, teachers have started uploading their PowerPoint presentations with audio records or explanatory notes, sometimes published with a significant delay. We assume that this lateness on home-learning-appropriate material is due to the fact that our teachers are usually health workers who must be having frenetic and stressful workdays, but this issue is making e-learning harder and slower for students. Moreover, most universities, like the University of Barcelona, have declared the end of presential classes for this semester,5 what will make us lose face-to-face classes even if the lockdown ends before the academic year does. To make everything more complicated, confinement has several negative psychological effects,6 which we can expect to be influencing our academic performance and that will become worse as the isolation is prolonged.

Even though that every situation that I have described is negative, that is not all the picture. Communication between teachers and students has increased spectacularly and workload is trying to be progressively adjusted. Exams are being rescheduled and the topics that are included in each one are being reevaluated, giving us more time to prepare for them. In addition to this, lots of exams are being planned to be taken online, avoiding a high load of tests when the isolation ends.

A highly relevant concern to take into account is the lack of planned alternatives for clinical practices. On March 9th, all the Catalan medicine faculties cancelled this practices, which are required for the degree.7 I have been lucky enough to be in second year, the last year without clinical practices and, therefore, my knowledge on how it is being managed is very limited, so I will not discuss this topic.

What do we expect for the next weeks of isolation?

It is a common thought between my classmates that the issues previously exposed will eventually disappear. Predictably, communication between teachers and students will continue to increase, and it will help teachers prepare content that is more useful for us. Another important change we will surely experiment is that we will eventually get used to the situation, and thus develop routines and habits that will allow us to decrease isolation-related psychological effects and increase our productivity.

Summary

The COVID-19 outbreak is the biggest health emergency that Spain has faced since it became a democratic country in the late 70s and it is affecting every aspect of its citizens life. For medical students, it is being though to keep up to date with the degree in this new and unexpected situation, but the teaching community is making considerably efforts to make their subjects more accessible.

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Experience

COVID-19: Experience from Vietnam Medical Students

Duc Nguyen Tran Minh,[1] Tung Pham Huy,[1] Dung Nguyen Hoang,[1] Minh Quach Thieu.[1]

The Experience

Living in Ho Chi Minh City, one of the most crowded places in Vietnam, and also being a medical student, I have never imagined that my life would change so much due to a virus like this. In the beginning, people feel quite confident because we live in a place where people always joke that "this place is too hot for a virus to survive". But now, facing 255 cases positive with COVID-19 and more than 2000 cases are being suspected infection, nervous is something undeniable.[1] Since the announcement of the first case of COVID-19 on 22nd January 2020, Vietnam underwent 2 phases of the pandemic. The first phase ended with only 16 patients within one month. Unfortunately, the second phase occurs with the 17th patient in Hanoi, and the number is rising.

Back to school or not: In a stressful situation of the COVID-19 pandemic, many chancellors of the university have very confused when deciding whether to get students at home or return to school, particularly medical schools after a long break of Lunar New Year. I have a bit nervous myself after I kept getting urgent announcements about a return to the school, which usually appeared on weekends when students studying aloof from home must return to the city early to begin a new school week. However, when considering everything comprehensively, I have realized that each decision sent to our students has got to undergo many meetings. From the view of our university steering committee, medical students should return to school soon. I have thought this was the best choice as not only made us have more obtained knowledge about the disease and preventive measures but also medical students ought to seem of the core forces complementing the missing positions of medical staff when an outbreak or further spreading.[2]

Shifting to online classes: After the country announcement of 15-day social distancing on 1st April, the only choice now is online learning.[3] Online courses address the issue of providing clinical knowledge for medical students to some extent; nevertheless, this type of studying is never a close replacement to hall lectures and clinical rounds. Learning online via meeting software means participants can only interact with one person at a time, which means there would be no group discussions, no debate on clinical decisions. Also, professors will find it difficult to collect all student's ideas or to perceive the overall understanding of the class.

As William Osler "He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all", due to the pandemic, medical students should be on their clinical rotations in hospitals for their own and the society's safety.[4] This comes with drawbacks that medical students in their clinical years will suffer from a lack of clinical experience as well as the skills to make on-point clinical decisions, which is of utmost importance for to-be doctors.

"Raising the line": In brief, the method of mitigation, including social distancing, practicing good hygiene, and isolation of confirmed cases, is the act of flattening the curve. Besides, raising the line is about expanding the health care capability to meet the rising demand so that every sick patient has enough medical support depending on their infection severe.[5] Our city now has the plan to recruit final-year medical students to support the situation when the thing is getting worse.[6] Until now, the public health final year students are sent to the Ho Chi Minh CDC to support in contact tracing of suspected and confirmed cases, detecting clusters, answering the hotline, and classify imported suspected cases.[7] According to our peers, the first day felt a bit uncomfortable due to the unfamiliar work. Days later, they were gaining emotional support and began to enjoy the job thanks to their training and the flow of work. These support, belief, and strict rule of personal protective make them more confident when confronted with their daily task at CDC.

To conclude, it is not exactly what I pictured myself doing when learning to become health care providers, but medical students should consciously avoid panicking. Getting highly emotional makes it hard to think clearly and act effectively during a crisis. It's been an excellent opportunity to be needed, to be trained to help safely and to learn valuable lessons from being involved. It is, after all, a different but meaningful way.

