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International Journal of Medical Students
The International Journal of Medical Students (IJMS) is a peer-reviewed open-access journal (ISSN 2076-6327) created to share the scientific production and experiences of medical students and recently graduated physicians worldwide.

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EDITORIAL STAFF

IJMS

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The *International Journal of Medical Students* (IJMS) is an open-access, peer-reviewed scientific journal (ISSN 2076-6327) that publishes original research in all fields of medicine. The Journal was created in 2009 to share the scientific production and experiences of medical students (*i.e.*, MBBS students, MD students, DO students, MD/MSc students, MD/PhD students, etc.) and recently graduated physicians from all over the world. Our objective is to be the primary diffusion platform for early-career scientists, using standards that follow the process of scientific publication.

The *IJMS* receives submissions where there is at least one author enrolled as a medical student in any medical school in the world or a recently graduated physician worldwide. For research articles, early-career scientists must be accompanied by a senior researcher that must be also responsible for the research, guaranteeing the quality of the work. We publish Original Articles, Short Communications, Reviews, Case Reports, Interviews, Experiences, and Letters, which follow an innovative and unique two-step, double-masked peer-review process, in brief:

> *The first step of revisions is carried out by two Student Editors (medical students with publications indexed in the US National Library of Medicine (NLM) with the supervision of an Associate Editor. The aim of this step is to improve the quality of articles and identify those that can proceed to external peer-reviews. The second step of revisions is carried out by external peer-reviewers who are researchers with publications indexed in the NLM related to the topic of the submission.*

The time between submission and final publication in most cases has been two to four months depending on the diligence of Peer-Reviewers and Authors.

The *International Journal of Medical Students* is published online quarterly (March, June, October, December) by the University of Pittsburgh Library System, a member of the Open Access Scholarly Publishers Association, as part of its Pitt Open Library Publishing imprint.

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The *IJMS* acceptance rate is 18% of the almost 350 annual submissions. Published articles in 2021 came from 32 different countries. The average days to a first decision is 14 days, 143 for acceptance, and 31 to decline a submission. The time between submission and final publication in most cases has been three to four months depending on the diligence of Peer-Reviewers and Authors.

The journal's website got over 75 thousand visits only in 2021. The *IJMS*'s reach includes a growing social media presence (more than 19,000 followers on Twitter, Facebook, Instagram, YouTube, and LinkedIn). Only in the last 2 years, the Journal has been visited from nearly every place in the world (+190 countries). You can find more of the *IJMS* statistics here.

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There are no article processing charges, submissions fees, or any other costs required of authors to submit, review or publish articles in the IJMS.

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All papers submitted to the International Journal of Medical Students will undergo a two steps peer-reviewers process. The first step of revisions is carried by two anonymous Student Editors who will work together with one Associate Editor. In the second step, the manuscript will be reviewed by two anonymous reviewers (Editorial Board members, Associate Editors and/or invited reviewers with expertise in the subject matter). Authors will remain anonymous to all the referees.

The *IJMS* review process guarantees and supports the quality and validity of the work published at the *IJMS*. Reviewers are given three weeks to complete their tasks.

Reviewers and editors are obliged to retain the contents as privileged and confidential until publication. The Editor in Chief and the Editorial Board will have final authority over an article's suitability for publication.

The *IJMS* also strive towards the training of a new generation of Editors and Peer-reviewers promoting different training strategies among our Editorial Team that includes the Web of Science Academy courses and the Committee on Publication Ethics (COPE) courses available to its members (*IJMS* is a member of COPE).

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

Global Needs and Barriers for Medical Research Education: Initiatives to Solve the Physician-Scientist Shortage

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In a recent interview, Dr. Anthony Fauci said the words that physicians worldwide must embrace and apply: "…You're a scientist."[1] There is a little romanticism in the belief that all physicians are scientists, but it is our deepest wish that all physicians find a passion for research. It is easier said than done. Research requires rigor, knowledge, the use of validated methods, resources, mentors, adherence to ethical guidelines, sometimes the endurance and hardships of data collection, the ability to write in a "scientific manner", and the patience to get the results published. Through all those barriers is where we, as a society, begin to lose physician-scientists from the tracks. People like research until they find the above-mentioned barriers or get tired of fighting against them, and this can happen at any stage of a physician's career, as a medical student, resident, clinician, or faculty.

Moving away from barriers after medical school, medical students' education includes the encouragement of independent study to stay up to date. Some efforts are also made to train them as potentially independent researchers. These efforts sometimes are just shy attempts to teach research methodologies and statistics without proper applicability or the resources to carry out real-life research. One of the very few ways to get real training in most of the cases is to pursue a graduate diploma in research being a master's or a Ph.D. or a combined program (i.e., MD/MSc, MD/Ph.D., etc.). Nevertheless, and besides all the barriers that a medical student can face to carry out research, some (should be everyone but that will be discussed in the next editorial) reach the goal of a scientific publication. A scientist not only reads critically, but they must also write and publish. We at the International Journal of Medical Students are committed to the publication of medical students and early career-scientist research and we try our best to help authors get their papers out. Our innovative, 10-year tested and validated, two-step peer-reviewing process help us achieve high quality early-career scientists publications.[2-4] It includes a step of real peers (medical students with publications) reviewing and suggesting ways to improve the research or the way that is being described or analyzed to make it into a publishable scientific article.

Medical student barriers to research have been widely studied and still, the issue has not been fully addressed. Several different efforts, like journals focusing on medical students' research or initiatives to mentor and help medical students to carry out research (https://ijms.info/IJMS/Conference/sponsors) are among the few options that medical students have to become those scientists that the world needs.[5-7] Humankind is lucky enough that some medical students are not satisfied with what medical school provides. They go the extra mile to change their environment to be able to become scientists. In this issue, we found some interesting research and medical students' activities that are aligned with the above arguments. Medical students experience more barriers to research compared to residents or faculty, and still they are asked to have publications or research experience to get into a residency. This can go against the promotion of research and could encourage predatory publishing behaviors.[9] These barriers to do research are reinforced by gender bias and its effects on women wanting to pursue a career in science.[10] Mentorship and medical curricula reforms are needed to encourage medical students to explore the field of medical research,[9] and evidence-based decisions,[11,12] ensuring that they will continue publishing after graduating,[13,14] have better employment opportunities,[13] and can be better clinicians.[15]

How to Make Editors and Scientists: An IJMS Initiative

For a decade, the IJMS has striven to develop an international society of young scientists via education and mentorship. Building

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opportunities for the community of medical students and freshly graduated physicians has led to immense growth not just for the Journal itself and medical students' research quality, but also for the Editorial Team behind the journal.

The nourishing soil for this successful history is founded on integrity and the will to develop a new generation of editors and scientists.[16] Training via the Web of Science Academy and the Committee on Publication Ethics (COPE) courses constitutes the backbone of the Journal and is mandatory for the whole Editorial Team, which also underlines the objective of the IJMS: to be the leading platform for early-career scientists' medical research. The generations of physician-scientists that have been part of IJMS are highlighted on our Alumni website section: https://ijms.info/IJMS/about/editorialTeam/alumni

The IJMS creates opportunities for medical students to get involved in the development of original articles. The initiative strives to bring young scientists together and mentor them to improve their research. Having built a network of more than sixty young research enthusiasts, we are happy to share that there are numerous research collaborations within the IJMS network that are of the highest quality and published in high-impact journals. We see the successfully published articles of these collaborations as a transcript of our efforts. The manuscripts tackled topics in the fields of hematology and oncology,[17-23] ethics (e.g., diversity, equity and inclusion),[24-27] infectious diseases,[28,29] surgery,[30,31] pediatrics,[32] and physical and rehabilitation medicine.[33-35] We invite you to read them and encourage you to include students and early career scientists in your research projects.

The quality of our team is also expressed in the statistics of the Journal. In 2022, excluding editorials, our team was able to process a total of 58 articles from submission to publication (acceptance rate=29%). We were able to provide the first decision in only four days for most papers. The authors received the first revision request on an average of 49.2 days (SD=63.4, median=32.5, IQR: 23-49, range: 3-433) after the initial submission. With this fast pace, we were also able to accept articles on average after 187.9 days (SD=130.1, median=147.5, IQR: 114-224, range: 34-662) from the initial submission. And finally, from acceptance to publication, it took an average of 31.8 days (SD=40.1, median=9.5, IQR: 3-53, range: 0-145) to produce publishable articles.

Announcement of the 2023 World Conference of Medical Student Research

After steadily gaining popularity and a successful conference in 2022, the IJMS is pleased to announce the 2023 World Conference of Medical Student Research (WCMSR) to be held on October 7th, 2023. Sparking the idea to foster a new generation of physician-scientists and to enable international networking, we aim to further develop the WCMSR as the fundament for an inclusive scientific society. Again, the format will be fully online allowing participants to present their research to an international audience.[36] The presentations will be evaluated by an expert jury, and the top 10 works will have the possibility of a fast-track peer-reviewing process. Each abstract accepted will receive its own digital object identifier (DOI) and publication in Volume 11 Supplement 1 in December 2023. Please refer to the website for more information: https://ijms.info/IJMS/Conference/welcome.

Other Papers in This Issue

Turning away from the training aspect, this issue features an interesting study by Zhou et al. The authors propose the use of a new decell process in tracheal transplantation that involves removal of epithelial, mucosal, and submucosal cells while preserving chondrocytes. This procedure was carried out on the trachea of Yorkshire pigs and achieved by an adaptation of the sodium dodecyl sulfate cycle protocol. This novel procedure particularly improves the short-term viability of chondrocytes with the limitation on long-term viability.[37]

Soleymani et al.'s manuscript focuses on promoting physical activity amongst people who use wheelchairs by predicting the accuracy and precision of research tools, e.g., ActiGraph accelerometers and SMARTwheels, which can be used to measure pushes. The study reports that SMARTwheels had a minor undercount of the total number of pushes across workloads versus ActiGraph accelerometers (worn on the arm) which recorded an overcount of the same parameters. Thus, the authors advocate for more accurate research in this area.[38]

Ng and Velanthren report the case of a 69-year-old Chinese man in Malaysia with a windswept deformity caused by pseudogout. The patient presented with pain in both knees and right shoulder, and deformed windswept knee requiring the use of a walking stick, with full painless flexion in both knees and shoulders. Imaging studies showed complete destruction of the knee joints. As the patient could not afford surgery, he was placed on steroids and colchicine. This case report shows how devastating pseudogout can be and the need for affordable surgical care to promote health equity.[39]

Munoz-Valencia et al. described an association between the availability of blood banks and the incidence of deaths due to traumatic hemorrhagic shock. The authors used national datasets from Colombia and analyzed clusters of municipalities. They concluded that the more banks the lower the incidence of deaths due hemorrhagic shock. Interestingly, the authors mention the lack of research on geographic determinants of blood products' availability and the need for granular data to enhance conclusions.[40]

Peñafiel-Pallares et al. report the case of a 51-year-old female presenting with a three-month history of headache and diplopia. She was found with fundoscopic abnormalities, with absent clinical history of hemophilia. She was diagnosed with an uncommon combination of a hemophilic protein C type 1 deficiency and a cavernous sinus thrombosis complicating sphenoidal rhinosinusitis. The authors point out the importance of early recognition and treatment in such cases.[41]

Revisiting the beginning of a worldwide catastrophe, Gajare et al. share their experiences during their COVID-19 travelers screening activity by explaining protocols, guidelines, and screening procedures of international passengers for symptoms of COVID-19 at one of the largest airports in India.[42]

As suicide is the second leading cause of death worldwide in 15-29-year-olds, Keuch et al. investigate the prevalence of suicidal ideation as an indicator for future suicide attempts among German medical students and suggest further development and implementation of preventive strategies.[43]

Gabralla et al. present a case of exacerbated, previously well-controlled, myasthenia gravis (MG) following the second dose of the AstraZeneca COVID-19 vaccine. Despite rehydration therapy and steroids, the 37-year-old patient passed away after failed attempts to obtain IV immunoglobulins.[44] Although this is not the first MG case to suffer from disease exacerbation after receiving the COVID-19 vaccination,[45-49] nearly a fifth of MG patients were found to experience exacerbations during or after COVID-19 infection in a study conducted by Peric et al.[50]

Even if high-income countries have limited the wearing of white coats in healthcare facilities to decrease hospital-acquired infections or healthcare-associated infections (HAIs),[51] most of the world still sticks to wearing them. Daraniyagala et al. conducted a cross-sectional study on medical students to assess the rate of white coat contamination, the responsible pathogens, and antibiotic resistance phenotypes. Nearly half of the participants had coats contaminated with bacteria associated with HAIs, including methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococci. Therefore, it is important to limit wearing white coats and switch to scrubs, or to have strict rules as to how and when to wear white coats.[52]

Conclusion

In a world where changes are inevitable and challenges particularly in healthcare emerge every day, research has become an essential problem-solving tool. Physician-scientists are needed more than ever. The IJMS has and will continue to provide an open platform for medical students and junior doctors to explore their areas of interest in research and share their findings with their peers and the world at large. Our platform has also encouraged collaborations across the world and led to the publication of innovative research papers. Furthermore, the introduction of the WCMSR is another mind-blowing progress to unveiling the work done amongst the students and junior doctors. The IJMS is on a wheel of progression, and in the near future, an even bigger impact will be made to achieve the goal of creating positive change in healthcare through research in the global society.

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Original Article

De-Epithelialization Protocol with Tapered Sodium Dodecyl Sulfate Concentrations Enhances Short-Term Chondrocyte Survival in Porcine Chimeric Tracheal Allografts

Kevin Xiang Zhou,[1] Fabio Gava Aoki,[2] Alba Marin,[3] Golnaz Karoubi,[4] Siba Haykal,[5] Thomas K. Waddell.[6]

Abstract

Background: Tracheal transplantation is indicated in patients with extensive defects that are unable to be repaired via primary reconstruction. However, transplantation is currently considered a high-risk treatment option partly due to high morbidity and mortality associated with graft rejection. Recently, decellularization (decell) has been explored as a technique for creating bioengineered tracheal grafts. However, this method increases risk of post-operative stenosis due to the death of chondrocytes, which are critical to maintain the biochemical and mechanical integrity of tracheal cartilage. In this project, we propose a novel decell protocol that adequately removes epithelial, mucosal, and submucosal cells while maintaining a greater proportion of viable chondrocytes. **Methods:** The trachea of adult male outbred Yorkshire pigs were extracted, decontaminated, and decellularized according to the original and new protocols before incubation at 37 °C in Dulbecco's Modified Eagle Medium (DMEM) for 10 days. Chondrocyte viability was quantified immediately following post-decellularization and on days 1, 4, 7, and 10. Histology was performed pre-decell, post-decell, and post-incubation. **Results:** The new protocol showed a significant ($p < 0.05$) increase in chondrocyte viability up to four days after decell when compared to the original protocol. The new protocol also preserves extracellular matrix (ECM) composition to a similar degree as the original protocol. When scaffolds created using the new protocol were re-epithelialized, cell growth curves were near identical to published data from the original protocol. **Conclusion:** Despite limited improvements in long-term chondrocyte viability, the new protocol may be used to engineer chimeric tracheal allografts without the need for cartilage regeneration up to four days post-decellularization.

Key Words: Tissue Engineering; Decellularization; Allograft; Trachea; Bioreactor; Regenerative Medicine; Chondrocyte; Stem Cell; Graft; Transplantation; Transplant; Surgery; Bioengineering; Stenosis; Cartilage; Viability; Cell Viability; Medicine (Source: MeSH-NLM).

Introduction

Tracheal transplantation is a surgical procedure that aims to restore the airway in patients with extensive defects that are unable to be repaired via primary reconstruction. Transplantation is indicated in cases where injury exceeds 50% of the organ in adults and 30% in children.[1] However, tracheal replacement therapy is currently considered a high-risk procedure, and is mostly offered as a treatment option in compassionate use cases. A major reason behind the relatively high rate of complications is the plethora of immunological compatibility issues created by orthotopically transplanting a donor organ.[2] A possible solution to this problem may be found in tissue engineering-based approaches for whole-trachea regeneration. Recently, significant progress has been made in engineering bioartificial organs de novo from pluripotent stem cells and acellular extracellular matrix (ECM) scaffolds.[3–6] Somatic cells have been differentiated into functional lung epithelial cells after transformation into induced pluripotency.[7] Also, stem cell-seeded tracheal grafts from cadaveric donors have been transplanted into patients with end-stage airway diseases.[4] Despite these milestones, recellularized tracheal allografts still demonstrate increased risk of stenosis, resulting in post-operative complications.[3,4,8]

Decellularization (decell) of donor trachea is a relatively well-studied technique for creating natural scaffolds for whole-trachea

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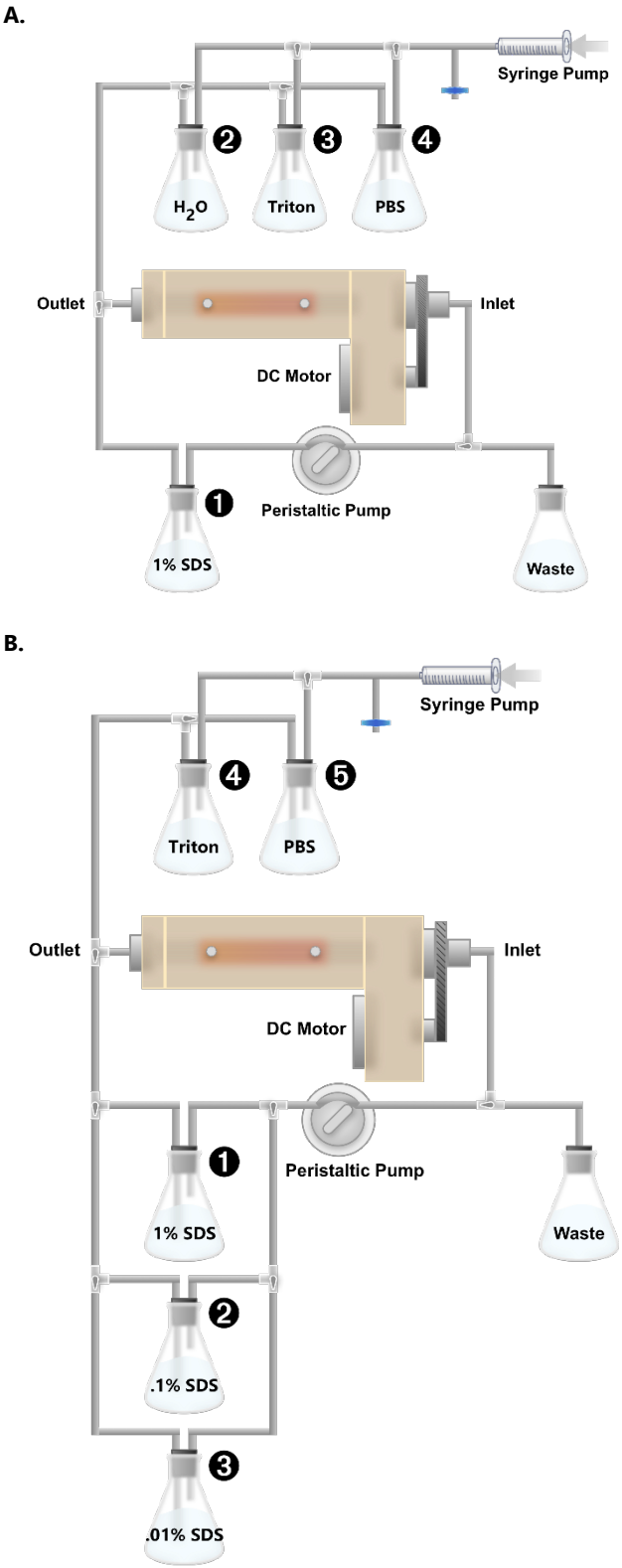
regeneration.[9–15] One such decell approach involves the use of detergents to remove donor cells from a cadaveric trachea, leaving behind the ECM scaffold.[11,16,17] Recipient-derived induced pluripotent stem cells (iPSCs) may then be seeded onto such scaffold, thereby reconstituting the respiratory epithelium.[4] The benefits of this approach are twofold. Firstly, risk of graft rejection is reduced because the immunogenic donor tracheal epithelium and submucosa are removed and replaced with autologous cells.[8,10,18–20] Secondly, the use of a native biological scaffold rather than synthetic materials preserves the important tissue architecture and ultrastructure, which allows for greater mimicking of the cellular niche later during scaffold seeding.[17] However, the full thickness decell protocols currently in use are harmful to chondrocytes, leading to deficiencies in the biochemical and mechanical integrity of hyaline cartilage.[14,17,21] This may increase the risk of post-operative stenosis and other complications upon implantation.[22] To address this issue, the Waddell lab uses a de-epithelialization (de-ep) technique pioneered by Aoki et al. in 2019 to remove only the immunogenic epithelium while maintaining chondrocyte viability.[17,23] This de-ep technique can be followed by re-epithelialization (re-ep) using autologous cells to produce chimeric tracheal allografts.

Despite these advances, the original de-ep protocol is suboptimal due to relatively low chondrocyte survival rates (68.6 ± 7.3%).[17] A new de-ep protocol has recently been developed by the Waddell lab based on the postulated chemical and osmotic effects of various decellularization agents on chondrocytes. This protocol is believed to provide milder de-ep conditions that may increase chondrocyte survival while providing similar removal of epithelial cells. When designing this new protocol, the following hypotheses were made: 1) removal of the standard 40 minute ddH_2O wash cycle will decrease osmotic stress on cells perforated by sodium dodecyl sulfate (SDS) detergent, the most common decellularization agent used in previous protocols, and 2) using decreasing concentrations of SDS rather than a static concentration will remove greater amounts of residual SDS in submucosal tissue, thus protecting cartilage. An initial high concentration (1%) is required for decellularizing epithelium and mucosa, after which lower concentrations of SDS (0.1%, 0.01%) are more appropriate for minimizing damage to cartilage. This study intends to serve as a proof-of-concept to demonstrate that a modified de-ep protocol can allow the removal of immunogenic tissue (epithelium, mucosa, submucosa, and perichondrium) while preserving a greater portion of the chondrocyte population. The objectives of this study are to: 1) evaluate chondrocyte viability in porcine trachea after the use of the new de-ep protocol, 2) evaluate the preservation of ECM biochemical composition after the new protocol, and 3) evaluate the degree of epithelial cell attachment and viability during re-ep after the new protocol. We hypothesize that the new protocol will produce de-epithelialized scaffolds with improved chondrocyte viability while demonstrating similar biochemical composition and re-epithelialization performance as compared to the current protocol.

Figure 1. **A**: The Perfusion Circuitry Designed for the Original de-ep Protocol.[17] Order of Perfusion is Numbered from 1-4 and Corresponds to the Solutions in Table 1. **B**: The Perfusion Circuitry Designed for the new de-ep Protocol. Order of Perfusion is Numbered from 1-5 and Corresponds to the Solutions in Table 2.



Methods

Tracheal extraction

Adult male outbred Yorkshire pigs (30-40 kg) (n = 18) sourced from the University Health Network (UHN) Animal Resources Centre were used as donor animals due to the physiological similarity of their cardiopulmonary system to that of humans. After anesthesia by isoflurane administration, a median incision of the neck was made to expose the larynx and upper trachea. Next, a median sternotomy was performed to open the chest wall and provide access to the lower trachea. Using Mayo scissors, the trachea was bisected just below the cricothyroid membrane and lifted away from the esophagus. Surrounding connective tissue was dissected away using curved Mayo scissors. To detach the trachea, the left and right main bronchus were bisected just below the carina. The extracted trachea was immediately placed in decontamination solution at 0 °C until transported out of the operating room. The decontamination solution contained Hank's balanced salt solution (HBSS, ThermoFisher, USA) supplemented with 2% (w/v) bovine serum albumin (BSA, ThermoFisher, USA), fluconazole (4 µg/mL, Gibco, USA), colistimethate (5 µg/mL, Gibco, USA), imipenem/cilastatin (25 µg/mL, Gibco, USA), ceftazidime (154 µg/mL, Gibco, USA), penicillin (200 U/mL, Gibco, USA), streptomycin (200 µg/mL, Gibco, USA), amphotericin B (2.5 µg/mL, Gibco, USA) and gentamicin (50 µg/mL, Gibco, USA). The tracheas were subsequently incubated at room temperature on a rocking platform (30rpm) for 2 hours. After this incubation, the decontamination solution was replaced with fresh solution, and luminal mucus was scraped off using a micro-tapered stainless-steel spatula. The tracheas were incubated at 4 °C overnight until de-ep was performed the next morning.

Animals selected for tracheal extraction surgery were screened against the following exclusion criteria:

- Respiratory pathologies,
- Participation in concomitant respiratory studies (ex: bleomycin lung injury model), and
- More than 30 minutes since cardiac death (donor warm ischemia time).

All animals received humane care in compliance with the ''Principles of Laboratory Animal Care'' formulated by the National Society for Medical Research and the ''Guide for the Care of Laboratory Animals'' published by the National Institutes of Health. The study was approved by the Animal Care Committee of the Toronto General Research Institute.

De-epithelialization and incubation

The following solutions were prepared under sterile conditions and adjusted to a pH of 7.4: 1%, 0.1%, and 0.01% SDS; 1% triton X-100; Dulbecco's phosphate buffered saline (DPBS). A perfusion system was constructed using polyvinyl chloride (PVC) tubing and 4-way Luer connection stopcocks as illustrated in *Figure 1*. A rotating perfusion bioreactor was used, modified from Haykal et al. Using three 2/0 silk sutures, the trachea was anastomosed to the bioreactor with its proximal end facing the inlet of the chamber (*Figure 2*).[4] De-ep was performed according to the original, new, and control protocols outlined in *Tables 1-2*.[17]

Table 1. Original de-epithelialization Protocol.[17]

Step	Reagents*	Time	Vol. (mL)	pH	Temp. (°C)
1†	1% SDS	3 hr	75	7.4	37
2†	ddH_2O	30 min	140	7.4	37
4‡	1% Triton	30 min	140	7.4	37
5‡	DPBS (-/-)	30 min	140	7.4	37

Legend: * Reagents inside trachea (Lumen). Outside the trachea, DMEM with 10% FBS + 1% Penicillin-Streptomycin solution remains circulating.
† De-epithelialization process – pulsatile perfusion
‡ Washing steps – continuous perfusion
DMEM = Dulbecco's Modified Eagle Medium
SDS = Sodium Dodecyl Sulfate
DPBS = Dulbecco's Phosphate-Buffered Saline

Following de-ep, the proximal and distal ends of the trachea were trimmed such that only the portions exposed to the decellularization media were used for the subsequent 10-day incubation. The tracheal segments were then placed in decontamination solution for 48 hours at 4 °C on a rocking platform (30 rpm). Finally, the tracheae were incubated at 47 °C with 5% CO2 (ThermoFisher, USA) in a 250 mL Erlenmeyer flask fitted with a 20-micron filter allowing for gas exchange. The media used was Dulbecco's Modified Eagle Medium (DMEM, Gibco, USA) supplemented with 10% (v/v) fetal bovine serum (FBS, Gibco, USA), fluconazole (4 µg/mL), colistimethate (5 µg/mL), imipenem/cilastatin (25 µg/mL, Gibco, USA), ceftazidime (154 µg/mL, Gibco, USA), penicillin (200 µg/mL, Gibco, USA), streptomycin (200 µg/mL, Gibco, USA), amphotericin B (2.5 µg/mL, Gibco, USA) and gentamicin (50 µg/mL, Gibco, USA). Media was changed every 48 hours.

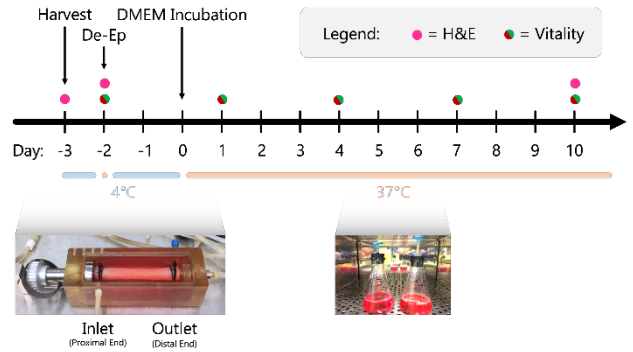
Table 2. New De-Epithelialization Protocol.

Step	Reagents*	Time	Vol. (mL)	pH	Temp. (°C)
1†	1% SDS	1 hr	75	7.4	37
2†	0.1% SDS	1 hr	75	7.4	37
3†	0.01% SDS	1 hr	75	7.4	37
4‡	1% Triton	30 min	140	7.4	37
5‡	DPBS (-/-)	30 min	140	7.4	37

Legend: * Reagents inside trachea (Lumen). Outside the trachea, DMEM with 10% FBS + 1% Penicillin-Streptomycin solution remains circulating
† De-epithelialization process – pulsatile perfusion
‡ Washing steps – continuous perfusion
DMEM = Dulbecco's Modified Eagle Medium
SDS = Sodium Dodecyl Sulfate
DPBS = Dulbecco's Phosphate-Buffered Saline

To accurately compare the two de-ep protocols being tested, two negative control groups were employed. The first control was a decontaminated native trachea that immediately underwent static incubation for ten days without any de-ep procedure, henceforth referred to as "control-native." The second control was exposed to the same conditions as the trachea that underwent the new protocol, except with DPBS replacing all steps that required SDS, henceforth referred to as "control-DPBS" (*Table 3*).

Figure 2. Timepoints for live/dead Staining and Histology used in this Study. Bottom left: Appearance of the Bioreactor with lid Removed. Trachea is Visible, Surrounded by Dulbecco's Modified Eagle Medium (DMEM).



Two control groups are necessary to rule out any potential negative effects on chondrocyte viability arising from tracheal harvesting and installation into the bioreactors. If both controls demonstrate similar levels of near-100% viability, the study can conclude that the primary determinant of chondrocyte viability is the protocol itself, in other words, the series of SDS decellularization steps. Three biological replicates – each consisting of a single trachea harvested from a random Yorkshire pig – were performed for the original protocol, the new protocol, and the two control groups.[17] Day 0 was defined as the start of the bioreactor incubation period, hence day −2 was when the decellularization protocol was performed. *Figure 3* illustrates the study protocol as a flowchart diagram.

Histological analysis

Histological samples were taken from the trachea before de-ep, after de-ep, and after incubation (*Figure 4*). Specimens were fixed with 4% paraformaldehyde for 24 hours and processed with an automated vacuum tissue processor (Leica, USA). Tissue was sectioned into 5 µm slices and stained with hematoxylin and eosin (H&E), Masson's trichrome (Sigma-Aldrich, USA), Verhoeff's elastin (Sigma-Aldrich, USA), and Alcian blue (NovaUltra™, IHC World, USA).

Figure 3. The Experimental Protocol Followed in the Current Study, Illustrated as a Flowchart Diagram.

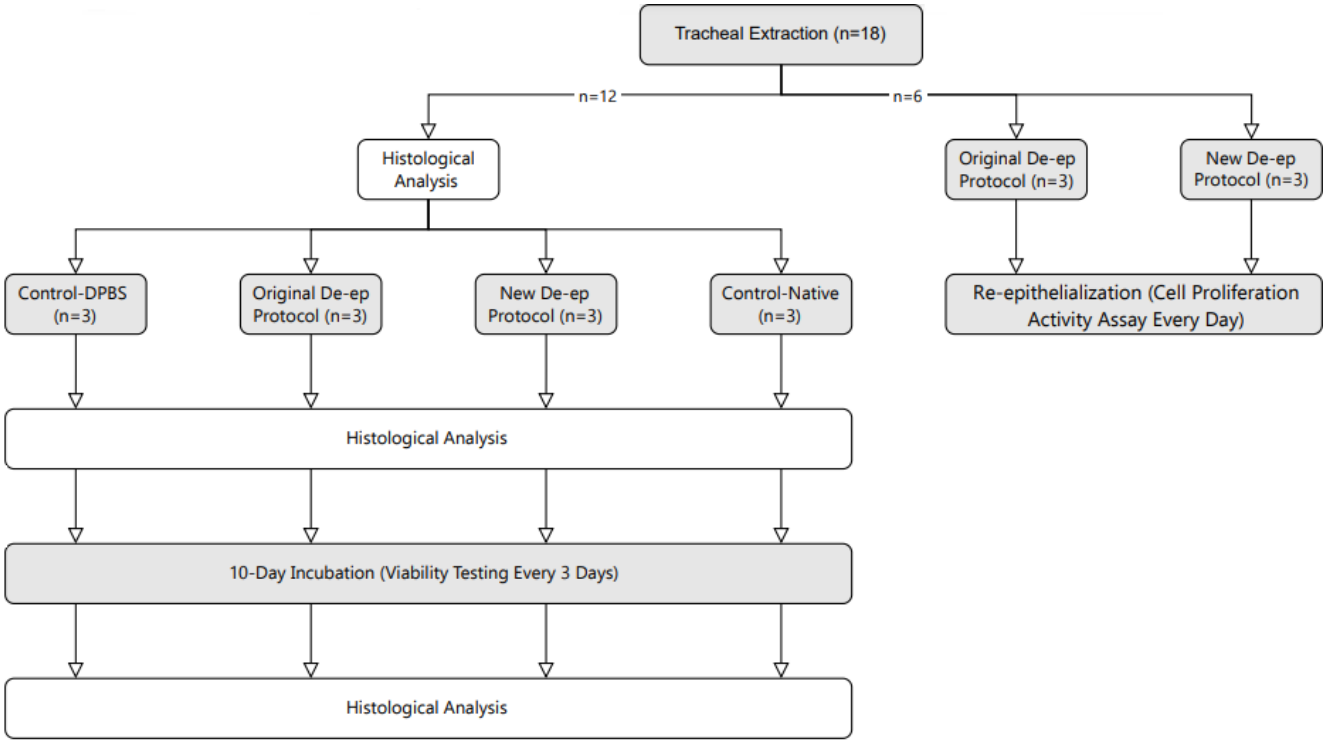


Table 3. Control – New De-Epithelialization Protocol without SDS. Identical Conditions as new Protocol, Except Perfused with DPBS Instead of SDS for Preparation of Control-DPBS Trachea.

Step	Reagents*	Time	Vol. (mL)	pH	Temp. (°C)
1†	1% DPBS	1 hr	75	7.4	37
2†	1% DPBS	1 hr	75	7.4	37
3†	1% DPBS	1 hr	75	7.4	37
4‡	1% Triton	30 min	140	7.4	37
5‡	DPBS (-/-)	30 min	140	7.4	37

Legend: * Reagents inside trachea (Lumen). Outside the trachea, DMEM with 10% FBS + 1% Penicillin-Streptomycin solution remains circulating. † De-epithelialization process – pulsatile perfusion. ‡ Washing steps – continuous perfusion. DMEM = Dulbecco's Modified Eagle Medium. SDS = Sodium Dodecyl Sulfate. DPBS = Dulbecco's Phosphate-Buffered Saline

Quantification of chondrocyte viability

Chondrocyte viability was quantified immediately after de-ep and on days 1, 4, 7, and 10 (*Figure 3*). Two to three rings were obtained from each trachea for a membrane integrity-based viability assay. The mucosa and submucosa were dissected away from the cartilage using fine forceps. The cartilage ring was opened and manually cut in cross section into thin (<1 mm) slices. An ethidium homodimer assay (LIVE/DEAD™ Viability/Cytotoxicity Kit, Invitrogen, USA) was performed as per manufacturer directions. The slices were imaged under confocal microscopy at 20x magnification (A1R, Nikon, Japan). Images were then examined manually by a blinded experimenter. Portions of the image containing viable chondrocytes were circumscribed and the area was calculated. The percentage viability of an image was calculated through the following formula:

$$\%\ chondrocyte\ viability = \frac{Area\ of\ viable\ chondrocytes}{Total\ cartilage\ area} \times 100\%$$

Three technical replicates were performed per trachea.

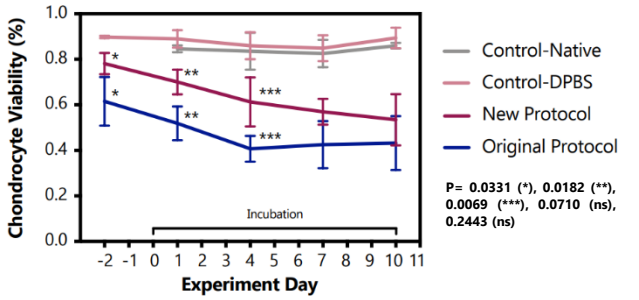
Re-epithelialization

The de-ep bioreactor circuitry from Haykal et al. was modified to include media reservoirs for oxygenation, in addition to syringe ports for media changes and sample collection.[4] A 1 mL suspension of BEAS-2B human bronchial epithelial cells (~1×10^6 cells/cm^2) was injected into the lumen. Cells were allowed to adhere for 2 hours under bidirectional flow at a rate of 1.5 mL/min. After the initial 2 hours, we started unidirectional perfusion of the lumen at the same rate for seven days. During re-ep, media in the luminal circuit (30 mL) was changed every 24 hours and media in the outer circuit (250 mL) was changed every 48 hours.

Cell proliferation activity assay

Cell proliferation during re-ep was measured using a resazurin-based cell viability assay as per manufacturer instructions (PrestoBlue®, Invitrogen, USA). Briefly, a 20 mL solution of 1:20 (v/v) PrestoBlue/DMEM + 10% FBS was prepared. Three 0.5 mL volumes were separated for use as a negative control. The remaining 18.5 mL of reagent was injected into the luminal perfusion circuit of the bioreactor and allowed to circulate for 1 hr. Afterwards, the PrestoBlue solution was aspirated out of the luminal circuit and aliquoted into three 0.5 mL replicates in a 24-well plate for fluorescence analysis at 560 nm (Cytation™ 5, BioTek Instruments).

Figure 4. Chondrocyte Viability Following De-epithelialization and 10-day Incubation in Static Media. Statistically Significant Differences as Determined by a Two-Way Analysis of Variance (ANOVA) with Tukey's Post Hoc Multiple Comparisons Test are Indicated. P-Values Given as: <0.0332 = *, <0.0021 = **, <0.0002 = ***, <0.0001 = ****



Statistical analysis

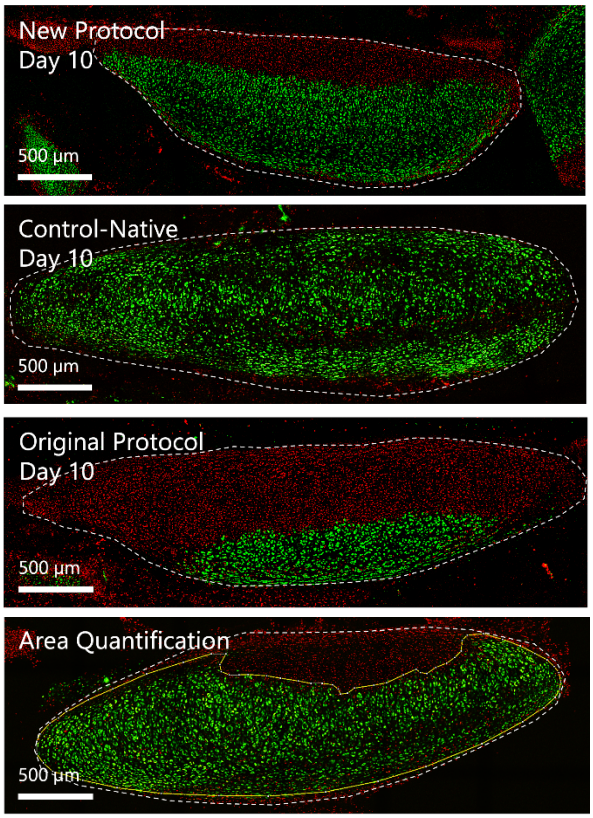
Commercial statistical software (GraphPad Software Inc., USA) was used for statistical analysis. A 2-way analysis of variance (ANOVA) was used to determine statistically significant differences ($p \leq .05$) between the three protocols (original, new, control-DPBS), with Tukey's post hoc multiple comparisons test. Values in figures are presented as means with standard deviations (SD).[17]

Results

Quantification of chondrocyte viability

There exists an overall negative correlation between days since de-ep and percentage chondrocyte viability (*Figure 4*). Both the original and new protocols significantly reduce viability compared to the control protocol (no SDS) and unprocessed native trachea.[17] However, the new protocol provides significantly ($p = 0.0069$) improved viability compared to the original protocol in the first four days, after which there is no detectable difference.[17] The most marked improvement in chondrocyte viability occurs on day 4 (61.3±10.8% vs 40.7±5.7%), yet the benefit of the new protocol towards chondrocytes is seen as early as immediately after de-ep on day −2 (78.1±4.7% vs 61.5±10.7%). In other words, long-term chondrocyte survival remains unchanged. Qualitative inspection of live/dead staining reveals the most chondrocyte death at the luminal surface of each cartilage ring (*Figure 5*). There appears to be a smaller "wavefront" of chondrocyte death in the new protocol compared to the original protocol. The average chondrocyte viability of two replicates (n=2) after a 7-day re-ep was 63%.

Figure 5. Chondrocyte Viability in new Protocol, Original Protocol, and Control-Native Trachea on day 10 of Static Incubation.[17] Confocal Microscopy Images Depicting Calcein-AM for live (Green) and Ethidium Homodimer-1 for dead (Red) Cells in Cross-Sections of Cartilage Rings (Marked as the area within the White Dotted Line). Bottom Right Image Shows the Calculation for Percentage Viability as the area within the Solid Yellow Line (Live Cells) Divided by area within the White Dotted Line (Total Cross-Sectional Area).

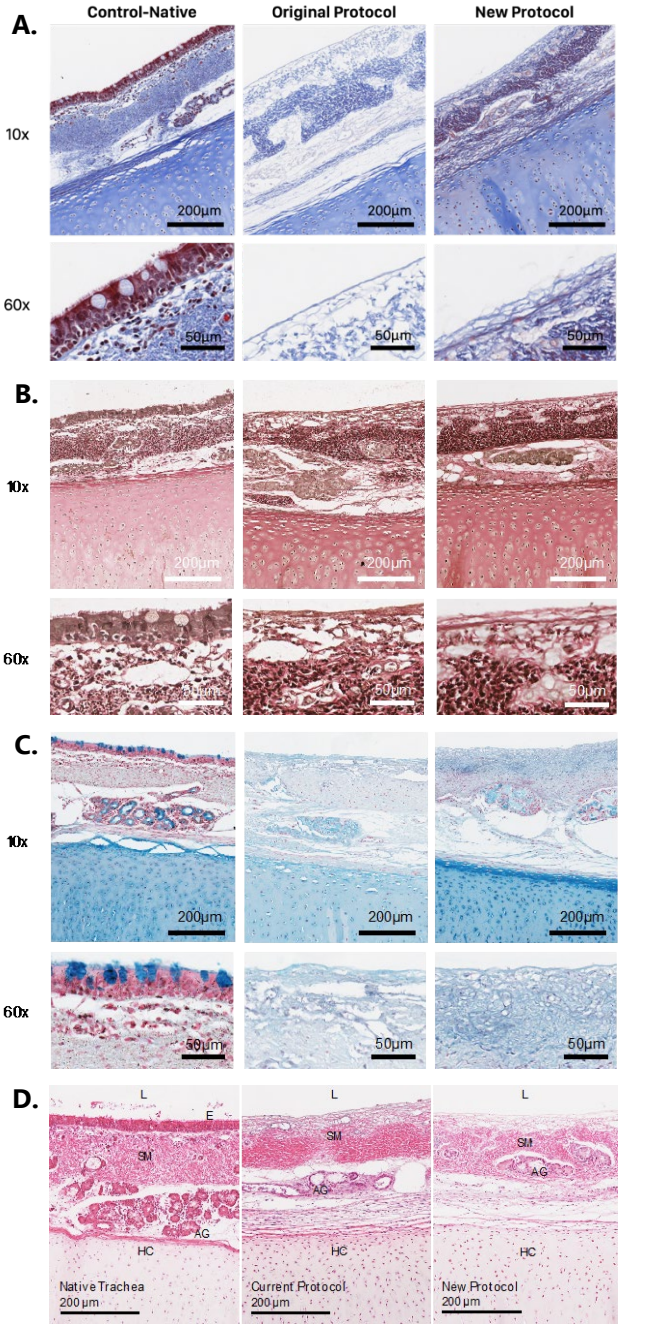


Histological analysis

In the native trachea control, H&E staining showed the expected pseudostratified columnar epithelium with cilia and goblet cells (*Figure 6*). In both the original and new de-ep protocols, H&E showed a denuded epithelium, with no residual cellular material.[17] No nuclei or cytosolic elements were found in the epithelium. However, both protocols resulted in some nuclei remaining in the deep submucosal regions. Residual acinar gland cells were also visible in both protocols. The hyaline cartilage appears morphologically unchanged.

Masson's trichrome stain showed good collagen preservation throughout the ECM in both the original and new protocols (*Figure 6*).[17] Keratin fibers in the deep submucosa appear better preserved in the new protocol. Verhoeff's elastin stain showed good preservation of elastin fibers in the mucosa and submucosa of both the original and new de-ep protocols (*Figure 6*).[17] Alcian blue stain showed good preservation of acidic polysaccharides such as glycosaminoglycans in cartilage, in both the original and new protocols (*Figure 6*).[17]

Figure 6. **A)** Masson's trichrome stain **B)** Verhoeff's elastin stain **C)** Alcian blue stain **D)** Hematoxylin and eosin stain of control-native; trachea processed with the original/current de-ep protocol; and trachea processed with the new de-ep protocol.[17] 10x and 60x magnifications are shown in the top and bottom rows respectively. The lumen (L), epithelium (E), submucosa (SM), acinar glands (AG) and hyaline cartilage (HC) are labelled.

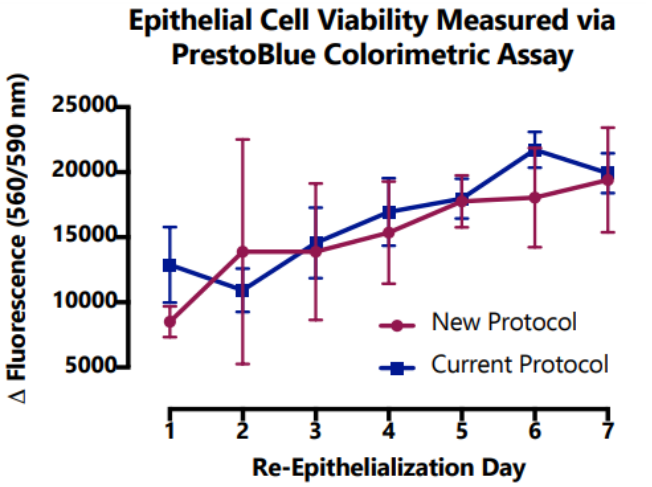


Cell proliferation activity assay

When the new protocol's re-ep cell proliferation curve is compared with that of the original protocol from Aoki et al., there is similarity in the rate at which fluorescence increases (*Figure 7*).[17] The difference between the two growth curves is

nonsignificant (p=0.15, 0.59, 0.86, 0.59, 0.89, 0.20, 0.84) as indicated by a multiple t test (false discovery rate approach). Although not a focus of this study, chondrocyte viability after the 7-day re-ep with BEAS-2B was evaluated with two tracheae. The average chondrocyte viability was 63%.

Figure 7. Growth Curves of BEAS-2B on the New and Old Protocol's Scaffolds over Seven-Day Re-Epithelialization Period.



Legend: p = 0.15, 0.59, 0.86, 0.59, 0.89, 0.20, 0.84.

Discussion

It has been demonstrated in previous literature that SDS reduces cell viability by acting as an anionic detergent, perforating the cell membrane and causing osmotic lysis.[11,12,22] The original protocol contains a 3 hour 1% SDS wash that can leave residual detergent trapped in tissue, thus causing ongoing damage after the protocol is terminated.[17] Furthermore, the original protocol includes a 30 minute ddH_2O wash that can cause further chondrocyte death via osmotic imbalance leading to cytolysis.[17] The new protocol made two changes to the original protocol: 1) the 3 hour SDS cycle has been replaced with three 1 hour cycles at decreasing SDS concentrations (1%, 0.1%, 0.01%), and 2) The 30 minute ddH_2O wash has been removed.[17] It is believed that the first change limits deep penetration of residual SDS into tissue, while the second change reduces cytolysis of chondrocytes. In other words, this new protocol was designed to provide milder de-ep conditions that increase chondrocyte survival while providing similar removal of epithelial cells. Both negative controls (control-native and control-DPBS) showed close to 90% viability. Therefore, it seems that SDS retention in the ECM is a major contributor to chondrocyte death after de-ep, overshadowing the cytolytic effect of the ddH_2O wash and other potential minor contributors. Attempts at quantifying the amount of residual SDS in de-epithelialized tissues using a methylene blue assay were unsuccessful. Future studies should investigate the relationship between residual SDS levels and chondrocyte viability. The short-term nature of the improvement in chondrocyte viability observed in this study was likely due to an initial reduction in residual SDS concentration in submucosal tissues, followed by eventual permeation of the SDS through submucosa and into cartilage due to passive diffusion. Confocal images of the cell viability assay show a clear delineation between calcein-AM (live cells) and ethidium homodimer-1 (dead cells), suggesting a progressive "wavefront" of cell death that is consistent with diffusion of residual SDS. Confirmation of this theory is required, although preventing the diffusion of SDS through submucosal tissue would be difficult or impractical to accomplish in any de-ep protocol.

Examination of H&E slides shows that both protocols were extremely efficient at denuding the epithelium. However, neither protocol appears to sufficiently decellularize acinar glands. Furthermore, the new protocol seems to be less efficient at decellularizing deep submucosal layers. This result was expected since the new protocol uses decreasing concentrations of SDS and is less aggressive overall compared to the original protocol, among others.[17,24,25] Therefore, with the current detergent-based methods of de-ep, the goal of selectively preserving chondrocyte viability seems to depend on the careful titration of SDS concentrations, walking a fine balance between over- and under-decellularization. The current study shows that the new protocol sacrifices decellularization performance in return for better chondrocyte survival.

Previous studies have shown that decellularization cycles can reduce several ECM components that are critical to structural integrity, including elastin, collagen, and glycosaminoglycans.[17,25,26] Qualitative histological analysis demonstrated that the new protocol is not any more damaging to ECM components than the original protocol.[17] Elastin, collagen, and glycosaminoglycans were found to be preserved after de-ep to a similar degree as with the original protocol.[17] Tracheal compliance and viscoelasticity were not tested because previous studies by Aoki et al. have confirmed no difference in these mechanical properties after the more aggressive original de-ep protocol.[17]

The cellular proliferation assay suggests that the new protocol has no negative effects on metabolism and growth of the BEAS-2B cells used for re-ep. This suggests that ECM scaffolds created using the new de-ep protocol can support epithelial cell attachment and viability during re-ep, allowing for the creation of chimeric allografts.

This proof-of-concept study is not without limitations. To longitudinally measure chondrocyte survival, we incubated the de-epithelialized trachea in static Dulbecco's Modified Eagle Medium (DMEM) to simulate implantation of the grafts. This does not fully recapitulate the complex cell-environment interactions present in vivo. Therefore, conclusions regarding chondrocyte viability should be validated in a bioreactor environment that simulates nutrient perfusion, hydrodynamic stimuli, and mechanical stimuli.[27,28] The current study did evaluate chondrocyte viability of de-epithelialized trachea after a 7-day re-

ep in a double-chamber bioreactor, yielding a percentage viability of 63% over 7-days. This result is promising given that previous studies have demonstrated that a 50% chondrocyte viability was associated with successful tracheal transplantation in dogs, with no lethal stenosis.[29] However, future studies should be conducted with a larger number of replicates.

In conclusion, we introduce a new de-ep protocol with improved short-term chondrocyte viability. The results of this study have indicated that improvements in the protocol can still be made. However, the data presented sheds light on the potential mechanism of chondrocyte death during and after de-ep.

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Original Article

The Association of Blood Banks per City with Mortality Due to Traumatic Hemorrhagic Shock in Colombia: A Population-Based Analysis

Alejandro Munoz-Valencia,[1] Francisco J. Bonilla-Escobar,[2] Juan C. Puyana.[3]

Abstract

Background: Hemorrhagic shock is the second leading cause of death for injured people and disproportionately affects low resource economies. The potential role of spatial allocation of blood banks and the unmet transfusion needs of patients are yet to be characterized. We aimed to estimate the effect of the number of blood banks in mortality due to traumatic hemorrhagic shock (THS) in Colombia. **Methods:** We performed a population-based cross-sectional study using secondary data from the Colombian Government: including annual reports from the Blood Bank Network, mortality, and population estimates for 2015-2016. International Classification of Disease 10th code T79.4 identified THS as the primary cause of death. A city-clustered multivariate negative binomial regression, weighted by violent deaths rate, was used to obtain incidence rate ratios (IRR) of death due to THS with 95% confidence intervals (95%CI). **Results:** Of the 59,030 violent deaths in Colombia in 2015-2016, 36.76% were due to THS. Only 3.13% of Colombian municipalities had a blood bank. THS incidence decreased as the number of blood banks in a city increased, and the lowest incidence was observed at ten banks (IRR:0.18, 95%CI:0.15-0.22). Receiving medical care in a city with blood banks had a more substantial impact on THS (IRR:0.85; 95%CI:0.76-0.96). **Conclusion:** The number of blood banks per city was associated with lower incidence of THS deaths. These findings may highlight the inequitable distribution of blood systems and their association with preventable deaths. Further studies with more focused clinical and geographical data might clarify the geographic determinants of blood products' availability.

Key Words: Blood bank; Blood transfusion; Injury; Mortality; Hypovolemic shock (Source: MeSH-NLM).

Introduction

Injury-related deaths are a growing public health concern worldwide. According to the World Health Organization (WHO), injuries represented 8.6% of global deaths in 2016.[1] The latest report stated that injuries took the lives of 4.4 million people in 2019 and constituted 8% of all deaths globally. Among the injury-related causes of death include road traffic accidents (29%), drowning (5%), falls (15%), burns (3%), poisoning (2%), and violence against oneself (16%) or others (11%).[2] As for the WHO Americas region, injury-related deaths vary across countries, with an average of 9.4%. While the United States (US) has one of the lowest rates in the region (6.55%), Colombia has one of the highest injury-related death rates worldwide to the present day (15.04%).[1] The impact of injury-related deaths on society is noteworthy. In 2013, the cost of a single fatal injury was estimated at $1.1 million, which accounted for medical and work-loss costs. Thus, the total cost of injury-related deaths across the US is estimated at around $214 billion annually.[3] For 2019, this cost has gone up to $4.2 trillion, including medical care, work loss, the value of statistical life, and quality of life losses.[4]

The main threats to life in injured patients are hemorrhage and central nervous system (CNS) damage, regardless of the injury mechanism.[4] Approximately one out of every three trauma patients die from a hemorrhage.[5] Moreover, hypovolemic shock in patients with CNS damage increases mortality up to three-fold,[6] and plays a causative role in subsequent organ failure and late mortality.[7] Managing acute hemorrhage in severely injured patients involves timely interventions to stop the bleeding and prompt administration of blood products. Multiple guidelines and clinical management algorithms recommend the use of blood components in the setting of hypovolemic shock after trauma.[8,9] Additionally, the WHO determined blood banking

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capabilities and blood products as essential components for all health facilities and systems providing care to injured patients.[10]

Despite the importance of blood banks as a source of essential blood products, the response of blood bank systems to the immediate transfusion need of everyday injured patients is yet to be thoroughly characterized. Assessments on whether blood banking systems meet the population's needs remain unexamined, especially in low-resource settings. Current global strategies focus on national blood donation thresholds with scarce guidance on the spatial distribution of blood bank infrastructure. For instance, the WHO recommends a donation threshold of at least 1% of the population (10 donations every 1,000 population), while the Lancet Commission on Global Health recommends 1.5%.[11] Geographic distribution and subsequent distance to healthcare facilities are known determinants of access to health services and resources.[12] Thus, understanding the distribution of national blood banking systems could facilitate measuring equity and timeliness of access to safe blood and blood products, particularly for those patients with hypovolemic shock after injury. Previous studies have mainly analyzed hypothetical scenarios of national emergencies or local mass-casualty scenarios.[13,14]

In this study, we aimed to characterize the distribution of a national blood banking system in a middle-income country with high injury-related mortality rates, Colombia, to evaluate the relationship between the number of blood banks and mortality rates due to THS at the city level. Our approach and results may contribute to understanding the impact of blood banking systems on the outcomes of patients with acute transfusion needs.

Methods

Study Setting and Design

This study is a retrospective cross-sectional and population-based research analyzing data from 2015 to 2016 at the city level. We used secondary data from the Colombian National Network of Blood Banks [Red Nacional de Bancos de Sangre], the National Mortality Registry, and population estimates from the National Administrative Department of Statistics [Departamento Administrativo Nacional de Estadisticas].[15,16] The mortality registry contains deidentified data from all death certificates issued across the country– including date, location, age, sex, injury intent (natural death, violent, or under investigation), and causes of death, according to the International Classification of Disease 10th revision (ICD-10). Colombia, a middle-income country in South America, is organized into 33 departments and divided into 1,119 municipalities, including cities and towns. It is the 24th largest and the 29th most populated country in the world, with a blood donation estimate of 2.1%, or 21 donations for every 1,000 population.

Data and Variables

We included in our analyses all violent deaths registered from January 2015 to December 2016 that occurred in a city with at least one blood bank. Data were obtained from the National Mortality Registry– including sex, marital status, age, healthcare coverage, educational level, place of occurrence (urban vs. rural), geographic location (city), type of violent death, the primary cause of death, and whether or not medical assistance was provided prior to death. The cause of death was the dependent variable in all analyses. Specifically, we used the ICD-10 code T79.4 to identify those who died due to shock immediately or later after injury.[17] The National Blood Network served as the source for location data of active blood banks. Each bank was coded using unique national identifiers, and its location was determined through the Colombian national coding system for municipalities.[18] A similar process was conducted to obtain the location of mortality registry data. Finally, population estimates were acquired from the Colombian National Administrative Department of Statistics.[16]

Statistical Analysis

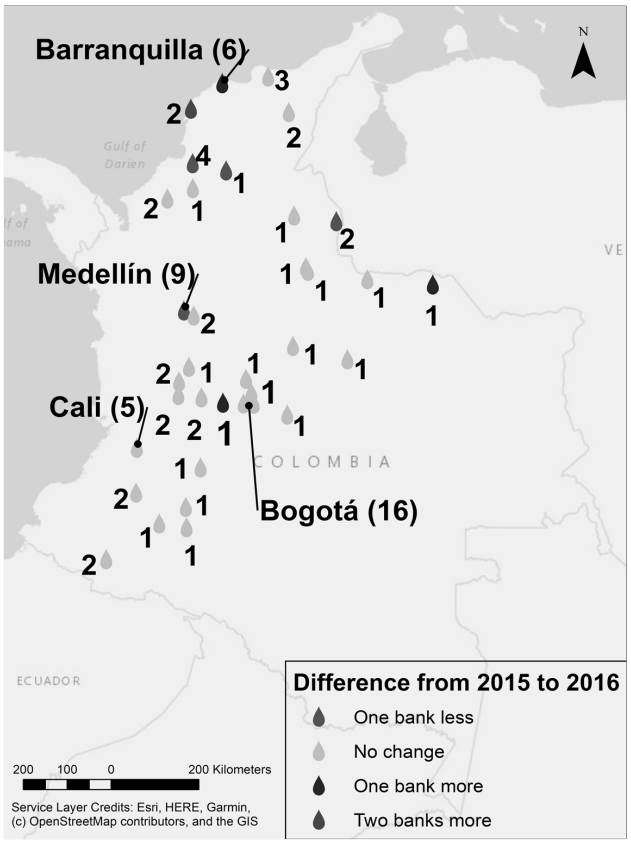
Datasets for counts of violent deaths, number of blood banks, and population estimates as the number of inhabitants were merged into a single database using the location coding system as the joining variable. As deaths are a count variable, we assumed a Poisson data distribution. We used bivariate Poisson regressions with clustered estimators of variance by city and overall violent deaths rate (1/rate) as the sampling weight to identify confounders. Statistical significance for confounders was set at a p-value<0.1019.

The Pearson goodness-of-fit test for the Poisson adjusted model was significant (p<0.001); therefore, the Poisson model was not a proper regression to be used. We used a multivariate negative binomial regression model adjusted by sex, age, health insurance status, rurality, type of violent death, whether or not health care was provided prior to death, and year of death, weighted by the rate of violent deaths and clustered by city. Incidence of ICD-10 code T79.4 (Traumatic Hemorrhagic Shock – THS) as a primary cause of death was described as Incidence Rate Ratios (IRR) using 95% Confidence Intervals (95%CI) and considering statistical significance at p-value <0.05. All the statistical analyses were conducted in Stata 16® (StataCorp, TX). Ethical approval to conduct this study was granted by the Institutional Review Board of the University of Pittsburgh, code HRP-723.

Results

In this middle-income country, there were 82 active blood banks in 2015 as compared to 81 in 2016. Uneven distribution of banks was observed across the country. (*Figure 1*) Only thirty-five (3.13%) of the 1,119 municipalities had a blood bank, and the number of banks per municipality ranged from 1 to 16. In this country, with 47.61 million inhabitants, 24.16 million (50.73%) live in a municipality without a blood bank. Of those with a bank, 8.03 million live in a city with 1 or 2 blood banks; 1.49 million with 3 or 4 banks; 3.59 million with 5 or 6 banks; and 10.34 million in a city with 9 or 16 banks. In fact, 25 (30.48%) of the banks are located in the two largest cities.

Figure 1. Blood Banks Geographic Distribution in Colombia, a City-Specific Description of the Situation in 2016 Compared with 2015.



From January 1, 2015, through December 31, 2016, there were 59,030 violent deaths. THS was found to be the primary cause of death in 21,731 (36.76%). *Table 1* shows the characteristics of all violent deaths categorized by cause of death and blood bank presence. Males had more deaths in the THS and non-THS groups, 87.64% and 81.48%, respectively. Most THS deaths were observed in the 20-29 and 30-39 age groups, accounting for more than forty percent across groups (39.43% - 60.57%). While homicide (50.33%) and Road Traffic Accident (RTA) deaths (43.90%) were frequently caused by THS, suicide and other injuries were primarily due to other causes. Regarding the place of occurrence, THS represented a greater proportion of rural deaths (42.55%) compared to urban deaths (34.78%). There were no significant differences in medical assistance or year of occurrence.

Overall, the proportion of violent deaths attributed to THS was significantly less in those cities with a blood bank 33.50% vs. 40.68% (p<0.001). Similarly, the proportion of THS deaths significantly varied across age groups from 20 to 89 years, ranging from 4.19 to 11.94 percentage points less among violent deaths in cities with at least one blood bank (p<0.001). Regarding the type of violent death, homicide accounted for most deaths in cities with and without blood banks, 40.25% and 43.23%, respectively.

Table 1. Description of Violent Deaths by Blood Bank Availability and Cause of Death in Colombia 2015-2016 (N=59 030).

Characteristic	Blood Bank in the city				p-value*
	No		Yes		
	Death by THS		*Death by THS*		
	No Freq (%)	*Yes* Freq (%)	*No* Freq (%)	*Yes* Freq (%)	
Sex					
Female	2575 (66.76)	1282 (33.24)	4277 (75.45)	1392 (24.55)	<0.001
Male	13431 (58.08)	9694 (41.92)	16988 (64.57)	9321 (35.43)	<0.001
Age in years					
<10	895 (84.20)	168 (15.80)	839 (86.85)	127 (13.15)	0.09
10-19	1970 (61.68)	1224 (38.32)	2154 (62.63)	1285 (37.37)	0.42
20-29	4045 (54.97)	3313 (45.03)	5024 (59.16)	3468 (40.84)	<0.001
30-39	2929 (54.90)	2406 (45.10)	3537 (60.57)	2303 (39.43)	<0.001
40-49	1997 (55.70)	1588 (44.30)	2455 (66.01)	1264 (33.99)	<0.001
50-59	1605 (60.11)	1065 (39.89)	2187 (70.43)	918 (29.57)	<0.001
60-69	1004 (63.14)	586 (36.86)	1750 (75.08)	581 (24.92)	<0.001
70-79	784 (67.35)	380 (32.65)	1499 (77.91)	425 (22.09)	<0.001
80-89	495 (77.34)	145 (22.66)	1295 (83.60)	254 (16.40)	0.001
>89	160 (85.11)	28 (14.89)	398 (88.05)	54 (11.95)	0.31
Unknown	164 (67.49)	79 (32.51)	147 (80.33)	36 (19.67)	0.003
Type of death					
Suicide	1879 (85.02)	331 (14.98)	2321 (88.66)	297 (11.34)	<0.001
Homicide	5570 (47.67)	6114 (52.33)	6631 (51.48)	6250 (48.52)	<0.001
RTI	3243 (48.56)	3435 (51.44)	4969 (62.42)	2991 (37.58)	<0.001
Other	3145 (79.26)	823 (20.74)	3447 (79.06)	913 (20.94)	0.82
Unknown	2211 (88.80)	279 (11.20)	3917 (93.69)	264 (6.31)	<0.001
Medical assistance					
No	11884 (58.50)	8429 (41.50)	9124 (62.54)	5464 (37.46)	<0.001
Yes	3275 (61.58)	2043 (38.42)	10705 (70.10)	4565 (29.90)	<0.001
Unknown	889 (63.55)	510 (36.45)	1456 (67.97)	686 (32.03)	0.006
Place of occurrence					
Urban	8694 (61.08)	5539 (38.92)	20082 (67.19)	9807 (32.81)	<0.001
Rural	7243 (57.34)	5389 (42.66)	1114 (55.90)	879 (44.10)	0.23
Unknown	111 (67.27)	54 (32.73)	89 (75.42)	29 (24.58)	0.14
Healthcare coverage					
Contributory	3566 (56.37)	2760 (43.63)	6134 (67.43)	2963 (32.57)	<0.001
Subsidized	8898 (61.67)	5531 (38.33)	7584 (66.81)	3768 (33.19)	<0.001
No insurance	2683 (58.02)	1941 (41.98)	3835 (62.97)	2255 (37.03)	<0.001
Unknown	901 (54.57)	750 (45.43)	3732 (68.34)	1729 (31.66)	<0.001
Year					
2015	8078 (58.77)	5666 (41.23)	10433 (65.73)	5440 (34.27)	<0.001
2016	7970 (59.99)	5316 (40.01)	10852 (67.29)	5275 (32.71)	<0.001

Legend: THS: Traumatic Hemorrhagic Shock. RTI: Road Traffic Injury. * Chi-square or exact tests comparison across groups by row.

RTAs accounted for 24.88% in cities with a bank and 24.71% in those without one. The place of death occurrence was significantly different across groups. Although most of the deaths occurred in urban areas of municipalities with and without blood banks, urban location accounted for 93.40% among those with a bank and only 52.66% in municipalities without a bank. Moreover, of the 14,625 rural deaths, 86.37% occurred in a municipality without a blood bank compared to 32.26% of urban deaths in a city without a bank (p<0.001).

Medical care prior to death was received by 47.72% of the casualties in municipalities with blood banks. In contrast, only 19.67% of deaths received care before death when it occurred in municipalities without a bank (p<0.001). Health insurance status was similar between groups. Subsidized regime accounted for most deaths among municipalities with and without blood banks, 35.48% and 53.38%, respectively. The proportion of the uninsured showed no significant differences.

In *Table 2*, we show regression analysis results described in terms of adjusted and unadjusted IRR of THS. Compared to municipalities with only one blood bank, those with 2 or 3 banks did not show a significant difference in THS incidence. However, cities with four banks were associated with a reduction of 45.88% (p<0.001); five with a reduction of 58.38% (p<0.001); and six with a reduction of 71.93% (p<0.001), in the incidence of THS. A significant association was also found with 16 banks per city, showing a reduction of 29.06% (p<0.001). Cities with 9 or 10 banks did not have a significant difference. When comparing those that received medical care prior to the death against those who did not, the former had less incidence of THS (IRR: 0.90, p=0.013). Age was significantly associated with an IRR of 0.99 (p<0.001). As for the type of death, there were significant differences between suicide, homicide, and RTA. Suicide deaths showed significantly less incidence of THS (IRR: 0.48, p<0.001) compared to other types of death. Conversely, homicide and RTA deaths were associated with significantly higher incidence rates of THS (IRR=2.38, p<0.001, and IRR=.1.80, p<0.001, respectively). Incidence in rural areas compared to urban areas was not significantly different (p=0.35). No significant differences were found when comparing violent deaths by year (2015 vs. 2016, IRR=0.93, p=0.09).

Discussion

This study explored the association between blood bank availability and the incidence of deaths caused by THS. To our knowledge, this is the first study to use comprehensive population-level datasets of blood bank distribution, mortality, and population density to analyze this issue at a national level. Adjusted analysis showed a continuous reduction in death rates due to THS as the number of blood banks in a city increased. The association was statistically significant at four or greater blood banks. This trend reached its lowest value at ten banks per city (IRR=0.18, p<0.001). In addition, receiving medical care before death was not significant when considered independently (IRR=1.02, p=0.62); however, it resulted in a lower incidence of THS deaths when paired with blood bank availability (IRR=0.85, p=0.009).

These findings may reveal the role of the geographic distribution of blood banking facilities as vital elements for those strategies that aim to meet the transfusion needs of injured patients. The 28th World Health Assembly in 1975 first mentioned the idea of an adequate supply of blood products.[20] This concept has evolved towards the commitment of countries to ensure national blood supplies only by volunteer donors as well as the safety of blood units.[21,22] But, neither the geographic distribution nor target quantity of blood banks has been systematically addressed. Additionally, national estimates have historically set self-sufficiency goals that may not reflect disparities among the population.[22-25] For instance, we observed that only 35 cities in Colombia (3.13%) had at least one blood bank in 2015 and 2016. This fact would be overlooked if only national aggregated data were analyzed and regional geographical differences not considered.

Table 2. Incidence Rate Ratios of Death due to Traumatic Hemorrhagic Shock in Colombia 2015-2016.

Characteristic	$_u$IRR	95% CI	p-value	$_a$IRR	95% CI	p-value
Blood Banks per municipality						
1	-	-	-	-	-	-
2	0.79	0.75-0.84	<0.001	0.76	0.51-1.15	0.192
3	1.09	1.00-1.19	0.060	0.94	0.67-1.33	0.735
4	0.56	0.49-0.66	<0.001	0.54	0.45-0.66	<0.001
5	0.55	0.52-0.59	<0.001	0.42	0.34-0.23	<0.001
6	0.35	0.30-0.42	<0.001	0.28	0.23-0.34	<0.001
9	1.03	0.95-1.11	0.525	0.91	0.75-1.10	0.331
10	1.01	0.94-1.09	0.795	0.97	0.79-1.18	0.738
16	0.68	0.64-0.72	<0.001	0.71	0.59-0.86	<0.001
Medical assistance						
No	-	-	-	-	-	-
Yes	0.80	0.77-0.83	<0.001	0.90	0.82-0.98	0.013
Sex						
Female	-	-	-	-	-	-
Male	1.44	1.36-1.53	<0.001	1.11	1.06-1.015	<0.001
Age, in years	0.96	0.95-0.97	<0.001	0.99	0.98-0.99	<0.001
Type of death						
Other	-	-	-	-	-	-
Suicide	0.54	0.48-0.62	<0.001	0.48	0.39-0.59	<0.001
Homicide	2.32	2.16-2.48	<0.001	2.38	1.86-3.05	<0.001
RTI	1.79	1.67-1.93	<0.001	1.80	1.57-2.07	<0.001
Place of occurrence						
Urban	-	-	-	-	-	-
Rural	1.34	1.26-1.44	<0.001	1.06	0.94-1.20	0.352
Year						
2015	-	-	-	-	-	-
2016	0.95	0.92-0.99	0.016	0.94	0.86-1.01	0.090

As for 2019, the circumstances have remained unchanged, with almost the same number of blood banks (83 actives) and an identical distribution, with a difference in the number of violent deaths that has gone down to 28,220 (47% of 2015 -2016).[26,27]

Overall, the relevance of blood transfusion in preventing deaths in the trauma setting is exemplified by the emphasis on transfusion protocols as one of the first critical actions in the setting of hemodynamic instability due to hemorrhage.[9,28,29] These results align with those approaches, as we observed that blood bank availability, coupled with medical care, impacts the incidence of deaths by exsanguinating causes among injured patients.

The proportion of THS deaths and demographic characteristics within this population of trauma deaths are similar to previous descriptions of trauma settings reported by other authors from the National Trauma Data Bank.[30,31] However, the absence of key variables (blood bank data availability and geographic location) in other national trauma datasets and academic reports hinders the proper comparison that could have provided further meaningful conclusions. The Colombian reports of violent death do not show all data regarding each death since they only account for the cause of death of patients who received medical assistance before their death, making it challenging to create conclusions from these cases. Additionally, we cannot assess the severity score, such as shock index or the state of the patients if we do not have the complete history of each patient and whether or not the patient had one or multiple transfusions or if blood was available in their local blood bank. According to the National Institute of Health, only 220,000 nationals donated blood in the country with a population of 49.28 million in 2018, indicating a lack of donors countrywide.[27,32,33] Previous authors have found similar difficulties when analyzing trauma datasets.[34,35] Consequently, multiple endeavors have been proposed to overcome obstacles related to data reporting and data accessibility, especially in LMICs.[36,37] Nonetheless, non-standardized reports generated at local and rural hospitals still account for lack of reliability in the absence of more accurate registrations at a national level.