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Experience

COVID-19 Pandemic: Other Perspective. Saudi Arabia

Osama A. Zitoun.[1]

The Experience

As of April 2020, the novel COVID-19 Pandemic has permeated nearly our entire world. In response to the unreasonable number of deaths and infected people, many governments have taken actions in an aim to limit the spread. In the Kingdom of Saudi Arabia, the suspension of schools and universities took place on the 8th of March, and all academic activities were to be carried out through online education.[1] Shut-down of all social gatherings and special events and announcements of lockdown and curfews have followed.[2] Indeed, for a senior student in the final year at medical school, this was rather frustrating. My college was beginning in the preparation of graduation ceremony before the winds of COVID-19 degraded all arrangements.

Fear and Social Media.

Overwhelming news captions added fear and anxiety to the preexisting situation as well as promoted rumors and overemphasized information that unqualified individuals provided.[3] Many resources and newspapers refer to the COVID-19 as to be caused by a *Chinese Virus*, influencing the public to target the Chinese People blame them for spreading the disease.[4] Moreover, deceptive rumors and conspiracy hypotheses about the emergence of the COVID-19 have spread around the globe through social media channels to cause what can be called as: (Pandemic of Social Media Panic).[5]

The Ethical Dilemma.

Few emerging infectious diseases have constituted many ethical challenges as dramatic as the novel COVID-19. The shortage of health-related resources will certainly affect patients other than COVID-19 patients, such as heart disease, diabetes, and cancer patients.[6] Disarrangement of the health care system may cause more deaths of patients with a diversity of critical health needs other than that of COVID-19 patients. Thus, in a crisis, we have to adjust the standard of care to highlight the demands of the community and still provide the best achievable individual-level health care.[7] If vulnerable and poor individuals of a community are not capable of practicing physical distancing or accessing health care services, then all members of that community will be at substantial risk.[8]

Other Perspective.

Well, if I want to have a pure pessimistic view of our current situation, this brief experience account will not be adequate to discuss all negative aspects. Nevertheless, our current isolation and quarantine are not disadvantageous all the way. The main question that I was thinking about recently was: What if this pandemic with the same statistics was to happen at the beginning of the 21st Century? I believe that nearly all educational activities and work will be halted. Most aspects that can be substituted by digital tools and replacements will be simply discontinued. In our current case, thanks to the new technologies, we are nearly on track by actively engaging in our education and even social communication. We are now having much free time, which many of us have formerly longed for. We can now take the online courses which we have ever since procrastinated. We could make use of this time to finish pending projects, learn new skills, or just get together with our families. Of course, during quarantine, we may expect a decrease in productivity, state of distraction, low motivation, and difficulty in maintaining concentration.[9] We can try to manage these inconveniences' threshold by prioritizing sleep, eating well, exercising, and most importantly being optimistic.

Conclusion.

Public health education about COVID-19 and its prevention should be intensified to soothe panic and assemble the general population to cooperatively withstand the pandemic.[10] While the COVID- 19 is now a global public health issue, stigma and discrimination should not be neglected as their effects may pull-down the worldwide efforts to control this pandemic. Finally, as the valid measures at hand to oppose COVID-19 are nonpharmaceutical interference procedures such as physical distancing and quarantine, social media should be used to promote the public to follow these measures and maintain the spread of uncertainty and fear.

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Experience

COVID-19: Where Do We Go from Here? An Experience from Medical Students in India

Tanisha Kalra,[1] Nikhita Kalra.[2]

The Experience

As animals saunter down the roads erstwhile earmarked for humans, we begin to think of the enormous thrust of this pandemic on our lives and yours…

Lockdown. Curfews. Containment zones. Hotspot regions sealed. All these are words that have become a part of our life now. Four weeks ago, who would've imagined that life would take such a drastic turn, whether good or bad is a highly individual perspective!

As we step into these uncertain times, we have become cognizant of "service before self" in the true sense. We wear our ammunition, our personal protective equipment (PPE) and go into the dark to combat an enemy that we have very little knowledge about. But the hurdle is the lack of ammunition, the scarcity of PPEs, forcing doctors to rummage through their inventories in this dire time. Who could've anticipated the dearth of masks, including the N95! It was this interlude offered by the lockdown which inspired us to ponder and read-up and we were shocked by the paucity of studies on nitty-gritty like N95 mask reuse vs extended single use. It was only a recent assessment that supported prioritising N95 extended use over reuse.[1]

The gloom that preceded COVID-19 cases forced government organizations to sweat and slave, but enough attention was not paid to the importance of PPE. And now, the after-effects are evident, as an inadequately protected healthcare worker, is unknowingly spreading the virus. For instance, in Delhi when a patient with a travel history to an affected area went to see a doctor in a government run clinic and turned out to be positive for COVID-19 because of which the doctor and around 800 patients he had come in contact with had to be home quarantined for 14 days.[2]

This disease has all eyes glued to the news as we learn something new every day, protocols change by the hour. In light of new evidence, the CDC now recommends that everybody should wear at least a cloth mask when outside.[3] Several states in India have made wearing a mask mandatory and anybody not wearing a mask in public could face legal action.

Something which we can proudly say for our government is that it has excelled in its hour of trial. Its dedication to keep its citizens safe, implementing new strategies every day to flatten the curve and making it a point to ensure that people stay at home even if means taking legal action, is admirable. For most of us, this period of complete lockdown is unprecedented, something which we'll recount to our future generations.