These limitations also highlight the nature of trauma settings in LMICs, which are often represented as unfavorable environments not equipped to collect all relevant and reliable information.[38] For these reasons, further analyses are required with multiple datasets that include more detailed geographic and clinical data such as injury descriptions, severity scores, and trauma mechanisms, as well as information about blood products' management and delivery circumstances in order to achieve a fuller understanding of the blood banking system's response to the transfusion need of injured patients.

Conclusion

In this study, we described the association of blood banks' availability with the number of violent deaths caused by traumatic hemorrhagic shock at a population level. Between 2015 and 2016, in this middle-income country, there was an inequitable distribution of blood facilities where the incidence of THS decreased as the number of blood banks in a city increased. Without any changes in neither distribution nor the number of blood banks in recent years, this study may suggest novel elements for strategies that aim to meet the transfusion needs of injured patients by inquiring about the importance of the geographic distribution of blood bank facilities. Such strategies could further tailor local and national policies to consider geographic and non-geographic determinants of blood products' availability and delivery, eventually developing successful strategies from blood banking systems to meet the populations' transfusion needs.

Summary – Accelerating Translation

Las muertes relacionadas con lesiones son un problema de salud pública creciente en todo el mundo. Aproximadamente uno de cada tres pacientes traumatizados muere a causa de una hemorragia. Múltiples pautas y algoritmos de manejo clínico recomiendan el uso de componentes sanguíneos en el contexto de un shock hipovolémico después de un trauma. Además, la Organización Mundial de la Salud (OMS) determinó que las capacidades de los bancos de sangre y los productos sanguíneos son componentes esenciales para todas las instalaciones y sistemas de salud que brindan atención a los pacientes lesionados. A pesar de la importancia de los bancos de sangre como fuente de hemoderivados esenciales, la respuesta de los sistemas de bancos de sangre a la necesidad inmediata de transfusiones de los pacientes lesionados cotidianos aún no se ha caracterizado a fondo. En este estudio, nuestro objetivo fue caracterizar la distribución de un sistema nacional de bancos de sangre en un país de ingresos medios con altas tasas de mortalidad por lesiones, Colombia, para evaluar la relación entre el número de bancos de sangre y las tasas de mortalidad por SHT en el país. nivel de la ciudad.

Este estudio es una investigación transversal retrospectiva y de base poblacional que analiza datos de 2015 a 2016 a nivel de ciudad. Se utilizaron datos secundarios de la Red Nacional de Bancos de Sangre de Colombia, el Registro Nacional de Mortalidad y estimaciones de población del Departamento Administrativo Nacional de Estadística. Los datos se obtuvieron del Registro Nacional de Mortalidad, incluyendo sexo, estado civil, edad, cobertura de salud, nivel educativo, lugar de ocurrencia (urbano vs. rural), ubicación geográfica (ciudad), tipo de muerte violenta, causa principal de muerte, y si se proporcionó o no asistencia médica antes de la muerte.

En este país de ingresos medios, había 82 bancos de sangre activos en 2015 en comparación con 81 en 2016. Se observó una distribución desigual de los bancos en todo el país. Solo treinta y cinco (3,13%) de los 1.119 municipios contaban con banco de sangre, y el número de bancos por municipio varió de 1 a 16. En este país, con 47,61 millones de habitantes, 24,16 millones (50,73%) viven en un municipio sin un banco de sangre. Del 1 de enero de 2015 al 31 de diciembre de 2016 hubo 59.030 muertes violentas. Se encontró que el shock hemorrágico traumático era la principal causa de muerte en 21.731 (36,76%). En general, la proporción de muertes violentas atribuidas al shock hemorrágico traumático fue significativamente menor en aquellas ciudades con banco de sangre 33,50% vs. 40,68% (p<0,001). En cuanto al tipo de muerte violenta, el homicidio representó la mayoría de las muertes en las ciudades con y sin banco de sangre, 40,25% y 43,23%, respectivamente. Las lesiones de tránsito representaron el 24,88% en las ciudades con banco y el 24,71% en las que no lo tenían. Aunque la mayoría de las muertes ocurrieron en las áreas urbanas de los municipios con y sin bancos de sangre, la ubicación urbana representó el 93,40% entre los que tenían banco y solo el 52,66% en los municipios sin banco. Además, de las 14.625 muertes rurales, 86,37% ocurrieron en municipio sin banco de sangre frente a 32,26% de muertes urbanas en ciudad sin banco (p<0,001). La atención médica previa a la muerte fue recibida por el 47,72% de las víctimas en los municipios con bancos de sangre. En contraste, solo 19,67% de las muertes recibieron atención cuando la lesión ocurrió en municipios sin banco (p<0,001). En comparación con los municipios con un solo banco de sangre, aquellos con 2 o 3 bancos no mostraron una diferencia significativa en

la incidencia de shock hemorrágico traumático. Sin embargo, las ciudades con cuatro bancos se asociaron con una reducción del 45,88% (p<0,001); cinco con una reducción del 58,38% (p<0,001); y seis con una reducción del 71,93% (p<0,001), en la incidencia de shock hemorrágico traumático. También se encontró asociación significativa con 16 bancos por ciudad, mostrando una reducción del 29,06% (p<0,001).

El análisis ajustado mostró una reducción continua en las tasas de mortalidad por shock hemorrágico traumático a medida que aumentaba el número de bancos de sangre en una ciudad. La asociación fue estadísticamente significativa en cuatro o más bancos de sangre. Esta tendencia alcanzó su valor más bajo en diez bancos por ciudad (razones de tasa de incidencia [IRR]=0,18, p<0,001). Además, recibir atención médica antes de la muerte no fue significativo cuando se consideró de forma independiente (IRR=1,02; p=0,62); sin embargo, resultó en una menor incidencia de muertes por shock hemorrágico traumático cuando se combinó con la disponibilidad del banco de sangre (IRR=0,85; p=0,009). Estos hallazgos pueden revelar el papel de la distribución geográfica de los bancos de sangre como elementos vitales para aquellas estrategias que tienen como objetivo satisfacer las necesidades de transfusión de los pacientes lesionados.

Sin embargo, este estudio también conlleva sus propias limitaciones. Los informes colombianos de muerte violenta no muestran todos los datos de cada muerte, ya que solo dan cuenta de la causa de muerte de los pacientes que recibieron asistencia médica, lo que dificulta sacar conclusiones de estos casos. No podemos evaluar la severidad de los casos si no tenemos el historial completo de cada paciente y si el paciente recibió o no una o múltiples transfusiones o si había sangre disponible en su banco de sangre local; según el Instituto Nacional de Salud, solo 220.000 personas donaron sangre en el país con una población de 49,28 millones en 2018. Estas limitaciones también resaltan la naturaleza de los entornos de trauma en los países de bajos y medianos ingresos, que a menudo se representan como entornos desfavorables que no están equipados para recopilar todos los datos relevantes e información confiable. Por estas razones, se requieren análisis adicionales con múltiples conjuntos de datos que incluyan datos geográficos y clínicos más detallados, como descripciones de lesiones, puntajes de gravedad y mecanismos de trauma, así como información sobre el manejo de los productos sanguíneos y las circunstancias de entrega para lograr una comprensión más completa de la respuesta del sistema de banco de sangre a la necesidad de transfusiones de pacientes lesionados.

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Original Article

Accuracy and Precision of Actigraphy and SMARTwheels for Measuring Push Counts Across a Series of Wheelchair Propulsion Trials in Non-disabled Young Adults

Hunter Soleymani,[1] Brenda Jeng,[2] Beshoy Abdelmessih,[1] Rachel Cowan,[3] Robert W. Motl.[2]

Abstract

Background: There has been a growing interest in "Lifestyle Physical Activity" (LPA) among wheelchair users. LPA can be quantified via "pushes" as an outcome metric. This study examined the accuracy and precision of research-grade devices for counting pushes across a series of wheelchair propulsion trials. **Methods:** Eleven non-disabled, young adults completed 19, 1-minute wheelchair propulsion trials at self-selected speeds with a wheelchair equipped with a SMARTwheel (SW) device while being video recorded. Participants also wore 2 ActiGraph accelerometers, one on the wrist and one on the upper arm. Video footage enabled manual counting of the number of pushes (gold standard). Total pushes were averaged across 16 workloads (3 trials of repeated workloads were excluded) for each device and compared to manually counted pushes. **Results:** Compared to manually counted pushes, SW demonstrated the greatest accuracy (mean difference [MD] compared to video of 2.3 pushes [4.5% error]) and precision (standard deviation of the mean difference [SDMD]) compared to video of 4 pushes, (Coefficient of Variation [CV] =.04), followed by the upper arm-worn accelerometer (MD of 4.4 pushes [10.4% error] and SDMD of 10, [CV= .06]) and the wrist-worn accelerometer (MD of 12.6 pushes [27.8% error] and SDMD of 13 [CV=.15]). **Conclusions:** SW demonstrated greater accuracy and precision than ActiGraph accelerometers placed on the upper arm and wrist. The accelerometer placed on the upper arm was more accurate and precise than the accelerometer placed on the wrist. Future investigations should be conducted to identify the source(s) of inaccuracy among wearable push counters.

Key Words: Wheelchair; Actigraphy; Physical Activity; Health Promotion; Disability (Source: MeSH-NLM).

ClinicalTrial.gov identifier. https://clinicaltrials.gov/ct2/show/NCT04987177

Introduction

There has been a growing interest in the study of physical activity for management of health outcomes among wheelchair users and this has largely focused on participation in intentional, structured, and planned exercise training.[1, 2] Nevertheless, there are many barriers for participation in this type of physical activity, and such barriers may underlie the low number of wheelchair users who achieve the recommended physical activity levels.[3-6] To that end, researchers have recently advocated for a paradigm shift towards organic incorporation of health-promoting physical activity into daily life, termed "Lifestyle Physical Activity" (LPA).[1, 5] The paradigm shift advocats for an application of concepts regarding LPA among those who use manual wheelchairs as a primary or only means of mobility (i.e., spinal cord injury, multiple sclerosis, cerebral palsy, and spina bifida). The paradigm shift includs suggestions for a working definition and metrics of LPA for manual wheelchair users followed by a brief discussion of LPA correlates, consequences, interventions, and safe movement considerations.

One of the key steps in meeting the challenges of this paradigm change involves tools for monitoring "pushes" as a metric of LPA. To date, little is known regarding the accuracy and precision of research-grade devices, such as SMARTwheels [SW] and ActiGraph accelerometers, for monitoring pushes as a metric of LPA. Such research is important for documenting changes in LPA pre/post intervention and for better identifying associated outcomes of LPA in wheelchair users. SWs have a long history of providing reliable data and being a critical instrument for wheelchair research studies involving the relationship between the type of wheelchair, set-up, activity, technique, anatomy, physiology, and repetitive strain injury.[7] SW devices are considered the gold standard but are not cost-effective and currently no longer in production (SW cost: $15,000 USD in 2012,

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ActiGraph Accelerometer cost: $430 USD, Apple Watch Series 8 cost: $399 USD, and Fitbit Flex 2 cost: $229 USD). There has been recent interest in the accuracy and/or precision of commercially available wearable devices such as Apple Watch[8-11] and Fitbit.[8] The Apple Watch Series 4 has demonstrated a mean absolute percentage error (MAPE) of 9.2-13.9%[8, 9] compared with manual counting of pushes during wheelchair propulsion, and this was substantially better than the Fitbit Flex 2 (MAPE of 59.7%).[8] To our knowledge, there are currently no data on the accuracy and/or precision of research-grade devices for push counts.

The current paper extends previous research and explores research-grade tools for measuring pushes as an outcome metric of interventions designed for promoting LPA in wheelchair users. If we can provide accurate and precise measurements of pushes, future research can better examine the relationship between physical activity and its correlates in manual wheelchair users, so that clinicians may prescribe, promote, and monitor LPA. Accordingly, we examined the accuracy and precision of ActiGraph accelerometers and SW for measuring push counts during 19 bouts of manual wheelchair propulsion in healthy young adults. We expected that SW would demonstrate greater accuracy and precision than the wearable ActiGraph accelerometers. Additionally, we examined the accuracy and precision of research-grade accelerometers based on location on the arm (i.e., wrist vs. upper arm) and expected that the accelerometer on the upper arm would demonstrate better accuracy and precision for counting pushes than the accelerometer placed on the wrist. This study is a proof-of-concept pilot project conducted between August 2021 and November 2021 during the COVID-19 pandemic. We tested non-disabled individuals to enable a rapid evaluation of the accuracy and precision of research-grade devices. This was necessary as individuals with spinal cord injury, who are commonly enrolled in wheelchair studies, are particularly vulnerable to respiratory infections and other complications.[12-14] We sought to reduce risks of COVID-19 exposure by using non-disabled individuals.

Methods

Participants

This research protocol was approved by the University of Alabama at Birmingham Institutional Review Board (IRB-30007513) and registered with ClinicalTrials.gov (NCT04987177). Eleven non-disabled adults were recruited through local flyers, medical school interest groups, and word of mouth, and all participants provided written consent prior to participation. These data are secondary analyses of a parent study (Clinical trial registration number: NCT04987177). The parent study had 90% power at α=0.05 to detect a repeated measures correlation of 0.238 (two tail) with 12 participants, each completing 16 repeated measures. Our final sample size of n=11 was similar in size to many other wheelchair propulsion studies that enrolled wheelchair users[15-19] or non-disabled individuals.[20-24] Inclusion criteria were (a) age ≥18 years, (b) ability to safely participate in vigorous physical activity (assessed by the Physical Activity Readiness Questionnaire for Everyone [PAR-Q+], and (c) no current usage of a wheelchair. Exclusion criteria were failure to meet all the inclusion criteria. Inclusion and exclusion criteria were selected to maximize the participant safety and protocol completion. No adverse events occurred during testing.

Instrumentation and Configurations

All testing was performed using the same TiLite (TiLite, Permobil, Timra, Sweden) wheelchair (specifications in accordance with the recommendations of Fritsch et al. are in *Supplemental Table 1*).[25] The submaximal peak test was performed with SHOX (Custom Engineered Wheels, Inc., Baldwyn, MS, USA) solid tires mounted to TiLite Shadow 25″ wheels. The within-subject repeated measures protocol was performed with a 25″ Primo (Xiamen Lenco Co, LTD, Xiamen, China) pneumatic tire on the left side and a 25″ SMARTwheel equipped with matching pneumatic tire on the right side. During all testing, the wheelchair was secured to a WheelMill ergometer using two straps attached to the wheelchair backrest stabilizer bar and 1 strap across the foot plate.[26] We manipulated rolling resistance by adjusting the WheelMill parameters of testing decay and force multiplying coefficients,[26] which both are inversely related to rolling resistance (i.e., ↓ decay/force multiplying coefficient = ↑ rolling resistance). Participants were equipped with two ActiGraph GT3X+ accelerometers (ActiGraph, LLC, Pensacola, FL, USA); 1 on the right wrist above the distal radioulnar joint and 1 on the right upper arm at a point halfway between the lateral epicondyle of the elbow and the greater tubercle of the humerus. The accelerometers were calibrated by the manufacturer prior to the start of the study. The accelerometer is a lightweight, small device that contains a solid-state accelerometer that generates an electrical signal proportional to the force acting on it along three axes. Acceleration detection ranged in magnitude from 0.5-2.5g, and the frequency ranged from 0.25-2.50Hz. The signal was digitized by a 12-bit analog converter and integrated over 1s epoch intervals. The data were downloaded via the ActiLife software using a sample frequency of 100Hz and reintegrated into vector magnitude per 1s epoch with the low frequency extension applied and imported to Microsoft Excel for further processing. Vector magnitude was expressed as counts per minute across each bout of manual propulsion. 2D sagittal view video footage was collected from the right side.

Rating of Perceived Exertion (RPE)

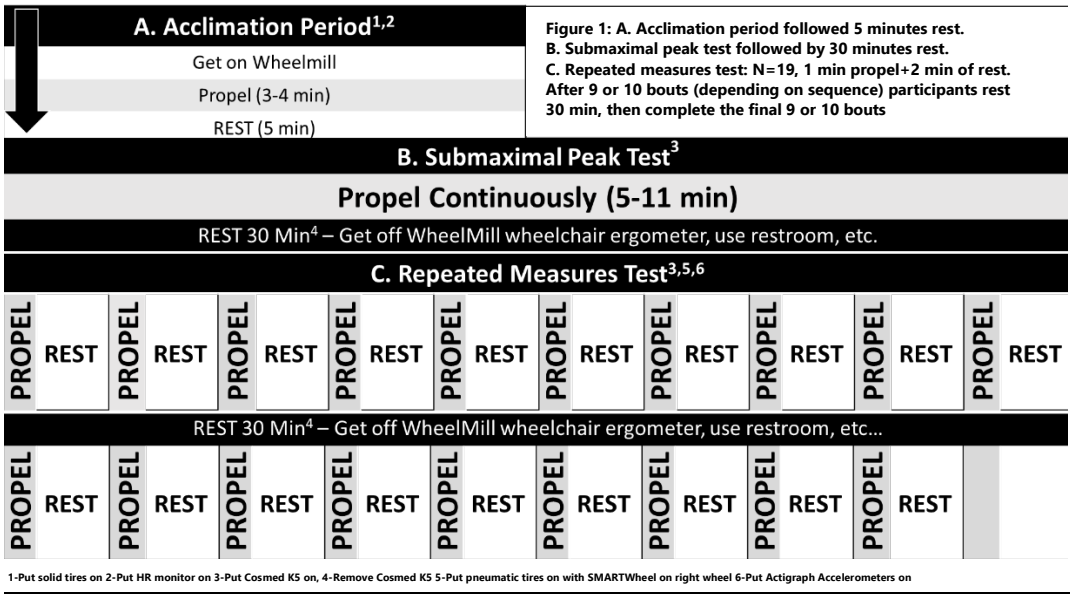
A non-differentiated 0-10 OMNI scale validated for use in manual wheelchair propulsion testing[27] was used to monitor perceived exertion during the acclimation period, submaximal test, and repeated measures protocol. Participants were introduced to the scale during the consent process and refamiliarized with the scale prior to the acclimation period, submaximal test, and repeated measures protocol.

Acclimation Period

A summary of the entire protocol can be found on *Figure 1*. Since participants were non-disabled persons with minimum previous wheelchair propulsion experience, we implemented an

acclimation period prior to the graded exercise test and repeated measures protocol. Participants were instructed to "propel at a casual pace that was comfortable for them" for 3-4 minutes. During this time, rolling resistance was manipulated, and RPE27 was collected every 30-45 seconds. Participants were allowed to change pushing speeds as resistances changed to maintain a comfortable pace, and this would naturally change pushing cadence. The starting resistance and resistance changes were based on the teams prior Wheelmill experience. The acclimation period was considered complete once the participant had completed a minimum of three minutes and we had identified at least one resistance rated as "easy" (RPE=2) and at least one rated as "hard" (RPE≥7). The "easy" resistance was used as the beginning resistance for the submaximal test. The speed pushed during the "easy" resistance was used as the target speed participants maintained during the submaximal peak test. We required experience of a "hard" rolling resistance to ensure participants had experienced it prior to the submaximal and repeated measures testing. Participants rested for at least 5 minutes following the acclimation period.

Figure 1. Summary of Testing Protocol.



Data Collection

Submaximal test to estimate maximum workload

The submaximal test estimated the maximum workload for use in the repeated measures protocol. Each participant completed the submaximal graded exercise test at the speed established during the acclimation period. Participants pushed continuously for the entire test, with workload (i.e., rolling resistance) increasing every minute until the participant reached RPE=8. The starting rolling resistance for each participant was established based on acclimation phase where RPE=2 rolling resistance (i.e., the same values for the WheelMill control parameters were input). Rolling resistance was increased each minute by a constant amount (i.e., a 0.04 unit decrease in the WheelMill parameter "force multiplying coefficient"). RPE was documented during the last 20 seconds of each one-minute stage. Participants rested for at least 30 minutes before starting the repeated measures protocol.

Each participant's maximum (i.e., 100%) workload capacity was estimated from the RPE-force multiplying coefficient relationship measured during the submaximal test. Maximum capacity (i.e., 100% workload) was defined as the estimated force multiplying coefficient at RPE=10. For each participant, RPE was regressed on force multiplying coefficient to generate the individualized linear equation of equation 1.

Equation 1:

(RPE × beta) + constant = force multiplying coefficient

RPE=10 was then plugged in to estimate the force multiplying coefficient at maximum capacity (i.e., 100% workload). This estimated force multiplying coefficient was set as the 100% rolling resistance level tested during the repeated measures protocol and was used to generate all other resistance levels tested using equation 2.

Equation 2:

Resistance level = target % × 100% force multiplying coefficient

Within-Subject Repeated Measures Test

Participants next completed a single-blind, within-subject, repeated measures experiment. Each participant completed 19, 1-minute propulsion bouts at a self-selected speed. The 19 bouts

consisted of 16 unique resistance levels between 25% and 100% in 5% increments of each participants estimated maximum capacity (i.e., 25%, 30%, 35%, etc.). Three resistance levels (25%, 50%, 75%) were completed twice, once in each block. To reduce potential fatigue effects, the 19 trials were divided into two blocks. Block 1 included 9 trials and block 2 included 10 trials. The trials were partitioned in a manner that total workload, defined as the sum of the resistance levels (% max), was equal between blocks. Within each block, trial order was designed to have an unpredictable pattern of increases/decreases in resistance and featured the highest rolling resistance trials towards the middle of the set. Participants completed the blocks in a counterbalanced order within gender (*Table 1*). Participants rested for 2 minutes after each one-minute trial and rested for 30 minutes between blocks. An automatic timer with a bell was used to instruct the participants when to begin and end each trial. Heart rate was recorded at the 40-second mark of each trial, and RPE was recorded immediately following the end of each trial.

Video Counting Process

Videos of each one-minute trial were deidentified, randomized, and divided into four batches for counting. Each one-minute clip was viewed by one person. A stroke count was recorded using a tap counter application using the following criterion: A stroke was counted at the end of each cycle after the subject touched the wheel, pushed forward, and then let go. Each batch was counted twice before moving onto the next batch (i.e., batch 1 counted twice, then batch 2 counted twice, etc.). Once the count was completed, the results were recorded into a spreadsheet, and any discrepancy was recorded and discussed.

Statistical Analysis

Data analyses were conducted for n=16 trials (the second trial for the 25/50/75% conditions were not analyzed) in SPSS version 28 (IBM, SPSS Inc., Chicago, IL). We evaluated accuracy and precision with absolute and relative metrics. Absolute accuracy was calculated as the mean difference between manually counted pushes and device-measured pushes. Relative accuracy was assessed as percentage error (i.e., [mean difference between manually counted pushes and device-measured pushes ÷ by manual pushes] × 100) and the frequency of large errors per device was based on ≥5%, ≥10%, and ≥25% error. Absolute precision was assessed as the standard deviation of the mean difference, and relative precision was assessed as the coefficient of variation (CV). We provided Bland-Altman plots to illustrate metrics of absolute accuracy and relative precision. We further conducted Spearman rho's bivariate correlation analyses among manually recorded push count difference, workload, rolling resistance, power output, and speed to evaluate sources of inaccuracy in counting pushes among ActiGraph accelerometers.

Results

Participants

Eleven (7 males, 4 females) non-disabled individuals with minimal previous experience propelling a manual wheelchair completed the study. Mean age (SD) was 24 years (+/-2.3 y), ranging from 22 to 29. Based on body mass index (BMI), 8 participants were normal weight (18.5-24.9 kg/m2), 1 was overweight (25-29.9 kg/m^2), and 2 were obese (≥30 kg/m^2) (*Table 1*).

Table 1. Participant Characteristics of the Sample of Non-disabled Young Adults (n=11).

Participant Number	Gender	Age (years)	Race/Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Sequence
	M	29	White	183	77.1	23.1	B
2	F	23	White	163	87.1	33.0	B
3	M	23	White	178	77.7	24.6	A
4	M	22	White	188	74.8	21.2	B
5	F	28	White	168	52.7	18.8	A
6	M	23	White	173	77.8	26.1	A
7	F	24	White	168	54.1	19.3	B
8	M	22	White/Asian	180	73.0	22.5	B
9	M	22	Asian/Hispanic	175	70.1	22.8	A
10	M	24	White	191	111.5	30.7	B
11	F	22	White	170	59.0	20.4	A
Average / Total	M=7 F=4	24±2.33	White only=9 All Other=2	176 ±8.43	74.1 ±15.69	23.8 ±4.32	A=5 B=6

Legend: Data are presented as number or mean +/- SD. M Male; F Female. Sequence A was block X, 30 min rest, block Y. Sequence B was block Y, 30 min rest, block X. Block X trial order (n=9, sum=575%): 55%, 50%, 70%, 75%, 100%, 90%, 25%, 30%, 80%. Block Y trial order (n=10, % sum=575%): 25%, 50%, 35%, 95%, 85%, 65%, 45%, 40%, 75%, 60%.

Accuracy

Metrics for absolute and relative accuracy are presented in *Table 2* and illustrated in *Figures 2-5*. Push counts captured by the wrist ActiGraph deviated from the manually counted condition by a mean of 12.6 (27.8% error) pushes. The frequency of small (≥5% error), medium (≥10% error), and large (≥25% error) errors were 115 (66%), 98 (56%), and 79 (45%), respectively. Push counts captured by the upper arm ActiGraph deviated from the manually counted condition by a mean of 4.4 (10.4% error) pushes. The frequency of small (≥5% error), medium (≥10% error), and large (≥25% error) errors were 44 (25%), 34 (19%), and 25 (14%), respectively. Push counts captured by the SW deviated from the manually counted condition by a mean of 2.3 (4.5% error) pushes. The frequency of small (≥5% error), medium (≥10% error), and large (≥25% error) errors were 25 (14%), 23 (13%), and 13 (7%), respectively.

Precision

Metrics for absolute and relative precision are presented in *Table 3* and illustrated in *Figures 2-5*. Regarding the wrist ActiGraph, the SD of the mean difference compared with video was 13 (CV=.15). Regarding the upper arm ActiGraph, the SD of the mean difference compared with video was 10 (CV=.06), whereas the SD of the mean difference for the SW compared with video was 4 (CV=.04).

Spearman's Rho correlations

Spearman's rho correlations between upper arm ActiGraph-Video push count difference and workload, rolling resistance, power

output, and speed are provided in *Table 4*. Upper arm ActiGraph-Video push count difference was significantly associated with rolling resistance (ρ=-0.174, p=0.022) and power output (ρ=-0.268, p<0.001). However, upper arm ActiGraph-Video push count difference were not associated with workload (ρ=-0.070, p=0.354) and speed (ρ=-0.137, p=0.072).

The study examined the accuracy and precision of the ActiGraph accelerometers and SWs for measuring push counts during manual wheelchair propulsion. The SW provided more accurate and precise estimates of push counts compared with accelerometers placed on the upper arm and wrist. The results further indicated more accuracy and precision of push count measurements with the accelerometer placed on the upper arm compared with the wrist. This preliminary study supports the accuracy and precision of SWs and perhaps upper arm-worn ActiGraph as research-grade devices for quantifying pushes as a metrics of LPA in persons who use manual wheelchairs.

Table 2. Accuracy of ActiGraph GT3X+ Devices Worn on the Wrist and Upper Arm and SMARTWheel for Capturing Pushes During Manual Wheelchair Propulsion Across 16 Trials of Increasing Workloads in a Sample of 11 Non-disabled Young Persons.

	Absolute Accuracy		Relative Accuracy			
	Mean (SD) of Total Pushes Averaged Across 16 Workloads	Mean Difference in Total Pushes Averaged Across 16 Workloads Compared with Video	Mean (SD) Percentage Error	n≥5% error (%)	n≥10% error (%)	n≥25% error (%)
Manually Counted	50(8)					
Wrist ActiGraph	63(12)	12.6	27.8(30.0)	115(66%)	98(56%)	79(45%)
Upper Arm ActiGraph	54(11)	4.4	10.4(24.8)	44(25%)	34(19%)	25(14%)
SMARTwheel	48(8)	2.3	4.5(8.8)	25(14)	23(13%)	13(7%)

Legend: SD standard deviation.

Figure 2. Bland-Altman Plot for Video 2. Negative Y-axis Values Indicate the 2nd Manual Push Counts Were Greater than the 1st Manual Push Count and Vice-versa.

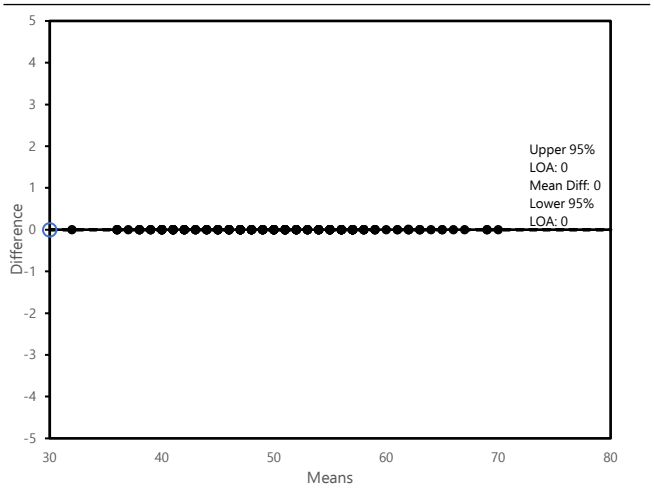


Figure 3. Bland-Altman Plot for the SW. Positive Y-axis Values Indicate SW Push Counts that Were Less Than Manual Push Counts and Vice-versa.

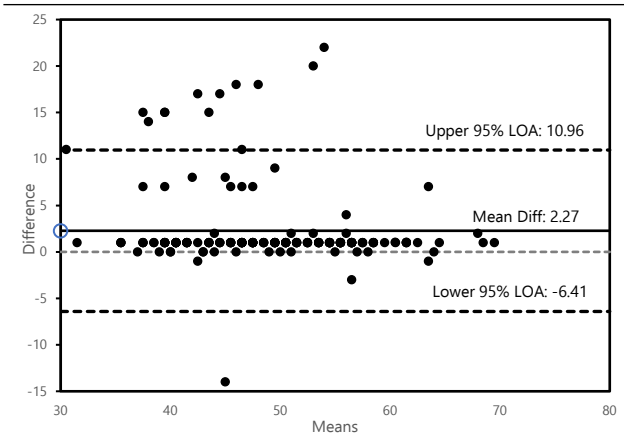


Figure 4. Bland-Altman Plot for the Upper Arm ActiGraph Accelerometer. Positive Y-axis Values Indicate ActiGraph Upper Arm Push Counts that Were Less Than Manual Push Counts and Vice-versa.

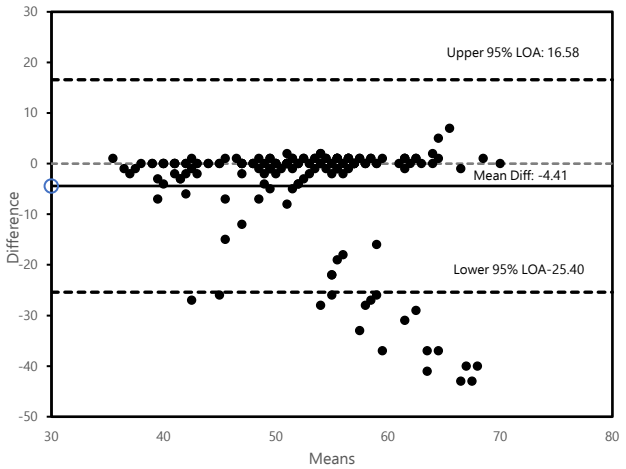
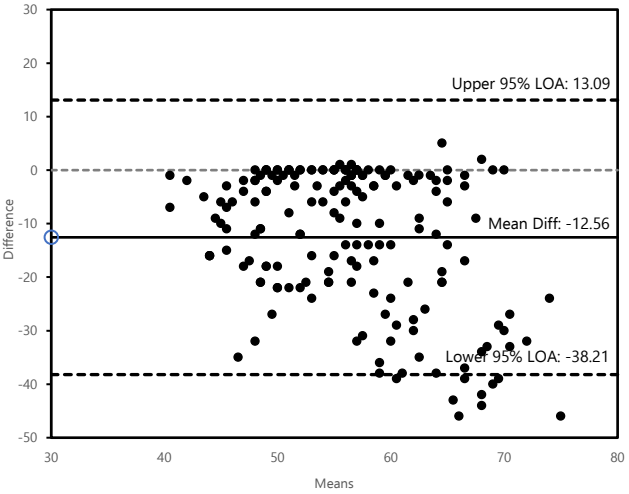


Figure 5. Bland-Altman Plot for the Wrist ActiGraph Accelerometer. Positive Y-axis Values Indicate ActiGraph Wrist Push Counts that Were Less Than Manual Push Counts and Vice-versa.



Discussion

Overall, compared to manual counting, SW slightly undercounted total pushes (SD) averaged across 16 workloads (manual: 50[8] pushes vs SW: 48[8] pushes). We suspect the SW undercounting could stem from discrepancies of defining a "push" or due to a push occurring on the wheel and not the push rim where the sensor on the SW is located. This could be the focus of future research examining the accuracy and precision of SW for measuring pushes in manual wheelchair users.

Conversely, compared to manual counting, both ActiGraph accelerometers overcounted total pushes (SD) averaged across all 16 workloads (upper arm: 54[11] pushes, wrist: 63[12] pushes, manual: 50[8] pushes). Due to limited research in using wearable devices for wheelchair push counts, comparisons of our study population with existing research are limited. Our finding of wearable push counters having the tendency to overcount is somewhat consistent with previous studies evaluating Apple Watch accuracy for counting pushes during wheelchair propulsion.[8-10] However, we identified one study that reported undercounting from the series 1 Apple Watch compared with manual counting during wheelchair propulsion through a 21-part obstacle course.[11] This may be due to differences in the definition of a "push" or in the methodology. For example, one group of researchers[11] defined a push as "any force that was applied to the rim of the wheel by the hand that resulted in movement of the manual wheelchair," including backwards pushes, and the testing protocol included multidirectional/backwards propulsion, whereas our protocol included only forward propulsion. Overall, this suggests that wearable device-measures of push counters tend to overcount during forward wheelchair propulsion. Further investigation is required to evaluate the accuracy and precision of wearable device-measures of push counts during backward wheelchair propulsion.

Table 3. Precision of ActiGraph GT3X+ Devices Worn on the Wrist and Upper Arm and SMARTWheel for Capturing Pushes During Manual Wheelchair Propulsion Across 16 Trials of Increasing Workloads in a Sample of 11 Young Persons.

	Absolute Precision	Relative Precision
	SD of the Mean Difference in Total Pushes Averaged Across 16 Workloads Compared with Video	Coefficient of Variation
Wrist ActiGraph	13	.15
Upper Arm ActiGraph	10	.06
SMARTwheel	4	.04

Legend: *SD* standard deviation.

The tendency for wearable push counters to overestimate can possibly be explained by increased "noisiness" of hand/arm motion during a push, resulting in falsely counted pushes. Based on ***Figure 3***, for a large portion of the time, the upper arm ActiGraph accelerometer was accurate, but there was a subset of trials in which the accelerometer push counts varied significantly from the manually recorded pushes counts (the gold standard). We evaluated hand-traced patterns during the wheelchair propulsion to determine if certain motions/hand patterns (i.e., vertical hand accelerations inherent in some certain push pattern trajectories) contributed to the inaccuracy of push counts recorded by accelerometers. However, we were not able to confirm this theory. Additionally, we evaluated bivariate correlations between upper arm ActiGraph-Video push count difference and workload, rolling resistance, power output, and speed. Our results suggest that rolling resistance and power output may have influenced the differences between the upper arm worn ActiGraph accelerometer and manually counted pushes. This warrants further investigations of whether or not vertical acceleration or other potential factors (i.e., wheelchair configuration, propulsion mechanics, individual factors) may contribute to these discrepancies in recorded push counts.

Table 4. Spearman's Rho Correlations Between Upper Arm ActiGraph-Video Push Count Difference and Workload, Rolling Resistance, Power Output, and Speed.

	Workload (%)	Rolling Resistance (N)	Power output (W)	Speed (m/s)
(n=11 participants)	-0.070 P=0.354 n=175	-0.174 P=0.022 n=175	-0.268 P<0.001 n=175	-0.137 P=0.072 n=175

Our results suggest that an ActiGraph accelerometer on the upper arm during wheelchair propulsion was more accurate (% error=10.4 vs 27.8) and precise (CV=.06 vs .15) than a unit worn on the wrist for measuring push counts. This further supports our suggestion that increased "noisiness" in arm/wrist motion is a contributing factor of overcounting. During wheelchair propulsion, the activity of the hand/wrist is higher and more variable than the mid humerus portion of the arm. Further work needs to be done to confirm if this pattern is present among more experienced wheelchair users.