But what bothers us a lot is the violence and atrocities that we as a medical community have to face in these times. Doctors and the paramedical staff are toiling away in hospitals, caring for patients despite a looming threat that they may also get infected with SARS-CoV-2 along with the apprehension of infecting their families. Despite all this, there are several reports across India of landlords evicting healthcare workers, residents not being able to enter their houses and incidences of violence against doctors and nurses all because people believe that they might get infected if somebody caring for COVID-19 positive patients stays in the same locality as them.[4,5] It's hard to digest such information because the same people were applauding and cheering for the frontline works from their balconies a few days ago.[6]

As medical students living in this pandemic amidst lockdown, the future sometimes seems bleak. Several national level exams for entering into a residency which were scheduled for this period have been indefinitely postponed. In such scenarios, when your preparation is complete and you are almost ready for the exam, for the exam to be deferred brings in a lot of anxiety. It becomes difficult to study with no end in sight and to keep studying the same topics repeatedly.

Most academic institutes have taken the onus on their shoulders to maintain a continuity in the curriculum by organizing online classes. Though theoretical lectures continue, clinical rotations in medical schools remain suspended with no light at the end of the tunnel due to conversion of hospitals to exclusive COVID-19 centers. Unpredictability in such times has led to fears about this year being wasted and not being able to follow the set timelines. The only silver lining is that everyone around the world is in the same boat.

Everything isn't gloomy though! The lockdown has brought in a much-needed break from the rigorous routine of medical school and its deadlines. The pandemic has ushered in loads of free time for recreational things. We can proudly say that we have impressed our mother by picking up the pieces of our co-curricular activities where they were left off before foraying into medical school! Most of all, there has been a lot of family time which the entire world had run out of, sharing anecdotes over the dinner table or pulling one another's leg makes time go by in a jiffy. These were the trivial aspects of life that had been lost in our daily hectic routine. Joyce Meyer very rightly put it into words, 'Patience is not simply the ability to wait, it's how we behave while we're waiting'.

The Earth, burdened by the enterprising humans, is recovering in all forms- pollution, wildlife, climate… As another peacock rambled down our street, we realized how nefarious the mankind has been in some ways.

We don't know what the future holds but aren't we all contriving with earnest sincerity of what we shall do when this phase ends! And definitely hoping to come out as stronger and better individuals. But for now, let's all hang in and have faith!

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

A New Reality: Experiences from Canadian Clerkship Medical Students during COVID-19

Jeffrey Leong,[1] Gurkaran S. Sarohia.[1]

The Experience

Medical students across the globe are being impacted by COVID-19 due to changes in teaching activities and patient care involvement.[5] We are third year Canadian medical students studying at the University of British Columbia (UBC) and were in our clerkship year when the COVID-19 pandemic started. We first began our clerkship in the summer of 2019 as cheerful and upbeat medical students, eager to see patients through a well-organized rotation schedule. Never would we have imagined that our lives as medical learners would have changed so drastically and suddenly. On March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization.[1] That same day, there were 46 cases in British Columbia (117 cases in Canada) occurring in health regions of Vancouver Coastal Health, Fraser Health and Island Health.[1] We were hopeful that our clinical duties as year 3 medical students would not be impacted as we were training in a rural town located more than 700 km away from these cases. However, on March 17, British Columbia (BC) declared a public health emergency and soon after on March 19, clinical duties for all the year 3 and 4 medical students at UBC were suspended.[1] We soon saw a new reality of physical distancing measures of 2 meters being implemented, along with restrictions of mass gatherings and closure of non-essential community services.[1] Undoubtedly, our once cheerful and upbeat disposition faded into one of vulnerability and anxiety given the ever-evolving situation.

Adaptations of Academic Bodies to COVID-19

While the impact of COVID-19 on medical students has yet to be explored, one may infer that the impact of COVID-19 will be similar or worse than the 2003 SARS outbreak. One study showed that the SARS outbreak and the subsequent suspension of clinical duties for University of Toronto medical students resulted in a negative impact on medical training and significant psychological stress.[2] Much like the 2003 outbreak, clinical duties for the roughly 600 year 3 and 4 medical students at UBC have been suspended during COVID-19. In fact, clinical duties have been suspended for all Canadian clerkship medical students, a decision made by the Association of Faculties of Medicine of Canada which governs all 17 Canadian medical faculties.[3] As for the some 300 year 3 UBC clerkship students like ourselves, curricular changes are being undertaken and a research-based course from fourth year is being pushed up to this year. In addition, online learning has not occurred for our year 3 class and written and oral exams are cancelled.

Medical Student Responsibility during COVID-19

In past acute health care problems, medical students have been deployed to provide patient care. Events including the 1918 flu pandemic and 2010 South American earthquake and tsunami have seen medical trainees being positioned to assist with health care.[4, 7] During COVID-19, we have seen Italian medical student graduation streamlined to allow for medical worker reinforcement, yet Canadian year 3 and 4 medical students are unable to participate in any clinical work.[5] One may argue that this comes at an opportunity cost to our learning and conflicts with a 2007 Canadian Federation of Medical Students (CFMS) policy which stated that "efforts should be made to educate medical students about their scopes of practice and emergency procedures before a disaster or emergency occurs".[6] This poses the question then of what our responsibility as year 3 Canadian medical students are during pandemics.