Our results suggest that SW (4.5% error) was more accurate than the wrist-worn ActiGraph accelerometer (27.8% error) and an upper arm-worn ActiGraph accelerometer (10.4% error) in our sample of non-disabled young adults. Previous studies have reported series 4 Apple Watch to have an accuracy (9.2-13.9% error),[8 9] which is comparable to the accuracy of our upper arm-worn accelerometer. However, the Apple Watch from the aforementioned study may be more accurate in measuring push counts than the wrist-worn accelerometer in our study. This is contradictory to what one would expect, as ActiGraph is a research-grade device while the Apple Watch is not. Future investigations are needed to identify the source(s) of inaccuracy among wearable push counters and to compare research grade devices to commercially available devices.

Some limitations should be considered when evaluating the results of this study. We included a relatively small sample size of

persons who were inexperienced with manual wheelchair propulsion. Future research may include a larger sample size of persons who use manual wheelchairs regularly (i.e., more than 50% of their daily life). Another limitation was that ActiGraph accelerometers were placed only on the right side, as there may differences in push counts between the dominant and non-dominant sides. Furthermore, we used a WheelMill ergometer rather than over-ground manual wheelchair propulsion for this study protocol. Wheelchair propulsion over-ground may have different biomechanical characteristics compared with wheelchair propulsion on an ergometer and may translate to daily life more readily. Another limitation is the use of research-grade devices to capture push counts. A potential avenue of research would be to compare accuracy and precision of commercially available activity monitors for measuring pushes in manual wheelchair users.

Conclusion

This study examined the accuracy and precision of ActiGraph accelerometers and SW for measuring pushes in non-disabled young adults. SWs demonstrated greater accuracy and precision than ActiGraph accelerometers placed on the upper arm and wrist, yet the accelerometer placed on the upper arm was more accurate and precise than the accelerometer placed on the wrist. An area for future investigation includes direct comparison of the accuracy and precision of available wearable devices, including ActiGraph accelerometers, Apple Watch, and Fitbit devices for manual wheelchair push counting. Once the most accurate and precise device is identified and deemed to yield acceptable data, future studies can then focus on furthering our understanding of physical activity and its correlates and consequences in manual wheelchair users. One potential example, among many, includes evaluating the relationship between daily push counts and health outcomes such as cardiovascular disease in wheelchair users.

Summary – Accelerating Translation

Title: Accuracy and Precision of Actigraphy and SMARTwheels for Measuring Push Counts Across a Series of Wheelchair Propulsion Trials in Non-disabled Young Adults

Main Problem to Solve: There has been a growing interest in the study of physical activity for management of health outcomes among wheelchair users. One key step in monitoring physical activity levels involves having tools for monitoring "pushes." To date, little is known about how well research-grade devices work for monitoring pushes. If we can provide accurate and precise measurements of pushes, future research can better examine physical activity among manual wheelchair users, so that clinicians may prescribe, promote, and monitor physical activity.

Aim of Study: Examine the accuracy and precision of SW and ActiGraph accelerometers for measuring push counts during 19, 1-minute bouts of manual wheelchair propulsion in healthy non-disabled adults.

Methods: Eleven (7 males, 4 females) non-disabled, young adults completed the protocol. All testing took place on a wheelchair machine that allowed us to control the resistance they pushed against. The same wheelchair was used for each participant, equipped with a device that counts pushes. Participants further wore 2 devices, one on the wrist and one on the upper arm that counted pushes. Video footage was recorded, which enabled manual counting of the number of pushes (gold standard). Participants underwent an acclimation period to get used to pushing a wheelchair. Then participants underwent an exercise test in which they pushed continuously for 5-10 minutes as the resistance they pushed against increased. Lastly, participants underwent 19, 1-minute pushing bouts against various resistances ranging from 25-100% of the estimated maximum resistance they could push against. We used the data obtained from the device on the wheel, the two devices on the participants arms, and the data from the video recordings to compare how accurate and precise each tool was for counting pushes. The manual counts from the video data were used as the gold standard and is what the other devices were compared to. We also evaluated various push mechanics to see if any certain factor may have caused the devices to count incorrectly.

Results: The device on the wheelchair most the most accurate and precise tool, followed by the device on the participants upper arm, followed by the device on the participants wrist. The device on the wheelchair tended to slightly undercount, while both devices on the participants arms tended to overcount. We were not able to identify a particular pattern of pushing that could be responsible for miscounting by the devices, but our results suggest that two push mechanical factors may be associated with miscounting by devices.

Conclusion: Among the three devices we evaluated, the device on the wheelchair is a better tool to use for counting pushes in manual wheelchair propulsion, followed by the device worn on the upper arm, and the device worn on the wrist. Further research needs to investigate potential factors that cause the devices to miscount. Once this is better understood, researchers can better examine physical activity among manual wheelchair users, so that clinicians may prescribe, promote, and monitor physical activity.

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Supplementary Material

Supplemental Table 1. Wheelchair specifications in accordance with the recommendations of Fritsch et al.[15]

Wheelchair Specification	Measurement
Rear wheel diameter solid tire	25″
Rear wheel diameter pneumatic tire	25″
Rear wheel camber with solid tires	11°
Rear wheel camber with pneumatic tires	8°
Handrim diameter for solid tire	21.5″
Handrim diameter for pneumatic tire	22″
Caster diameter	4″
Seat width x length	18″x18″
Seat height with solid tires	19″
Seat height with pneumatic tires	18.5″
Seat angle	1.5°
Backrest height	9″
Backrest angle	80°
Footrest size	6″ x 9″
From bottom of chair to footrest length	13″
Footrest angle	96°
Back of the seat fore-aft position with respect to the rear wheel axle	5″
Back seat height with respect to the ground with solid tire	28″
Back seat height with respect to the ground with pneumatic tire	28.5″
Fork axis angle	45°

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Original Article

Beck's Depression Inventory II Suicidal Ideation in Medical Students – Prevalence and Associated Factors

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Abstract

Background: Suicide is the second leading cause of death in 15- to 29-year-olds in Germany. Studies have shown that compared to the general population students are more affected by suicidal ideation, as one major indicator of an attempted suicide. This effect is observed all over the world, interestingly, it is also true for physicians. Therefore, we investigated whether medical students are at an even higher risk than their peers to develop suicidal ideation. **Methods:** N=1,103 medical students at a German university completed a self-reporting survey investigating socio-demographic, potential risk, and protective factors. The Beck's Depression Inventory (BDI)-II Item 9 "Suicidality" served as the dependent variable. **Results:** N=130 students (11.8% of the total sample) reported suicidal ideation within the last two weeks. Stepwise computed logistic regression models including all potential risk factors resulted in 40% explained variance. The most significant independent risk factors were the BDI-score, usage of tranquilizers, feeling lonely, insufficient time for hobbies and prior personal mental health issues, whereas focus enhancing drugs showed to be the only independent protective predictor. The BDI-II score correlated positively with the number of students suffering from suicidal ideation. **Conclusion:** The prevalence of suicidal ideation in our sample medical student population exceeds that of the general population greatly, confirming existing data and emphasizing the need to raise awareness and establish prevention programs.

Key Words: Suicidal Ideation; Suicide; Medical Students; Prevalence; Depression; Neuroticism (Source: MeSH-NLM).

Introduction

According to the World Health Organization (WHO) there are 800,000 deaths by suicide every year worldwide, and of those, 9000 suicides occur in Germany.[1] This exceeds deaths by road accidents by almost three times.[1] Worryingly, it is also the second leading cause of death in the age group of 15 – 29-year-olds,[1] an age group in which most people receive their education. Not only is suicide an unspeakable individual tragedy but it is also an immense economic and public health loss.

A reliable indicator for an actual suicide attempt in the future is a prevailing suicidal ideation. Therefore, it is important to get a better understanding of this stage, which is also a point in time where the society can still intervene.[2]

The nationwide prevalence in the general population for suicidal ideation in the two weeks prior to conducting out survey resulted at 2.8%.[3] According to Hawton and Van Heeringen (2009), there are several risk factors leading to suicide: demographic factors such as male sex (completed suicide) or female sex (attempted suicide or ideation), age (peak in adolescence and old age), low socioeconomic status, and single relationship status. Furthermore, there are biographic or psychobiological factors that often build a fundamental predisposition to develop suicidal behavior: hopelessness, social isolation and loneliness, impulsivity, genetics, childhood experiences, and suicide within family or friends. Additionally, psychological autopsies have shown that 90% of people who committed suicide suffered from a psychiatric disorder. The most important associated factor being depression, closely followed by substance abuse. Multiple co-morbidities increase the risk of suicidal behavior significantly.[4] Since neuroticism correlates positively with depression, it is also shown that people with a high personality trait of neuroticism suffer from suicidal ideation.[5]

Upon enrolling to a university, students are exposed to many of these risk factors, including loneliness due to moving away from home, relationship break-ups, poor financial status, performance

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pressure, substance abuse, and less time for hobbies and friends. Santos et al. (2017) confirmed that university students with low income, homo-/bisexual orientation, presence of depressive symptoms, high alcohol consumption and suicide attempts among friends or family have a higher prevalence of suicidal ideation than their peers.[6] The prevalence of college students' suicidal ideation varies from 10.6% - 13.3% within one year to 2.7% - 11.1% within the last month prior to survey.[7,8]

Within this particular age group, there is yet another subgroup this study aims to examine more closely, namely medical students. Trained to become physicians, thus maintaining everyone else's wellbeing, including mental disorders and suicide prevention, medical students' own mental health benefits the whole society. Once in professional life, the risk to commit suicide is 1.4 times higher for a male physician and 2.3 times higher for a female physician compared to the general population.[9] Studies attempting to shed light on whether this effect is already active for medical students show consistent results: an online-survey from France showed every fourth medical student to have thought of suicide,[10] and a Spanish study reported a prevalence of 15.8%.[11] According to Tyssen et al. (2001), who conducted a longitudinal study among Norwegian medical students, 14.0% have thought about suicide and within one year continue doing so after graduation.[12] A definite effect, albeit with lower prevalence, was found by Dyrbye et al. (2008) and Rotenstein et al. (2016) with 11.2% and 11.0%, respectively.[13,14] Finally, Schwenk et al. (2010) state that only 4.4% of medical students "seriously consider committing suicide during medical school", implying an already advanced action-oriented stage of suicidal behavior.[15] It is obvious that medical students' prevalence of suicidal ideation greatly exceeds that of the general population even though the precise percentages differ between studies. Therefore, it is long overdue to investigate the circumstances of those young individuals and help prevent drastic mental or even fatal consequences.

Since depression is one of the most important risk factors of suicide, it would be interesting to observe whether or not it is also more common in medical students than in the general population. A systematic review and meta-analysis of 24 international studies by Rotenstein et al. (2016) estimated 27.2% of medical students are suffering from depression or depressive symptoms.[14] After discovering this, a study on medical students' mental health was carried out. And indeed, we found almost every fifth student presenting mild to severe depressive symptom constellations. Compared to the 11.5% prevalence in 15–29-year-olds of the general German population, an additional mental burden cannot be denied.[16]

With the current literature findings and the increased presence of depressive symptoms within our previous study in mind, the following question arose: do the medical students of this study sample have a higher prevalence of suicidal ideation compared to the general population or students of other major graduate courses? Can additional risk factors be detected or known ones be confirmed? Knowledge of these factors is vital to implement effective prevention strategies in the susceptible age range and right before starting an even more demanding career. Therefore, this study aims to create a statistical basis for local projects and add to the understanding of students' mental health worldwide in order to better protect future generations by gaining prevalence and risk factors of suicidal ideation of medical students in a German university.

Methods

Study design

Between 2017 and 2018 we conducted an observational cross-sectional study in a medium-sized public university with about 20,000 enrolled students in order to study suicidality and depressive symptoms as well as sociodemographic, risk, and protective factors of medical students. The local Ethics Committee approved this study (approval code: 2017-138).

Setting

The questionnaire was distributed during compulsory seminars either at the beginning or end of an academic term and anonymously completed in classroom as paper-pencil survey in the German language. For this paper we used the English-version BDI-II for translation..

Participants

Initially we handed out the questionnaire to 1,124 students from pre-clinical and clinical semesters. The response rate of the population was 91%, resulting in a total sample size of n=1,103 study participants. Subjects participated on a voluntary basis without compensation and 9% refused to participate or did not fill out the survey accurately.

Measurements

Our study surveyed sociodemographic data, protective and risk factors, neuroticism, and depression symptoms including suicidality.

a) Suicidality and Depressive Symptoms

The Beck's Depression Index II (BDI II) was embedded in our survey to assess severity of depressive symptoms. It served as a self-assessed test consisting of 21 items measuring depressive symptoms within the last two weeks prior to the survey. Good reliability and validity in clinical samples were confirmed by Kühner et al. (2007).[17] Each item rated on a scale from 0 - 3 (no symptoms - severe symptoms), and the total score resulted in categories from mild to severe depression.

Item 9 "suicidal ideation" of this index served as the dependent variable for the present study. In accordance with several other studies, this item is a valid measure for suicidal ideation.[11,18, 23, 24] In the original questionnaire, suicidal thoughts were identified using the following options: 0= "I don't have any thoughts of killing myself"; 1= "I have thoughts of killing myself, but I would

not carry them out"; 2= "I would like to kill myself"; and 3= "I would kill myself if I had the chance." Since answers greater than "1" are usually very rare, we dichotomized the originally ordinal variable. Thus, creating a dichotomous variable (no suicidality vs. suicidality) for the following analysis. Item 9 (suicidality) was excluded to calculate the depression score for correlation analysis within this study.

b) Sociodemographic

Sociodemographic data consisted of extraneous variables on sex and gender, current age, region of origin, relationship status and duration, vocational training, number of children and siblings, and parents' highest school degree and professional qualification. During analysis we differentiated between growing up in former Western or Eastern Germany, as well as abroad.

c) Risk factors

For prevailing risk factors, we inquired whether or not a first degree relative or the subject was treated for a mental illness and if so, which one. Furthermore, we estimated the socioeconomic status by asking if the financial status fell into deprivation categories "sometimes too little," "often too little," and "I am mostly under great financial pressure." Additionally, we inquired into whether the subject was separated from a parent due to death or divorce and whether he or she abused alcohol, sedating, or focus enhancing drugs, and their frequencies of use. To scale current stress levels, we asked whether the subjects were satisfied with their amount of free and study time and the amount of pressure they felt. Moreover, social isolation was determined by whether sufficient quality time was spent with friends or family. Finally, we checked the ability of the subject to share problems and feelings of loneliness.

To measure the personality trait of neuroticism, we used a subcategory of the fully standardized NEO-Five-Factor Inventory (NEO-FFI) containing 12 items.[19] Neuroticism acted as a variable in our correlation analysis if a student scored a standard deviation of 2.54 above the age-adjusted mean.[20]

d) Protective factors

Protective factors included coping mechanisms such as time spent playing an instrument, importance of religion in everyday life and during childhood, frequency of engaging in hobbies with an emphasis on sports, enjoyment of studies, and the availability of support from friends, family and teachers. Additionally, we assessed the students' behavior towards diet and body conception.

Data analysis

Data analysis was performed using the software IBM Statistical Package for Social Sciences (SPSS 25.0). The evaluation of the frequency of suicidal ideations was done by descriptive statistics and the determination of relative frequencies of the respective item score. The initial sociodemographic description of the study sample was based on the descriptive distribution characteristic (mean, standard deviation, range) and relative frequencies. Depending on scale characteristics, correlation between risk factors and suicidal ideation was calculated using Kendall-tau or point-biserial correlation. The influence of risk factors that proved to be correlated was determined by binary logistic regression (forward).

Results

The cohort of students consisted of an almost exact split into 51.1% attending the preclinical and 48.9% attending the clinical part of medical school. Demographic data of the sample is presented in *Table 1*.

Table 1. Sociodemographic Characteristics of Study Participants.

Socio-demographic features	Pre-clinical n = 564	Clinical n = 539	Total n = 1103
Sex at birth – n (%)			
Males	188 (33.3%)	199 (36.9%)	387 (35.1%)
Females	376 (66.7%)	340 (63.1%)	716 (64.9%)
Age – Mean ± SD	21.5 ± 3.7	24.8 ± 3.6	23.1 ± 4.0
Vocational training[1] – n (%)	135 (23.9%)	142 (26.3%)	277 (25.1%)

Legend: 1 completed vocational training prior to medical studies.
n = Frequency; M = Mean; SD = Standard deviation.

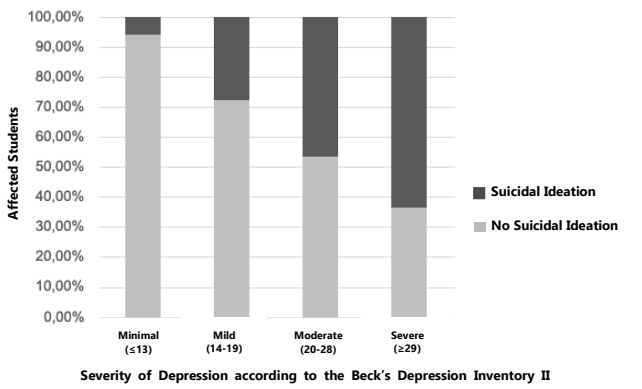
The participants' ages ranged from 17 to 45 years, with an average age of 23.1 years (Standard Deviation 4.0). The male to female ratio of 35% to 65% appropriately matches that of the overall men to women ratio of 38:62 in German medical students appropriately.[21] Suicidal ideation was stated by 130 students (11.8% of the total sample) students within the last two weeks. Most of these students (96.9%) showed the mildest form ("I have thoughts of killing myself, but I would not carry them out"), and only four students used more progressive options. The total 13.5% (n=76) prevalence of suicidal ideation was slightly higher in pre-clinical students compared to clinical students (n=54; 10.0%), however, this was not statistically significant (X^2 [df=1] =3.17; p=0.075).

Table 2 shows the correlation between suicidal ideation and potential risk factors. Highest coefficients were found for adjusted BDI-score (M±SD=8.2±7.0, point-biserial correlation (r_{pb})=0.456, p<0.001), neuroticism (M±SD=1.51±0.8, rpb=0.366, p<0.001), insufficient emotional support (17.7%, Kendall-tau (τ)=0.254, p<0.001), feeling lonely (13.2%, (τ)=0.274, p<0.001), using tranquilizers (6.5%, (τ)=0.211, p<0.001) and irregular meals (13.9%, (τ)=0.179, p<0.001).

Overall, 63% of students with suicidal ideation also showed at least mild symptoms of depression (BDI-II score ≥ 14). Conversely, only 13% of students with more than 14 BDI-II points

did not experience suicidal ideation. As displayed in *Figure 1*, the number of students suffering from suicidal ideation differs significantly between the groups of different levels of severity of depressive symptoms according to the corrected BDI-II sum score ($\chi 2$ [degrees of freedom = 3]=225.1; $p<0.001$; Standard error = 0.032): Suicidal ideation was reported by 6% students with no or minimal depressive symptoms (score ≤13). Nevertheless, 27.7% with a mild depression (score=14-19), 46.8% with a moderate depression (score=20-28) and 63.7% with a severe depression (score≥29) experienced suicidal ideation.

Figure 1. Relationship between Beck's Depression Inventory II Score and Percentage of Students Reporting Suicidal Ideation.



Stepwise forward logistic regression model including all potential risk factors resulted in 40% explained variance (Nagelkerke). Significant predictors for suicidal ideation were: "feeling lonely", "prior own mental health issues," "adjusted BDI-II-score," "confiding own worries to no one," "learning difficulties," "satisfied with time for hobbies," and "insufficient time for studies" (see *Table 2* for exponential value of B (Exp(B)) and 95% confidence interval (CI)).

Discussion

This study was conducted to highlight the mental pressure of medical students and found an 11.8% prevalence of suicidal ideation in this population. This suggests an immense problem not sufficiently addressed. The intention was to identify the main risk or protective factors for this high prevalence of suicidal ideation in order to raise awareness, reduce unnecessary stressors, and establish prevention programs. Our study showed several factors significantly correlated to suicidal ideation: mental health, sociodemographic factors, lifestyle, and study-related aspects. Variables concerning mental health such as current depressive symptoms, symptoms of fear, psychosomatic symptoms and prior mental health issues as well as a family history of mental illness, were associated. In terms of sociodemographic and lifestyle risk factors, we determined insufficient emotional support, loneliness, unsatisfying social relations, inability to share one's worries, insufficient financial funds, use of sedating or focus-enhancing drugs, irregular intake of meals, and weight issues were all players. The effects of medical school itself included stress factors such as time and performance pressure, mental overload, competition between class mates, learning difficulties, being an international student, and the uncertainty of being able to graduate.

To judge the correlation of neuroticism and suicidal ideation, one needs to keep in mind that current depressive symptoms alter self-perception, affecting the outcome of self-assessed neuroticism tests. Therefore, their correlation is likely to be overrepresented.[22]

All of the above are well established risk factors, confirming current knowledge. In a further step, we sought to identify the most important factors by using a logistic regression model. Here, feeling lonely, prior mental health issues, adjusted BDI-II-score, confiding own worries to no one, learning difficulties, satisfaction with time for hobbies, and insufficient time for studies significantly predicted suicidal ideation with 40% of variance explained. However, evolving suicidal ideation is complex and this gives future studies reason to investigate additional predictors.

As expected, the BDI-II-score predicted suicidal ideation reliably: 63% of students displaying suicidal ideation also suffered from mild to severe depression symptoms. Viewing it from the other side, only 13% of students with mild to severe depression symptoms did not state suicidal ideation.

Contrary to several findings,[6,8,23,24] we did not observe students with suicidal ideation consuming alcohol more frequently than their peers. This might be because alcohol consumption is more strongly associated with social activities and inclusion within this study's medical students, thus concealing alcohol consumption as coping mechanism for mental health problems. On the other hand, drug usage was associated with suicidal ideation and also served as a valid predictor. Studies show that drug abuse in general as a risk factor for suicidal behavior.[4] Likewise, our results show that consuming sedating drugs was correlated with suicidal ideation, as well as – to a smaller extend - consuming focus-enhancing drugs. These correlations suggest that the need for students to perform more effectively and reacting on their burdens may promote dysfunctional coping styles.

Prevalence

The prevalence found in our study is consistent with data from other medical student populations found in literature ranging from 9% - 15.8%.[11–13,15,25,26] In addition, Rotenstein et al. (2016) showed a mean prevalence of 11.1% within one year in a meta-analysis of 24 international studies on this topic.[14] Unfortunately, studies' inconsistent usage of screening tools (PHQ-9, CES-D, NCS-R, BDI, Meehan, individual questionnaires) and the time span of their questionnaires (two weeks, four weeks, one year, lifetime) lead to less comparable results. This emphasizes the importance of standardized survey methods for mental health studies.

Table 2. Correlation between Potentially Associated Factors and Suicidal Ideation and Exponents of Logistic Regression.

	Correlation	% of affected students or M±SD	Exp(B) [95%CI] in logistic regression
Sociodemographic			
Male sex[a]	-	35.1%	
Age[b]	-	23.1±4.0	
Loss of parent due to death/separation[a]	-	18.2%	
Being an international student[a]	0.067*	5.2%	
Lifestyle			
Regular meals[a]	-0.179***	86.1%	
BMI[b]	-	22.5±3.6	
Happy with weight[a]	-0.094**	58.3%	
Happy with diet[a]	-0.065*	27.3%	
Hours /w spent doing sports[b]	-	3.7±3.3	
Satisfied with time for hobbies[a]	-0.101***	24.2%	0.29 [0.14-0.61]
Number of days consuming alcohol / w[b]	-	1.4±1.4	
Number of smoked cigarettes / d[b]	-	0.8±3.0	
Using food to calm down[a]	0.099***	16.3%	
Using meds/drugs to calm down[a]	0.211***	6.5%	
Using meds/drugs to enhance focus[a]	0.088**	2.9%	
Social Life			
Living alone[a]	0.072*	41.8%	
Feeling lonely[a]	0.247***	13.2%	3.65 [1.97-6.79]
Relationship >3 months[a]	-0.069*	52.5%	
Happiness with relationship[a]	-0.143***	77.1%	
Happiness with family[a]	-0.164***	85.3%	
Happiness with friendships[a]	-0.169***	85.1%	
Insufficient emotional support[a]	.254***	17.7%	
Insufficient financial funds[a]	0.067*	19.6%	
Importance of religion[a]	-	22.9%	
Mental health			
Mental illness in FDR[1a]	0.064*	27.3%	
Prior own mental health issues[a]	0.193***	14.1%	2.73 [1.41-5.26]
Adjusted BDI-score[b]	0.456***	8.2±7.0	1.19 [1.14-1.24]
Symptoms of fear[a]	0.154***	56.0%	
Psychosomatic symptoms[a]	0.084**	44.7%	

Legend: 1 FDR: first degree relative.
a Kendall-tau, b point-biserial correlation.
* p<0.05; ** p<0.01; *** p<0.001; - no significance.
M = Mean; SD = Standard deviation; CI = Confidence interval; Exp(B) = Exponential Value of B.

The only other studies using the BDI item 9 as an indicator for suicidal ideation were Atienza-Carbonell & Balanzá Martínez (2020), Arria et al (2010) and Curran et al. (2009).[11,23,24] Curran's Irish medical student population showed a 6% prevalence within the last month. It is unclear why their prevalence is only half as high in a time period even longer compared to ours. One explanatory approach might be the difference in depression-prevalence of 14% compared to our 19%.[24] Arria's U.S. student population also showed a 6% prevalence but only within a few days compared to our two weeks.[23] Atienza-Carbonell's Spanish survey method resembles ours the most: their reported two-week prevalence of 15.8% exceeds ours by approximately 4% whereas, the prevalence of depression is around twice as high (39.1% vs. 19%).[11]

Overall, our results are generally in line with the observations described in literature, tending to exceed them. However, while comparing data, one must bear in mind that differences in results do not only stem from screening tools used and time frames captured but also from prevailing educational and socioeconomic systems.

The prevalence exceeded that of the general population by a factor of four, even though a comparison of those prevalences is limited due to different study methods, which is a cause for concern considering suicidal ideation as a main predictor for an actual attempt.[2] Few studies turned their focus on suicide cases in medical students. Those existing were reviewed by Blacker et al. (2019), concluding a lack of reliable recent sources but still finding medical students' suicide rates trending lower than those of the general population.[27] Furthermore, Barrios et al. (2000) showed students with suicidal ideations participated more frequently in "injury related risk behavior", such as driving after drinking alcohol or engaging in physical fights.[7] Therefore, supporting students with suicidal ideation is crucial to lower the risks not only for themselves but for others in society as well.

Additionally, the recent Covid-19 pandemic increased the presence of risk factors such as feeling lonely due to official social restrictions and decreased protective factors such as participating in clubs, team sports, in an orchestra or choir. Furthermore, fear of infection and unplanned changes in the curriculum added stress and anxiety. Earlier reviews suggest no change in prevalence but are still short on data.[28] Therefore, further longitudinal studies are needed to elucidate the causality of suicidal ideation related to the restrictions of social life like those during the COVID-19 pandemic.

Limitations

While analyzing the results of this study, several limitations must be kept in mind: even though our sample size of n=1,103 students and the resulting 130 students with suicidal ideation is substantial, the survey mirrors students' mental health of only one German university. Also, we did not include students of every year in school, potentially missing alternative risk factors. Additionally, our study was conducted at different points in time during classes or right after breaks, including acute stressful situations such as

exams or practical trainings, but not taking these into account during data analysis. As this study was originally designed to monitor depressive symptoms, important risk factors such as mood stability, suicides or suicide attempts in family and friends were not addressed. Fortunately, voluntary and anonymous participation should not have distorted our data since an actual response rate of 91% was achieved.[29] The environment the survey was conducted in (e.g., crowded classrooms, chitchatting) could have influenced self-reported responses, potentially concealing even higher rates of suicidal ideation or prevailing risk factors.

Prevention

Our findings show suicidal ideation is not a rarity amongst medical students. In order to help future generations of doctors, universities must establish prevention programs, educate fellow students and staff, and make psychological support more accessible to affected students. According to Givens et al. (2002), U. S. medical students were discouraged from using mental health services because of lack of time (48%), lack of confidentiality (37%), stigma associated with using mental health services (30%), cost (28%), fear of documentation on academic record (24%), and fear of unwanted intervention (26%).[30] Based on those findings, Thompson et al. (2010) established several intervention programs: staff training, distribution of mental health brochures among the students, mental wellbeing classes at another faculty, and free of charge sessions with psychologists. As a result, suicidal ideation was dramatically reduced from 30% to 3%.[31] Such measures are a great example of how to value and cater for the mental health of medical students, making student life more pleasant, safe, and healthy for everyone.

Summary – Accelerating Translation

„Beck-Depressions-Inventar II Suizidgedanken bei Medizinstudierenden – Häufigkeit und assoziierte Faktoren"

Selbstmord ist die zweithäufigste Todesursache unter den 15- bis 29-Jährigen in Deutschland. Studien zeigten bis jetzt, dass Studierende im Vergleich zur Gesamtbevölkerung häufiger unter Suizidgedanken leiden. Dieser Trend zeigt sich nicht nur in Deutschland, sondern weltweit. Zusätzlich wurde festgestellt, dass Ärzte eine höhere Suizidrate aufweisen. Um die mentale Belastung durch Suizidgedanken von Medizinstudierenden zu beleuchten und Risiko- sowie Schutzfaktoren ausfindig zu machen, führten wir also eine Querschnittstudie durch, in der wir die Medizinstudierenden der Martin-Luther-Universität Halle mit Hilfe eines Fragebogens analysierten. Die Rate der Suizidgedanken machten wir durch einen standardisierten Depressionsfragebogen ausfindig. Zudem erhoben wir Daten zu soziodemographischen Verhältnissen und potenziellen Risiko- bzw. protektiven Faktoren. Insgesamt berichteten 130 Studierende, das sind 11.8% der Befragten, von Suizidgedanken innerhalb der letzten zwei Wochen. Die wichtigsten Risikofaktoren waren das Vorhandensein depressiver Symptome, Gebrauch von Beruhigungsmitteln, das Gefühl von Einsamkeit, unzureichende Zeit für Hobbies und schon bestehende weitere psychische Probleme. Als protektiven Faktor konnten wir lediglich die Nutzung von Stimulanzien ausmachen. Es zeigte sich deutlich, dass die Schwere der Depression mit der Wahrscheinlichkeit vorliegender Suizidgedanken korrespondierten. Insgesamt konnten wir somit feststellen, dass Medizinstudierende eine erhöhte Rate an Suizidgedanken haben und das Studium selbst hierzu beiträgt. Es ist somit dringend notwendig unser vorherrschendes System an den Universitäten zu hinterfragen, psychische Gesundheit in den Fokus zu nehmen und Präventionsprogramme zu installieren.

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Original Article

Medical Students' Attitudes and Influential Factors Towards Conducting Medical Research

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Abstract

Background: Medical research has become an essential part of medical students' curricula at several medical colleges in Saudi Arabia. This study aimed to assess medical students' attitudes and identify factors influencing their willingness to conduct medical research. **Methods:** This cross-sectional study was conducted between December 2021 and April 2022 using the students' attitudes towards research and the students' perceived influential factors toward participating in research activities questionnaires. A 5-Likert scale to calculate the average of the students' responses, where 5 indicated 'strongly agree' and 1 indicated 'strongly disagree'. The survey was distributed to medical students at the College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Saudi Arabia. **Results:** A total of 500 responses were collected from the students (67.2% male and 32.8% female). Most students agreed with the following statement: 'Research is important for identifying and investigating problems in a subject matter' (N=399, 79.8%). More than half of the students agreed with the following statement: 'I am very interested in participating in research activities at the undergraduate level' (N=318, 63.6%). The top three influential factors for conducting medical research were 'to facilitate entry into competitive residency programs', followed by 'interest in specific research fields or medical topics' and 'to improve curriculum vitae (CV).' **Conclusion:** The majority of the surveyed students showed a positive attitude towards conducting medical research in King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia. Most students conduct research to gain a competitive edge and explore specialties of interest.

Key Words: Research; Medical students; Attitudes; Knowledge; Perception (Source: MeSH-NLM).

Introduction

Medical research has advanced medical practice because it helps physicians address the most pressing challenges in the healthcare sector, thereby reducing global health disparities by offering affordable treatments and rapid screening tools.[1,2] It is crucial for researchers and medical students to understand research principles in order to produce reliable and high-quality articles.[3] Previous studies have shown that early exposure to research can improve medical students understanding and the conduction of medical research. As a result, several medical colleges have incorporated research into their curricula.[4-6] There are a few methods to incorporate research training into medical school curricula: either by research-driven curricula, research electives, or mandatory research projects for graduation.[7,8] However, many medical students still do not have sufficient knowledge to conduct research projects and publish them.[6,9,10] Given the need to build a research-facilitating curriculum, it is important to determine the attitude of medical undergraduates towards research in Saudi Arabia.[11]

In the Kingdom of Saudi Arabia, there has been an increase in the number of medical undergraduates who have conducted research before graduation, though only a few have been the first authors.[6,9] Low number of graduates with research experience are commonly observed in colleges where research projects are not mandatory for graduation.[6,9] However, only seniors and students with a high Grade Point Averages (GPA) were more likely to participate in research.[6,9] A study conducted in Umm Al-Qura University in Saudi Arabia revealed that only 10.8% of health colleges' students have an adequate background in research, and only 6.6% had published a medical research paper.[10] Despite the increasing number of medical students involved in research for various reasons[12], studies have shown that students' research projects are often not of good quality, nor are they particularly impactful towards the scientific community.[13,14]

Currently, conducting a research project is a prerequisite for graduation in several Saudi medical colleges.[6,15] In addition, the Saudi Commission for Health Specialties (SCFHS), a regulatory commission that sets requirements for students' enrollment into Saudi residency programs, recently announced that participation in research activities and publications in specified journals are granted 6 points out of the total 20 points available for residency applications as of 2022.[16] There has been an increase in research summer schools to encourage students to gain hands-on

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experience with well-known researchers and physicians.[6] While this will improve the students' knowledge about research principles, many global studies have shown that these changes usually become controversial since they can influence the quality and quantity of students' future contributions to the field by encouraging them to publish more articles with lower quality to increase their chance of getting accepted into a competitive residency program.[6,12,16-18]

However, there is no available multi-campus study conducted in Saudi Arabia to thoroughly explore the attitudes of medical students toward conducting research, and the factors that influence students to do so. Multi-campus studies can provide better insights into students' attitudes and identify the influential factors in conducting research. Influential factors affect students' decisions to conduct research projects. The primary aim of this study was to assess medical students' attitudes towards conducting medical research and to identify the factors that influence their willingness to conduct research projects.

Methods

Study Design, Settings, and Participants

This cross-sectional study was conducted at the College of Medicine of King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Saudi Arabia, in the Jeddah and Riyadh campuses. The survey was distributed to medical students. Foundational and pre-medical students were excluded because the research course started during year three in the college curriculum. Interns were also excluded because they were more likely to be familiar with the process of conducting medical research as per the requirements of residency program application points, whereby at least one publication gives candidates an advantage over other applicants.

Questionnaires and Data Collection Process

This study utilized two self-administered questionnaires acquired with permission from recent studies: the Students' Attitude Towards Research (SAR)[4,] and the Students' Perceived Influential Factors Toward Participating in Research Activities questionnaires. This is a pre-piloted survey with high internal reliability (Cronbach's a coefficient = 0.88).[12] The survey included four sections. The first section investigated the students' attitudes towards research activities provided by the college. The second section identified students' opinions on faculty involvement in research projects. The third section examined the availability and quality of the infrastructural facilities offered by their colleges. The last section identified possible influential factors in conducting medical research. A 5-Likert scale was used to assess the level of students' agreement from 'strongly disagree=1,' 'disagree=2,' 'neutral=3,' 'agree=4,' to 'strongly agree=5.' Demographic information, such as sex, year of study, and GPA, which was collected in ordinal values, and previously published research, was collected. An online survey was distributed between December 12, 2021 and April 10, 2022. The estimated population was 1627 medical students from both campuses. Therefore, with a 5% margin of error and 95% confidence interval, the minimum recommended sample size was 311 students as suggested by the Raosoft Sample size calculator. Considering that the non-response rate was 20%, the final sample size was 373. This study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (Study number: SP21J/458/11).

Statistical Analysis:

The participants were asked to complete the survey through a Google webpage, which was exported to Excel and then to JMP software (version 10.0; SAS Institute Inc., Cary, NC, USA). Quantitative variables are presented as means and standard deviations (SD), and qualitative variables are presented as frequencies and percentages. The chi-square test was used to compare categorical values and report any differences. Disagreement responses (1: strongly disagree, and 2: disagree) were grouped as "disagree", and agreement responses (4: agree, and 5: strongly agree) were grouped as "agree"; while neutral responses (3: neutral) were simply presented as "neutral." All calculations of the mean and SD were based on the average of the 5-point Likert scale that was used. A *p*-value of less than 0.05 was considered statistically significant.

Results

Students' Characteristics

A total of 500 students completed the survey in both campuses. The majority were male students (N=336, 67.2%) and from the Riyadh campus (N=273, 54.6%). Most were fourth-year students (N=218, 43.6%). Most of the students had a grade point average (GPA) ranging between 4.5 and 5 (N=354, 70.8%), and were in their pre-clinical phase (N=366, 73.2%). Only a few students had prior research publications (N=67, 13.4%). Further characteristics are presented in *Table 1*.

Table 1. Participants' Characteristics

Characteristic	Descriptive Statistics
Campus [N (%)]	
Riyadh	273 (54.6%)
Jeddah	227 (45.4%)
Sex [N (%)]	
Male	336 (67.2%)
Female	164 (32.8%)
GPA* [N (%)]	
3 – 3.49	4 (0.8%)
3.5 – 3.99	34 (6.8%)
4 – 4.49	108 (21.6%)
4.5 – 5	354 (70.8%)
Level [N (%)]	
Freshmen	154 (30.8%)
Sophomores	218 (43.6%)
Juniors	87 (17.4%)
Seniors	41 (8.2%)
Phase of Study [N (%)]	
Pre-clinical phase	366 (73.2%)
Clinical phase	134 (26.8%)
Prior research publication [N (%)]	
Yes	67 (13.4%)
No	433 (86.6%)

Legend: *Grade Point Average; out of 5

Table 2. Attitude of Medical Students Towards Research.

Statement	Disagree N (%)	Neutral N (%)	Agree N (%)*	*p*-value**
Statement regarding Research Activities Offered in the College				
I am much interested in participating in research activities at the undergraduate level	91 (18.2)	91 (18.2)	318 (63.6)	0.331
My college organizes and gives priority to include undergraduates in research activities	63 (12.6)	123 (24.6)	314 (62.8)	0.360
Faculty members have adequate skills to handle research methodology	59 (11.8)	113 (22.6)	328 (65.6)	0.014*
Faculty do not have sufficient time to mentor undergraduate students in research	133 (26.6)	139 (27.8)	228 (45.6)	0.836
The degree of involvement of the faculty in the research program is good	108 (21.6)	148 (29.6)	244 (48.8)	0.338
Our college has adequate infrastructure to organize research programs	65 (13)	114 (22.8)	321 (64.2)	0.005*
I had been exposed to basic and advanced statistical tools needed for the preparation of a research report	100 (20)	117 (23.4)	282 (56.6)	0.207
Statement regarding Students Opinions of Faculty Involvement in Research				
Faculty members place great emphasis on research	64 (12.8)	126 (25.2)	210 (62)	0.258
Faculty members discuss their own research interests in class	182 (36.4)	162 (32.4)	156 (31.2)	0.484
Faculty members use research findings as a part of their teaching material	100 (20)	151 (30.2)	249 (49.8)	<.001*
Research is important for identifying and investigating problems in a subject matter	23 (4.6)	78 (15.6)	399 (79.8)	0.060
I am always getting the chance to discuss about the scientific/academic research in my class	168 (33.6)	166 (33.2)	166 (33.2)	0.022*
Statement regarding Infrastructural Facilities Offered by College for Research				
Our college provides good infrastructural facilities (i.e. laboratory) needed to conduct research at the undergraduate level	130 (26)	166 (33.2)	204 (40.8)	0.547
The library facilities available in my college are sufficient for us to conduct research activities	99 (19.8)	171 (34.2)	230 (46)	0.758
Sufficient funding is offered by the university for conducting research at the undergraduate level	125 (25)	219 (43.8)	156 (31.2)	0.674
Overall, I am satisfied with the research training program offered at the undergraduate level	95 (19)	140 (28)	265 (53)	0.056

Legend: *Disagreement responses (1: strongly disagree, and 2: disagree) were grouped as "disagree", and agreement responses (4: agree, and 5: strongly agree) were grouped as "agree"; while neutral responses (3: neutral) was simply presented as "neutral."

**A p-value of <0.05 was considered statistically significant.

Students' Attitudes

Table 2 shows the respondents' attitudes towards research. The agreement responses 'strongly agree' and 'agree' were grouped as 'agree', the disagreement responses 'strongly disagree' and 'disagree' were grouped as 'disagree, and neutral was recorded as 'neutral.' More than 60% of students (N=318) had an interest in participating in medical research at the undergraduate level, and 282 (56.6%) agreed that they had been exposed to the basic and advanced statistical tools needed to prepare a research report. Additionally, most students (N=399, 79.8%) agreed that research is important for identifying and investigating problems in a subjective manner. There was a significant difference in students' responses to the following statement: 'always getting the chance to discuss scientific/academic research in their class' (P=0.022). Only 265 (53%) of the students agreed that, overall, they were satisfied with the research training program offered at the undergraduate level, which was close to significance (P=0.056).

Female students significantly agreed more than male students that the faculty has adequate skills to handle research methodology (3.93±1.01 vs. 3.7±1.06, P=0.014). Less than half of the students (N=228, 45.6%) agreed that faculty members do not have sufficient time to mentor undergraduate students in research, but this was not significant (p=0.836). Only 108 (21.6%) students disagreed that faculty involvement in the research program was good. The majority of the students (N=210, 62%) agreed that faculty members place great emphasis on research. Furthermore, a significant difference was found in the following statement: 'faculty members use research findings as a part of their teaching material' (p <.001), but the difference among students' agreement regarding whether 'faculty members discuss their own research interests in class' was not significant (p=0.484).

More than half of the students (N=314, 62.8%) agreed that their college organizes and prioritizes the inclusion of undergraduate students in research activities. The students agreed that their college had adequate infrastructure to organize research programs (N=321, 64.2%, p=0.005). Moreover, there was a difference in the students' responses when they were asked if their college provided good infrastructural facilities (i.e., laboratories and libraries) needed to conduct research at the undergraduate level (p=0.547). Only 230 (46%) agreed that the library facilities available at their college were sufficient for them to conduct research activities. The majority of students (N=344, 68.8%) either disagreed or were neutral when asked if the university offered sufficient funding to conduct research at the undergraduate level.

Influential Factors & Motives

The 5-Likert scale was used to calculate the average of the students' responses, where 5 indicated 'strongly agree' and 1 indicated 'strongly disagree. The most influential factors chosen by the students were (1) facilitating entry into competitive residency programs, (2) interest in specific research fields or

medical topics, (3) improve curriculum vitae (CV), and (4) necessary competency for future clinical careers. On the other hand, the least influential factors were (1) good method to fulfill leisure time, (2) motivation by faculty/senior student researchers, (3) encouragement from previous participation in research activities, and (4) communicate research findings in scientific meetings. All influential factors are presented in *Figure 1.*

Figure 1. This Figure Demonstrates the Influential Factors Toward Conducting Research Among Medical Students

Legend: 'Facilitating Entry into Competitive Residency Programs' is the First Influential Factor and 'Having an Interest in Specific Research Field or Medical Topic' is the Second Influential Factor.

Discussion

This cross-sectional study aimed to assess medical students' attitudes and identify the influential factors in conducting medical research. The study outcomes revealed that most of the students recognize how vital research is in identifying clinical issues and trying to solve them in a subjective matter. Most of the students showed an interest in participating in research activities at the undergraduate level. Moreover, statistical analysis revealed that most students were exposed to basic and advanced statistical tools necessary for the preparation of a research report. These results are essential because medical students will eventually become physicians who need to incorporate evidence-based medicine into their practice to ensure the best health service outcomes, evaluate their practice in a critical but logical manner, and remain updated. The most influential factors for participating in research were (1) facilitating entry into competitive residency programs, (2) interest in specific research fields or medical topics, and (3) improving curriculum vitae (CV).

Similar to the outcomes of this study, several studies have demonstrated positive attitudes towards research among medical students who have been exposed to research activities.[5,6,14,15,19] Prior exposure to research activities may help students understand the importance of research and how it can advance science and medicine. This positive attitude may indicate that some students view research as a method to gain a more comprehensive understanding of medicine, but our results showed that it was ranked as the fifth factor, which may be because students prefer to understand medicine through textbooks and other sources recommended by their faculty. These outcomes emphasize the importance of establishing strong research programs and encouraging students to integrate research into their learning as it can increase the likelihood of students becoming more knowledgeable physicians.[2] Interestingly, our results regarding the influential factors in conducting medical research were very similar to another study conducted at Alfaisal University.[12] The top influential factor in the aforementioned study and this study was to facilitate entry into competitive residency programs. This shows that medical students, regardless of their institution, conduct research to gain a competitive edge to help them apply for residency. However, in our study, the second influential factor in conducting medical research was the interest in a specific research field. This stems from the fact that King Saud bin Abdulaziz University for Health Sciences students view research as a method to explore different specialties and build connections with physicians from different fields to decide which specialty they will eventually apply to.

Students agreed that their faculty members used research findings to teach, which may lead to research-oriented students subjectively investigating information. There was a difference in the students' responses regarding the opportunity to discuss scientific research in class, which may be due to the lack of understanding of research at their undergraduate level. Half of the students were satisfied with the research training curriculum in their college, indicating that most students are equipped to conduct research projects and try to integrate their research findings with the clinical theories they learn.

The students reported several barriers to conducting research at their colleges. Almost half of the students agreed that faculty members did not have sufficient time to mentor undergraduate students. Moreover, other studies have shown similar outcomes.[6,20-23] This may discourage interested students from participating in research projects and delay the advancement of research. Almost half of the students disagreed with or were neutral about their satisfaction with the research program offered at their college. This may be due to several reasons: (1) Saudi medical colleges focus on the fundamentals of medicine rather than research, (2) the research program is part of a curriculum that does not explain in detail complex research methodologies,

(3) most faculty members are not involved in student projects because it is time-consuming to mentor students and faculty members have various professional and academic commitments, and (4) some of the students may not be able to finalize their research projects due to busy schedule conflicts with their medical curriculum and examinations.

In this study, facilitating entry into competitive residency programs was the most influential factor in conducting medical research. In 2013, a study conducted in Pakistan reported the same reason as the second most common influential factor.[24] It was the second most common influential factor in another study conducted in Canada.[23] Facilitating entry into competitive residency programs is a common influential factor among medical students who conduct research projects. While improving the curriculum vitae (CV) was the third influential factor in our study, it was the most influential factor in several previous studies.[24-26] Medical students around the globe conducted research to advance their careers and build their resumes. This may be because residency programs and academic institutions emphasize research activities without examining the quality of the research conducted and/or published. This may pressure students to participate in research activities without having any interest in a career in research, and consequently, many published research articles remain unread and uncited for several years.

It has been reported that Saudi residency program directors in competitive specialties, such as plastic surgery, anesthesiology, and urology, prefer candidates who have high-quality research publications.[27-29] In contrast, specialties that are relatively less competitive in Saudi Arabia, such as internal medicine, obstetrics and gynecology, family medicine, and pediatrics have fewer publications.[30] This issue extends to the United States as orthopedic residency program applicants list research projects in their resumes as 'submitted'; but, in reality, remain frequently unpublished or published in low-impact journals.[31] Furthermore, this issue extends beyond residency applications, as the selection for fellowship programs requires more scholarly work.[32]

Local and international residency programs and academic institutions should consider enhancing research outcomes and improving evidence-based medicine. Many medical students conduct and publish research to get accepted into competitive programs, but it is unknown how many pursue a career in research once they are accepted into their desired specialty and program. Students' efforts should be directed toward basic/translational and clinical research that attempts to experiment and investigate various ways to contribute to medicine efficiently and productively.

Limitations

This study had several limitations. For example, this study utilized a self-administered, web-based survey. Therefore, the response rate was low. This was because the survey was distributed during the students' final examination. Additionally, this study was conducted at only one university, which means that the results and conclusions may not be applied to other universities. However, campuses in two different cities were included to ensure a diverse and large sample of students. King Saud bin Abdulaziz University for Health Science is a research-oriented university and has the King Abdullah International Medical Research Center (KAIMRC) within its campus, which may have impacted students' responses. This was a cross-sectional study, which means that it only represented students' attitudes at one point in time.

Conclusion

In conclusion, medical students at King Saud bin Abdulaziz University for Health Sciences generally showed a positive attitude towards conducting medical research. The most influential factor in conducting medical research was facilitating entry into competitive residency programs. The second influential factor was the interest in a specific research field or medical topic. The study outcomes revealed the importance of recruiting interested medical students in basic and/or clinical studies so that they can contribute to the scientific field in the early stages of their careers. This study is important for policymakers, residency program directors, and research center directors to reconsider published research and research activities as prerequisites for acceptance into competitive programs. Further studies should investigate whether medical students pursue research activities after college, their attitudes, and influential factors, as well as their research skills and how they acquired them.

Summary – Accelerating Translation

Title: Medical Students' Attitudes and Influential Factors Towards Conducting Medical Research

Main Problem: Currently, conducting a research project is a prerequisite for graduation in several Saudi medical colleges.[6,15] In addition, the Saudi Commission for Health Specialties (SCFHS)- a regulatory commission that sets requirements for students' enrollment into Saudi residency programs- recently announced that participation in research activities and publications in specified journals are granted 6 points out of the total 20 points available for residency application as of 2022. While this will improve the students' knowledge about research principles, many global studies have shown that these changes usually become controversial since they can influence the quality and quantity of students' future contributions to the field by encouraging them to publish more articles with lower quality as an attempt to increase their chance of getting accepted into a competitive residency program.

Aim: To assess medical students' attitudes towards conducting medical research and identify the factors influencing their willingness to conduct research projects.

Methodology: This cross-sectional study was conducted at the College of Medicine of King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Saudi Arabia, in the Jeddah and Riyadh campuses. The survey was distributed to medical students. This study utilized two self-administered questionnaires acquired with permission from recent studies. The first section investigated students' attitudes towards research activities provided by the college. The second section identified students' opinions on faculty involvement in research projects. The third section examined

the availability and quality of the infrastructural facilities offered by their colleges. The last section identified possible influential factors in conducting medical research. A 5-Likert scale was used to assess the level of students' agreement from 'strongly disagree=1,' 'disagree=2,' 'neutral=3,' 'agree=4,' to 'strongly agree=5.'

Results: A total of 500 students completed the survey on both campuses. More than 60% of students (N=318) had an interest in participating in medical research at the undergraduate level, and 282 (56.6%) agreed that they had been exposed to the basic and advanced statistical tools needed to prepare a research report. Additionally, most students (N=399, 79.8%) agreed that research is important for identifying and investigating problems in a subjective manner. Less than half of the students (N=228, 45.6%) agreed that faculty members do not have sufficient time to mentor undergraduate students in research. The most influential factors towards conducting medical research chosen by the students were (1) facilitating entry into competitive residency programs, (2) interest in specific research fields or medical topics, (3) improve curriculum vitae (CV), and (4) necessary competency for future clinical careers. On the other hand, the least influential factors were (1) good method to fulfill leisure time, (2) motivation by faculty/senior student researchers, (3) encouragement from previous participation in research activities, and (4) communicate research findings in scientific meetings.

Conclusion: In conclusion, medical students at King Saud bin Abdulaziz University for Health Sciences generally showed a positive attitude towards conducting medical research. The most influential factor in conducting medical research was facilitating entry into competitive residency programs. The second influential factor was the interest in a specific research field or medical topic. The study outcomes revealed the importance of recruiting interested medical students in basic and/or clinical studies so that they can contribute to the scientific field in the early stages of their careers. This study is important for policymakers, residency program directors, and research center directors to reconsider published research and research activities as prerequisites for acceptance into competitive programs. Further studies should investigate whether or not medical students pursue research activities after college, their attitudes, and influential factors, as well as their research skills and how they acquired them.

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Short Communication

Contamination of Clinical White Coats with Potential Pathogens and their Antibiotic Resistant Phenotypes Among a Group of Sri Lankan Medical Students

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Abstract

Background: Clinical white coats worn by medical students can be contaminated at hospitals and act as a potential reservoir for pathogens, including antibiotic-resistant bacteria. This study aimed to identify the contamination rates of clinical white coats worn by medical students with selected potential pathogens and their antibiotic resistant phenotypes. **Methods:** A cross-sectional study was conducted among 151 fourth-year medical students of the Faculty of Medicine of University of Peradeniya, Sri Lanka in September 2020. The participants belonged to two batches undergoing clinical training at two settings. Swabs from pockets and sleeves of the clinical white coats were taken. Potential pathogens and their resistant phenotypes were identified with routine tests. **Results:** Fifty-three participants (35.1%) had coats contaminated with *Staphylococcus aureus* (*S. aureus*) and 15 (9.9%) had coats contaminated with Methicillin-Resistant *Staphylococcus aureus* (MRSA). One enterobacterales (0.7%) was an AmpC producer. Enterococcus species were isolated from 19 (12.6%) coats and 2 participants (1.3%) had coats contaminated with Vancomycin Resistant Enterococci (VRE). Molecular testing on the MRSA isolates identified that 5 (20%) of the MRSA isolates were *PVL* positive, while all were *mecA* positive. Sex, type of clinical appointment, and frequency of washing white coats were not associated with contamination. The "batch" was significantly associated with contamination with *S. aureus* and Enterococcus species. **Conclusions:** We found that clinical white coats worn by medical students recruited for the study were contaminated with *S. aureus*, MRSA, and Enterococcus species. There was a notably high rate of contamination with *S. aureus*. All MRSA isolates were *mecA* positive, while the rate of *PVL* positivity was low.

Key Words: Drug Resistance; Microbial; Infection Control; Microbiology; Students; Medical (Source: MeSH-NLM).

Introduction

Clinical white coats are worn by healthcare workers, including clinicians and medical students in many countries. While most developed countries have moved away from clinical white coats to scrubs, white coats remain a part of the hospital attire in many developing countries, such as Sri Lanka.

Clinical white coats, however, are considered to be possible vehicles for transmission of pathogens.[1] Microorganisms may live on the fabric of clinical coats for several days, even up to three months.[2] Therefore, these can act as potential reservoirs for the transmission of antibiotic resistant bacteria. Medical students spend long hours in different clinical settings as per their training requirements, such as wards, clinics, and in-hospital teaching areas, in the same attire. Therefore, the contamination of their white coats can contribute to horizontal transmission of potential pathogens from patient to patient as well as between different locations within a single healthcare institute. This could also lead to an increase in the rates of healthcare-associated infections, including those caused by antibiotic resistant bacteria. Furthermore, this may contribute to the spread of antibiotic resistant bacteria to the community. Therefore, identifying if clinical white coats worn by medical students are contaminated with potential pathogens and their antibiotic resistant phenotypes would provide evidence to convince university and hospital policy makers to implement preventive measures, such as implementing standard operating procedures to clean hospital-wear, and establishing a mechanism to provide hospital laundered outerwear to be worn during clinical training.

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This study aimed to describe the patterns of contamination of clinical white coats among medical students in a Sri Lankan medical school, with selected potential pathogens and their antibiotic resistant phenotypes. This included *Staphylococcus aureus,* Methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacterales* species, Extended-spectrum Beta lactamase (ESBL)-producing *Enterobacterales,* AmpC producing *Enterobacterales*, *Enterococcus* species, and Vancomycin-resistant *Enterococcus* (VRE) species.

Methods

This cross-sectional study was conducted among fourth-year medical students of the Faculty of Medicine of University of Peradeniya, Sri Lanka in September 2020. The study site had two fourth-year batches (Batch A and B). Clinical training for the two batches were conducted predominantly in two separate institutes at the time of the study: the Teaching Hospital in Peradeniya, Sri Lanka and the National Hospital in Kandy, Sri Lanka. All except those who were wearing short or three-quarter-sleeved white coats were eligible to participate in the study. A self-administered data collection sheet was used to gather demographic data, current clinical appointment, predominant method of wearing the sleeve of the coat (rolled up or not), frequency of washing the coat, the date of when the coat was last washed, and the wearer's perception of the cleanliness of the white-coat. A pilot-test was done on ten medical students of the third-year batch. Ethics approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka (2020/EC/SP/01). Informed, written consent was obtained from all participants.

Two sterile swabs moistened with sterile 0.9% saline were used to obtain samples from both the pockets and the cuffs of the sleeves of each clinical white coat, as these are the sites that, respectively, are frequently handled by the wearers and come into contact with patients. Swabs were collected by the investigators according to a fixed protocol, with measures to prevent cross-contamination. The protocol called for the swab to be, inserted into individual plastic sheaths, transported to the lab immediately, and inoculated in 10 ml of Brain Hearn Infusion (BHI) broth (Oxoid, UK). BHI broth was incubated overnight at 37°C. The next day, 10 µl of each broth was plated on three different agars, a Mannitol Salt agar (MSA) (Oxoid, UK) plate, a MacConkey agar (Oxoid, UK) plate supplemented with Cefotaxime at 1 µg/ml (HiMedia, India) concentration to screen for potential *Enterobacterales,* and a Chromogenic agar plate (BioMaxima, Poland) to identify potential *Enterobacterales* and *Enterococcus* species. All plates were prepared according to manufacturer's instructions. Potential isolates were selected and identified using routine biochemical testing.[3]

S. aureus isolates were tested for sensitivity to cefoxitin in order to identify MRSA and Methicillin sensitive *Staphylococcus aureus* (MSSA) isolates. Sensitivity to cefotaxime and ceftazidime were tested in the *Enterobacterales* species to screen for possible ESBL producers. The *Enterobacterales* species that fulfilled the criteria for potential ESBL producers were subjected to combined disc testing and were additionally tested for AmpC production using the disc diffusion method (Mast, UK). Sensitivity to other relevant antibiotics were tested according to the CLSI guidelines.[4-6] Enterococci was tested for sensitivity to ampicillin using the disc diffusion method, and minimum inhibitory concentration (MIC) for vancomycin (Sigma-Aldrich, Singapore) was tested using macro-broth dilution method.[7]

DNA was extracted from the 20 MRSA isolates by boil lysis and presence of PVL and mecA genes were assessed by previously established conventional PCR.[8,9]

Student placements were categorized into two groups for the analysis. Medicine, pediatrics, and psychiatry appointments were grouped together as medical placements, while surgery, gynecology, obstetrics, and other surgical sub-specialties were grouped together as surgical placements. Wearers' perception of the cleanliness of the coat was thematically analyzed. The two themes that emerged were clean and contaminated, which were then used as a binary variable in further analysis.

In data analysis, percentages were calculated for contamination of white coats in each site with the selected potential pathogens and their antibiotic resistant phenotypes. A Chi-square test or Fisher's exact test were used to test for associations, while the Mann-Whitney U test was used to compare the differences in continuous variable. A p-value of less than 0.05 was considered as statistically significant. All analysis was done on SPSS (IBM) version 21.

Results

A total of 151 participants were recruited. Of these, 72 (47.7%) were from fourth-year batch A and 79 (53.3%) were from fourth-year batch B.

The numbers of female and male students were 78 (51.7%) and 73 (48.3%), respectively. The mean and median number of days from the last wash to sample collection was 6.2 (SD 5.8) and 4.0 (IQR 3 – 7) days, respectively. Other parameters of the two batches are provided in *Table 1*.

Among the 151 participants, *S. aureus* was isolated from one or both swabs in 53 (35.1%) participants. The coats of 15 of the 151 (9.9 %) participants were contaminated with Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. Twelve (7.9%) of the coats were contaminated with bacteria of the order *Enterobacterales*. None of the isolates were found to be ESBL producers; however, one (0.7%) coat was contaminated with an AmpC producing *Enterobacterales* species. Nineteen (12.6%) participants had coats that were contaminated with the Enterococcus species and two (1.3%) participants had coats contaminated with VRE (*Table 2*). The differences in contamination rates between pockets and sleeves were not statistically significant.

At least one potential pathogen of interest was found to contaminate 74 (49.0%) of the coats, while 18 coats (11.9%) were contaminated with at least one of the resistant phenotypes of interest (MRSA, VRE, or AmpC producers). Ten (6.6%) coats were contaminated with two types of potential pathogens, whereas 64 (42.4%) were contaminated with only one type.

Contamination rates with *S. aureus* and *Enterococcus* species was significantly different between the two fourth-year batches. Other parameters analyzed in relation to contamination with the selected bacteria did not differ significantly and are provided in *Table 3*.

Table 1. Description of the Study Population.

Variables	All participants n (%)	Batch A	Batch B	Difference
Sex				
Male	73 (48.3 %)	40 (55.6%)	33 (41.8%)	0.10
Female	78 (51.7 %)	32 (44.4%)	46 (58.2%)	
Appointment[1]				
Medical	86 (57 %)	47 (65.3%)	39 (49.4%)	0.07
Surgical	65 (43 %)	25 (34.7%)	40 (50.6%)	
Frequency of washing[2]				
< 1 once a week	118 (78.1 %)	62 (86.1%)	56 (70.9%)	0.03*
> Once a week	33 (21.8 %)	10 (13.9%)	23 (29.1%)	
Perception[2]				
Clean	30 (24 %)	12 (18.5%)	18 (30.0%)	0.147
Contaminated	95 (76 %)	53 (81.5%)	42 (70.0%)	
Time since washing				
Median (IQR)	4.0 (3 – 7)	3 (3 – 5)	4 (3- 10)	0.003^

Legend: 1: Medical includes medicine, pediatrics and psychiatry appointments. Surgery includes surgery, gynecology, obstetrics, and other surgical sub-specialty appointments. 2: Only 125 (83.8%) participants presented their perception on cleanliness of the coats. * Chi-square test, ^ Mann-Whitney U test.

Association between the pattern of wearing the sleeve (rolled up vs left long) and contamination with resistant bacteria was assessed. There was no significant association between rolling up the sleeves and colonization with *S. aureus* (18.8% vs 34.8%), MRSA (7.0% vs 8.7%), or *Enterococcus* species (6.3% vs 8.7%) ($p>0.05$, Fisher's Exact test).

Among the 53 white coats contaminated with *S. aureus*, 19 were contaminated only on the sleeves of the coats, 21 only on the pockets, and 13 were contaminated on both sites; leading to a total of 66 *Staphylococcus aureus* isolates. Among the *S. aureus* isolates, 20 (30.30%) were MRSA, while 46 (69.67%) were Methicillin-sensitive *S. aureus* (MSSA). The susceptibility rates for different antibiotics were higher among the MSSA isolates than the MRSA isolates, except for ciprofloxacin. The susceptibility rates for the different antibiotics among MSSA and MRSA isolates were; gentamycin (95.7% vs 85%), ciprofloxacin (50% vs 70%), clindamycin (91.3% vs 70.0%), erythromycin (58.7% vs 45%), and tetracycline (95.7% vs 90%) respectively.

Molecular testing on the MRSA isolates identified that five of the 20 MRSA isolates were PVL positive, while all were *mecA* positive. Of the 20 *Enterococcus* isolates, four were ampicillin resistant and two isolates were identified as VRE.

Table 2. Summary of Colonization Rates.

Organism	Sleeves only n (%)	Pockets only n (%)	Both n (%)	Either or both n(%)
S. aureus	19 (12.6%)	21 (13.9%)	13 (8.6%)	53 (35.1%)
MRSA	6 (4.0%)	4 (2.6%)	5 (3.3%)	15 (9.9%)
Enterobacterales species	5 (3.3%)	5 (3.3%)	2 (1.3%)	12 (7.9%)
ESBL producers	0	0	0	0
AmpC producers	0	1 (0.7%)	0	1 (0.7%)
Enterococcus species	9 (6.0%)	9 (6.0%)	1 (0.7%)	19 (12.6%)
VRE	0	2 (1.3%)	0	2 (1.3%)

Discussion

This study aimed to describe the pattern of contamination of clinical white coats with selected antibiotic-resistant bacteria. *S. aureus* was isolated from swabs of 53 participants (35.1%). Out of these, 15 were contaminated with MRSA (9.9%). All of the MRSA isolates were positive for *mecA* gene while only 5 were positive for *PVL* gene.

A number of studies has previously assessed the rates of *S. aureus* contamination of clinical white coats. Despite varying in frequency of contamination, *S. aureus* has been identified as the commonest isolate in many studies.[1,10,11,12] Similarly, MRSA isolation rates from white coats has ranged from 3.5%[13] to up to 79% (during outbreaks of infections in units).[14] These differences in contamination rates could be due to the differences in institutional environments, infection prevention, and control measures, as well as wearer habits such as hand hygiene.

While contamination rates of clinical white coats are not available for Sri Lanka, Munasinghe et al. has reported a colonization rate of 22.0% and 4.3% for *S. aureus* and MRSA respectively, from nasal swabs obtained from a group of university students of the same study site.[9] In the same study, 21.4% of the identified MRSA isolated were found to be PVL positive. We did not assess to see if the wearers of the coats were colonized with any of the pathogens tested for. However, using the *PVL* positivity rates we can hypothesize that most of the isolates obtained from the white coats are of hospital origin, as the *PVL* positivity rates were lower in the current study when compared to the colonization study. This is because *PVL*, a virulence factor in MRSA, is more commonly found in isolates of community origin. All isolates were found to contain *mecA*. *MecA* gene codes for an alteration in the penicillin binding protein, leading to resistance in beta-lactam drugs.[15,16] These findings indicate that the white coats are likely to have got contaminated in the health-care setting, rather than from the community.

Nineteen (12.6%) participants of the present study had coats that were contaminated with *Enterococcus* species and two of them (1.3%) were vancomycin-resistant. A study by C. Kannangara et al. has shown that Vancomycin-resistant Enterococci (VRE) had a rectal colonization rate of 5% among 218 patients in an intensive care unit of the National Hospital of Colombo, Sri Lanka.[17] It is undeniable that VRE isolates are circulating in healthcare settings in Sri Lanka and that contaminated cloths may act as a vehicle of transmission. Given the possibility of horizontal gene transfer for vancomycin resistance, this is a concerning situation.

Twelve (7.9%) of the participants' coats were contaminated with Enterobacterales and none of the isolates were found to be ESBL producers. However, one (0.7%) coat was contaminated with an AmpC-producing Enterobacterales species. A study done at Kilimanjaro Christian Medical Center in Tanzania found that 3 out of 180 coats were contaminated with *E. coli*.[12] This, and other studies indicate that the contamination of clinical white coats with Gram negative isolates is relatively less common than contamination with Gram positive isolates. While our study did not identify any contamination by ESBL producers, they are common in Sri Lankan hospitals and the community, both as causative agents for infections and as colonizers.[9,18] However, clinical white coats are often kept dry and Gram negatives do not usually thrive in such conditions, unlike *S. aureus* or *Enterococcus* species.

In this study, the rate of contamination of clinical white coats with *S. aureus*, MRSA, *Enterobacterales*, and *Enterococcus* was assessed in relation to several variables such as sex, batch, current clinical placement, frequency of washing the coat, and one's perception of cleanliness of his/her clinical white coats. Out of these variables, only the batch was found to have a statistically significant association with the rate of contamination. Batch A had a significantly higher contamination rate with *Enterococcus* species, while batch B had a higher rate of contamination with *S. aureus*. At the time of the study, the two batches had their clinical training at two hospitals, where the predominant environmental contaminants could have been different, which may explain the difference in the contamination rates. Furthermore, the frequency of washing coats significantly differed between the two batches; however, the impact of this on the association with different potential pathogens remains to be further explored. It is of interest to note that the frequency of washing and the duration since the last wash was not significantly associated with contamination rates.

Table 3. Association of Variables Studied with Contamination of Coats.

Variable	Contamination with *Staphylococcus aureus*			Contamination with MRSA			Contamination with *Enterococcus* spp		
	Contamination absent	Contamination present	p-value	Contamination absent	Contamination present	p-value	Contamination absent	Contamination present	p-value
Sex									
Male (n=73)	52 (71.2 %)	21 (28.8 %)	0.11	64 (87.7 %)	9 (12.3 %)	0.34	62 (84.9%)	11 (15.1%)	0.37
Female (n=78)	46 (59.0 %)	32 (41.0 %)		72 (92.3 %)	6 (7.7%)		70 (89.7%)	8 (10.3%)	
Batch									
4th year batch A (n=72)	53 (73.6 %)	19 (26.4 %)	**0.03***	66 (91.7 %)	6 (8.3%)	0.53	56 (77.8%)	16 (22.2%)	**0.001***
4th year batch B (n=79)	45 (57.0 %)	34 (43.0 %)		70 (88.6 %)	9 (11.4%)		76 (96.2%)	3 (3.8%)	
Appointment									
Medical (n=86)	58 (67.4%)	28 (32.6%)	0.45	78 (90.7%)	8 (9.3%)	0.77	76 (88.4%)	10 (11.6%)	0.68
Surgical (n=65)	40 (61.5 %)	25 (38.5 %)		58 (89.2 %)	7 (10.8 %)		56 (86.2%)	9 (13.8%)	
Frequency of washing									
<=1 once a week (n=118)	78 (66.1 %)	40 (33.9 %)	0.56	107 (90.7 %)	11 (9.3 %)	0.74	102 (86.4%)	16 (13.6%)	0.77
> Once a week (n=33)	20 (60.6 %)	13 (39.4 %)		29 (87.9 %)	4 (12.1 %)		30 (90.9%)	3 (9.1%)	
Perception									
Clean (n=30)	20 (66.7 %)	10 (33.3%)	0.86	26 (86.7 %)	4 (13.3%)	0.29	29 (96.7%)	1 (3.3%)	0.07
Contaminated (n=95)	65 (68.4 %)	30 (31.6%)		88 (92.6 %)	7 (7.4%)		78 (82.1%)	17 (17.9%)	
Time since coats were cleaned						0.07			
Mean (SD)	6.5 (6.6)	5.6 (3.9)	0.62	6.1 (5.9)	7.4 (4.5)		6.2 (6.0)	6.1 (4.4)	0.94
Median (IQR)	3.5 (3 - 8)	4.0 (3 - 7)		4.0 (3 - 6)	5.0 (3 - 11)		4.0 (3 - 7)	3.0 (3 - 8.5)	

Legend: * Chi-square test

One major disadvantage of this study is that we did not determine the contamination of *Clostridium difficile*. This was not possible, as the study site lacked anaerobic culture facilities. Also, the selection of the isolates depended on the available funding as it prevented us from focusing on all ESKAPE pathogens.

In conclusion, we identified a considerable high rate of contamination with potential pathogens, particularly Gram-positive isolates. This is a reason for concern. Furthermore, the association of *S. aureus* and *Enterococcus* species with the two batches, where the main difference was the hospital they were trained at, indicates that hospital environment may play a role in this.

The current study highlights the importance of establishing a protocol to ensure that the attire worn in healthcare settings are cleaned appropriately. While our study population is from a single university, in the current times of global travel, these findings are of global concern. With the escalation of the COVID-19 pandemic, Sri Lankan universities transitioned from white coats to scrubs as the attire for medical students. We hope that this will have had a positive impact on the possible contamination with potential pathogens, as scrubs directly contact the wearer's skin, and therefore, unlike white coats, are likely to be washed more frequently. Further, providing standard operating procedures for cleaning hospital wear and implementing mechanisms to provide faculty or hospital laundered cloths to be worn in the clinical setting along with adequate facilities for changing rooms could be considered.

Summary – Accelerating Translation

Contamination of white coats with germs

Clinical white coats had been switched for other alternatives in many countries, but in some countries like Sri Lanka it continued to be a part of the attire of medical students till the emergence of COVID-19 pandemic. In this study, we took samples from 151 white coats worn by medical students of the Faculty of Medicine, University of Peradeniya, Sri Lanka and tested to see if any germs causing infections are found. Regular laboratory methods were used for testing and samples were obtained from the cuffs and pockets of the white coats. We identified three types of infection-causing germs on the coats. We also found two types of germs that are resistant to antibiotics, namely Methicillin Resistant *Staphylococcus aureus* (MRSA) on 15 (9.9%) coats and Vancomycin Resistant Enterococci (VRE) on two (1.3%) coats. We emphasize the importance of having strict guidelines to ensure that those who wear white coats, including medical students, clean them more frequently so that their role as potential reservoirs of germs may be lessened.

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Review

Leadership Training in Undergraduate Medical Education: A Systematic Review

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Abstract

Background: This review seeks to characterize existing curricular interventions implemented to develop leadership skills in undergraduate medical students at LCME-accredited medical schools and elucidate best practices for leadership curriculum development. **Methods:** PRISMA guidelines were used to guide the review. Comprehensive literature searches of five databases retrieved peer-reviewed journal articles with empirical data published in English. Two phases of screening were conducted to identify studies describing leadership development curricular interventions, followed by data extraction and synthesis. **Results:** Comprehensive literature searching and hand searching identified 977 articles potentially eligible for inclusion, with a final set of 16 articles selected for the review. A majority of the leadership development programs targeted preclinical students, while others spanned the entire curriculum. "Mixed settings," including both classroom and clinical and community components were common. There was a wide range of cohort sizes spanning from over 100 students to fewer than 10. Using the competencies defined by Mangrulkar et al, we determined that all of the programs described leadership skills development, including conflict management and emotional intelligence. Out of the 16 selected studies, curricula that emphasized the development of skills were evidence-based medicine and practice, and 6 curricula targeted interprofessionalism. **Conclusions:** Leadership development needs to be standardized in undergraduate medical education, ideally using a competency-based framework to develop these standards. Longitudinal programs that had a didactic and project-based component received consistently high quality and effectiveness scores, as did programs with smaller cohort sizes that received more consistent mentorship and monetary investment from institutions.