As year 3 medical students, we are eager to assist with the COVID-19 pandemic and have witnessed overwhelming support among our year 3 colleagues as well. Student led initiatives such as basic childcare, grocery shopping, contact tracing, 8-1-1 helpline support have been organized by medical students where many students, including ourselves, have signed up to volunteer. While not direct patient contact, we do find some sense of fulfillment in volunteer duties and para-clinical work knowing that these tasks help to alleviate some pressure off the busy health care workers.

Summary

COVID-19 has caused disruption in everyday life, including medical education. It has side-lined clinical UBC medical students and created physical distancing measures with government policies for self-isolation after return from travel.[1] Life as we knew it at the beginning of our clerkship in the summer 2019 has drastically changed. There are questions we still have: What are the responsibilities of Canadian medical students? Are we prepared to assist in a pandemic if it occurs again? Should there be any curricular training for pandemic management in medical school? While we are in the midst of the pandemic, there will be important lessons learned once everything settles. One of the most important lessons learned thus far is from the late Canadian physician, William Osler, and his wise words of, "Soap and water and common sense are the best disinfectants".

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Experience

Medical Students Have a Powerful Role in Addressing Community Needs in the COVID-19 Pandemic: An Experience from the US

Carly O'Connor-Terry,[1] Tejasvi Gowda,[1] Ben Zuchelkowski,[1] Sarah Minney,[1] Jane Kwon.[1]

The Experience

"What are your thoughts on this? Would love to hear your feedback." If our readers are, or ever have been medical students, there is no need to explain the enormity of such a statement coming from individuals with titles, such as "Dean", "Chair" or "CEO." Oftentimes, our voices as medical students are--or at least we think they are--the quietest at the table. We enter the clinical world as "green", inexperienced, and overwhelmed.

This is not that story. We are five medical students with interest in social determinants of health, equity, and social justice. Our experience is one where we approached our classmates, faculty, public health officials and medical leaders with our ideas and concerns; they listened. This is our story, but our story expands beyond our work. It is also about the community with which we work.

Pittsburgh is known as the City of Bridges, with good reason--it is home to 446 of them.[1] These bridges unite neighborhoods filled with groups of people of different ethnic backgrounds, socioeconomic statuses, and cultures. This diversity ultimately makes Pittsburgh, a historical steel town turned hotbed for healthcare and technical innovation, a very special place to live. When we saw how the COVID-19 pandemic was affecting countries like China, Iran, and Italy, our thoughts turned to our home city. As medical students at the University of Pittsburgh, what could we do to support our patients and bolster local community efforts? As the COVID-19 crisis bore down on health systems across the country, us medical students stepped up to do what we came to medical school to do: help others.

The Influx

While we all had our own ideas of what we could do to help the Pittsburgh community during this pandemic, we were quickly overwhelmed by just how many needs surfaced in the aftermath of the shelter in place orders. Requests for childcare from healthcare providers sky-rocketed to the point that need outweighed our availability. Individual organizations reached out for food delivery. We were getting emails and calls about blood donation, supporting youths who suddenly were not at school, staffing a local free clinic and many more. Many of these required us to fulfill these requests in a short time frame. We had to mobilize quickly.

We connected with community organizations with whom we had previously worked and asked them to define their needs and how we could help. Free clinics needed to have medication delivered to their patients. Community organizations needed volunteers to check in on children or the elderly, and deliver food and hygiene kits. We were asked to help with delivering food to our frontline workers (***Figure 1***). One organization wanted us to create accessible information for people with disabilities.

Figure 1. *Left*: students deliver donated food from a local restaurant to community organizations. *Right*: Students assist with delivering medications to patients at a local free clinic.

Clinical Volunteering

Most students that signed up to volunteer were interested in clinical activities. It was not long before those opportunities began to present themselves, including case investigations with our county health department, telemedicine initiatives, and free clinic operations.

The pandemic has emphasized the value of the skills and training that we gain in medical school. We are uniquely positioned as learners in assessing, diagnosing, and making plans to address problems.[2] We are also very adaptable. Our entire training is based on month-long assignments where we quickly have to integrate ourselves into a new team. The environment of COVID19 is constantly in flux, but flux is our specialty.

The Future

At one of our virtual meetings (***Figure 2***), the Vice Dean of our medical school told us, "These will be the stories that you tell 10, 20, 30 years into your career." We cannot help but think about how the trajectories of our careers may be altered by our work during the COVID pandemic.

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Figure 2. Meeting remotely over Zoom®. From upper left to bottom right: Sarah Minney, Ben Zuchelkowski, Jane Kwon, Carly O'Connor-Terry, Tejasvi Gowda.

The work that we have accomplished alongside community organizations has been particularly humbling. While we all have clinical skills as medical trainees, we learned that sometimes other skills, like childcare or food delivery, can have higher priority. It highlights the occasional mismatch that may happen: we may try to treat problems as purely clinical issues when in reality, broken social support systems may be the issue. While non-clinical volunteer opportunities may not be as "glamorous" or appealing to medical students at first-glance, our classmates were willing and happy to perform these roles.