Key Words: Medical education; Undergraduate; Leadership; Undergrad Medical Education (Source: MeSH-NLM).

Introduction

Physicians bear immense professional responsibility: they are charged with the holistic promotion, protection, and restoration of their community's health, as well as with the offering of guidance and consolation in the face of chronic or terminal conditions.[1] Possessing effective leadership skills is essential to meeting these expectations. Leadership is defined in the U.S. Army Field Manual as "the process of influencing people by providing purpose, direction, and motivation while operating to accomplish the mission and improve the organization".[2] Leadership encompasses an array of difficult-to-master skills that must be effectively applied in clinical practice and within diverse relationships, as medicine is becoming increasingly interdisciplinary and team-based, veering away from decades of solo,autonomous practice, and driving an increase in demand for effective physician leadership.[1,3-4] Too often in medical education, leadership skills are learned "accidentally," in that it is dependent on the individual student passively observing leaders and internalizing their strategies.[1,3] The Liaison Committee on Medical Education (LCME), the body responsible for overseeing the accreditation of allopathic medical schools in the United States and Canada, makes references to leadership skills in multiple competencies that MD granting schools must fulfill in order to maintain accreditation.[4] The American Association of Medical Colleges (AAMC) has identified leadership as "the most critical component of success," for future medical professionals and describes various leadership skills in the Entrustable Professional Activities, a set of proficiencies medical students are expected to be able to perform upon entering residency.[5-6] Furthermore, Shaaban et al. argued in their systematic review that leadership should be the seventh competency used by the Accreditation Council for Graduate Medical Education (ACGME) to review residency programs.[7] An updated systematic review of the current strategies being deployed in undergraduate medical schools is a necessary foundation to begin building new leadership education that will equip students with the tools and confidence to meet the unprecedented opportunity this season presents.[8]

Methods

A protocol for this systematic review was developed by drawing on the work published by Boland et Al. and the Preferred Reporting Items for Systematic Review and Meta-Analyses

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(PRISMA) statement.[9,10] The protocol has been registered on the Prospero website, registration code CRD42021238892. International Review Board approval was not required for this study.

Comprehensive searches of literature published between 2014-2021 were conducted with databases: PubMed (MEDLINE), Embase, ERIC, PsychINFO, and Web of Sciences, using subject headings or index terms in combination with keywords including "medical students," "undergraduate medical education," "leadership," "curriculum," and "program development." A summary of search terms for each database can be found in the *Appendix*. Literature search results were downloaded and imported to Covidence software, which we used to perform the title and abstract review against inclusion and exclusion criteria determined a priori (see *Table 1*).[11] Screening of titles and abstracts was performed by ME, followed by full-text screening conducted by ME and MM in duplicate and independently. Any discrepancies in the full-text screening were resolved through discussion by the reviewers. Hand searching of references of selected articles were examined to identify any potential candidate studies for inclusion.

Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
- Curriculum interventions that prioritized the development of leadership abilities/skills, characteristics or competencies (i.e., the purpose of the intervention was to educate on leadership) -Leadership must be an explicitly stated feature of the intervention -Interventions implemented at LCME-accredited American and Canadian medical schools -Experimental or quasi-experimental studies, prospective and retrospective cohort studies, case-control studies	-Studies that did not include a leadership education intervention or that leadership development was not the primary purpose of the study -Studies solely including graduate medical students (residents and fellows) -Interventions implemented at graduate medical programs -Interventions only involving faculty or clinical faculty -Interventions utilized at medical schools not accredited by the LCME -Articles published without full text available -Articles not published in English -Comment, editorial, letter reviewed articles -Conference proceedings or abstracts without full research reports -Survey research without any leadership intervention implemented (investigation of students' perceptions without any leadership intervention)

A standard form was developed for data extraction, including information about various features of the interventions such as leadership competencies and cohort sizes.[12] We decided to use this framework to characterize the curricula in this review because it was developed collaboratively by educators at a variety of medical schools nationwide in an attempt to provide a consensus recommendation from diverse experiences.

This study also evaluated the effectiveness of the interventions using Kirkpatrick's four-level hierarchy (*Table 2*),[13] and the quality of the Interventions that formed the outcomes of the interventions outlined in the grading scale created by Hammick et al. (see *Table 3*).[14] Extracted data was placed in a shared spreadsheet. Data extraction in each of the described areas was done independently and in duplicate by two reviewers, ME and EJ, and then compared and discussed. Any discrepancies were discussed until a unanimous decision was reached, and if a unanimous decision could not be reached, the third reviewer served as a tiebreaker.

Results

Comprehensive literature searching and hand searching identified 977 articles potentially eligible for inclusion in the review. The removal of 175 duplicates left 802 studies for title and abstract screening. Of 47 studies selected for full-text screening, 31 studies were excluded during full text review, and 16 (1.6%)

Table 2. Inclusion and Exclusion Criteria.

Score	Definition	No. (%) of Curricula
0	None: Outcomes not evaluated	0 (0)
1	Reaction: Change in learners' attitudes	3 (18.75)
2	Learning: Modification or knowledge and/or skills	2 (12.50)
3	Behavior: Change in behaviors as a result of learning	6 (37.50)
4	Results: Tangible, as observed by change in the system/organizational practice; reduced cost, improved quality, efficiency, etc.	5 (31.25)

Table 3. Quality of Evidence Using the Hammick et al Data Evaluation Model.[14]

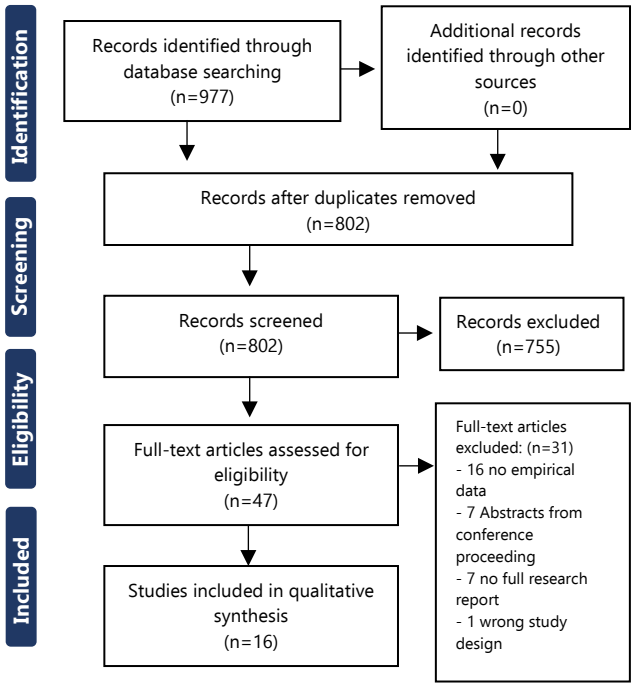
Score	Definition	No. (%) of Curricula
1	No clear conclusions can be drawn, not significant	1 (6.25)
2	Results ambiguous, but appears to be a trend	7 (43.75)
3	Conclusions can probably be based on the results	6 (37.50)
4	Results are clear and very likely to be true	2 (12.50)
5	Results are unequivocal	0 (0)

were included in this systematic review (*Figure 1*). Twelve unique interventions were described, with two pairs of articles publishing different data about the same intervention at the same school.[15-18]

Study Quality

The interventions had a mean effectiveness score of 2.6.. The mean score for quality of evidence was 2.56. Five interventions achieved the highest score for effectiveness, and none of the interventions achieved the highest score for quality of evidence. Only one study achieved the highest score for effectiveness and the next highest possible score for quality, making it the most successful intervention included in this review.[26]

Figure 1. PRISMA Diagram of Article Selection Process.



Educational Setting and Curricular Format

All studies included in this review implemented interventions at LCME-accredited medical schools. A variety of settings were utilized for interventions in the included studies. Most interventions (n=13, 81.25%) included a classroom-based setting for at least part of the intervention, but only two interventions were delivered exclusively in a classroom setting. The Peak Performance educational activity at the University of North Carolina used simulation learning to enable students to take on the role of a senior resident with multiple demands on their time and resources, so that the student could practice different leadership and coping strategies. The Uniformed Services University LEAD curriculum culminates in "Operation Bushmaster," a one-day field practicum where students are evaluated for a variety of elements including context adaptation, communication, and organizational skills.[23, 24]

Learner Levels

Leadership curricula were implemented at various stages within different medical schools. Interventions were most commonly offered only to preclinical students (n=7, 43.75%), followed by interventions offered only to clinical students (n=3, 18.75%), and then both groups (n=2, 12.5%). One intervention had a unique opportunity solely for MD-PhD students, and another for both clinical medical students and residents.[22] Learner level was not specified for two interventions.[19, 21]

Cohort Sizes and Intervention Duration

There was a wide variation in sample size, intervention length, and curricular formats across the studies. The largest cohort size was over 200 participants in the Chicago's UMed Program of University of Illinois College of Medicine, and the smallest was six participants in the University of Colorado's Health Innovation Scholars Program.[18,19] The average cohort size across all interventions was 53 students. Length of intervention ranged from longitudinal programs spanning all four years of the medical curriculum, such as the Quality Improvement Track implemented at the University of Chicago, to programs lasting only a summer or less than a single day, such as half-day leadership workshops offered to MD-PhD students at Vanderbilt University.[20,21] There was a slight majority of stand-alone experiences (n=10, 62.5%) lasting less than 6 months as opposed to longitudinal experiences lasting multiple semesters (n=6, 37.5%).

Leadership Competencies and Topics

A wide variety of leadership skills and competencies were targeted for development by the different interventions. Using the competencies defined by Mangrulkar et al., we determined that all (n=16, 100%) of the interventions promoted the development of leadership skills, including conflict management and emotional intelligence. This was closely followed by change agency (n=15, 93.75%), professionalism and ethics (n=14, 87.5%), and teamwork (n=13, 81.25%).[12] Furthermore, 11 (68.75%) interventions emphasized development of skills in evidence-based medicine and practice, and six (37.5%) interventions included inter-professionalism as a competency in their program. All interventions incorporated at least two of Mangrulkar et al's leadership competency domains into their program, which include team management, change agency, teamwork, interprofessionalism, evidence-based medicine and practice, and professionalism and ethics, and two (12.5%) of the programs incorporated all six domains.

Leadership topics were often catered to the specific objectives of each program. The Business and Leadership for Medical Students course at Boston University and the Health Innovation Scholars Program at the University of Colorado instructed students on the executive management topics and how it is affected by the healthcare policy and the supply chain's impact on resource utilization.[17,18] Project management, creating an effective meeting agenda, and adjusting to changing conditions were the focus of many interventions, such as Leaders in Innovative Care Program

(LINC) at Brody School of Medicine.[25] The Student Leadership Committee at Harvard Medical School provided pairs of students the opportunity to facilitate executive meetings and give presentations, followed by an opportunity to receive feedback from faculty on their performance; most survey respondents found this to be an effective approach to learn and apply principles.[26] Leadership workshops conducted at Vanderbilt University solicited requests for topics from participants prior to the start of the program, and the most requested topics by students were conflict management and building a team, which became the focus of most sessions.[21] The focus of the Patient-Centered Exploration in Active Reasoning, Learning and Synthesis course at the Zucker School of Medicine helped students to "think outside the box" and develop innovative approaches to running teams and solving problems through the use of complex biomedical science scenarios that students worked through in groups.[15,16]

Assessment and Outcomes of Leadership Interventions

The majority of studies (n=9, 56.25%) utilized a pre- and post-intervention survey to evaluate the impact on participants. A smaller proportion of studies (n=5, 31.25%) only distributed post-intervention surveys to students. The surveys sought feedback on the student's experience with any speakers or mentors they engaged with, their opinion of the overall organization and value of the program, as well as the student's perceptions of their own growth in various domains of leadership. Agarwal et al. specifically designed a Business and Leadership for Medical Students elective course to foster student interest in pursuing a Master in Business Administration, and the survey results noted a modest increase following the intervention, highlighting the benefit of writing questions directly related to the specific aims of the program.[27] Two studies surveyed their participants both immediately and one year after the conclusion of the intervention in order to gauge the long-term impact on participants and the utility of learned skills.[22,28] The Health Innovation Scholars Program (HISP) at the University of Colorado created an alumni network for all participants to join that allow them to share career developments, and consequently, many alumni have held "spread events" at their own institutions that are modeled after HISP.[18] Additionally, 88% of HISP participants were involved in quality improvement in their career and 70% held leadership positions.[17] Operation Bushmaster at the Uniformed Services University was unique in that intervention participants were not surveyed or interviewed to evaluate their own leadership skills and experience during the intervention.[24] Instead, the participants were evaluated by superior officers before and after the intervention to assess for leadership development.[24] Smithson et al. combined pre- and post-intervention surveys with reflection workbooks that participants were required to use throughout their participation in the educational activity in order to routinely evaluate their strengths and weaknesses.[23] This provided robust qualitative data for program directors to improve the curriculum for future students.

Discussion

The purpose of this review is to contribute to the ever-growing body of knowledge regarding best practices for leadership education in undergraduate medical education. An accurate and practical understanding of these practices is crucial to developing effective programs that will prepare medical students to be confident and effective leaders as residents and attending physicians. The 16 studies included in this review provide the basis of our recommendations.

Impact of Educational Setting and Program Format on Effectiveness Score

We found that most interventions (n=11, 68.75%) achieved a score of 3 or 4 for effectiveness, reflecting changes in behavior and tangible results, respectively, and that the overwhelming majority of interventions used a mixed-method approach (n=14, 87.5%) consisting of didactic lectures, projects, seminars, simulations, among others. The interventions that achieved lower scores of 1 or 2 often lacked an opportunity for students to apply what they had learned in a didactic setting, such as the Business and Leadership course at Boston University.[27] The purpose of the course was to explore nontraditional physician career paths, such as pursuing an MBA and spending most of one's career in hospital leadership as opposed to clinical medicine. This course gave students a better understanding of the healthcare system in the United States and increased interest in pursuing leadership positions but failed to give students the chance to practice what they had learned or produce tangible results in the form of a project or presentation. The same could be said for the Physician as Leader course and the First-Year Leadership Program at the University of Michigan.[28,29] The Peak Performance educational activity at the University of North Carolina utilized a simulation to give medical students the opportunity to act as senior residents with multiple demands on their time and resources so that the student could practice different leadership and coping strategies. However, when evaluating participants, it was unclear whether or not their involvement in the intervention had any specific or tangible impact on their behavior.[23]

The studies that achieved high scores for effectiveness described interventions that were designed for the purpose of generating a tangible result or an observable change in behavior that could be objectively assessed. We suggest using the mixed-method approach when developing leadership curricula for undergraduate medical students, to include both the benefit of supported learning and independent application of acquired skills. The ideal setup would be to begin with a didactic or instructional component that defines program goals and expectations, and follow this with an opportunity for students to work individually and in groups on a project or simulation to apply what they have learned in a meaningful way.

Optimal Intervention Duration and Sample Size

The interventions described in this review represent a diversity of durations and cohort sizes. There was a slight majority of stand-

alone programs that lasted less than six months with respect to longitudinal programs that extended beyond six months, and within each of those categories there were programs lasting for a single half day to spanning the entire four years of the curriculum. Most programs hosted fewer than 50 students per cohort (n=12, 75%), while the other four hosted well over 100. Longitudinal programs had a higher average effectiveness score than stand-alone programs, as did programs with cohort sizes under 50 students compared to larger programs. This poses a challenge for educator, as interventions would ideally be made available to the entire student body with opportunities to engage with the program throughout the curriculum. However, a large ratio of students to faculty, financial limitations, and the packed nature of undergraduate medical curricula make it difficult for students and staff to give high-impact investment for a long period of time. Providing high impact programming for a small number of students over a short period of time is one solution, and is the strategy that was utilized by the LINC Scholars Program which received the highest scores for both quality of evidence and effectiveness in this review.[25] LINC provided a group of 5 students, during an 8-week summer immersion program, with both a stipend and additional resources to fund quality improvement projects, thereby developing 15 new hospital protocols and giving students the opportunity to present their work at regional and national conferences.[25] This contrasts with the University of Illinois' UMed program, a longitudinal program spanning the entire 4-year curriculum and with more than 200 students per cohort. However, this intervention had different objectives, focusing on humanizing attitudes in its students towards marginalized community members and seeking to inspire more graduates to pursue careers in primary care, both of which were ultimately achieved.[19] If the purpose of a leadership development program is to generate new, high-impact hospital or medical school policy in a short period of time, a stand-alone structure with a small group of students that can receive extensive mentoring and more substantial financial support to participants could be a promising and beneficial structure. However, if the primary goal is refining student's leadership attitudes, developing new career interests, and creating meaningful bonds between students with common passions, a long-term program with a larger cohort might be beneficial.

Standardization of Leadership Competencies and Evaluation

Since Webb et al. published their systematic review on leadership training in undergraduate medical education, which called for improved standardization of leadership competencies and assessment strategies, very little progress has been made in this area.[30] There also needs to be improved standardization in the assessment of leadership training effectiveness. Many of the programs described in this review created an in-house pre- and post-intervention survey to gauge effectiveness, and the variety between them made it difficult to assign an appropriate effectiveness score. Using a pre- and post-intervention self-assessment might have some utility for participating students, giving them a chance to reflect on strengths, weaknesses, and growth over the course of the program. Smithson et al. described an additional technique by having students complete a "reflection workbook" throughout their experience.[23] The majority (14/18, 77%) of student participants completed their workbook and 91% of the students that completed their workbooks found them valuable. Some programs opted not to use surveys or self-reflection workbooks, and simply reported the number of projects completed throughout the program and a grade for their impact.[17,19] During Operation Bushmaster at the Uniformed Services University, students were evaluated by faculty members for their performance, and data regarding the students' perspective of their performance or experience was not published.[24] We suggest creating a standardized rubric for faculty to evaluate students prior to and following the intervention, and basing survey questions on specific standard competencies and aims of the program.

Strengths and Limitations

There were several significant strengths of this review. Comprehensive literature searches were conducted by an expert searcher (medical librarian) who ensured the quality of the review.[31] Furthermore, the review encapsulated a wide range of interventions in terms of geographic setting, demographics of student cohorts, and methods of delivering content that might be adaptable to a wide range of contexts.

In terms of limitations, we acknowledge that this literature review describes only published literature and articles written in English regarding leadership education in undergraduate medical education and therefore cannot account for all interventions being staged around the world. Additionally, this review only encapsulates interventions at LCME-accredited medical schools, excluding those taking place at osteopathic medical schools in the United States and medical schools around the world. It is also possible that the leadership educational domains we attempted to classify are limited or misrepresented due to the language choices or undescribed context of the study and hence, not captured in this review. Finally, this review does not include searches of all available databases; Google Scholar, Scopus and others were not included, which limits the catchment of this review.

Summary – Accelerating Translation

In this article titled "Leadership Training in Undergraduate Medical Education: A Systematic Review," the authors explore what medical schools in the United States are currently doing to develop leadership skills in their students. By understanding what is currently being done, the authors describe the practices that are most effective and might be helpful to other medical schools in creating their own curriculums for leadership development. Being an effective leader is important in medicine: physicians make decisions and manage teams in crucial settings that can be life altering for their patients, which is why it is important that leadership skills are taught early, consistently, and well. The authors reviewed multiple large databases for articles about leadership development and found 977 possible articles to include in the review. Using pre-determined inclusion and exclusion criteria, the pool was

narrowed to a final set of 16 articles that were included in this review. These articles found that most medical schools begin their leadership education in the first half of a student's medical school tenure, but very few extended the curriculum for the entirety of medical school. We also found that most medical schools used a combination of classroom-based teaching and clinical or community settings in their curriculum. Some curriculums allowed greater than 100 students to participate per class, and some had more limited cohort sizes that included 10 or fewer students to participate at a time. Furthermore, we found that different medical schools emphasized different leadership skills in their curriculums, ranging from emotional intelligence and communication to professionalism and ethics. To understand how effective these programs were at developing leadership skills and how accurate their data was, we used scoring systems from previously published articles and assigned each article a score for effectiveness and data quality. We found that the average effectiveness score for the programs was a 2.6/4, meaning that the leadership curriculums led to learning and possible changes in the behavior of learners, and the average score for quality of data was 2.56/5, which meant that the articles had some convincing data as well as some ambiguous data. When analyzing the data, we formed the following recommendations: medical schools should extend their leadership curriculums for as long as possible- ideally the entirety of medical school, the curriculum should include both didactic and practical components so that learners can have a foundation of knowledge and an opportunity to apply it in their own way, and that smaller cohort sizes with a larger amount of funding from their medical school for projects are the most effective. Finally, we found that there is no set of leadership competencies or abilities that medical schools are required to develop in their students prior to graduation. This makes it difficult for schools to be held accountable to creating effective leadership development curriculums, and to collaborate with each other. We would encourage governing bodies in the United States and around the world to world to prioritize the creation of such a standard so that schools and students can be better prepared to meet the needs of our world as physicians.

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Author Contributions

Conceptualization, M.A.E and M.M; Methodology, M.A.E and M.M, Formal Analysis, M.A.E, E.J.J, and M.M; Investigation, M.A.E, E.J.J, and M.M; Data curation, M.A.E and M.M; Writing- Original Draft, M.A.E; Writing- Review & Editing, M.A.E, E.J.J, and M.M; Visualization, M.A.E and M.M; Supervision, M.M.

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Supplementary Material

Appendix
Search Strategies

Database	Platform	Search Strategies
PubMed	NLM	students, medical [mh] OR schools, medical [mh] OR education, medical, undergraduate [mh] OR "medical student" [ti] OR "medical students" [ti] OR "medical school" [ti] OR "medical schools" [ti] OR "undergraduate medical education" [ti]) AND (leadership [mh] OR leadership[ti]) AND (education [mh] OR learning [mh] OR program development [mh] OR program Evaluation [mh] OR curricul* OR course*[ti] OR program* [ti] OR educate* [ti] OR learn*[ti] OR teach*[ti] OR instruct*[ti])
Embase	ELSEVIER	('medical school'/exp OR 'medical students'/exp OR 'undergraduate medical education'/exp) AND 'leadership'/exp/mj AND ('education'/exp OR 'learning'/exp) OR ('medical student' OR 'medical students' OR 'medical school' OR 'medical schools' OR 'undergraduate medical education') AND leadership AND ('program development' OR 'program evaluation' OR curricul* OR course* OR program* OR educat* OR learn* OR teach* OR instruct*)
ERIC	ProQuest	(MAINSUBJECT.EXACT("medical schools" OR "medical students") OR "medical student" OR "medical students" OR "medical school" OR "medical schools" OR "undergraduate medical education") AND (MAINSUBJECT.EXACT("Leadership") OR leadership) AND (MAINSUBJECT.EXACT("program evaluation" OR "program development" OR "curriculum" OR "courses" OR "learning" OR "instructional development" OR "instructional design" OR "instructional development") OR "Program Development" OR "Program Evaluation" OR curricul* OR course* OR program* OR learn* OR teach* OR instruct*)
PsychINFO	ProQuest	("medical student" OR "medical students" OR "medical school" OR "medical schools" OR "undergraduate medical education") AND leadership AND ("Program Development" OR "Program Evaluation" OR curricul* OR course* OR program* OR learn* OR teach* OR instruct*)
Web of Sciences	Clarivate	("medical student" OR "medical students" OR "medical school" OR "medical schools" OR "undergraduate medical education") AND leadership AND ("Program Development" OR "Program Evaluation" OR curricul* OR course* OR program* OR learn* OR teach* OR instruct*)

Summary of Systematic Review Findings

First Author, Date	Length of Intervention, Number of Students per Cohort	Learner Level (number of students)	Curricular Format	Educational Setting	Curricular Domains based on Mangrulkar et al #	Quality of Evidence Score using Hammick et al	Effectiveness Score using Kirkpatrick's 4-level Hierarchy
Agarwal 2015[27]	2 years, 22	Preclinical	Stand-Alone	Mixed (didactic, case-based)	A, B, D, F	2	2
Barry 2018[24]	1 day, >100	Clinical	Stand-Alone	Field practicum	A, B, C, F	2	3
Cadieux 2017[28]	1 week, 172	Preclinical	Stand-Alone	Mixed (didactic, TBLs, small group discussion)	A, B, C, D, F	2	1

Coutinho 2019[32]	1 year, 36	Other (Clinical and Residents)	Stand-Alone	Mixed (projects, online, workshops)	A, E	2	4
Ginzburg 2018*[15]	2 years, 44	Preclinical	Longitudinal	Mixed (PBL, CBL, workshop)	A, B, C, E, F	4	3
Ginzburg 2018*[16]	2 years, 44	Preclinical	Longitudinal	Mixed (PBL, CBL, workshop)	A, B, C, E, F	3	3
Girotti 2015[19]	4 years, >200	Preclinical and Clinical	Longitudinal	Mixed (seminar, online, project)	A, B, C, E, F	3	4
Gottenborg 2020**[17]	5 weeks, <10	Preclinical	Stand-Alone	Mixed (didactic, project, workshop)	A, B, C, D, E, F	3	4
Hsiang 2018[21]	6 months, 23	Not described	Longitudinal	Mixed (didactic, workshop, project)	A, B, C, E, F	2	4
Lawson 2019[25]	8 weeks, 5	Clinical	Stand-Alone	Mixed (project, workshop)	A, B, C, D, E, F	4	4
Meador 2016[22]	1 day, 23	Clinical (M4 MD-PhD students)	Stand-Alone	Mixed (didactic, workshop)	A, B, C, F	3	3
Rotenstein 2019[26]	1 year, 33	Not described	Longitudinal	Mixed (didactic, project)	A, B, C, D, E, F	2	3
Smithson, 2020[23]	4 weeks, 18	Clinical	Stand-Alone	Simulation	A, B, C, D, E, F	2	1
Sweigart 2016**[18]	5 weeks, 6	Preclinical	Stand-Alone	Mixed (seminar, workshop, project)	A, B, C, E, F	3	3
Vinci 2014[20]	4 years, 23	Preclinical and Clinical	Longitudinal	Mixed (project, workshop)	A, B, E	3	2
Wagenschultz2019[29]	1 year, 166	Preclinical	Stand-Alone	Didactic	A, B, C, F	1	1

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Case Report

Myasthenia Gravis Exacerbation Following COVID-19 Vaccine: A Case Report

Thoybah Yousif Ibrahim Gabralla,[1] Hayat Abdoallah Ahmed Bashir,[2] Omaima Abdalla Hajahmed Mohamed.[3]

Abstract

Background: Vaccination remains the mainstay of strategy for prevention of Coronavirus Disease-2019 (COVID-19). AZD1222 (AstraZeneca vaccine) was distributed in Sudan by the COVID-19 Vaccines Global Access facility in March 2021. It was added to the emergency use list by the WHO in mid-February 2021. However, vaccine safety among patients with autoimmune diseases, such as myasthenia gravis (MG), is yet to be established. MG is a relatively rare illness that could result in life-threatening complications. Myasthenic crisis is considered the most serious complication of MG that can lead to death due to aspiration and respiratory failure. **The case:** We report the case of a 37-year-old Sudanese female who presented to the emergency room with an exacerbation of her normally well-controlled MG following her second dose of AZD1222 vaccination. She continued to deteriorate and was admitted to the intensive care unit, where she was intubated and placed on a mechanical ventilator. The low-income setting was a major barrier in obtaining intravenous immunoglobulin until the patient died. Our study aims to present an MG case with features of MG exacerbation following administration of a second dose of AZD1222. **Conclusion:** Little is known about the effect of different COVID-19 vaccines on subgroups of patients with autoimmune diseases like MG. In our case, an exacerbation of MG may have been precipitated by the COVID-19 AstraZeneca vaccine. Therefore, more efforts and experimental studies may be needed, with closer vigilance in MG patients.

Key Words: Myasthenia gravis; COVID-19; Vaccine; Case report (Source: MeSH-NLM).

Introduction

To date, the Coronavirus disease-2019 (COVID-19) pandemic has resulted in millions of deaths worldwide. As of December 2021, the World Health Organization (WHO) reported 280,119,931 confirmed cases of COVID-19 and 5,403,662 COVID-19-related deaths.[1] While COVID-19 continues to be a major cause of deaths in Sudan, the COVID-19 Vaccines Global Access (COVAX) facility distributed more than 800,000 doses of AstraZeneca vaccine (AZD1222) in Sudan in March 2021.[2] According to the WHO, AZD1222 is a novel recombinant replication-deficient chimpanzee adenovirus carrying a gene encoding the S protein antigen of SARS-CoV-2.3 It is synthesized by SK Bioscience Co. Ltd (SK Bio) in the Republic of Korea.[3]

AZD1222 was added to the emergency use list by WHO in mid-February 2021.[4] Five Clinical trials in UK, Brazil, and South Africa, which included 23,745 participants, were conducted to assess its safety. The vaccine was well tolerated with minor side effects such as injection site inflammation, headache, nausea, fever+/-chills, muscles and joint pain, and fatigue.[3] Thrombosis and thrombocytopenia were uncommon, but serious side effects were reported in few cases after administration of AZD1222.[5] However, vaccine safety among patients with autoimmune diseases, such as myasthenia gravis (MG), is yet to be established and needs further studies. MG is a relatively rare illness with a worldwide prevalence rate of 12 per 100,000 population.[6] The principal underlying pathology is the destruction of the postsynaptic membrane at the neuromuscular junction by autoantibodies, mostly anti-acetylcholine receptor antibodies (Anti-AChR). It manifests clinically as fatigable weakness of ocular, bulbar, proximal extremities, neck, and respiratory muscles. Common exacerbating factors are physical exertion, high temperature, drugs, emotional stress, surgical procedures, infections, menses, or pregnancy.[7] MG exacerbation can present with a progressive pattern over a few days or up to one month. It should be considered as a potential

Highlights:

- COVID-19 is a relatively new pandemic that was first reported in Wuhan, China in 2019.
- COVID-19 vaccines were created to curb the spread of the disease.
- The effects of COVID-19 vaccines on pre-existing diseases such as Myasthenia gravis patients is still questionable.
- By sharing this case, we aim to elucidate the effects of the AstraZeneca COVID-19 vaccine on a Myasthenia gravis patient.

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imminent crisis. The main features of myasthenic crisis are weakness in respiratory and oro-pharyngeal muscles, which can deteriorate in a short period of time and be complicated by aspiration and respiratory failure. Plasma exchange (PLEX), Immunoadsorption (IA) and Intravenous Immunoglobulin (IVIG) are the first-line treatments for myasthenic crisis. It is also proven that cortisone has a positive effect when used as add-on therapy with PLEX/IA and IVIG.[8]

Our study aims to present a myasthenia gravis case with features of MG exacerbation following the administration of a second dose of AZD1222.

The Case

A 37-year-old Sudanese female with known MG since 2011 had been maintained on pyridostigmine (60 mg tablet once daily), and reported compliance to treatment. She received a first dose of the COVID-19 AstraZeneca vaccine, followed by a second dose a month later. She reported experiencing mild generalized weakness after the first dose that did not significantly limit her daily activities, and she did not seek any medical help at that time. After receiving the second dose, she had been experiencing severe generalized body weakness that increased overtime and inability to walk for about one month, for which she was on sick leave from her work. This was the presenting complaint at the emergency room (ER), along with a complaint of shortness of breath for one day. Dyspnea was not associated with fever or cough. Examination of other organ systems was non-significant. She had been missing her menstruation during this exacerbation. Her last MG exacerbation was about 10 years ago and had been treated accordingly. Thereafter, her disease was well controlled. Her last visit to the ER was about 4 years ago, where she had severe anemia that necessitated blood transfusion. There was no hypertension, diabetes mellitus, asthma, or any other diagnosed comorbidity. Moreover, there was no history of recent surgical procedures or administration of any drugs other than pyridostigmine. On examination, the patient was not cyanosed, pale or jaundiced. Vitals were as follows: pulse rate of 95 beats per minute, blood pressure of 175/125 mmHg, and respiratory rate of 24 breaths per minute. The patient's temperature was within normal range and the Glasgow coma scale was 6/15. Chest was clear on auscultation with the trachea being central. The abdomen was soft, with no tenderness, superficial masses, or organomegaly. After almost half an hour from the presentation, the patient developed cardiopulmonary arrest. Cardiopulmonary resuscitation was initiated immediately and was revived with the return of spontaneous circulation. She was intubated and ventilation was assisted with an Ambu® bag.

Thereafter, she started to breathe spontaneously. A few hours later, the patient developed respiratory arrest again and was assisted with an Ambu bag for about 6 hours until she was admitted to the intensive care unit (ICU), where a mechanical ventilator was utilized. Laboratory results were significant for hyperglycemia (470 mg/dL) at the time of presentation. Complete Blood Count was within normal ranges and a malaria blood test, which was done as per routine in Sudan, was negative. Computerized tomography of the chest was performed, and it revealed no evidence of COVID-19. Management at the ER started with rehydration and IV methylprednisolone 1g, followed by IV hydrocortisone 200mg. IVIG was requested, but could not be obtained, and fourteen days after admission, the patient died due to circulatory collapse. We obtained an informed consent for publication from the patient representatives due to the patient's death.

Discussion

We reported a case of MG exacerbation after a second dose of AZD1222. Present findings are consistent with the findings from another case that reported an exacerbation of MG after a second dose of the Moderna COVID-19 vaccine. The symptoms of exacerbation were dysphagia, non-specific joints pain, on and off fevers with chills, and fatigue.[9] In a recent case report, the patient developed fatal MG crisis after receiving AZD1222, but exacerbation occurred after the first dose.[10] Single-center case series investigated 22 MG patients and reported that 90.9% of patients had no exacerbation of symptoms four weeks after receiving vaccines (all of them received inactivated vaccines), and only 9.1% (n=2, one received an inactivated vaccine and the other received a recombinant vaccine) reported mild symptoms like neck and limb weakness.[11] In a study concerning neurological complications after the first dose of COVID-19 vaccines, AZD1222 was associated with an increased risk of hospitalization and death among MG patients. This increased risk was significantly associated with the age group of 50 years or below.[12] In a cohort study that evaluated 80 MG patients, where most of them received the BNT162b2 (Pfizer) vaccine, five patients received the Moderna vaccine, while three received AZD1222, the results showed that only four patients experienced myasthenic exacerbation. These four patients experienced MG exacerbation after the second dose of the BNT162b2 (Pfizer) vaccine.[13]

It is worth noting that almost all of the aforementioned vaccines that led to worsening of symptoms, including AZD1222, used genetic material to encode for specific proteins in order to activate the immune system. On the contrary, the administration of whole virus vaccines (inactivated vaccine) to 21 MG patients in a single-center case series did not lead to a worsening of symptoms, except in one patient who experienced mild symptoms. It could be that the difference depends on the type of vaccine itself. Although it has not been elucidated how COVID-19 vaccine provokes autoimmunity, several theories have been proposed. The molecular mimicry theory explains how the genetic material of a virus could provoke autoimmunity due to the cross-reactivity of antibodies produced against proteins encoded by viral genetic material with the proteins located at the post-synaptic membrane.[14]

MG can be classified according to etiology into Congenital Myasthenic Syndromes, Transient Neonatal due to maternal anti-

AChR antibodies, Drug-Induced, or Acquired Autoimmune.[7] A new MG diagnosis was reported in a patient who experienced slurred speech after receiving the BNT162b2 vaccine.[15] Additionally, other two individuals were newly diagnosed with MG following a second dose of the same vaccine.[16]

We noticed that the exacerbation, in most cases, occurred after the second dose instead of the first. MG patients have defective lymphocytes[17] which may respond to the vaccines in a different way. Sensitization may have occurred following the first dose, and since the second dose was administered after their lymphocytes already developed immunologic memory, a cytokine storm could have been stimulated.[18] This is still a hypothesis as it is yet to be proven in preclinical studies and in a clinical setting.

Infections are a well-known trigger of MG exacerbation.[7] Likewise, the COVID-19 infection is reported to cause an exacerbation of symptoms in MG patients and causes symptoms such as dysphagia, weakness, and respiratory failure.[19] Outcomes can include: ICU admission, mechanical ventilation, and death.[20] Nevertheless, a single-center study that assessed 83 MG patients with COVID-19 infection reported a favorable clinical outcome in 79 patients.[21] We can conclude that MG outcome in relation with COVID-19 infection is still controversial. This may raise questions about whether the vaccines' benefits outweigh the risks in MG patients or not. However, we believe that MG patients should be informed about the benefits and risks of COVID-19 vaccination.

The management of exacerbations involves steroids and IVIG.[19] Our patient was on steroids at the ICU, and IVIG was requested, but due to the high cost of this medication, it is not easily accessible in Sudan, and it was not possible to obtain it prior to her death. The use of immunosuppressive therapy is controversial. Some studies suggest that the use of immunosuppression can lead MG patients to a more severe course of COVID-19 disease,[22] while others suggest that MG patients infected with COVID-19 may need increasing immunosuppressive doses but should be stopped if sepsis occurs.[23]

Although the safety profile of AZD1222 is generally reassuring, people with severe underlying diseases were excluded from trials.[3] This report highlights the potential risks of vaccine use in individuals with pre-existing illnesses such as MG, in which its safety is unknown.

Conclusion

In summary, we reported a case of MG exacerbation following a second dose of AZD1222. The course of illness started with shortness of breath and generalized weakness, which deteriorated to respiratory arrest and necessitated ICU admission, followed by a fatal outcome. Little is known about the effect of different COVID-19 vaccines on subgroups of patients with autoimmune diseases such as MG. Therefore, more efforts and experimental studies may be needed, and closer vigilance in MG patients is recommended.

Summary – Accelerating Translation

العنوان: تفاقم الوضع الصحي لمريض الوهن العضلي الوبيل بعد تلقي لقاح مرض فيروس كورونا المستجد ٢٠١٩: تقرير حالة

ملخص:

تهدف الدراسة الى عرض حالة لمريضة مصابة بالوهن العضلي الوبيل اظهرت أعراض تفاقم مرض الوهن العضلي الوبيل بعد تلقي الجرعة الثانية من *AZD1222* لقاح مرض فيروس كورونا المستجد ٢٠١٩. تتوفر قليل من المعلومات عن تأثير لقاحات مرض فيروس كورونا المستجد ٢٠١٩ المختلفة على المرضى المصابين بأمراض المناعة الذاتية مثل مرض الوهن العضلي الوبيل .

بالرغم من أن درجة سلامة اللقاح مطمئنة الا أن المرضى المصابين بأمراض المناعة الذاتية استبعدوا من التجارب السريري، بالتالي هنالك حاجة ملحة للمزيد من الدراسات مع متابعة يقظة و لصيقة لمرضى الوهن العضلي الوبيل.

حاليا لا توجد معلومات عن الطريقة التي يقوم بها لقاح مرض كورونا المستجد ٢٠١٩ بتحفيز المناعة الذاتية لكن توجد نظريات عديدة, أشهرها نظرية التمويه او المحاكاة الجزيئية يمكنها تفسير كيف المواد الجينية للفيروس يمكنها تحفيز المناعة الذاتية. يوجد خلاف حول هل فائدة اللقاح بالنسبة لمرضى الوهن العضلي الوبيل أكبر من المخاطر التي يمكن أن يتعرضوا لها بعد تلقي اللقاح أم لا, وبالتالي يجب مناقشة فوائد و أضرار اللقاح مع مريض الوهن العضلي الوبيل.

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Case Report

Windswept Deformity from Pseudogout: A Diagnostic Challenge of an Extreme Presentation, A Case Report

Yuki Julius Ng,[1] Kauseliya Velanthren.[2]

Abstract

Background: Twenty percent of the population globally is affected by musculoskeletal conditions. These conditions significantly impair mobility and dexterity. Pseudogout is similarly a debilitating disease that significantly increases morbidity and the disability adjusted life years of a person. We report a case of pseudogout in its advanced stage, causing total joint destruction of the knees and shoulders that manifested and presented as a windswept deformity. **The Case:** Our patient is a 69-year-old man who complained of bilateral knee pain, shoulder pain during active flexion, and an obvious knee deformity. His familial history was not significant, and there was no history of injuries, infection, or congenital diseases. His knees were severely deformed, with extremely laxed collateral ligaments. Both of his shoulders had a limited range of movement with coarse crepitation on passive movement. X-ray of his knees showed a destroyed joint, reduced joint space, subchondral cysts, and chondrocalcinosis. X-ray of his shoulder joint showed a subluxated joint, subchondral cyst, and subchondral sclerosis. His joint aspirate was positive for rhomboid crystals in the birefringence test, consistent with pseudogout. Joint replacement surgery is the definitive management for this disease, but the patient and caretaker were not able to afford the implants. **Conclusion:** We discussed the diagnosis of pseudogout in this patient and how the policies in place do not provide adequate coverage for these populations. This marginalizes those who need surgery and limits their access to affordable surgical care when needed.

Key Words: Chondrocalcinosis; Calcium Pyrophosphate Deposition Disease; Global Surgery (Source: MeSH-NLM).

Introduction

One in five persons globally is affected by musculoskeletal conditions.[1] These conditions significantly impair mobility and dexterity, causing early retirement and reducing the ability to participate in social activities. Pseudogout equally affects patients' quality of life. Approximately 20% of patients with osteoarthritis requiring total knee replacement have calcium pyrophosphate deposition (CPPD) crystals in their joints.[2] Although CPPD continues to be underdiagnosed, it is not difficult to confirm the diagnosis. Polarizing light microscopy with a red filter can accurately diagnose CPPD crystals. The hallmark of the crystal is its classical rhomboid shape and its relation to the light source. The crystal turns blue when the light axis is parallel and turns yellow when it is perpendicular under microscopy. This contrasts with monosodium urate crystals which turns blue perpendicularly and yellow parallel to the crystal axis in relation to the light source.[3,4] The morphology of monosodium urate crystals appears as a needle-like rod-shaped crystals.[4] We present a case of CPPD disease at its extreme stage of pathogenesis and discuss the diagnostic and social challenges faced.

Highlights:

- Severely destroyed knee joints can be caused by pseudogout.
- Policies in place are still not covering the extremely poor population in Malaysia.
- Transitioning countries to high-income status should reform their policies to ensure adequate health coverage.
- Implant manufacturers and companies have a big great role in deciding setting the cost of implants.

The Case

A 69-year-old Chinese ethnic man with underlying hypertension presented with bilateral knee pain and windswept deformity, associated with right shoulder pain (*Figure 1*). He had no history of fever, numbness, leg weakness, trauma, or congenital anomaly. The knee pain started 3 years prior and his windswept deformity progressively worsened over the past 1 year. The bilateral knee pain was sharp in nature, did not radiate, and was exacerbated by walking and weightbearing. He scored his pain as 5/10. He was able to ambulate with a walking stick. His shoulder pain progressed over 8 years and was exacerbated with movement. He was primarily concerned with the prolonged nature of the pain. He was a construction worker before the deformity severely affected his joints.

Upon examination, there was a large, boggy effusion of the shoulder joints bilaterally. The left shoulder had a reduced range

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of movement with gross crepitations during passive movement. Active abduction was up to 100° and frontal flexion was up to 90°. The right shoulder had a significantly reduced range of movements. Both active abduction and frontal flexion were up to 30°. The pain in both shoulders was localized with a pain scale of 5/10. Biceps bilaterally presented with Popeye deformity (*Figure 2*). Rotator cuff tests were abandoned due to the pain they caused.

There was an obvious windswept deformity of the knee towards the left while bearing weight. Knee flexion and extension had a full range of motion on active and passive movement. Gross crepitus was felt with passive movement bilaterally. The left knee was able to passively angle medially up to 50° and the right knee was able to passively angle laterally up to 70° according to his deformity as shown (*Figure 1*). The knees were bilaterally tender upon performing the stress test with a pain scale of 5/10. McMurray's test was inconclusive bilaterally due to the severely deformed anatomical structures.

Investigation

His full blood count, renal profile, electrolytes, liver function, coagulation profile, fasting lipid profile, cortisol, and thyroid function tests were within normal ranges.

The radiographs of his shoulders and knees are described (*Figures 3* and *4*).

Management

This patient was initially planned for bilateral total knee replacement as the definitive treatment, but the patient decided to opt out due to the cost. Not only was he within the low socioeconomic group, but the social welfare department was unable to fund the two knee implants. Arthrocentesis was done over both shoulders and both knees for symptomatic relief. We managed to aspirate a total of 200ccs of synovial fluid from all four joints and immediate pain relief was reported from the patient. The fluid was immediately examined under compensated polarizing light microscopy with a red filter (*Figure 5*). The diagnosis of pseudogout was established with the presence of rhomboid crystals in the classical birefringence test. He was discharged with oral Prednisolone 20mg once a day for 14 days and oral Colchicine 0.5mg once a day for 14 days. The pain was significantly reduced, and the patient was satisfied with the treatment.

The patient was followed up with in the rheumatology clinic. Physical examination had similar findings from his initial presentation such as the windswept deformity, joint crepitations, and laxed joints. However, his pain had significantly reduced. He had no further complaints and was happy with his current medical management plan. He was discharged with the same prescriptions of Prednisolone and Colchicine. However, he expressed his hopes for the definitive surgery and regaining basic walking function in the future if fundings became available.

Figure 1. Knee Examination Bilaterally while Bearing Weight. Windswept Deformity towards the left of the patient.

Figure 2. Left and Right Popeye Deformity.

Discussion

Pseudogout is caused by the deposition of CPPD, which is predominantly found in the elderly over 60 years of age. Clinically, the most commonly affected joints are the knees, followed by the wrist, shoulder, ankle, elbows, and hands.[4] These crystal formations are found in the extracellular matrix of the midzone chondrocytes, which are usually found on the surface. Multiple factors such as excessive cartilage pyrophosphate production are thought to then cause CPPD and inhibit basic calcium phosphate mineralization. Animal studies have shown that the overactivity of

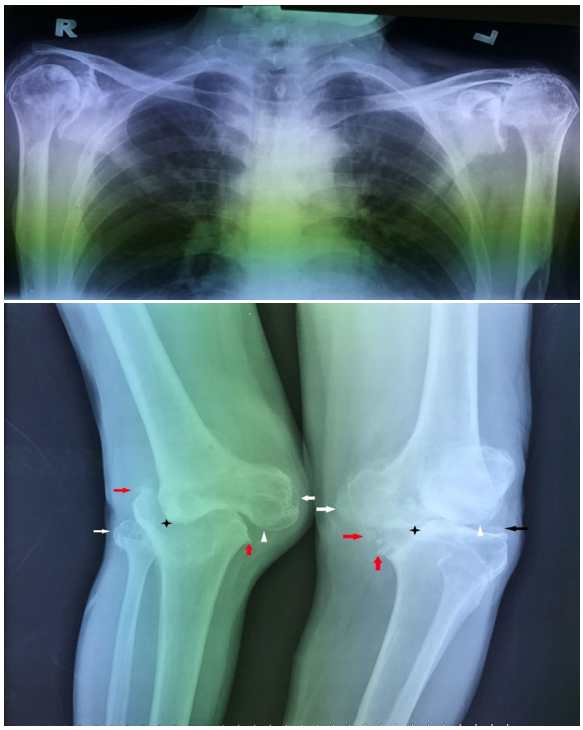
the enzyme ectonucleotide pyrophosphatase/ phosphodiesterase-1(ENPP1) catalyzes pyrophosphate production via hydrolysis of extracellular adenosine triphosphates.[12] Deficiencies of ENPP1 in mice showed increased pyrophosphate production and inhibition of basic calcium phosphate mineral formation.[13] In vitro studies have also shown Transforming Growth Factor β1 can overtly stimulate chondrocyte pyrophosphate production. Other factors such as increased osteopontin and cross-linking of extracellular matrix proteins with transglutaminase may increase CPPD formation.[12]

The ANK gene coding for a protein ANKH, produces a transmembrane protein that facilitates the transport of pyrophosphates across cell membranes into the extracellular matrix. Mutations in this ANK gene promote an excessive buildup of pyrophosphates within chondrocytes and promote CPPD. These crystal deposits have also been found to induce the promotion of osteoclastogenesis, a cause of crystal-induced joint damage.[13] Although the exact mechanism of crystal formation is still unknown, the saturation of CPPD within cartilage as the cause is generally accepted. The inflammatory responses are similar to gouty arthritis in terms of inflammatory markers and the activation of synovial mononuclear phagocytes and neutrophils. CPPD crystals as a destructive amplifying factor are likely, as shown in our case. This destructive property was also evident in our patient as he presented with bilateral Popeye deformity (*Figure 2*). This was most likely due to the destruction of his shoulder joints (*Figure 3*), extending to the tendons of the long head of the brachialis muscle. CPPD is usually not seen in the early stage of osteoarthritis, however, it is associated with severe progression of osteoarthritis.[13]

CPPD is commonly asymptomatic and can be observed via radiographic changes as demonstrated in our patient.[2,3,13] The presentation varies between acute cases and chronic cases. An acute case of pseudogout presents commonly with monoarthritis affecting the large joints, such as knees and wrists, with severe inflammation and painful swelling of the joints.[4,11] Unlike gout, it is usually self-limiting and typically resolves within 10 days. Chronic cases of pseudogout clinically resemble osteoarthritis, as seen in our case, and can present with a more severe pain than similarly-staged osteoarthritis.[11,13] CPPD imitates the characteristics of gouty arthritis, thereby increasing the difficulty for clinicians to diagnose this condition. For this reason, the birefringence test of the joint aspirate examined under compensated polarizing light microscopy with a red filter to observe the rhomboid-shaped crystals is pathognomonic for CPPD.[11]

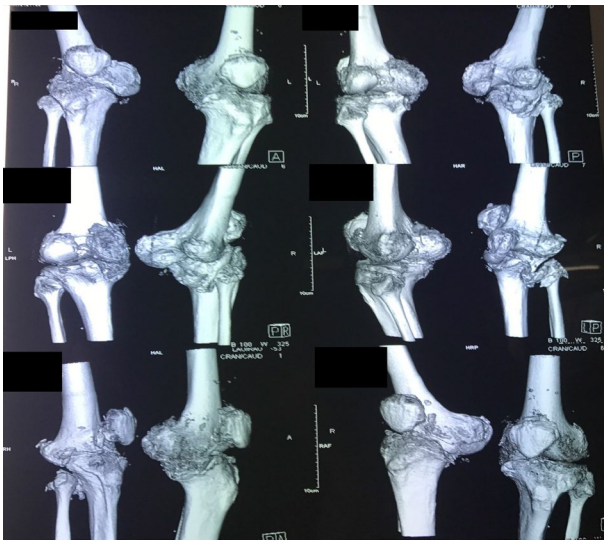
This case had a particular diagnostic challenge presenting at a late stage of the disease. To the authors' knowledge, CPPD disease causing windswept deformity has not been described in medical literature to date. His physical examination was jarring, causing additional constraints to reach a definitive diagnosis, which additionally delayed the execution of his management plan.

Figure 3. Bilateral Shoulder Xray and Bilateral Knee Xray (Non-Weight Bearing).



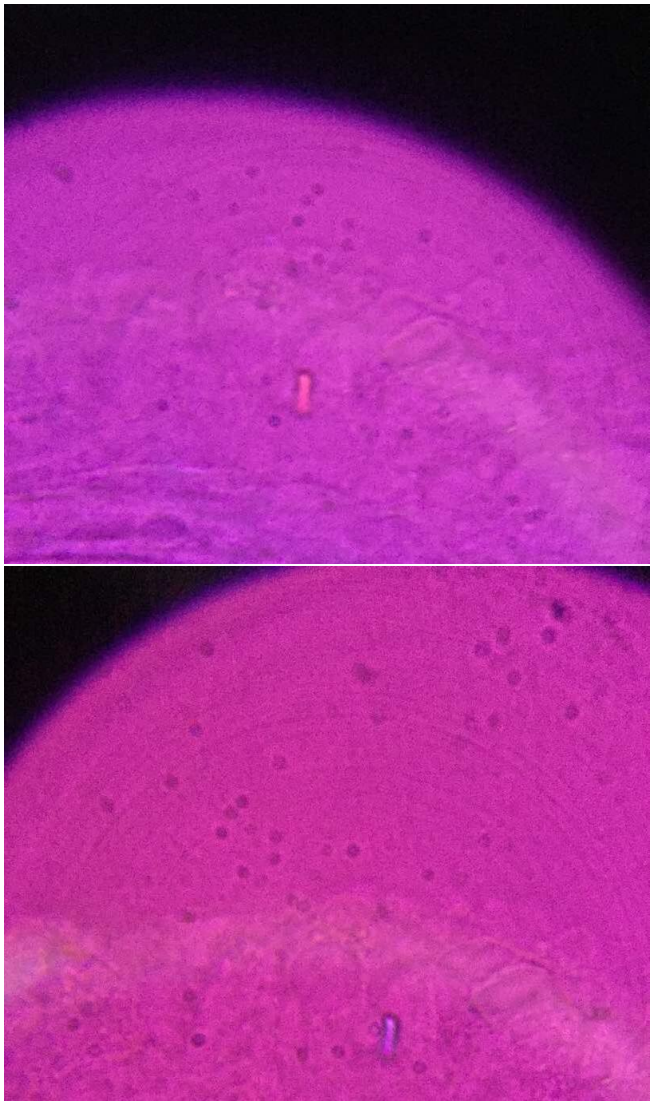
Legend: Left shoulder subluxed and dislocated with a presence of subchondral cyst and subchondral sclerosis. Right shoulder shows subchondral sclerosis and subchondral cysts. Bilateral knee x-ray shows a destroyed knee joint with absent anatomical landmarks of the knee joint. Black star – destroyed tibia plateau and reduce joint space. Red arrows – variable osteophyte formation.
Black arrow – chondrocalcinosis. White arrowhead and white arrows – subchondral cyst.

Figure 4. 3D Reconstruction CT scan of Bilateral Knee.



Legend: Findings from 3D reconstruction of bilateral knee joint suggest similar findings as the bilateral knee x-ray findings. This CT scan demonstrates a destroyed knee joint with reduced joint space, variable osteophytes formation, and subchondral cyst formation.

Figure 5. The Birefringence Test of the Synovial Aspirate was Examined under Compensated Polarizing Light Microscopy with a Red Filter. Examination Shows a Rhomboid Crystal.



Operative management of total knee replacement was considered the definitive management for this patient. However, there was no public or private funding available. Joint replacement is expensive, this can risk financial catastrophe. Because of the cost, this further limit its application for the extreme poor.[6] The patient and his caretaker were unable to afford the implant as they live below the poverty line. In Malaysia, a knee replacement surgery costs approximately USD 12,000.[9] The Malaysian guidelines for obtaining facilities, welfare, and healthcare are covered for some medical conditions eligible to request financial aid. Nevertheless, it can only be applied with a minimum amount of an upfront payment to purchase the implant.[10] The large cost for these procedures forces the population with a lower socioeconomic status to reject surgery.

This family is categorized into both the vulnerable poor, whose families' monthly income is USD 605.91 and below.[7] This healthcare financial aid is a great advantage for middle to upper-income earners, yet it is a conditional privilege. A new system is needed to address the lack of access for the vulnerable poor.

In conclusion, CPPD disease is a debilitating disease that can destroy large joints and, in rare cases, cause significant morbidity and deformity. With the ongoing COVID-19 pandemic there is a strong need to offer reasonable financial aid for surgical care to prevent progressive and lifelong disabilities among this vulnerable group. It is integral for citizens to have complete healthcare coverage including surgical care, despite their socioeconomic status.

Potential differentials

1. Osteoarthritis
2. Milwaukee Shoulder Syndrome (hemorrhagic shoulder effusions)
3. Gonarthrosis

Learning points

1. Policies should allow access to surgical care for definitive management to reduce disabilities and allow the elderly population below the poverty line to receive the best treatment.
2. An invasive procedure should be employed to further examine the underlying pathology of indeterminate joint disease. In this case, arthrocentesis was pivotal in the diagnosis and management plan.
3. Diagnosis of calcium phosphate deposits should always be a differential in a destroyed joint.

Summary – Accelerating Translation

Windswept Deformity from Pseudogout: A Diagnostic Challenge of an Extreme Presentation, A Case Report.

Our patient is a 69-year-old male retired construction worker who presented to the hospital with bilateral knee pain and right shoulder pain with movement. He also had a severely deformed windswept knee deformity, requiring a walking stick to ambulate. His family was well and did not have similar issues with his complaints. Previously, he did not have any history of injuries, infection, or birth deformity. His knee pain was of moderate intensity, localized to the knee, and did not radiate elsewhere. Both knees and both shoulders were swollen with some fluid effusion. The range of motion of both shoulders were limited by pain and the rotator cuff examination was abandoned because of the pain it caused. He could actively perform flexion and extension of his knees with a full range of motion without pain. All four joints had gross crepitation upon movement. His knees could be passively bent to the side according to his deformity up to 70°. Other tests for his knees were abandoned because of the pain. His blood investigations (full blood count, renal profile, electrolytes, liver function, coagulation profile, fasting lipid profile, cortisol, and thyroid function test) were within normal range. X-rays and computed tomography studies showed a destroyed knee joint with osteoarthritis changes and chondrocalcinosis. His joints were decompressed using a needle under aseptic technique, which gave immediate pain relief. The fluid was examined under a microscope and pseudogout was diagnosed from the birefringence test. Although aspirating the fluid provided immediate pain relief, the definitive management for this condition is total joint replacement. However, surgery was not an option as this patient was extremely poor. He was given steroids and colchicine tablets to manage the pain and inflammation. Although the surgical service is free, the cost

of implants and the replacement of both knees are expensive. Policies in countries such as Malaysia may provide good health coverage to those who need surgery and belong to the middle-income group or above, but those living in extreme poverty are neglected. Therefore, health policies for this group of the population should be revised.

Pseudogout is caused by the deposition of calcium pyrophosphate deposition (CPPD) crystals into joint surfaces. Usually, it affects the knees, followed by wrist, shoulders, ankles, elbows, and hands. There are multiple factors that can increase CPPD crystal formation and deposition into joints. The deficiency of the ectonucleotide pyrophosphatase/ phosphodiesterase-1 enzyme can increase pyrophosphate deposition and the presence of Transforming Growth Factor β1 can stimulate pyrophosphate production, ultimately forming CPPD crystals. Genetic factors such as the ANK gene increase the levels of the protein ANKH and can cause excessive pyrophosphate deposition into cartilage and promote crystal formation. These crystal deposits can induce osteoclastogenesis, which leads to joint damage, as shown in our patient. The exact mechanism of crystal formation is unknown, however, the saturation of CPPD in cartilages causing the deposition of crystals is generally accepted by the scientific community. CPPD has similar inflammatory responses as gout in terms of activation of synovial phagocytes and neutrophils. For this reason, the current mode of treatment of pseudogout is with colchicine, to down-regulate multiple inflammatory pathways and modulate innate immunity.

Conclusion

Pseudogout is a debilitating disease that increases morbidity and reduces one's quality of life. It can progress to destroy joints as shown in our patient. It can be treated by decompressing the joints and slowing down the progression of disease with medication. When pseudogout destroys the joint, a joint replacement surgery is required. Current policies do not provide adequate coverage to the low socioeconomic group in Malaysia. This marginalizes those who need surgery and limits their access to affordable surgical care when needed.

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Case Report

Hypercoagulability and Cavernous Sinus Thrombosis due to Protein C Deficiency. A Case Report

Wilson S. Peñafiel-Pallares,[1] Camila Brito-Balanzátegui,[1] Jaime David Acosta-España.[2,3,4]

Abstract

Background: Thrombophilia due to Protein C deficiency is a rare condition, present in 0.2% of general population. Cerebral venous thrombosis has an incidence of 3-4 cases per million in adults. A combination of both is very uncommon. Patients with these conditions are prone to life-threatening superinfections. **Case:** A 51-year-old woman presented with pressing frontal headache accompanied with left periorbital edema, fever, diplopia, and disorientation. Laboratory findings showed low protein C levels. Computed tomography demonstrated sphenoidal rhinosinusitis. Magnetic resonance venography revealed cavernous sinus thrombosis. The patient was started on empiric antibiotic treatment (vancomycin, ceftriaxone, and metronidazole) and anticoagulants. **Conclusion:** This case report emphasizes the importance of early diagnosis and appropriate management of patients with protein C deficiency complicated by septic cavernous sinus thrombosis.

Key Words: Thrombophilia; Protein C deficiency; Cavernous sinus thrombosis; Case report (Source: MeSH-NLM).

Introduction

Protein C deficiency (PCD) is a rare disorder with a prevalence of approximately 0.2% in general population.[1,2] Protein C is a vitamin K-dependent glycoprotein activated by the thrombin-thrombomodulin complex on the endothelial surface. Activated Protein C degrades factors Va and VIIIa of the coagulation cascade, thereby inhibiting coagulation. In addition, it is involved in regulating the expression of endothelial proteins related to inflammation and cell survival.[3] PCD, therefore, promotes thrombus formation. Inheritance of the gene can be either an autosomal dominant inherited disease with an alteration of the Protein C Inactivator of Coagulation (PROC) gene or, less commonly, as an acquired disease.[4] Expression of the PROC gene can be decreased in certain pathological states, including right heart failure, severe liver disease, acute inflammation, and respiratory syndromes, by consumption and the dysfunctional production of activated Protein C.[2] There are two phenotypes of PCD: Type 1 is described as a mutation that reduces the plasmatic concentration of Protein C antigen and its activity, whereas Type 2 is characterized by normal concentrations of the protein, but with dysfunctional activity.[2] This deficiency has a wide range of manifestations from asymptomatic to life-threatening conditions.[4]

Cavernous sinus thrombosis (CST) belongs to the group of cerebral venous thromboses. It has nonspecific clinical manifestations such as headache, painful ophthalmoplegia, conjunctival chemosis, and ocular proptosis.[5,6] CST can be either septic or aseptic; septic form being the most common, with Methicillin-resistant Staphylococcus aureus (MRSA), followed by Methicillin Sensitive Staphylococcus aureus (MSSA) being the most reported causative organisms.[7,8] In a literature review, it was found that 57% of patients with septic CST had sphenoidal rhinosinusitis (inflammation of the nasal mucosa (rhinitis) and the mucosa of the paranasal sinuses (sinusitis)).[8]

Highlights:

- Patients with undiagnosed thrombophilia have a 3-8% risk of developing cerebral venous thrombosis.
- 3-4 per million cases may develop cerebral venous thrombosis, which can be later complicated by a septic cavernous sinus thrombosis.
- Patients complicated with septic cavernous sinus thrombosis demonstrated to have sphenoidal rhinosinusitis in 57% of the cases.
- A middle-aged patient without any medical or family history of thrombophilia, can develop a cerebral venous thrombosis due to Protein C Deficiency.
- A combination of a septic cavernous sinus thrombosis and a thrombophilia can be correctly managed with early anticoagulation and antibiotic treatment.

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The Case

A 51-year-old female patient with an unremarkable medical history (no previous similar events, nonsmoker, no surgical history, no miscarriages, no contraceptive pill use) and without family history of thrombophilia, presented to the emergency department with a bilateral pressing frontal headache present for 3 months that gradually increased in severity and did not respond to acetaminophen. A non-contrast computed tomography showed sphenoidal rhinosinusitis and a parenchymal lesion was excluded. The patient was diagnosed with migraine and NSAIDs were prescribed. No treatment for rhinosinusitis was indicated.

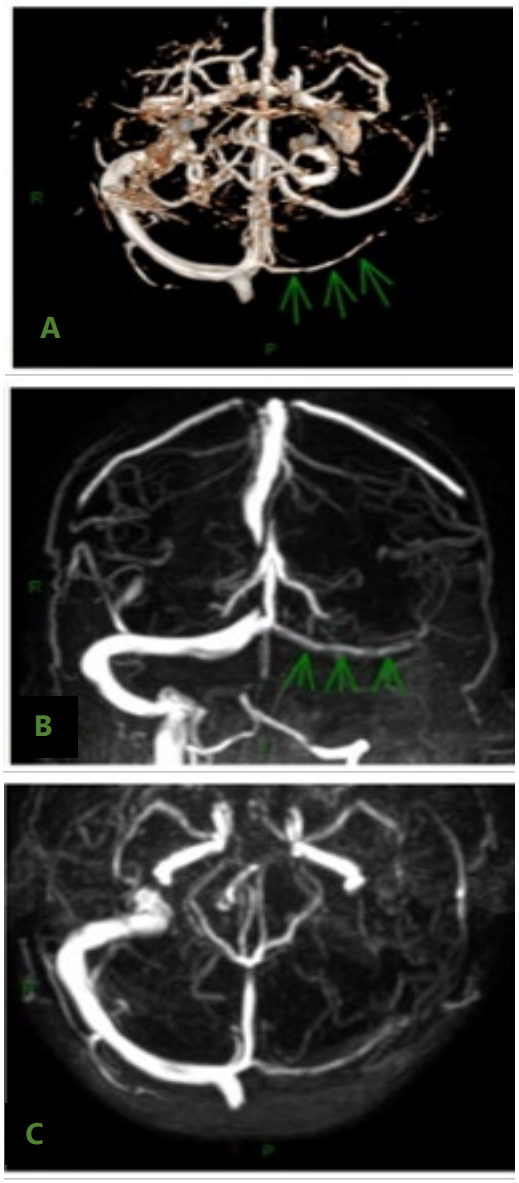
After 2 weeks, the headaches worsened, and her family took her back to the emergency department. During this admission, the patient had left periorbital edema, diplopia, and disorientation to time and place. Physical examination revealed left eye proptosis, nystagmus, limitation of extraocular movements, and papilledema with tortuous left retinal veins on fundoscopy. Remarkable vital signs included a respiration rate of 22/min, temperature of 38.1°C, and pulse rate of 110/min. Based on clinical presentation, differential diagnosis was: subarachnoid hemorrhage, epidural hematoma, bacterial/viral meningitis, and periorbital infection.

Procalcitonin level was 0.783 ng/ml (<0.5 ng/ml normal range); neutrophil level was 14107 mm^3 (2000-8000mm^3 normal range); C-reactive protein level was 235.9 mg/L (0-10mg/L normal range); and D-Dimer level was 819 mg/ml (0-500 normal range). Prothrombin time, INR, and Partial Thromboplastin Time were within normal ranges. Lipid panel, liver, and renal function markers were normal. Antinuclear antibodies and anti-dsDNA were negative. Due to the possibility of periorbital cellulitis and infection, intravenous empiric antibiotic treatment was started with vancomycin (loading dose of 15mg/kg/ BID), ceftriaxone (2g/BID), and metronidazole (500mg/ TID). Urine and blood cultures were taken prior to antibiotic treatment, and both resulted negative. Based on the neurological findings, imaging studies of the brain were indicated. Magnetic Resonance Venography showed filling defects of the left cavernous sinus compatible with cavernous sinus thrombosis. As a result of the radiological findings, anticoagulation therapy was started with enoxaparin (1mg/kg BID, total dose 60mg BID). Hemorrhage and infections of the central nervous system were excluded based on clinical presentation and laboratory and imaging studies.

Hypercoagulability tests revealed a Type 1 Protein C deficiency with reduced functionality and antigenic plasmatic Protein C levels at 30.98% (70%-140% normal ranges). Antiphospholipid antibodies, protein S, antithrombin III, and homocysteine levels were within normal ranges. Factor V Leiden and prothrombin mutations were not detected.

After seven days of hospitalization, laboratory findings were consistent with resolution of the infectious process (procalcitonin of 0.208 ng/ml, C-reactive protein of 40.10mg/L, and neutrophils of 5239mm^3). Blood and urine cultures remained negative. The patient showed significant clinical improvement and was discharged on oral antibiotics (amoxicillin/clavulanic acid 1g/ BID for 5 weeks) and long-term oral anticoagulants (Dabigatran 150mg/ BID). Follow-up with hematology department was indicated after 6 months of discharged and then every year. At eight months follow up, imaging studies were consistent with complete resolution of the thrombotic event and the sphenoidal rhinosinusitis.

Figure 1. Brain Magnetic Resonance Venography Confirming Cavernous Sinus Thrombosis.



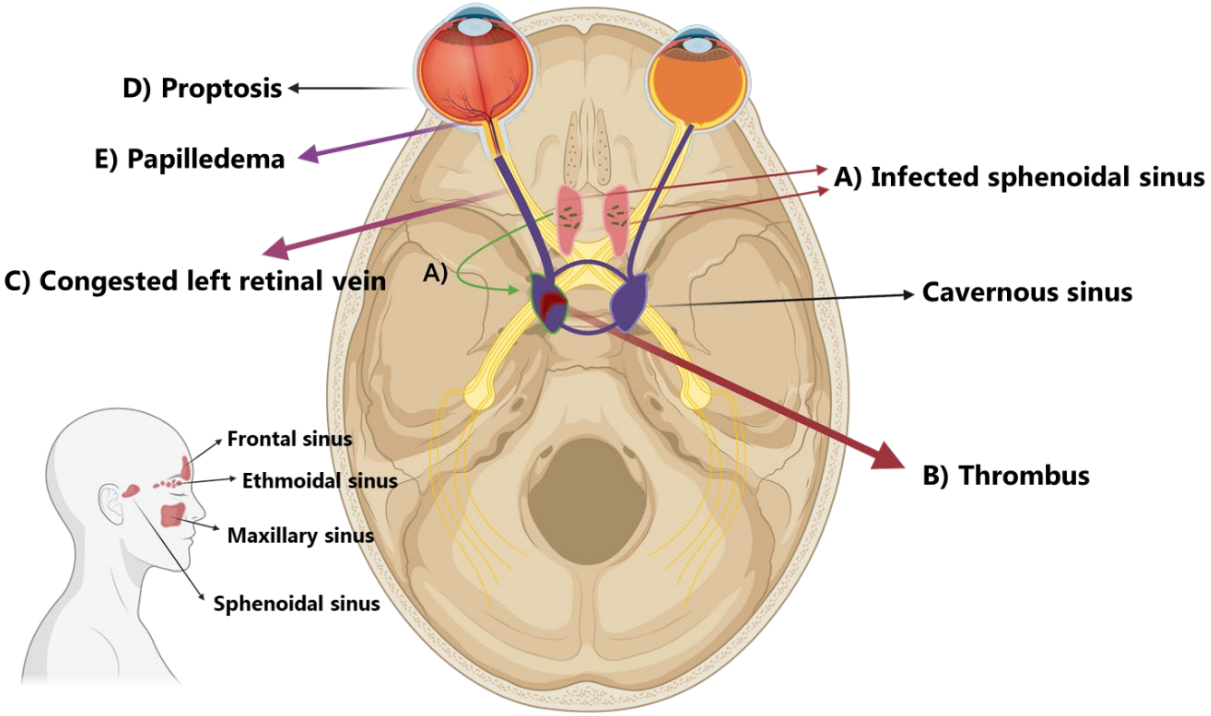
Legend: **A:** 3D Reconstruction of a Magnetic resonance cerebral venography. Axial section, cranial view. **B:** Magnetic resonance cerebral venography. Coronal section. **C:** Magnetic resonance cerebral venography. Axial section, cranial view. All of them show decreased diameter, signal intensity and filling defects of the left transverse sinus and ipsilateral internal jugular vein (green arrows). Tortuosity and dilatation of the left ophthalmic veins are also present.

Discussion

This case report presents a patient with thrombophilia due to Type 1 PCD complicated by cavernous thrombosis. Septic CST was supported by periorbital cellulitis and laboratory findings. Weerasinghe & Lueck et al. reported a similar case with septic CST caused by MSSA, however the patient did not have a three-month headache history, diplopia, or fundoscopic abnormalities.[8] Type 1 PCD was suspected in this case due to low Protein C plasmatic levels associated with a thrombotic event. This is unlike a case described by Fukushima et al. where normal plasmatic Protein C levels increased the suspicion of type 2 PCD and their patient presented with seizures and paralysis.[9] The diagnosis of our patient was established by referring to the Protein C activity assay using the immunofluorescence method. However, genetic analysis was preferred in Fukushima´s et al report.[9]

The risk of venous thromboembolism in patients with PCD is around 3-8%.[1] Cavernous thrombosis as a complication of an infectious process is more common in patients that have prothrombotic risk factors, such as deficiency of coagulation factors, trauma, smoking, oral contraceptive pills use, or previous surgery (*Figure 2*).[2,5] The aforementioned risk factors were not declared by the patient during the clinical interview. This supports the hypothesis of a possible inherited PCD triggered by an unidentified infection.[4] There have been some cases reported of patients without any family history of hypercoagulable states that developed a thrombotic event and found to have thrombophilia.[2]

Figure 2. Simplified Graphic of an Infected Cavernous Sinus Thrombosis.



Legend: **A)** An infected sphenoid sinus causes septic thrombosis in the cavernous sinus, **B)** In cavernous thrombosis, the facial vein, and superior and inferior ophthalmic veins **C)** cannot drain properly, resulting in facial and periorbital edema, ptosis, proptosis **D)**, chemosis, eye movement discomfort, papilledema (**E)**, retinal vein dilation, and vision loss. This image was created with Biorender.