We often reflect back on how we felt before the pandemic. We thought that our voices were quiet and that our knowledge and skills were limited. However, with the way the world is changing and the way medical students have been addressing the needs of their community, we learned that our voices are loud and heard. Not only do we have enough clinical knowledge to help answer many of the questions of our friends, loved ones, and neighbors, but we also have the work ethic, leadership skills, and social skills to meet the wide-range of needs of our community. The imposter syndrome many of us feel has been replaced with confidence.[3] We are uniquely adept at managing the stress that this chaotic time triggers, while maintaining the big-picture vision needed to address structural and societal inequalities. As a result, faculty, leaders in the medical community, and public health officials are the ones who are turning to us.

For the medical students feeling overwhelmed and powerless in this crisis -- know that your voices matter. For students that have been organizing -- we see you and are proud to call you our colleagues. For our mentors and administrators that have been working with us -- we thank you for valuing us.

For those interested in our specific projects, please see our website at www.412med.com.

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ULS

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Experience

The Voice of a Psychiatry Resident Doctor During COVID-19 Outbreak in Mumbai, India

Pooja Kapri,[1] Pawan Gadgile.[1]

The Experience

As the world has been brought to a standstill with the recent COVID-19 outbreak declared a pandemic on 11th March 2020, we both junior resident doctors in the Department of Psychiatry, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, India would like to share our experiences in this situation.

The first recorded case of COVID-19 infection in India was on 30th January 2020 and with the rising cases since then the Government of India issued a nationwide lockdown, starting 22nd March 2020 and further extending it to 30th April 2020. The current statistics of total open cases in India have surpassed 9000 as of 14thApril 2020. The decree limits the movement of general public for procurement of essential goods and services while our frontline warriors, like doctors, nurses and paramedical staff, essential goods' manufacturers and distributors, police forces and sanitation workers have been tirelessly at work.

Being resident doctors, we have been in the center of this pandemic. We have seen an unprecedented increase in number of anxious patients developing panic disorder and patients going into substance withdrawal in the past few weeks. Many people developed what is called Corona anxiety and they feel that they may contract the virus. Mild fever and cough were thought of as COVID and anxiety developed. Excessive protection and obsessiveness about social distancing and protection developed in people.1

A number of patients on maintenance medications of psychiatric illnesses have been having difficulty in reaching out to the doctors for prescriptions as a result of the lockdown, and have had acute exacerbation of their complaints. Telemedicine has been proposed as the need of the hour, although highly debatable. The Ministry of Health & Family Welfare, India has recently released guidelines to be followed.

There is no stringent body that would monitor the quality of these services and whether ethical standards are adhered to. It is important that professionals and agencies offering telepsychiatry services have professionals who are qualified and trained in this regard to some extent.2

Even compliant patients that came to our Out Patient Department had sleep and appetite disturbances, easy irritability, breakdowns over trivial issues and anxiousness. We also received innumerable queries and concerns in the recent days from relatives and friends having difficulties in managing their stress, culminating into emotional outbursts. Lending an open ear, simple reassurances and general directives for prevention against COVID infection as well promoting mental well-being and self-care has been the way forward for us. We have emphasized that social distancing should not mean emotional distancing, and in these trying times we need to stay connected with our family, friends and loved ones via electronic means.

The medical and paramedical fraternity have been under tremendous stress themselves with the mounting number of daily new cases and deaths, long and tiring work hours (14-18 hours a day), scarcity of hospital beds, lack of treatment protocols and Personal Protective Equipment (PPE), constant worry about contracting the infection and taking it home; thus putting our families at risk, staying in the hospital premises for days together; away from our own family has all been taking a toll on our mental health as well.

Good mental health care for these doctors, nurses and ancillary staff is very important and this will help in developing a stable healthcare infrastructure to combat COVID. There is also a need for training these staff in communication skills and building their resilience for the tough times that they shall face ahead.3

Many psychiatrists have felt that the current pandemic has made psychiatry appear as a non-essential field. Hospitals and many centers have allowed that their non-essential staff to stay home which include basic sciences and psychiatry in some quarters but the question of essentiality and non-essential is a personal one that we have to answer. We cannot shy away as we are doctors first and psychiatrists later. Consultation-liaison psychiatrists work closely with the medical and surgical teams and also know about the worries that their colleagues undergo. Consultation-liaison psychiatrists usually traverse through the hospital and multiple specialties system and will be on the frontline in this pandemic.4 While we use telepsychiatry to manage our patients, it is vital that we realize we are as important on the frontline as we are on a video screen or telephone call.

India has been facing one of the biggest crises of recent times both socially and economically, putting a physical, mental and emotional strain on patients, general public and healthcare providers alike. The World Health Organization has praised India's commitment in combating and containing the pandemic, setting an example for others to follow. Only time will tell about the final outcome, as we give in our best fight against COVID-19 while providing help, support and empathy to fellow beings.

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Experience

Lessons from COVID-19: The Perspective of an International Medical Student Back in the United States

Avnee Nulkar.[1]

The Experience

While applying to medical schools, I was advised to refrain from the "common cliché" – that helping people was my principle reason for aspiring to practice medicine. During interviews, I emphasized my fascination with the human body, my desire to bridge treatment and prevention, and my hope to lead the US' healthcare reform. Above all, I always circled back to my primary passion for impacting patients in a personally significant way – one that is only present in the field of medicine. The current pandemic, which has revealed the weaknesses in healthcare systems and highlighted the strength of healthcare workers globally, has re-affirmed my motivation for entering medical school and serving others.