The imaging studies recommended for the diagnosis of CST are contrast-enhanced computed tomography, magnetic resonance imaging, or magnetic resonance venography.[7] In this case report, all these imaging studies were used. Magnetic Resonance Imaging was normal, and contrast enhanced computed tomography revealed sphenoidal rhinosinusitis. Magnetic Resonance Venography showed enlargement and filling defect in the left cavernous sinus after contrast administration. Tortuosity and dilatation of the left ophthalmic veins were present. Central filling defects in the left transverse and sigmoid sinuses accompany these findings (*Figure 1*).

Due to undetermined timeline of sphenoidal rhinosinusitis, the recommended 10 days antibiotic treatment was extended to 5 weeks by the infectious disease department. According to the management of chronic rhinosinusitis described by Baron & Durand in 2017, a minimum of 3 weeks of antibiotic course is recommended. Some symptoms of chronic rhinosinusitis tend to reappear after 10 days of treatment.[10]

At 8 months, imaging studies were consistent with complete resolution of the thrombotic event and sphenoidal rhinosinusitis. The continuation of anticoagulation with a direct oral anticoagulant (Dabigatran) after hospitalization showed no

recurrence of thrombotic events, similar to what was reported by Fukushima et al. [9]

The limitation of this case is the uncertainty about its infectious etiology. Cultures resulted negative and a nasopharyngeal swab for bacteria was not performed. Due to a possible chronic sphenoidal rhinosinusitis as the infectious source, empirical prolonged antibiotic treatment was prescribed (this is debatable). Moreover, because of diplopia, confrontation visual field examination could not be assessed correctly

Conclusions

Although rare, a patient without medical and family history of thrombophilia may develop cerebral venous thrombosis because of Protein C Deficiency. Sinus infection may worsen the clinical state. Early recognition with clinical examination and imaging studies, followed by prompt intervention with anticoagulation and broad-spectrum antibiotics, is associated with a good prognosis for patients with septic CST due to hypercoagulability.

Summary – Accelerating Translation

Este reporte de caso presenta a un paciente con trombofilia debido a una deficiencia de proteina C (DPC) tipo 1 complicado por una trombosis del seno cavernoso (TSC). La TSC séptica fue confirmada por celulitis periorbitaria y hallazgos de laboratorio. El paciente también presentaba historia de dolores de cabeza de 3 meses, diplopía y anormalidades fundoscópicas. La sospecha de DCP tipo 1 surgió debido a bajos niveles plasmáticos de Proteína C asociados con un evento trombótico. La tomografía computarizada mejorada con contraste y la resonancia magnética venográfica mostraron un aumento y un defecto de llenado en el seno cavernoso izquierdo después de la administración de contraste, así como tortuosidad y dilatación de las venas oftálmicas izquierdas. Se recomendó un tratamiento prolongado de 5 semanas con antibióticos debido a una posible rinosinusitis esfenoidal crónica como fuente infecciosa. En el seguimiento a los 8 meses, se observó una resolución completa del evento trombótico y de la rinosinusitis esfenoidal. Se realizó anticoagulación oral (Dabigatrán) después del alta hospitalaria, lo que evitó la recurrencia de eventos trombóticos. Las limitaciones del caso incluyen la falta de cultivos positivos y la ausencia de una muestra de hisopado nasofaríngeo para bacterias.

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Experience

Women in Science: A Student Workshop at a University in Mexico

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Abstract

Women have participated in science since the earliest of times. However, their valuable contributions are not as widely acknowledged throughout our history and women still face several barriers throughout their professional career. We developed and hosted a half-day Women in Science seminar organized by students, for students. The main goal was to promote ways to involve more women in research activities and to strengthen the scientific community within our medical school. The workshop consisted of three main sections, where we shared relevant statistics, resources, and strategies among a community of students interested in science. At the end of the workshop, participants shared their insights proving the necessity and utility of such events to strengthen the development of science as an inclusive field.

Key Words: Gender; Bias; Women; Science; Medicine; STEM (Source: MeSH-NLM).

The Experience

Gender bias is an "unfair difference in the way men and women are treated."[1] This phenomenon has many different forms and extends to many work environments, including the scientific world.[2-4] Gender bias affects women in hiring decisions, perceptions of the quality of their work, research publications, peer-review processes, citation patterns, and leadership positions, among others.[5-9] Barriers such as gender wage gaps, sexual harassment, and maternity and paternity policies often prevent women from advancing in their professional careers, particularly in science.[10-14] Studies have shown that gender bias begins early in education and has deleterious effects throughout many aspects of academia.[15] It affects grading, mentoring, and letters of recommendation, which could certainly affect the progress of a woman in science.[16, 17]

Addressing this issue is key to pursuing gender equality in science, a problem that women have fought especially hard to overcome. Thus, we designed, developed, and hosted a half-day research-focused workshop to highlight the gender gaps in science and to provide information on research opportunities available for medical and clinical chemistry students. This workshop aimed to achieve the following goals:

- Provide information about ways to get involved in research as medical and clinical chemistry students.
- Instill confidence in students by providing examples of women with research experience
- Foster a sense of community in our school among women in research
- Motivate and inspire women to pursue their scientific abilities
- Increase women's participation in research activities at our university

Implementation of The Workshop

The workshop was a hybrid event where students were invited to attend in person or online. Although the invitation was open to all students, each of the 50 participants identified themselves as women. The workshop was divided into the following three phases:

Phase One: History of Women in Science

The first speaker was a fifth-year medical student from our university with previous research experience. Her session started with an implicit association exercise to assess unconscious bias in the audience. She continued with a talk titled "Women in Medical Sciences Throughout Time." This talk presented women who have made essential contributions in the field of medical sciences. It included notable individuals such as Agnodice, an important figure of Ancient Greece[18] and the first woman to be acknowledged as a gynecologist; Doctor Alice Hamilton, the first

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woman to become a faculty member of Harvard University;[19] and Nobel Prize winners Doctors Emmanuelle Charpentier, Jennifer Doudna, and Rita Levi-Montalcini among other scientists and doctors.[20] The purpose of this introduction was to show how women have been actively participating in medicine from ancient times to the present and how their contributions have played a great role in global and human development.

Phase Two: Current State of Affairs

The second speaker was a first-year clinical chemistry student from our institution with previous research experience. The speaker focused on the National System of Researchers or SNI, a government-led program established in Mexico, in which scientific researchers across the country subscribe to receive funding for their projects and apply for academic positions. According to the data provided by SNI, only 37.2% of Ph.D. researchers are women.[21] Thereafter, the speaker described some of the structural barriers that could explain the disparity between men and women in professional settings, such as the theory of the "glass ceiling and the sticky floor," which addresses the challenges women face for being promoted in science, technology, engineering, and math (STEM) careers, as well as the increasing difficulty in securing a grant for research.[22-25] At the end of this presentation, we conducted an activity in which the audience was encouraged to write down thoughts and ideas on how to improve women's situation in science in the present and near future (*Figure 1*).

Figure 1. Audience Participation Proposing Ways to Address Gender Bias at the University.

Phase Three: Leadership and Empowerment Seminar

The third speaker was a fourth-year medical student from our institution with previous research experience in the field of Psychiatry. The talk focused on empowering and instilling confidence in leaders, promoting empathetic and respectful communication, and suggesting ways to establish boundaries in the workplace. We continued with a pre-recorded interview with Sonia Hernández-Díaz, MD, PhD, a professor at Harvard T.H Chan School of Public Health. Her main area of research is Pharmacoepidemiology of Women's Health. She spoke about the difficulties she faced in academia and shared insights on how she found her passion. We also displayed a video of women researchers around the world giving advice to inspire young students who are interested in research.

We ended the workshop with a question-and-answer panel in which the participants and the presenters could share their doubts and experiences. Participants shared ideas and opinions, and advice based on personal experiences and on how they found research opportunities within our university (*Figure 2*). Some of the attendees were already involved in research activities, therefore their input was of great importance to younger students who did not know where to begin.

Figure 2. Round Table.

Recommendations and Lessons Learned

This workshop accomplished its objective of motivating women to pursue and embrace science as a career. The participants were asked about their opinions and feelings regarding the workshop, they described it as an inspiring, deep, and informative experience. Here we propose specific actions so as to continue to address gender issues in science:

- **Raise Awareness, Create, and Participate in Inclusive Events**

The extended discussion following the presentations offered different ideas and possibilities for future projects. We encourage institutions to carry out and implement workshops that promote the inclusion of minorities and educate the majority. We hope these activities continue to generate interest in students and help everyone consider ways to move forward in an inclusive manner in today's scientific community.

- **Increase Women's Representation in Science and Promote Gender-Neutral Mentoring**

According to the United Nations Educational, Scientific, and Cultural Organization (UNESCO), less than 30% of researchers worldwide are women.[26] We suggest increasing the number of women in high leadership positions in order to make fairer decisions and to motivate more women to be involved in these fields. To achieve this, we must first recognize the women who have participated in science throughout history and acknowledge

their contributions. Illustrating more women in books, scientific media, and even on television communicates diversity and raises awareness in young girls on their importance in scientific development. As for current research, we support the concept of gender-neutral mentoring to help account for barriers such as gender bias in grants and scholarships for the funding of research projects led by women.

- **Share and Learn from Each Other**

We suggest that women in the scientific community look for support and guidance from other women in leadership positions including older students, research trainees, professors, specialists, and researchers. We recognize that groups are beneficial for forming better ideas through brainstorming, as well as for intellectual discussions and proposing solutions. Forming support networks of women, incorporating inclusive language in science, and promoting a sense of community that empowers women are actions that contribute to making a change (*Figure 3*).

- **A Job for Everyone**

This is not only a job for women, but a job for everyone. We must all be conscious, inclusive, and account for everyone's needs to bring equity into the workplace and achieve better results that, in the aggregate, benefit everyone.

Figure 3. The Seminar.

Conclusion

Is it hard to be a researcher? Undoubtedly yes. Should we try despite the difficulties we are supposed to overcome? Definitely. This workshop allowed us to reflect on that. Although we have made a lot of progress over the past few years, we still have a long way to go to reduce and eventually close the gender gap in science. The impact of the event on the women of our institution proves the efficacy and the need for such interventions to enhance the development of women in science.

Participant Experiences and Perspectives

"This workshop was a genuine experience. It was a space created by women for other women, which made me reflect upon the value and importance of us women helping each other, highlighting our skills, and reminding us that instead of competing, we can be allies. Without a doubt, I could say that more than one of us went home wishing to become a woman in science."

Claudia Ramírez Mata, first-year clinical chemistry student.

"Going to the workshop was enriching. I felt comfortable and safe, it was a very empowering environment. I loved that the speakers encouraged us to participate and even share our own experiences. It made me realize that there are many paths to follow in the world of science. They gave us advice to start doing research, and most importantly, they made us feel connected with other women as there is still work to do to achieve equality and lay a foundation for future events."

Lourdes Gil Flores, fourth-year medical student.

"'Women in science' was a delightful event, full of emotions, knowledge, and women empowerment. At the beginning, it was quite frightening to listen to data about discrimination against women and gender inequality in professional life. But as the event went on, there were suggestions of what we can do to be part of the change, sharing of testimonies, and support from the whole auditorium. By the end of the event, I was sure that our generation can make a change, that there are people willing to help and redirect to the correct areas to seek change, and that with small actions we can start to eliminate the injustices that exist nowadays. Honestly, it was an event that I wish everyone, not just women, would attend."

Daniela Ortega Mata, sixth-year medical student.

Summary – Accelerating Translation

Mujeres y Ciencia: El Horizonte en Investigación

Las mujeres han participado en la ciencia desde el inicio de los tiempos. Sin embargo, sus logros no son tan vastamente reconocidos dentro de la historia. Actualmente, las mujeres enfrentan barreras asociadas al género cuando se trata de avanzar en su carrera profesional. Debido a esto, decidimos crear un espacio dirigido a estudiantes para hablar de la historia de la mujer en la ciencia y difundir estrategias para fortalecer la comunidad de mujeres en investigación. Durante este taller se compartieron estadísticas, experiencias personales y consejos sobre la trayectoria de distintas mujeres que se desarrollan en campos científicos alrededor del mundo. Al finalizar el taller, la retroalimentación de las participantes puso en evidencia la utilidad y necesidad de este tipo de espacios para motivar y enriquecer la comunidad científica de mujeres.

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Experience

Acquiring Medical Statistical Competencies in a Demanding Evidence-Based World: Thoughts and Experience from a Student Statistical Team in a Mexican Academic Center

Carlos de la Cruz-de la Cruz,[1,2] Humberto de León-Gutiérrez,[3] Juan Manuel Millán-Alanís,[4] Andrea Judith Bautista-Gómez,[5] Braulio Hernán Velasco-Sepúlveda,[6] Adrián González-Martínez,[1] Neri Alejandro Álvarez-Villalobos.[7]

Abstract

Training and encouraging students to critically review the evidence and make evidence-based decisions should be one of the goals of medical education. We report our experience developing an extracurricular university student statistical team that offers statistical aid to other students and faculty. This includes supervised training sessions and mentoring in diverse scientific research projects at work in our university.

Key Words: Medical Student; Statistics; Education; Personal Narrative (Source: MeSH-NLM).

The Experience

In an era of constant emergence of advanced scientific knowledge, staying up to date can be overwhelming for many physicians, especially for medical students and residents who must leap into the race and learn to maneuver through the vast amount of information available. Due to this, training and encouraging students to critically review the evidence and make evidence-based decisions should be one of the goals of medical education.[1] Learning statistics and epidemiology is important for physicians, as it is expected for them to be able to make decisions according to what is best for the patient, with the best possible evidence available. Having such competence will also enable future physicians to contribute to critically reviewing articles and publishing.

The understanding of epidemiological and statistical principles is essential for the performance and critical appraisal of clinical research. However, many clinicians excel throughout their various levels of medical training with poorly perceived knowledge of these concepts.[2] At our institution, biostatistics and epidemiology are integrated into the undergraduate (pre-clinical/clinical) curriculum, however the delivery of the content is often inadequate. For instance, there is insufficient application of the knowledge, which we consider an area of opportunity that should be included in our school's curriculum. Although the importance of learning statistics has been established, there exists barriers to exploring this field. For example, there is a common fear that the course is too challenging and demanding.

To demonstrate this problem in teaching medical statistics at a national level in Mexico, our team carried out a study in which most available curriculums from medical schools across the country were reviewed. In this study, we found that less than half of the curriculums included at least one subject of medical statistics over the entire undergraduate course, independent from the requirements of the medical education national board accreditation.[3] This was an important finding because the academic expectation is that physicians have reached a theoretical competence in this subject upon graduation. The National Bachelor's Degree Exit Exam evaluates statistical and

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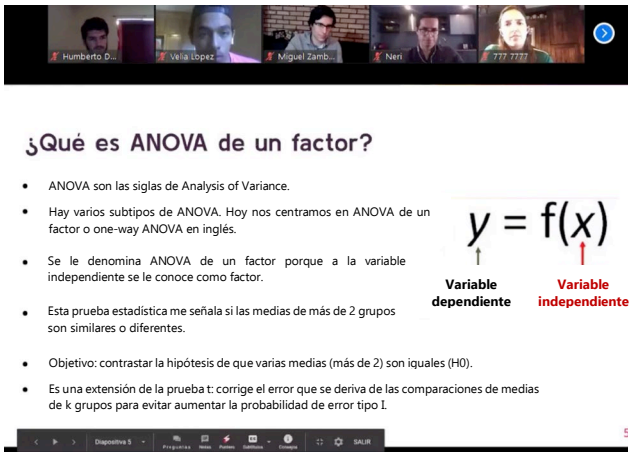
epidemiological concepts in its syllabus,[4] thus emphasizing the need to teach epidemiology and statistical courses in undergraduate programs.

One of the greatest privileges of our medical school is the vast availability of professors who engage in research, thereby providing ample guidance to students interested in the field. Students, therefore, have role models and are inspired to become academic physicians through participation in publishing, conferences, and presentations. In essence, the authors of this work have become statistical enthusiasts with some level of expertise obtained after supervised training sessions and mentoring with real scientific work performed in our university. We have had the opportunity to aid in decision-making for research protocols being performed by other undergraduate and postgraduate students and professors who reached out to the statistical consultation services offered by our school (*Figure 1*).

Figure 1. During the COVID-19 Pandemic, our Statistics Team Continued Training via Internet Video Meetings. One of the Team Members is giving a Workshop (in Spanish) on Statistical Tests performed for comparing more than two groups, such as the One-way ANOVA Test.

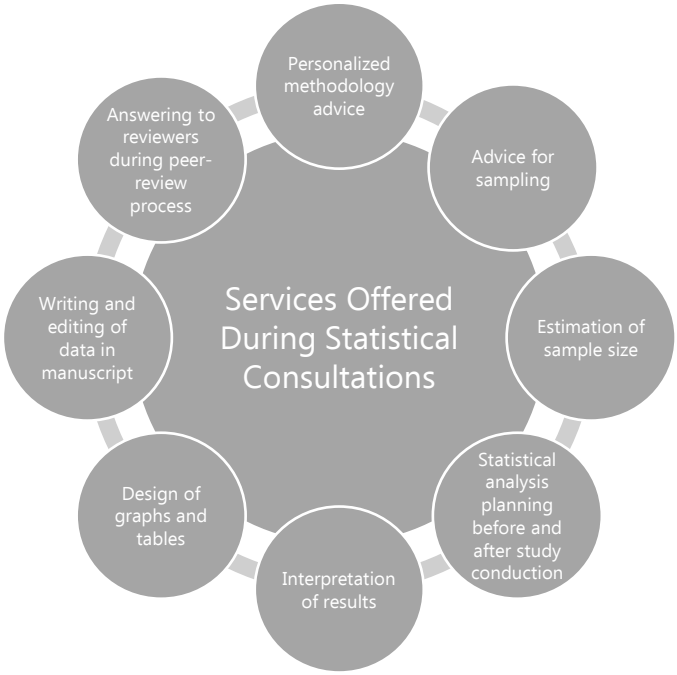


To give readers context, some of the activities that we were able to perform during the statistical consultations were related to methodological advice personalized to each research protocol design, ideas for sampling and estimation of sample size, performance of statistical tests in accordance to the needs and objectives of each study, advising in the interpretation of results and design of graphs and tables, presentations of medical statistics topics, and even getting the opportunity to be involved in research when there was a need for an additional collaborator (*Figure 2*). During the consultations, the petitioner usually came at different phases of their project (from the idea, writing the protocol, processing data, statistical analysis, and final report for diffusion). Our task was to aid each fellow researcher adhere to the research methodology, provide help in performing and interpreting statistical tests, and give guidance in merging the components of their project.

Although teaching basic epidemiologic and statistical theories are essential for understanding more advanced practical notions, we recommend that these subjects include more practical approaches and therefore, spend less time teaching impractical concepts such as manually calculating a standard deviation or performing frequency tables. We believe that the subjects related to these topics should invest more time in teaching students how to access data, critically appraise the available evidence, design and complete a database, use statistical software for analyzing, interpreting, and contrasting data from other prior knowledge, and earn the competence to make inferences and conclusions from other studies, aside from the authors' criteria.

Although many of the activities and skills that we have been trained in have been obtained on an extracurricular basis, most of these scenarios could be replicated in the classroom. From this perspective, each student would be able to understand and agree on the need for the acquisition of these essential scientific abilities for his/her clinical practice and possibly further activities related to work or achievement of a postgraduate degree.

Figure 2. Supervised Statistical Services Offered in the Consultations by the Student Statistical Team in Training.



To overcome these barriers, it is required for both medical education providers and students to acknowledge that there is an increasing need for physicians to be competent in delivering evidence-based decisions and that medical education must supply tools for addressing this demand. To resolve this issue, medical schools should consider obligatory and complete courses related to these subjects, as well as other elective courses that meet the needs of different student interests. For students who are interested in clinical statistics and research, we believe the best way to learn, at least in our setting, is to reach out to a

fellow researcher who is actively engaged and willing to consider a mentoring relationship in the field you have most interest. Even though many medical students can change their fields of interests as they advance in medical school, the knowledge that they will obtain from these experiences can be universally applied to any field involved in clinical statistics and research. .

Summary – Accelerating Translation

Entrenar y alentar a los estudiantes a revisar críticamente la evidencia y tomar decisiones basadas en evidencia debe ser una de las metas de la educación médica. Presentamos nuestra experiencia en el desarrollo de un equipo estadístico extracurricular de estudiantes universitarios que ofrece ayuda estadística a otros estudiantes de licenciatura y posgrado, y a profesores. Esto incluye sesiones de formación supervisadas y tutorías en diversos campos de la investigación científica realizadas en nuestra Universidad.

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Experience

"*Passengers, May I Have Your Attention Please...*" – The Airport Diaries of Young COVID-19 Warriors

Shweta Gajare,[1] Alhad Mulkalwar.[1]

Abstract

This article summarizes the novel experiences of a team of medical interns posted at Chhatrapati Shivaji Maharaj International Airport, Mumbai in the midst of the COVID-19 Pandemic. The authors describe the protocols, guidelines, duties, and procedures that were to be followed while deputed to screen the incoming international passengers for possible exposure and symptoms of coronavirus. For the young healthcare workers in the early days of their internship, being a part of this team was no less than a roller coaster ride. From anxiety and excitement to fatigue and crippling exhaustion, the authors narrate their ordeal as young COVID warriors on duty.

Key Words: COVID-19; Airport; Screening; Quarantine; Internship (Source: MeSH-NLM).

Experience

"Passengers, May I Have Your Attention Please..." even in the wildest of our imaginations, we never would have guessed that this would be our first announcement as healthcare workers. After a gruesome final year of M.B.B.S., we were now ready to enter our hospital internship as doctors. While some may find it hard to equate interns with doctors, in our minds, we were no less than integral and indispensable pillars of the healthcare system. It was the time to don that prestigious white coat and apply, in practice, the five years of rigorous training that we had endured. However, little did we know that along with our clinical internship, this was also the beginning of a new global event with unprecedented ramifications - the COVID-19 pandemic, which would alter everything and anything we thought we knew.

It was as early as our third day of internship at the hospital when 15 interns from our batch were summoned by the Dean. Clueless as to what this was all about, we rushed to the office where we were informed that our team was to be a part of the delegation to the Chhatrapati Shivaji Maharaj International Airport, Mumbai to screen the incoming passengers in view of the ongoing pandemic. We collected our PPE (Personal Protective Equipment) and immediately departed for the Airport Health Organization (APHO). There was a surge of mixed feelings amongst us - the thrill of doing something important for the nation and the excitement of a novel experience as medical professionals, alongside the fear of fighting an unknown adversary. On the way to the airport, we were briefed about the safety guidelines, including the signs and symptoms and management protocols used by other countries at that time. As India had reported only a couple of cases by then, domestic protocols were still evolving. At the beginning of the pandemic, we had little data on all these characteristics of the SARS-CoV-2 virus. However, we resolved to face the challenge 'head-on' with the guidance of our mentors. We reported to the APHO and were handed our airport staff ID cards. After the documentation and other official formalities were completed, we were directed to the staff canteen for lunch where we got an opportunity to interact with interns and residents from other colleges who were also deputed at the airport for the same duty. We were then handed our schedules and briefed on the screening protocols to be followed and given instructions regarding management of passengers, positioning of stanchions and use of megaphones for crowd control at the arrival terminal of the airport.

Our work profile included the screening of all incoming international passengers and members of the cabin crew. Once all passengers on-board a particular flight were screened completely, we would then issue clearance to the airlines. There were multiple counters set at the arrival terminal for the screening, thereby ensuring a one-meter distance between the passengers and the Medical Officers (MO). Passengers were given in-flight self-health declaration forms by their respective airlines. They were asked to fill the forms during their journey and then submit the same at the screening counters. A copy of the form was to be kept by the MO for records and the original was given back to the passenger with the APHO stamp after clearing the screening procedure. All passengers were required to produce the APHO stamped health forms at the immigration counter, and failure to do so would impact the immigration process. The

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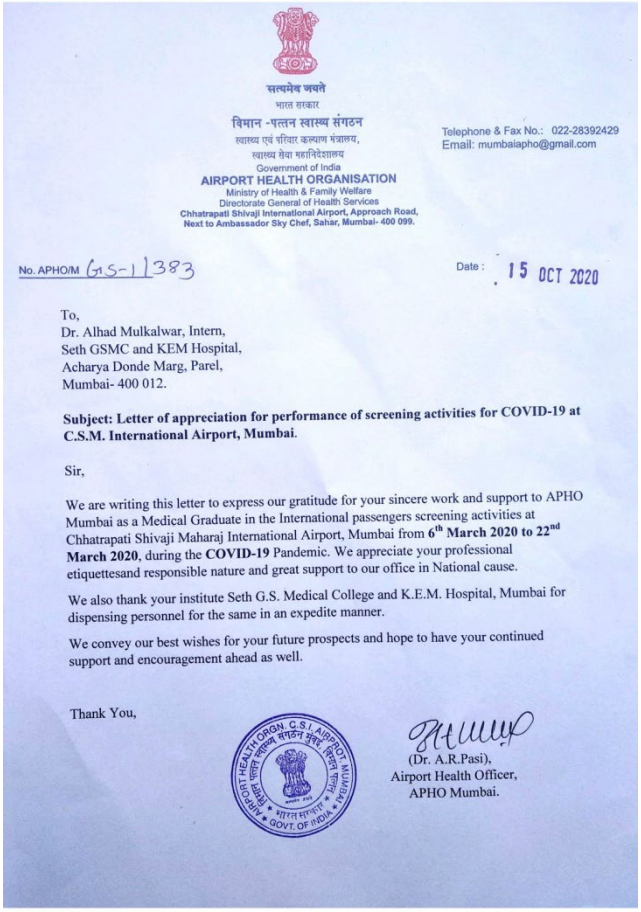
screening procedure consisted of recording the body temperature using a thermogun (infrared thermometer), identifying the basic symptoms of ILI (Influenza-like illness), making a note of any comorbidities, and asking about travel history to Wuhan, China within last 14 days, as this was the location of patient 0 and the known incubation period of coronavirus. Those passengers who were at a higher risk (positive travel history or greater than 60 years of age) or those who showed any symptoms were directly transferred to the nearest hospital for further work-up. By that time, India had banned all the flights from China to avoid any possible exposure to the virus. However, we were very apprehensive about the lack of information and studies on the infectivity and communicability of the virus. Also, constant news of the exponential spread of the infection across the world and failure of even the developed countries to contain the same was demoralizing. Assuring our worried and concerned families amidst this catastrophe was another Herculean task. It was like fighting a mysterious evil. Little did we know that this was no less than a forest fire. Almost every alternate day, the list of red countries (to check for travel history to countries with higher infection rates and/or increasing case load for high risk of exposure to COVID-19) became longer and longer. After China, many European countries were added to the list. Gradually, the issuance of new visas was suspended and those with old visas had to carry a negative COVID test report, which was to be conducted within 48 hours prior to the departure of the flight. Then, on March 11th, 2020, the World Health Organization declared the COVID-19 spread a pandemic.

With the escalating situation of pandemic and increasing mortality rates, the guidelines were frequently updated and we ensured to obey the new protocols. Initially, we used the health declaration forms and thermoguns to screen the passengers. Healthy international passengers who would clear the screening were stamped on the dorsum of hand, indicating that they were to mandatorily quarantine themselves. The stamp read 'HOME QUARANTINE' along with the date until which the person was to be quarantined. They were generally asked to be quarantined for 14 days at home, if possible, or at a government facility.

Figure 1. Our Team of Doctors at Work at the International Arrival Terminal of CSI Airport, Mumbai.

Figure 2. Appreciation Letter Received from the Airport Health Authority, Mumbai.



सत्यमेव जयते
भारत सरकार
विमान -पत्तन स्वास्थ्य संगठन
स्वास्थ्य एवं परिवार कल्याण मंत्रालय,
स्वास्थ्य सेवा महानिदेशालय
Government of India
AIRPORT HEALTH ORGANISATION
Ministry of Health & Family Welfare
Directorate General of Health Services
Chhatrapati Shivaji International Airport, Approach Road,
Next to Ambassador Sky Chef, Sahar, Mumbai- 400 099.

Telephone & Fax No.: 022-28392429
Email: mumbaiapho@gmail.com

No. APHO/M GIS-1/1383 Date : 15 OCT 2020

To,
Dr. Alhad Mulkalwar, Intern,
Seth GSMC and KEM Hospital,
Acharya Donde Marg, Parel,
Mumbai- 400 012.

Subject: Letter of appreciation for performance of screening activities for COVID-19 at C.S.M. International Airport, Mumbai.

Sir,

We are writing this letter to express our gratitude for your sincere work and support to APHO Mumbai as a Medical Graduate in the International passengers screening activities at Chhatrapati Shivaji Maharaj International Airport, Mumbai from **6th March 2020 to 22nd March 2020**, during the **COVID-19** Pandemic. We appreciate your professional etiquettesand responsible nature and great support to our office in National cause.

We also thank your institute Seth G.S. Medical College and K.E.M. Hospital, Mumbai for dispensing personnel for the same in an expedite manner.

We convey our best wishes for your future prospects and hope to have your continued support and encouragement ahead as well.

Thank You,

(Dr. A.R.Pasi),
Airport Health Officer,
APHO Mumbai.

The last week of airport duty, which was also the week before the lockdown, was the busiest of all. The Government of India had declared a Pan-India lockdown beginning on March 24th, 2020 – this resulted in huge number of Indian citizens abroad making last minute reservations to return home. By then, we had started quarantining all passengers aged greater than 60 years old and those with any existing comorbidities for 24-48 hours at the nearest government facility for observation. All such passengers underwent Rapid Antigen Test or RT-PCR, as indicated, and were kept under observation until a negative report was produced. If positive, they were isolated and treated accordingly. This helped to reduce the mortality rate to a greater extent as many cases were detected in this screening process amongst the high-risk patients, facilitating early intervention and recovery.

The 12 hour night shift of March 22nd – 23rd was our last shift at the CSI Airport. It was a Sunday and India had already implemented a weekend curfew by then. The streets were deserted, which was a rare sight for the usually chaotic city. On arrival, a long queue of the passengers awaited us. All the flights were arriving at maximum capacity as it was the last day for entry into India before the international borders were to be closed. That night proved to be our most hectic duty as we screened an enormous number of passengers.

The next morning, at 8am, was the end of this riveting journey at CSI airport Mumbai and the end of Phase 1 of our internship or "The COVID Internship"! While returning from the airport, something did not feel right; it was if someone had stopped time. This was something that will never be forgotten - the only vehicle running on the roads of the busiest city was our bus! The city of dreams, known for its speed, was as calm as the adjoining sea. The police check points on the roads ensured enforcement of the lockdown. As fascinating as the experience was, we would never wish to relive it. Hopefully, we will not experience such a disaster again. Even if such a time comes, let us hope that we will have learnt from our prior mistakes and are able to mitigate accordingly.

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Letter

Navigating Research Enthusiasm in Medical Students Towards Clinically Impactful Articles

Muhammad Abdul-Qadeer,[1] Danish Ramesh,[2] Samar Mahmood.[3]

Abstract

Learning medical research is an integral part of the development of a holistic physician. Although not all physicians become clinician-scientists, those who do enjoy significant privileges over their clinician-only counterparts, mainly in terms of faster career progression and higher employability. To produce more well-rounded clinician-scientists, academic physicians and medical scientists need to make themselves available and be willing to work with and mentor medical students. A curriculum reform is warranted where students should be encouraged to start learning and conducting research in their first year of medical school. To make the process even easier and help scale these ideas, students should be encouraged to replicate previous highly cited studies, as they can provide a walkthrough for students to follow, thereby necessitating lesser supervision while maintaining the clinical impact that can be made with their time and effort.

Key Words: Research; Medical Students; Journal Impact Factor; Mentorship; Learning; Evidence-based Medicine; Curriculum; Medical School; Medical Education (Source: MeSH-NLM).

Introduction

Learning research as a medical student is important for various reasons, such as the growing acknowledgement that clinician-scientists perform better as physicians.[1] In addition, publishing prior to graduating from medical school has shown to carry an even greater promise for the learning physician, both in terms of opportunities for postgraduate training and in academia.[2,3] This awareness has increased the accessibility to basic research training and skill development, with numerous online and in-person courses to support learning. In order to progress from just the development of an exceptional idea to publication and gauging its clinical relevance, adequate experience in the specific field is required, and this is where students find themselves lost and without the help of a mentor. As a result, such students' articles only make it to journals with very limited readership and scope and the impact of their work remains limited.

According to two scientific studies, students who publish during their time in medical school were significantly more likely to continue publishing ($p < 0.001$), publish more frequently ($p < 0.001$), and have a mildly greater citation impact after graduation ($p = 0.005$).[2,3] One of these studies also suggested that most students (87%) who perform research as part of their curriculum (research internship) complete medical training in the minimum amount of time.[2] These students were also likely to have a higher chance of securing employment in academic medical centers.[2] Working under a mentor who focuses on clinical research, as well as one who has prior publication(s) with prior mentees, has shown to increase the likelihood that the mentee/student will publish research articles by successfully completing their tasks.[4] Furthermore, students who were involved in research during their academic careers had increased motivation, while doctors, who had been involved in the same, formed accurate diagnoses.[5,6]

It is apparent that publishing research in medical school years is difficult.[2] Therefore, there needs to be a systematic change, whereby medical schools adopt research as part of their curriculum.[2] For a start, clinical physicians with clinically relevant ideas could be paired with students who are available and interested in developing their skills to conduct research. Such a setting would also teach medical students valuable skills and traits that are deemed necessary for a future physician to possess, such as appropriate behavior towards team members, building team spirit,[1] and developing a strong work ethic, early in their careers.[2] Within their curriculum, students should be encouraged, and even guided, to read recent articles relevant to their module of study in widely acclaimed journals. This would help them understand the characteristics of good quality articles, making writing seem like a less daunting task. An effective first step towards execution would be to conduct the research module for students in their first year, as opposed to introducing it in the

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clinical years, so as to equip them with the researcher's perspective and the necessary skills at an early stage. Additionally, plenty of funding needs to be allocated to hire professors who are proficient in research methodology, to make latest guidelines and articles more accessible to students, as well as to enable the conduction and completion of research projects without a shortage of funds.[6] In addition to this, motivating students to participate in research competitions and then sharing their experiences with their juniors will encourage more participation in research.[6] Moreover, integrating compulsory, practically-focused statistics courses in their curricula will help students hone the much needed skillset of applying statistics in data analysis to make their own inferences.[7] Furthermore, replication studies are a good opportunity for students to gain an initial insight, as they provide a rough walkthrough for researchers to conduct their study while allowing them to work on what has already been highlighted as clinically relevant. Many frequently cited studies are seldom replicated- a necessary step in improving the credibility of the scientific theories derived from these studies.[8,9] The results obtained from these studies on the same topic across varying demographics, such as age, gender, geographical locations, or even time period, may present with diverse results and thus could aid in broadening previous hypotheses and/or generating new predictions.[8,9]

In conclusion, performing a study and writing a research article is undoubtedly a learning curve, with students starting small and progressing as they refine their skills. However, with the help of more experienced academic doctors and medical scientists, the growing interests of new researchers can be channeled towards clinically relevant and impactful research studies - a steer that will benefit both the students and academia at large.

Summary – Accelerating Translation

The importance of learning about research has increased for medical students around the world. As a result of their increased skill set, it helps individuals climb the job ladder more quickly and increase their employability. Academics in the medical field need to be more willing to offer their time to teach medical students who want to become academic physicians about their profession in order to make this all more feasible. If their curriculum pushes them to learn research, it can also aid in the objective of creating more academic physicians. This can be made simpler if students do previously published high-impact research because the same research can still have a significant influence when conducted on a different or even similar demographic. Because it takes less mentoring to replicate a study than it does to create one from scratch, replicating studies can also reduce the scarcity of academic mentors.

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Author Contributions

Conceptualization: MAQ, SM. Project administration, Writing – original draft: MAQ, DR, SM. Writing – review & editing: MAQ, SM. Supervision: SM.

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Errata: Volume 10; Issue 4, 2022

Executive Committee of the International Journal of Medical Students.

Errata

The following items published in the International Journal of Medical Students (IJMS) Volume 10, Issue 4 of 2022 were corrected on February 20, 2023:

"A Cross-Sectional Study of p66Shc Gene Expression in Liquid Biopsy of Diabetic Patients. Is it Possible to Predict the Onset of Renal Disease?" was corrected for capitalization errors in the title.[1]

"Elective Courses in Global Surgery for Undergraduate Medical Students: A Narrative Review and a Proposal for European Universities" contained an error in the DOI on the footer of page 395. The correct DOI is: 10.5195/ijms.2022.1598.[2]

"Why the Furor about Polio?" was corrected for a spacing error in the title in the PDF version.[3]

In the article entitled "Research Experience of Medical Students Collaborating in an International Peer Research Mentorship Program", there were errors in the fourth and fifth authors' names. The correct names are: Aysha Zulfiqar and Tejaswini Ashok.[4]

"'First, Do No Harm'... A Call to Re-evaluate the Wellbeing of Healthcare Staff" was corrected for a spacing error in the title.[5]

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