I first learned of COVID-19 as an American student attending an Irish medical school. Quicker than expected, cases spread across the country, and the virus soon infiltrated our teaching hospitals. Within two weeks, we were quarantined and encouraged to return home. Since 2019, I had meticulously planned my 2020, which I anticipated as the most important year of my career thus far. I was slated to complete US licensing exams and third-year medical school exams between March and May, and my US rotations would follow during Summer 2020. Instead, what initially appeared to be a contained virus evolved rapidly into a pandemic. Within days, my classmates and I returned to our home countries, with hopes of reuniting with our families and caring for our communities.

During my two-week self-isolation at home in California, my restless mind overwhelmed all rational sense. I was in limbo awaiting the decision to cancel or continue my US licensing exams, unsure how much study time to allocate towards my licensing exams versus medical school exams. I was also attempting to conceal my unremitting worry and fear for my family and friends, as the case number at home seemed to climb daily. More importantly, I felt, in the most realistic sense, useless. Here I was, with three years of medical knowledge, yearning to be helpful in hospitals, whether taking bloods, triaging patients, comforting families, or collecting personal protective equipment, yet a diploma was lacking – my perceived ticket into clinical settings to aid the fight against COVID-19 in California.

In time, I reframed these obstacles as challenges. I researched volunteer organizations in which I could deliver food to community members, tutor children, and foster shelter animals. Although my student status did not qualify me to aid in clinical settings, I was soon eligible to register with California Health Corps' COVID-19 Response Team and my local response team, thanks to Governor Gavin Newsom's appeal for increased aid.[1]

While volunteering and awaiting my response call, I had time to reflect. This pandemic has revealed that the existing connection between healthcare and employment must be terminated. In 2012, 61% of health insurance coverage was linked to employment, while 49% of coverage was employee sponsored in 2019.[2,3] Although the percentage has decreased, too many Americans who experienced job security this past year are now unemployed, still resulting in loss of insurance.[4,5] Compared to universal coverage, insufficient health coverage is associated with premature death and decreased health status, suggesting that the health of those who lose insurance is likely to suffer.[6] Healthcare is a human right, not an employee benefit. The government should seize this opportunity to question the inner workings of our healthcare system and implement changes to prevent such losses in the future.

Contemplating the flaws in our current system has reiterated the significance of healthcare reform as well as strengthened my resolve for pursuing medicine. Doctors have a duty to care for their patients, which includes advocating for their right to access healthcare. Extra time, funding, and critical dialogue should be dedicated towards healthcare restructuring. Additionally, this pandemic has shed light on how grateful I am to have a home, healthy family members, and basic necessities. One month ago, my mind was consumed with exams and rotations. Now, I feel thankful for my family's safety and health and will do my best to advocate for patients' safety and health while refusing to take such comforts for granted.

Although I have yet to be called by the response teams, I recently learned that medical teams and volunteer organizations within California are reaching capacity. This news immediately filled me with gratitude. The inherent good of people in our community has provided a sense of unity and hope during a time of uncertainty and distress, inspiring me to provoke a similar feeling in those around me. The mode of doing so is irrelevant, whether it occurs in a clinical setting, from my desk at home, or in a car between food banks and homes. Personally and professionally, my purpose is to help people to the best of my ability – the "common cliché," or reason I pursued a medical career.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Being an American 2nd Year Medical Student in the COVID-19 Pandemic

Benjamin D. Liu.[1]

The Experience

Four months ago, nobody could have guessed just how disruptive COVID-19 would be. The first case was reported in Washington, United States on January 20th, 2020.[1] While spreading rapidly, it mainly spared the mid-west United States where my medical school is located. Just over a month and a half ago, cases were still low in my state and I was fully expecting to finish my school year and take my Step 1 medical licensing exam with minimal disruptions. By the time March 12th, 2020 rolled around, several cases appeared in our state and thus my school decided to move all classes completely online while keeping exams on campus. A week later, all school services went remote, including exams and all non-essential employees after the community spread intensified. Most importantly, the one exam that essentially determines which residency programs or even which area of medicine you can apply to, is cancelled until April 30th (likely much longer). Today, the United States remains the hardest-hit region in the world standing at 829,000 cases as of April 22nd, 2020.[2]

For most 2nd year US medical students, March-June is basically quarantine. While yes, a bit overstated, most students spend at least a month dedicated to 8+ hours per day of reviewing, doing practice questions, and flashcards in preparation for the Step 1 medical licensing exam. With a test date near the end of June, the lockdowns currently in effect have not changed my plans very much. However, for many 2nd year medical students who normally study on campus, in coffee shops, or libraries, are struggling to focus studying at home all day. Even worse, a substantial number of students were supposed to take Step 1 in March or April. Reading their posts in online medical student forums, I cannot imagine spending all that time to prepare, just to have the exam they were supposed to take ***the next day*** canceled and delayed for another month and a half at least. Communication from the testing company has been poor, and anger and frustration from medical students is strong. Many students describe feeling unmotivated, anxious, and aimless even. I identify with these feelings and feel the cabin fever that many medical students are feeling as I approach day 42 of quarantine. Nevertheless, as I hear about what our fellow 3rd and 4th-year American students are going through - canceled in-clinic learning opportunities, uncertainty about graduation and rumors about being forced to work as an unpaid, tuition-paying 4th-year student at a resident level - I understand that the big takeaway is that medical students, as a community, are going through unprecedented difficulty and need to support each other.[3]

Beyond Step 1, not much has not changed. Reading an Italian Medical Student's experience during the outbreak, a major difference between my experience and theirs was the fact that most of our lectures were already streamed online.[4] It's well known that many U.S. medical students do not go to class; over a third (34.9%) of medical students never or "occasionally" attend virtual classes and almost half (48.1%) do the same for in-person classes.[5] As a result, besides the change of no longer having to go to mandatory classes, the daily 2nd-year medical student class experience has not changed. For our exams, our school (like a significant number of other medical schools at this moment) are currently being delivered remotely. When taking the exam, we need to have the webcam open and are not allowed to look anywhere but the screen. If we do, it will be flagged for review by exam proctors later. Nevertheless, other than the "big brother" feel to it, the exam situation has been quite reasonable as our exams were taken electronically before the pandemic as well.

Finally, any extracurriculars that 2nd-year students may be involved in are generally on hold. Because of the Step 1 dedicated period, most of our extracurriculars have already been handed off to the first-year students for leadership, therefore 2nd-year students were not generally affected. Nevertheless, seeing the ability of first-year students to adapt the organizations to this time has been amazing. For example, the free clinic associated with our school has now moved completely online to telehealth, while dispensing any medications in person with protective measures in place – all thanks to the leadership of the 1st year student director board.

In conclusion, a significant portion of 2nd year US medical students' class and extracurricular experience have not been affected very much. Instead, many of our Step 1 licensing exam plans have been completely disrupted leading to anger and uncertainty over this extremely important exam. Organizations should remember that communication with their patrons is very important, especially in times of crisis. US medical students should continue support each other and remember that this too shall pass.

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Experience

Medical Students in Low- and Middle-Income Countries and COVID-19 Pandemic

Chatpol Samuthpongtorn,[1] Krit Pongpirul.[2]

The Experience

The novel coronavirus disease (COVID-19) pandemic has attacked nearly every country—high- and low- and middle economies. The dividing line that dichotomizes the global population into medical staff who provide care and patients who receive care has never been this thin. In fact, healthcare providers have more likelihood of not only getting infected but also spreading the virus.[1-3]

As of April 14, 2020, there were over 2,500 cases in Thailand and more than 2,000,000 cases worldwide. While these figures attracted the attention of any young individual to a similar extent as other international news. In many countries, schools were closed and students were asked to study at home. Likewise, pre-clinical medical students were asked to do the same. Nonetheless, medical students who are in their clinical years like myself are not qualified as a healthcare professional, yet are not regarded as layperson either. Things are complicated as conventional medical knowledge as well as clinical care and personal protective skills of medical students have not saturated, not to mention the unclear pathophysiology of the emerging virus.

During the inception of the 6th year of my medical training in Thailand,[4] in the emergency room, a 45-year-old male presented with dyspnea on exertion for one day. Despite no obvious respiratory symptoms, his oxygen saturation was about 91-92%. Electrocardiogram showed sinus tachycardia with partial right bundle branch block and a chest x-ray was within normal limits. As pulmonary embolism was suspected, his blood was checked and found a significantly high D-dimer level of 700 mg/L. Consequently, computerized tomography pulmonary angiography was performed but found no blood clots in the pulmonary vessels. Instead, peripheral infiltration of both lower lungs compatible with COVID-19 was revealed. The patient was immediately moved to an airborne infection isolation room. Nasopharyngeal swab that was obtained from the patient tested positive for SARS-CoV-2 on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay.

The positive COVID-19 result in an afebrile patient with no obvious respiratory symptom was no longer a surprise,[5,6] but it inevitably 'scary'. As a good medical student should do, history taking and physical examination were done intensively to approach a patient—approximately 45 minutes per patient on average in my own experience. Performing an echocardiogram on this patient to rule out structural heart disease added up exposure time. Thai medical students have been taught to take care of patients as if we were looking after our family members; it was partially acceptable to make an inconclusive diagnosis or treatment plan but unacceptable for a medical student to show inadequate compassionate care, especially in the Thai context. Unfortunately, the longer time we spend with an infected patient, the higher chance we get infected ourselves.

The moment I knew that the patient was COVID-19 positive, I started asking myself so many questions, including about the reliability of the personal protective equipment that I wore that day. Did I wear it correctly? Did I clean my hand adequately afterward? Despite the anxiety and stress while waiting for the result from laboratory investigations of hospital staff who contacted the patient, I did not feel discouraged from taking care of patients. I believe in remaining calm and finding a way to learn and practice skills through this situation. One mandatory skill for any general practitioner is endotracheal intubation. Although intubation was presumed to pose a high risk for healthcare staff during the procedure to save the life of an infected patient, such presumption might distract us from the fact that the virus could be transmitted from an asymptomatic carrier. Although physical protection is essential, I learned that ability to remain focused is crucial during the pandemic. There have been several atypical presentations of COVID-19 cases; abdominal and testicular pain, sudden loss of smell, shortness of breath without fever or respiratory symptoms,[7] for example. Patients came to the hospital without a clue of COVID-19 so it is very difficult to indicate which patient is 'high risk'. Hence, the medical school policy to limit exposures or procedures in high-risk patients for medical students is practically questionable.

COVID-19 has a potentially significant impact on medical students and medical schools. A 26-year-old University of Louisville medical student became ill while at school but tested negative.[8] After returning to her home, she was taken to the Baptist Health Lexington emergency room, tested positive for COVID-19, and had to be admitted to the intensive care unit for weeks. After she had gotten better, she still had a mildly depressed mood. Moreover, she did not know who she got infected from although nosocomial infection was likely.

Medical students in preclinical years in Thailand teaching have replaced classrooms with online sessions; the objective was to decrease the gathering of children into the crowded community and reduced physical interactions. Those in clinical years were in their questionable roles and responsibilities during their educational transition. On the contrary, the American Association of Medical Colleges (AAMC) reported at least 13 U.S. medical schools allow students to graduate early in response to the COVID-19 pandemic.[6] While I hope that approach is not necessary for other countries, I am still not sure if I prefer a clear and legitimate role and responsibility as a doctor to being an in-training medical student with unclear safety skills.

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We believe the knowledge and skills regarding infection control in the medical curriculum, at least in low- and middle-income countries like Thailand, have been minimal to none. The COVID-19 pandemic introduced an unprecedented opportunity for medical students and a majority of medical staff to learn about the personal protective equipment (PPE) for the first time.[3] This is a great starting point of a new norm in our medical society, along with the other emerging social norms such as wearing a mask and washing hands.

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ULS

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

The COVID-19 Pandemic Through the Lens of a Medical Student in India

Surobhi Chatterjee.[1]

The Experience

The pandemic has brought an unprecedented challenge before the global community. It can be labeled as one of the most severe pandemic which has already affected 210 countries including India.[1] One of the communities hardest hit is the student body. Much akin like every other medical student, I was extremely anxious. I am an Indian. I am from Lucknow, Uttar Pradesh, one of the most densely populated areas in the world. When just put in plainly, this is not a lot to concern about but once you understand the vulnerability of the population in my country and the immediate restriction measures the government had to take to restrict infection, being anxious, just comes naturally. Being a medical student who had just arrived home after the end-semester exams; the closing of universities, schools, public places, any forms of social interaction beginning from 13th March,[2] was just the silence before the storm. Since March 24th, the entire nation of a 1.3 billion people is in complete lockdown.[3] Most universities had to cancel their examinations, the Undergraduate national examinations for premier medical and engineering institutes, the board examinations of senior secondary and high school and internal school exams were postponed indefinitely. The lockdown was implemented for 21 days which had to be extended till 3rd of May taking into account the increasing number of cases and the impact of social distancing in fighting the pandemic.

How did universities and schools respond?

With the government's advisory on immediate closing of institutions, the student and education bodies both were faced with the challenge of provision of quality education via online platforms.[2] Most universities started live-online classes. Schools even started their own e-learning platforms for students. Everybody had their reservation regarding this complete shift from lecture discussions to an online portal altogether. In a low- and middle-income country (LMIC) like India, the internet connectivity and global access to it is still not a universal privilege. Learning of these new skills by the senior faculty members was though difficult and time-intensive, but it has yielded a significant impact in decreasing the psychosocial trauma and anxiety the student community faced.

Medical schools and their transformation

Medical schools are known for their intense curriculum and workload. They have adhered to their traditional in-house lectures and bedside teaching since a long time. The pandemic brought a diabolic change in this rigorous teaching schedule. Doctors and healthcare workers being the backbone of the community's fight against pandemic are already in testing times. It was difficult at first for medical schools to adapt but with the passage of time and dawn of realization, they were quick to resort.

My experience with online teaching has not been a smooth sail either, though it is important to understand a few points here. There is poor internet connectivity in some areas, (mine thankfully being an exception) which is partly even due to heavy traffic. Complaints ranging from the access, audio and video quality to sometimes even about the background noises were raised regarding the live streamed classes, which was faced by me too, though rarely. The online streaming of lectures by senior faculty wearing masks and some in their full gear kept making me realize the precipitous amount of workload the medical community is drenched with. Here, it is even important to understand that my institute, King George's Medical University and associated hospitals, a premier tertiary-care medical school of India, is also combating the immense workload of regularly screening and treating a large number of COVID-19 suspects from around the state and, like, many other medical institutes, is also trying its level best to provide quality education to students. There are several factors that acts as barriers for online education, with a) academic skills, b) technical skills, c) cost and internet access, d) time and motivation for studies and e) technical issues, being some of them.[4]

In brief, India, which is at the face of this unprecedented crisis, since the Spanish Flu, the turmoil both economically and mentally, has been immense. The world's 2nd most populous country has been under complete lockdown since 25th March. Universities though have responded by providing e-learning platforms for its students, a lot still needs to be done especially for the medical students, who are next in line for this fight. Student-centered approach needs to be implemented including doubt clearing sessions via online portals, virtual bedside-stimulation software, creative conceptualization and student engagement, keeping in mind the 4 key pillars- skills, resources, institutional strategies and support and attitude.[5] The interdepartmental co-ordination needs to be ensured as well.[6] India, with its stringent lockdown measures is an example for most low- and middle-income and even affluent countries and was applauded by WHO[7] and by the Oxford COVID-19 Government Response Tracker (OxCGRT) for the same.[8] Hence, India can revolutionize the field of cost-effective online education for others to learn from.

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